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Seminar Report

Child Health Priorities for the 1990s

The Johns Hopkins University
Institute for International Programs

Child Health Priorities for the 1990s

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Introduction

Background

A seminar was held in 1988 under the auspices of the Johns Hopkins Institute for International Programs concerning issues for the 1990s in child survival programs[1]. Gadomski and Black (1988), in a paper prepared for the seminar, presented assembled evidence that strongly suggested an impact of direct child survival programs in reducing child mortality. However, the strength of the evidence of mortality effects of national intervention programs varied widely from one intervention to another. In many cases, the empirical basis available for drawing conclusions about the impact of large scale programs was very weak.

A follow-up seminar, "Child Health Priorities for the 1990s", organized by the Institute for International Programs with financial support from the United States Agency for International Development and the World Bank, was held at the Johns Hopkins School of Hygiene and Public Health in June 1991. There were two main objectives of this second meeting: first, to examine in more depth, making use of important new data, the question of the impact of child survival interventions, disease by disease, and second, to attempt to examine the issue of cost effectiveness of the various child survival interventions potentially available. The seminar program, and a list of participants, appear at the end of this volume.

In order to achieve the first purpose, assessing program impact, a number of commissioned papers reviewed what is known about the impact of a wide range of child survival interventions. These papers, which make up the bulk of this volume, have been divided into four groups: those dealing largely with vaccine programs; those dealing largely with case management interventions; those addressing nutritional interventions; and those addressing behavioral interventions. These distinctions are not always clear, of course. For example, tuberculosis programs include both vaccination and case management, but here the discussion of both types of intervention is included under vaccine programs. Another example is acute respiratory infections, for which case management is the predominant intervention at present in the developing world, although vaccine development has shown promise. In many cases, the papers go beyond a review of evidence of impact to discuss future priorities and potential for further developments. The papers and the discussion that they generated will be reviewed briefly in this introduction.

The second purpose -- putting interventions in a cost-effectiveness perspective -- was undertaken in collaboration with the World Bank Health Sector Priorities Review. This Review aims to evaluate the cost effectiveness of interventions against a wide range of

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[1] See Child Survival Programs: Issues for the 1990s. Report of a seminar held November 21-22, 1988. Baltimore, MD: The Johns Hopkins University.

health problems, not limited to those of childhood, by applying a consistent methodology based on an assessment of discounted healthy years of life gained. Draft chapters of the Review relating to diseases primarily of childhood were presented to and discussed by the participants of the seminar. However, neither the draft chapters nor the discussion of them will be reported in this volume, since the overall Review is to be published in due course by the World Bank. The chapters discussed, with the names of their presenters and discussants, appear in the seminar program in Appendix 1.

Trends in Child Mortality

The first paper, by Shea Rutstein, presented data on trends and differentials in child mortality in the developing world, drawing heavily on recent data from the Demographic and Health Surveys (DHS) program. These data tend to confirm earlier studies indicating that declines in child mortality observed for the 1960s and 1970s have continued into the 1980s in almost all countries surveyed. Using data from the DHS surveys, the probability of dying by age five (the UNICEF 'Under-5 Mortality Rate') declined over the period 10 to 14 years prior to the survey to the period 0 to 4 years prior to the survey in all 25 countries for which DHS figures are available. For seven countries, the decline over the ten year period exceeded 50 deaths per thousand live births, for a further 15 countries, the decline ranged between 20 and 50 deaths per thousand, and for the remaining three countries, the decline was less than 20 deaths per thousand, the smallest fall being seven per thousand in Uganda. A bivariate analysis of differentials indicates that in general urban children have lower mortality risks than rural children (particularly in high mortality settings), children of educated mothers have much lower mortality risks than children of uneducated mothers, male children have higher risks than female children (though the differences are not large in some countries), and children of young mothers, first births, and births following short intervals are all at above average risk.

Kenneth Hill, in his discussion, showed that estimates of child mortality for the period 1960 to 1985 from a recent United Nations (1990) review were in agreement with the DHS findings on trends. Specifically, the pace of child mortality decline for regions of the developing world has continued almost unchanged over 25 years. DHS data also show a relation between child mortality risks and levels of immunization coverage, though differences in both variables could reasonably reflect variation in some third factor such as health service efficiency. Recent survey estimates of child mortality for two countries suggest some role for program impact. In Bangladesh, child mortality remained virtually unchanged from the 1960s to the early 1980s, but has begun to decline in recent years, at a time when primary health care measures have been expanding. In Egypt, child mortality has been falling for at least two decades, but the pace of decline accelerated greatly around 1985, at the time the national oral rehydration program was taking effect (a point returned to by Rashad in a subsequent session, confirming with the survey data patterns previously reported using national vital registration data for Egypt). The continued decline in child mortality in most regions of the developing world in the face of at best anemic economic performance suggests that some other factor, in all probability program interventions, played an important role in the declines.

Immunizations

Two sessions of the seminar were devoted to a review of the effect of vaccines on child mortality and morbidity. In the first paper, Michael Koenig reviewed evidence of the impact of measles and tetanus vaccination on child mortality.

In the mid 1980s, measles was estimated to be responsible for nearly two million deaths world wide of children under age five each year. In a review of five community studies of the impact of measles vaccination, mortality in the age range of roughly nine to 60 months was reduced by some 40 percent, the results being surprisingly consistent across studies. Results from the studies provide no support for the 'replacement mortality' effect sometimes postulated, whereby deaths averted by measles vaccination succumb to some other disease in a short period, thus reducing the impact of the vaccination on overall mortality. Neither seasonality, nor the patterns of survival curves to age five, nor the impact on high risk groups supports such an effect, tending indeed to suggest some beneficial synergy, whereby vaccination against measles reduces mortality from other causes also.

Neonatal tetanus was estimated to be responsible for some 800,000 infant deaths annually in the mid 1980s. Immunization of the mother before or during pregnancy provides a high level of protection for the child. Studies from Matlab in Bangladesh indicate a reduction in neonatal mortality (typically the age range with the mortality rate most resistant to change) of over 30 percent (reducing the rate by 20 to 35 per thousand) for the children of mothers who received two doses of tetanus toxoid. Similar large reductions in neonatal mortality were reported from studies in New Guinea and Colombia. Clearly, however, the impact of tetanus immunization on child mortality depends on the pre-existing incidence of neonatal tetanus, which varies substantially by culture and ecological zones. The Matlab data, based on a population in which tetanus toxoid had been used as a placebo in an earlier cholera vaccine trial, also indicate that the duration of protection of newborns of mothers receiving tetanus immunization may be much longer than previously thought, up to at least 15 years, and that even one dose may provide some short-term protection.

Looking at the combined effects of both measles and tetanus immunization, Koenig indicates that in a study population in Bangladesh, the potential impact of measles and tetanus immunization would be to reduce the probability of dying by age five from the baseline level of 206 per thousand live births to 140, a reduction of one-third.

The discussant, Felicity Cutts, emphasized the lack of clear evidence of a replacement mortality effect of measles immunization, in particular the erroneous conclusions about this effect drawn from the Kasongo study. With regard to measles, the case for impact was clear. Vaccination should ideally be given as early as possible, at around age nine months, but studies show that vaccination at later ages also confers survivorship benefits relative to non-vaccination. Thus attempts should be made to attract older children for measles vaccination if they were missed in early childhood, perhaps through linking vaccination with school enrollment. Cutts saw the findings from Matlab of prolonged protection of tetanus immunization as of great programmatic importance. The need to reach potential mothers with tetanus immunization adds an important family dimension to programs.

The ensuing discussion focused largely on the issues of age at measles vaccination

and the development of vaccines that can be given before nine months of age in populations with substantial incidence levels in early infancy. Concerns were expressed about immunological responses to high titre vaccines given prior to nine months. The lack of investment in recent decades in vaccine development was pointed out as a barrier to progress against both measles and neonatal tetanus.

In the second paper, Mark Steinhoff reviewed the role of respiratory tract infections in child mortality, and the possible impact of future vaccines against influenza and pneumonia infections. Respiratory infections account for some 30 percent of child deaths worldwide. The Expanded Programme on Immunization (EPI) incorporates DPT vaccine, providing protection against diphtheria and pertussis. Diphtheria appears not to be a major cause of morbidity or mortality in the developing world, but pertussis is estimated to have been responsible for some half a million child deaths annually in the mid 1980s. Clinical trials have shown pertussis vaccine efficacy to vary widely, though most authorities regard it as being 80 to 90 percent efficacious. No impact studies have been carried out in developing countries, though experience from developed countries is relevant. Pertussis cases declined sharply with the universal introduction of DPT some 50 years ago, but coverage declined in the 1970s and 1980s as a result of concerns about side effects. This decline was followed by scattered pertussis epidemics, including deaths, though the epidemics moderated as vaccine use increased again. New acellular vaccines with lower risks of side effects are in the process of development and testing.

A major portion of acute respiratory infection mortality arises from the bacterial agents Streptococcus pneumoniae and Haemophilus influenzae type b. Introduction of H. influenzae type b conjugate vaccine into existing EPI programs could reduce pneumonia mortality in children under five by seven to 16 percent. Given that the vaccine is safe and effective, consideration should be given to adding the conjugate vaccine to standard EPI programs as soon as the cost of the vaccine has fallen far enough. Further information would be useful on the prevalence of H. influenzae serotypes in developing regions. The currently available pneumococcal vaccine is effective against the most important serotypes, but is not immunogenic in children under age two, and would thus be difficult to incorporate into standard EPI programs. However, work is in progress to develop a septavalent conjugate vaccine that would be immunogenic in young children, to be administered at 2, 4 and 6 months. This vaccine would have the potential to be integrated into standard EPI programs. Illustrative calculations show that the 23-valent current pneumococcal vaccine could avert 25 percent of pneumonia deaths in children aged two to four, but would thus reduce overall childhood pneumonia deaths by only some three percent. The septavalent vaccine could reduce childhood pneumonia deaths by some nine percent because of providing protection from six months, albeit against a much smaller range of serotypes. Immunization of mothers during pregnancy could further reduce pneumonia mortality by providing immunity for the child under six months of age.

The discussant, James Gibson, expressed concerns about the use of Haemophilus conjugate vaccines. Given the lack of field trials, questions arise about the implications for efficacy of multiple simultaneous vaccinations of the type that would be necessary for delivery strategies. Questions also arise about the prevalence of non-type b H. influenzae serotypes in target populations, and about the efficacy of the vaccine in malnourished children. Similarly, the effects of maternal immunization during pregnancy are not

known. Respiratory infections are more syndrome specific than organism specific, so case management may be more appropriate than immunization, at least in the short term. From a cost point of view, case management may also have an advantage, since people are willing to pay for curative services but are unwilling to pay for prevention. The rest of the discussion followed these points, in particular covering the issue of whether, and if so, how to incorporate pneumonia vaccines into an EPI program.

The third paper, by Joseph Melnick, reviews evidence about the impact of polio and hepatitis B vaccines. In the absence of vaccine use, it is believed that about five out of every 1000 children suffers some form of disability, most frequently lameness, as a result of polio infection. National data show clearly that polio vaccination has greatly reduced cases of paralytic polio in developing countries. In Brazil, for example, there were several thousand cases of paralytic polio each year in the late 1970s, falling to an average of only 80 per year in the early 1980s, and essentially no cases in the early 1990s. Even quite low vaccination coverage rates can produce large effects: in Yaounde, Cameroon, for example, only 35 percent of the target 12 to 24 month old children received three doses of oral (OPV) vaccine, but cases of paralytic polio fell by 85 percent. Current OPV programs are preventing at least 400,000 cases of paralytic polio per year. Melnick also discusses the relative merits of oral versus injectable (IPV) vaccine delivery. The OPV seems in most respects to have the edge, largely because it provides gastro-intestinal immunity eliminating the excretion of virus. The vaccine virus also circulates in the environment, competing with the wild virus and thus reducing exposure to the wild virus. However, there are doubts about the 'take' of OPV in very young children, whereas IPV provides an immediate immune response regardless of age.

Hepatitis B is an important disease of childhood not because it kills children directly, but rather because if contracted in childhood it greatly increases the likelihood of an individual becoming a carrier, and of dying prematurely in adulthood of chronic liver disease. It is estimated that there are some 300 million carriers of hepatitis B in developing countries; in highly endemic areas, notably sub-Saharan Africa and Southeast Asia, up to 95 percent of adults have been infected. Of those infected, about 10 percent become persistent carriers, of whom about 25 percent will die of chronic liver diseases, generally at economically productive ages. The probability of becoming a chronic carrier if infected falls sharply with age at infection, from about 90 percent in infancy to about 10 percent after age six. Thus immunization at young ages could be highly effective in reducing numbers of carriers in the population. A series of three intramuscular doses of Hepatitis B vaccine (HBv) at 0, 1 and 6 months induces adequate antibody response, with 80 to 95 percent efficacy in preventing infection or clinical disease. Although antibody levels fall to undetectable concentrations after seven years, protection apparently continues. In an intervention in Indonesia in 1987, introduction of HBv into the existing EPI program boosted the coverage of other vaccines, and reduced HB carrier levels among children aged nine months to two years from 6.7 percent to 1.7 percent in only two years. Efforts are needed to reduce the cost of HBv, currently about US$1 per shot, and to integrate its delivery into the standard DPT vaccine, before incorporating it into EPI programs.

In his role as discussant, Ciro de Quadros reported that the Western Hemisphere polio eradication campaign is close to complete. Wild polio virus affected only 14 out of 14,000 health districts in the Americas in 1990, and only two cases have been

identified in 1991. Though eradication strategies varied from country to country, routine EPI systems were used to provide an infrastructure for control activities. Identified cases were then isolated by massive vaccination campaigns in surrounding areas. One serendipitous side effect of the eradication campaign has been increased coverage with all other EPI vaccines. De Quadros was less enthusiastic about HBv. The cost of US$1 per shot is prohibitive for developing countries. What is needed is the development of risk group profiles, so that high risk groups can be targeted for administration of the vaccine.

The discussion focused largely on two issues, the question of whether a surveillance system had to be established prior to an eradication campaign, and the question of whether eradication campaigns were worth the effort. The necessity of introducing a surveillance system at the start of the program was supported by one speaker on the grounds that it had enabled planners in the polio eradication campaign to identify low serological response to type three vaccine as a barrier to program impact, and thus to demonstrate that a modified vaccine, which was subsequently introduced, was needed. In response, other speakers pointed out that the existing vaccine had done a perfectly adequate job eliminating polio from Europe and North America, and that a surveillance system should not be seen as a necessary precondition of a campaign. The question was raised of the costs and benefits of eradication as opposed to regular EPI activities. The answer depends on the relative magnitude of the extra costs of the eradication campaign versus the discounted future costs of continued immunization, but nobody knows the values involved.

The fourth paper, by Hans Rieder, is concerned with tuberculosis interventions, and bridges the gap between vaccine-preventable and case-manageable diseases. There are estimated to be eight million new cases of tuberculosis per year, some 10 to 20 percent of them among children. The main effect of BCG vaccination is through limiting serious complications of childhood tuberculosis such as miliary disease or meningitis, which are generally fatal if not treated. BCG vaccination does not have additional indirect effects through limiting new adult infections and thus reducing potential transmission to children. The problem of tuberculosis in children, Rieder argues, is most effectively addressed through the aggressive treatment of sputum-positive cases (largely in adults), thus cutting the chain of transmission, combined with preventive therapy of small children who are household contacts of infectious cases. The main constraint on such a strategy is compliance: the so-called 'short-course' drug therapy requires six to nine months of treatment with expensive drugs. In developing countries, the combination of incomplete case finding (perhaps only 30 percent of cases), lack of compliance (perhaps only 50 percent of identified cases) and lack of regimen efficacy (perhaps only 85 percent because of drug resistance) results in the successful treatment of only some 10 percent of cases. What is needed in developing country contexts is a focus on new short course regimens using powerful drug combinations for the first few weeks of therapy, during which period the patient would be hospitalized to improve compliance.

In his discussion, Christopher Murray supported Rieder's point about BCG vaccination providing no reduction of transmission. Thus as infection risks fall, the benefits of BCG are reduced, and case management becomes relatively more cost-effective. He also pointed out that the burden of tuberculosis in children is hard to estimate. He questioned the impact of BCG vaccination on reducing serious

complications, citing the levels of BCG vaccination in Heliojang province of China, above 98 percent, and the occurrence of some 1500 cases of tuberculosis-associated meningitis among children in the same province. Since case detection appears to be lower among women than men, much in-household transmission to children may occur through women; in the developing world, tuberculosis may be the largest killer of women of reproductive age.

The discussion raised doubts about the feasibility of ensuring case management compliance in a developing country setting. However, case management interventions in eastern Africa have apparently been successful in identifying cases, and in case holding, with 90 percent of patients continuing with treatment for eight months or more. The implications of AIDS for treatment strategies were also discussed, the general feeling being that the same strategy, of reducing transmission through case identification and management, was appropriate.

Case Management Interventions

The next section of the seminar was concerned with the impact of case management interventions, specifically the use of oral rehydration therapy to combat diarrheal mortality and the use of antibiotics to limit mortality from acute lower respiratory infections.

The first paper, by Hoda Rashad, examined the impact of the Egyptian National Control of Diarrheal Disease Program (NCDDP) on reducing child mortality in Egypt. A focus on this one program was felt to be justified since it represents by far the largest single-focus oral rehydration program ever implemented. Rashad started by laying down rules by which evaluations should be governed, first determining whether intermediate objectives of the program have been met, and then considering whether any apparent mortality impact was consistent with the intermediate objectives achieved. The NCDDP started in 1984 with the objective of achieving increased use of ORT (consisting of both the use of oral rehydration salts and the continuation of normal feeding during a bout of diarrhea) through training health workers and through a media campaign focused on the recognition of symptoms of dehydration and on the prompt initiation of ORT. Impact studies indicate that the campaign did result in major changes in behavior, with some 40 percent of diarrhea cases in children under age five being treated with ORS, the percentages being substantially higher for cases perceived by mothers as being severe or associated with dehydration. Studies suggest however that the quality of use is not high. Thus program aims have largely been met in terms of frequency of use, if not in quality. To identify a mortality impact, Rashad uses regression discontinuity analysis to examine trends in infant mortality from the mid 1970s to 1988. This analysis reveals a statistically significant change of intercept (indicating a discontinuity in the underlying trend) from 1984 to 1985, exactly the time when the NCDDP should have been showing its most pronounced effects. The change, in infant mortality, post-neonatal mortality, and diarrhea-associated infant mortality, was of about eight per thousand, a decline of about 15 percent in infant mortality and about 30 percent in diarrhea-associated infant mortality. Although Rashad feels that this impact is rather larger than would be consistent with indicators of quantity and quality of ORT use, she concludes that the timing of the discontinuity, with no alternative explanation in terms of coincident changes

in socio-economic factors, is strong evidence of a mortality impact of the program.

The discussant, Norbert Hirschhorn, commented that Rashad's estimate of impact was probably conservative, because it excluded any of the post-1985 decline in infant mortality. Demonstrations of impact using vital registration data are very nice to have, but the inevitable delays are a disadvantage to program managers, who want quicker results. For the impatient, Hirschhorn illustrated the parallel between declining infant mortality in Egypt and the numbers of children receiving intravenous fluids in a particular hospital; the two series follow practically identical trends, suggesting that the latter could be used, at least in Egypt, as a proxy for the former. A similar indicator is provided by the proportion of cases of children with severe dehydration among those with visible signs of any dehydration, which, for the same hospital, showed a sharp decline as total cases declined. Finally, Hirschhorn commented that the ORT campaign in Egypt has probably achieved as much as it can; further declines in child mortality from diarrhea will require reductions in incidence, requiring in turn large social and behavioral changes, perhaps reinforced by the development of vaccines. Others pointed out the important contributions of malnutrition and persistent diarrhea and of dysentery to child mortality and the need for programs to take a more comprehensive approach to diarrhea management.

In the general discussion that followed, it was stressed that the success of the NCDDP in Egypt owes something to the Egyptian context, which is particularly favorable to impact of the type of campaign used. First, access to health services is virtually universal and easy in Egypt. Second, media penetration is extremely high, with a very high proportion of households having their own television. Results in Egypt might not be generalizable to other contexts.

The second paper considered the impact of case management interventions for acute lower respiratory infections (ALRI). The justification for such interventions is that a large proportion of life-threatening acute respiratory infections are caused by bacterial pneumonias, the bacteria responsible for which are treatable by antibiotics. The authors, Robert Black and Sunil Sazawal, carried out a 'meta-analysis' of studies of efficacy, assessing and pooling existing studies as a way of synthesizing their results and increasing potential significance. The results of six field trials were used in the analysis. Each study was ranked by methodological quality and by the extent of co-intervention, and outcomes were analyzed by age categories, study design, and both overall and ALRI-specific mortality. The effects on mortality were not found to vary by methodological quality, and though changes in mortality were largest where co-intervention was most pronounced, significant impacts were identified even in studies with minimal co-intervention. Significant mortality reductions were found for all outcomes, though the absolute magnitudes of the reductions were largest for infant mortality (a reduction averaging some 16 per thousand) and ALRI-specific infant mortality (a reduction averaging some 11 per thousand). The cumulative reduction in under-five mortality from effective case management of ALRI could reach 36 per thousand, roughly equivalent to a 20 percent reduction in infant mortality and a 25 percent reduction in under five mortality. The authors conclude that case management for ALRI can have an impact on child mortality, at least in settings where child mortality is high. Research is needed to determine how to implement a case management strategy effectively within existing primary health care systems.

James Heiby, the discussant, focused on the issue of how to move from evidence of clinical efficacy to national implementation. Quality of care issues become of great importance for implementation, since the treatment is complex. The World Health Organization implementation algorithm defines detailed and readily-measurable standards for the process of care. Quality of care is a measure of the degree to which care actually provided resembles program standards. Impact studies such as those reviewed by Black and Sazawal do not explicitly examine process of care, and program managers and supervisors also frequently fail to monitor this process. Extensive training, careful supervision and emphasis on monitoring quality of care will be necessary components of an effective national (or population-based) program.

The discussion reinforced Heiby's points, several speakers pointing out that implementation processes have been relatively neglected, and that whole new methods of supervision are needed. Existing interventions have been particularly ineffective in early infancy, suggesting that new approaches to case identification and management for very young children could substantially increase the impact of an intervention.

Nutritional Interventions

Three papers were presented to the session on the broad topic of nutritional interventions, the first by Donald Rose and Reynaldo Martorell on protein-energy supplementation programs, the second by Chris Kjolhede on micronutrient supplementation, and the third by Mary Ann Anderson concerning breastfeeding.

Rose and Martorell point out that few studies exist of food supplementation in isolation, since most supplementation programs are combined with broader primary health care delivery. Of the three 'pure' studies identified, perhaps the best, in rural Guatemala, shows a 19 percent decline in infant mortality in the treatment village, compared to a slight increase in the control village. However, since there was only one village of each type, the significance of the mortality difference cannot be determined. Supplementation programs combined with provision of health services show large infant and child mortality declines in a number of settings, but the impact of food supplementation per se cannot be separated out from other program components; surprisingly, in an INCAP study in Guatemala, energy intake was not a significant predictor of time spent sick with diarrhea among six to 18 month old children. Although good direct evidence of the mortality impact of food supplementation is thus lacking, such supplementation has clearly demonstrated effects on intermediate outcomes such as anthropometric status and (through supplementing diets of pregnant women) birthweight. Links have been established between anthropometric status and morbidity: the immune system is clearly affected by malnutrition, and satisfactory anthropometric status appears to be related to reduced episode duration more than to reduced incidence of diarrhea. A number of studies have also shown links between anthropometric status and mortality in childhood, though the nature of the relationship (that is, linear, curvilinear, or threshold) has varied from study to study. The authors conclude that evidence supports the view that supplemental food programs can reduce child mortality and morbidity, though it is difficult to say by how much. It is also difficult to know whether the effects of clinical interventions could be replicated with general supplementation provided through the primary health care system or with a health education program concerning

improved diets in pregnancy and childhood.

In his discussion, Jean-Pierre Habicht characterized the Rose-Martorell interpretation of the evidence as conservative. The role of malnutrition stressed by Habicht is of synergy with disease; disease incidence is little affected, but case-fatality rates vary greatly. The relationship of mortality with degree of malnutrition is proportionately constant across varying levels of mortality, so that, for children below 60 percent of standard weight for age, mortality risk is increased by a factor of ten. However, although risk rises steeply with degree of malnutrition, moderate malnutrition kills more children than severe malnutrition because of the much larger numbers of children involved. The cost-effectiveness of interventions will vary by setting; in a community where purchasing power is adequate, a nutrition education program may be optimal, whereas in a community with inadequate resources, supplemental feeding may be an essential component of a successful intervention. Supplementation of mothers, with beneficial consequences for birthweight, may be a cost-effective way of reducing child mortality.

The general discussion picked up on the need for targeting, and for the provision of technical support for supplementation programs. Such programs need to be integrated into broader primary health care programs, and for efficiency require effective targeting to those in need, targeting that can be provided by widespread growth monitoring.

Kjolhede reviewed the evidence of impact on mortality of micronutrient supplements, with particular emphasis (given its pre-eminence in studies to date) of vitamin A supplements. The prevalence of vitamin A deficiency is hard to establish, but it appears to be most prevalent in the rice staple communities of south and east Asia. In terms of intermediate effects, vitamin A deficiency is associated with increased risk of diarrhea, and diarrhea reduces absorption of vitamin A. There is some evidence of a relationship between ARI risk and mild or moderate vitamin A deficiency, but definitive clinical and field trials are still under way. Measles-related eye disease is more common among those with vitamin A deficiency, and there is clear evidence of reduced measles mortality and shortened morbidity as a result of vitamin A treatment of cases. Most studies show a clear reduction in child mortality as a result of vitamin A supplementation every six months, the reduction being about 30 percent. However, the generalizability of this level of impact is unclear, since most studies were carried out in populations of children with rather high levels of malnutrition and vitamin A deficiency. More needs to be known about the risk populations that would benefit from vitamin A supplementation, as well as about the optimal way of delivering the intervention (capsules, fortification of staples, dietary education, etc.).

The discussant, Ronald Gray, raised concerns about the selection of sites for efficacy trials on the basis of presumed high vitamin A deficiency. Some of the trials also suffer from compliance or observation failures, though the consistency of results across trial sites (with the exception of the Hyderabad study in India) supports the general findings. The case for mortality impact is also supported by the clear evidence of the effect of adjuvant vitamin A therapy on measles mortality and complications. This finding raises the question of whether vitamin A (or other micronutrients) may have a therapeutic role for diseases other than measles.

This latter point was elaborated upon in the general discussion, with emphasis on the need to look at the immune system responses to a wide range of micronutrients, among

them iron (with well-known benefits in pregnancy) and zinc. Specifically for vitamin A, studies would be justified of the mobilization of vitamin A stores during infection, to support the case for a vitamin A supplementation impact on morbidity and mortality.

Mary Ann Anderson reviewed the evidence of health effects of breastfeeding. In any study of the health impact of breastfeeding, it is essential to distinguish between different types: exclusive, predominant, partial, and none. Studies show a dose-related response of mortality and morbidity to breastfeeding, so any collapsing of categories, for instance into breastfeeding or not, may miss important parts of the pattern of the relationship, and also instill false optimism on the basis of high proportions breastfeeding, possibly combined with low proportions breastfeeding optimally. The strongest evidence about health effects of breastfeeding relates to its effect on morbidity. Exclusive breastfeeding appears to be associated with major reductions in morbidity from both diarrhea and acute respiratory infections, the impact being on both incidence and duration of episodes. Similar but smaller advantages are conferred by predominant and partial breastfeeding. A number of studies show a mortality impact of breastfeeding, but many of the studies suffer from one sort of bias or another, the most serious being that of reverse causation, whereby the causal route is sickness on breastfeeding rather than vice versa. However, Anderson suggests that it is safe to assume that the mortality risks of bottle-fed babies would be at least twice those of breastfed babies in the developing world. A recent study in Brazil shows dramatic effects on diarrhea-related mortality (the relative risk of no breastfeeding relative to exclusive breastfeeding being an astonishing 15) and to a lesser extent on acute respiratory infection related mortality. Using recent Demographic and Health Survey data on breastfeeding patterns and a set of assumptions about relative risks, Anderson estimates that the adoption worldwide of optimal breastfeeding patterns (exclusive breastfeeding to age four to six months, and continued partial breastfeeding well into the second year of life) would reduce by two million the current figure of 13 million annual deaths under age five in the developing world.

In her discussion, Julie DaVanzo argued that more information is needed about within-country variations in breastfeeding practice. The advantages of breastfeeding are likely to be largest in the subpopulations with the poorest sanitation conditions, and unfavorable interactions of practice and conditions could be used for intervention targeting. DaVanzo cited recent evidence, partly from a reinterview of a Malaysian population and partly from the DHS, showing that downward trends in breastfeeding do seem to have been reversed in many parts of the developing world, though more work is needed on why. A final problem for setting policy guidelines that must be confronted is that of Acquired Immune Deficiency Syndrome (AIDS), and the risks of transmission from mother to child through breastmilk.

The serious problem raised for studying both morbidity and mortality effects of breastfeeding by the cessation of breastfeeding when a child becomes sick was discussed further. In the Cebu study in the Philippines, an attempt was made to avoid the resulting bias by incorporating birthweight into the regression analysis of impact, but there is no perfect way of avoiding bias altogether. Other intermediate effects of breastfeeding provide useful confirmation of impact, however, such as the improved vitamin A status of breastfed children, and the avoidance of growth stalls during bouts of diarrhea for children that continue to be breastfed. Optimal practice appears to involve four to six months of exclusive breastfeeding, but such a regimen is associated with slower growth

than infants on a mixed diet; new growth curves are needed to reflect the slower, but nonetheless satisfactory, growth of exclusively-breastfed children.

Behavioral Interventions

The session on behavioral interventions consisted of two papers, one by Alonso et al. presented by co-author Allan Hill on the impact of treated bed nets on child mortality in The Gambia, and the other by Bonita Stanton on more directly behavioral interventions.

Alonso et al. present data from a carefully designed study of the use of treated bed nets in rural villages in The Gambia. The intervention should not strictly be described as behavioral because the main behavior involved, sleeping under bed nets, was already well-established. The intervention consisted of washing bed nets in insecticide in one group of villages (and also administering malaria prophylaxis to a sub-group of the children) but not in another group. Vital events were monitored by registrars, and basic rates were checked against direct and indirect retrospective methods. Verbal autopsies were used to identify cause of death for children. The effects of the intervention were dramatic. The probability of dying in the bed net villages dropped by more than 50 percent, whereas in the control villages it increased slightly. The declines were most pronounced in the age range one to four (70 percent decline), but the decline in infant mortality was over one third. For specific causes of death, mortality from malaria fell, but a number of other cause-specific mortality rates fell sharply also, particularly for acute respiratory infections. The use of anti-malarials appeared to reduce the mortality from malaria still further, though the numbers were too small to establish a clear effect. The authors draw particular attention to the apparent frailty protection dimension of the intervention.

The discussant, Clive Shiff, noted that malaria has been largely ignored by standard child survival interventions, although the disease is of paramount importance in Africa, where there are very high proportions of children parasitemic with associated anemia and impaired immune competence. The use of treated bed nets can be seen as a community vector control strategy to replace the vertical vector control programs which were used, often very effectively, in the 1950s and 1960s, but have not been sustained. The main effect of bed nets is as transmission blockers; only about 75 percent compliance is needed in order to reduce dramatically the number of mosquitos able to maintain the extrinsic parasite cycle.

The discussion raised a number of issues about replicability and sustainability. The insecticide dipping of bednets was largely carried out by village women with some supervision from community health workers, so costs were minimal and the intervention could be readily replicated. However, in communities where sleeping under nets is not the norm, such as in much of eastern Africa, behavioral modification through health education would be necessary. Mosquito resistance to the insecticide is not seen as a major problem, since it is only those mosquitoes that come indoors to feed that get killed. It remains to be seen whether mosquito behavioral modification, such as biting during the day, will take place. In general, the simplicity of the intervention, the lack of viable alternatives, and the apparently huge synergistic gains in child survival, make it a very attractive candidate for widespread implementation in areas where malaria is a

serious problem.

Bonita Stanton's paper takes a rather different approach from that used by other authors. She takes it as given that behavioral interventions can work to change behavior and hence improve health outcomes, and then proceeds to discuss how the interventions should be conceived, planned and implemented. Interventions can be aimed at reducing risk-associated behaviors or promoting protective behaviors. A behavioral intervention selects a mechanism through which change is thought to operate, a method of communication, a target audience, and a dose thought to be sufficient to bring about change. Using a framework for the development of a behavioral intervention, designed to make full use of existing knowledge relevant to the task in the social and epidemiological disciplines, the literature concerning hygiene and diarrheal disease is reviewed to determine how fully the different parts of the framework are utilized and described. Though the articles considered all included citations of relevant epidemiologic literature, there was minimal reference to findings from the social science literature. Much more needs to be done to incorporate the relevant findings of social science research into the development and implementation of behavioral interventions.

In her discussion, Margaret Bentley noted that there has been a major shift in recent years towards interest in health behaviors, evident, for example, in the World Health Organization Control of Diarrheal Diseases program. Continual reinforcement is necessary for behavioral messages, in the health field just as in any advertising activity.

The main theme of the general discussion was the complexity of engineering behavioral change. It is not just the message itself that is important (though the behavior change can be pleasant, such as bed nets, or unpleasant, such as giving oral rehydration to a small child), but also a whole range of other levers, such as subsidies, costs, coercion, or penalties (such as requiring immunization certificates for school admission) that reinforce compliance. Nor should behavioral change be seen only as of value for recipients of health care: providers also need to change. Further, behavioral models need to be simplified in order to be of value for planning interventions.

Service Utilization

Ties Boerma presented information from the DHS on utilization of health services. Immunization trends have been strongly upward in the second half of the 1980s. Knowledge of oral rehydration therapy is quite widespread, though actual use is still fairly low, and has probably not had any impact on mortality until the late 1980s. The declines in breastfeeding seen in the 1960s appear to have been halted and in some cases reversed in the 1980s, with increases in some cases both in proportions ever breastfeeding and duration. Large fertility declines are observed in almost all the DHS countries, in many cases as large as 15 to 20 percent of total fertility in a decade. Given the timing of the increases in immunization coverage and oral rehydration use, the child mortality declines observed in the early 1980s cannot be ascribed to them. However, relationships do appear in the cross-national data between antenatal and delivery care and infant mortality, and between measles vaccination and mortality in the age range one to four, though of course no causal link can be assumed, because in each case changes in the dependent and independent variable may be driven by some third variable such as health service efficiency. There is still much that can be done in analyzing service use

data from the DHS program.

Disease Synergy

Becker, Black and Brown reanalyzed data from Bangladesh on weight gain, energy intake, and days sick with diarrhea or fever. The original analysis had shown that, after allowing for age of child and energy intake, weight gain was adversely affected by the proportion of days sick with either diarrhea or fever. However, the original analysis did not examine the issue of the joint effect of suffering from both conditions at the same time. A new variable, the proportion of time suffering from both diarrhea and fever, is found to have a significant negative effect on weight gain, whereas the proportion of time with either diarrhea or fever is not significant. The implications for public health practitioners are that children with both diarrhea and fever are exposed to especially high risk of growth faltering and possible negative sequelae, and thus merit special attention from health professionals. It cannot be determined from this data set whether the concordance of diarrhea and fever represents two illnesses, or a subset of diarrhea episodes that are associated with fever.

The discussant, Michel Garenne, expressed concerns about the small size of the sample in the Bangladesh study, and about the impact on results of inaccuracies in measuring weights, and hence weight gain. However, these problems should really only serve to obscure significant results, rather than to create spurious ones. The results, particularly the conclusion of the original study that the main cause of reduced weight gain is inadequate energy intake, raise questions about how the problem of malnutrition can be incorporated into child survival programs. The new indications of synergy between diarrhea and fever in impeding weight gain suggest that dietary recommendations to mothers should form a routine part of case management for both fever and diarrhea.

In the general discussion, it was suggested that the inclusion of energy intake in the analysis could result in underestimates of the impact of infections on weight gain, because of possible effects of the infections on food intake itself. Although on average the effect of illness on energy intake was not found to be large, the effect was found to vary by average level of intake, such that the intake of children with high average energy intakes was not significantly affected by illness, whereas the intake of children with low average intake was significantly and substantially reduced by infection.

Conclusions

The papers presented to the seminar, and the discussion that was generated, leave no real doubt that child survival interventions have reduced child mortality in the developing world over the last decade. Consensus on this conclusion was much clearer at this seminar than at the previous seminar in 1988. It is clear that measles immunization has contributed to falling child mortality, that oral rehydration therapy and antibiotic management of pneumonia have reduced child mortality in some settings, and that tetanus toxoid given to women of childbearing age could reduce neonatal mortality substantially. Further, the widespread use of polio vaccines, leading to the virtual elimination of polio from the western hemisphere, has greatly reduced the prevalence of flaccid paralysis

among children. On the other hand, child mortality has been falling anyway for several decades, and not all of the recent decline can be attributed to child survival interventions. Numerous other interventions have been shown to work in efficacy trials, and further declines in child mortality can undoubtedly be achieved if these additional interventions can be implemented effectively.

Priorities for the rest of the decade include consolidating the gains that have already been achieved, that is, continuing with the main components of the 1980s interventions. At the same time, it is necessary to develop research activities into better, or more effective, or broader programs (for instance, on improved EPI vaccines, on new multivalent vaccines, and on effective case management strategies). As programs become broader, they need to become more context-specific. A critical issue is maintaining financial and other support for child survival programs. The field of public health needs to do a better advocacy job in order to maintain or improve funding levels. The ultimate objective is universal access to a system of primary health care that offers adequate preventive and curative services, plus a referral system. In practice, political appeal drives funding allocation, and high visibility 'magic bullet' programs attract funding easily, but do not necessarily use it efficiently. Part of the advocacy job that is needed for the lower profile primary health care approach depends on demonstrating impact, which in turn requires regular monitoring and evaluation activities. Ultimately, good health for children requires not only technological fixes but also behavioral and social changes. The challenge for the 1990s is to make sure not only that children survive, but also to enable them to achieve their full potential.

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Levels, Trends and Differentials in Infant and Child Mortality in the Less Developed Countries

Shea Oscar Rutstein

I. Introduction

In the past two decades, more reliable estimates of infant and child mortality levels have become available for many countries of the developing world due to the implementation of large-scale fertility surveys. These surveys contain information that permits the direct calculation of infant and child mortality levels without resorting to assumed patterns. The Demographic and Health Surveys program is the current sponsor of many of these surveys as was the earlier World Fertility Survey program. Although mortality estimation was not originally a principal goal of these types of surveys, it is now widely recognized that on the whole they can be used to provide reasonably accurate estimates of levels and recent trends. These surveys have an additional benefit in that estimates can be produced of important mortality differentials, such as for demographic and socio-economic characteristics, that are usually not available from either registration or census data.

II. Levels of Mortality in the 1980s

Levels of infant and child mortality are presented in table 1 for the 28 countries that have undertaken a Demographic and Health Survey and have published the survey report. For comparison, estimates are included from several other countries with sizeable populations that have reports since 1980. However, most of the data for these other countries are from civil registration and are of doubtful quality. They will therefore not be used in the following discussions. Figure 1 presents the levels graphically. Both the table and the figure are ordered by level of under five mortality within each region.

The variation in mortality level is very great overall and substantial even within most regions. The countries with the lowest percentage of children dying before their fifth birthday are Trinidad and Tobago and Sri Lanka with 3 and 3.5% dying, respectively. The countries with the highest levels are Mali and Liberia with 25 and 22% percent dying. If we group countries according to the level of under five mortality as was done in the comparative report for infant and child mortality using WFS data,[1] the following emerges:

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DHS Countries grouped by level of under five mortality
(percentage of children dying before their fifth birthday)

Low (<3%)	Moderate (4-7%)	Moderate to high (8-11%)	High (12-15%)	Very high (16-19%)	Extremely high (20% or more)
Sri Lanka	Tunisia	Egypt	Bolivia	Senegal	Mali
Trin & Tob	Zimbabwe	Morocco		Uganda	Liberia
Colombia	Botswana	Ondo State		Togo	
	Thailand	Kenya		Ghana	
	Mexico	Indonesia		Burundi	
	Paraguay	Peru			
		Guatemala			
		El Salvador			
		Domin Rep			
		Brazil			
		Ecuador			

The ranking of countries by the level of infant mortality tends to follow that of mortality under age five years. However, there is much more variation in mortality for ages one to four years than there is for infant mortality: from 25 to 144 infant deaths per 1000 births and from 3 to 158 age one-to-four deaths. Indeed, in six of the countries surveyed, all in sub-Saharan Africa, the risk of dying between ages one and five is higher than infant mortality.

Neonatal deaths are those that occur in the first four weeks of life. The DHS rates, however, refer to deaths occurring within the first month of life or within 30 days rather than the conventional 28 days.[2] Because of the shape of the relationship of mortality with age at the beginning of life, the effect on the rates is negligible. Overall, neonatal deaths make up slightly over half (52%) of infant deaths, but this proportion varies substantially among the countries surveyed.

In general neonatal mortality varies with the level of under five mortality, but the range of variation is reduced. This is due to the fact that neonatal deaths occur for both "endogenous" or internal reasons such as birth defects and for "exogenous" or external causes such as neonatal tetanus whereas later child mortality is mostly related to the exogenous causes. As under five mortality rates become low, the reduction occurs more in external than in internal causes of death.

III. Trends of Infant and Child Mortality

Data obtained through the use of full birth histories can provide information on recent trends of infant and child mortality. There is a limitation in using the data from a single survey for more extended time periods: Because the data are obtained from women up to a given age at the time of the survey (49 years for most DHS surveys and 44 years for Brazil and Guatemala), as periods of time successively further into the past are studied, the data available of births is restricted to those occurring to successively

younger mothers at the time. Comparisons between two surveys remove the effects of this restriction but differences in coverage and in quality must be taken into consideration.

Table 2 presents under five mortality rates from the DHS for periods 0-4 and 10-14 years prior to the survey and from the WFS for countries with both surveys. Some of the decreases in mortality levels indicated by the DHS data are indeed spectacular: a decrease of 108 deaths per 1000 births in ten years for Mali, 95 for Senegal and 81 for Egypt. Seven countries have declines that exceed 50 deaths per 1000 births, fifteen have between 20 and 50 and three countries have a decrease of less than 20, including Uganda with a decrease of less than 7 deaths per thousand births. These declines are shown graphically in figure 2.

For sixteen countries comparison can be made with WFS estimates. The time trends including both the DHS and WFS data are shown in figure 3[3].

To evaluate whether the decline of mortality slowed in the 1980s due to the generalized economic and balance of payments crises in the less developed countries, comparisons can be made within each survey program between periods 0-4 and 10-14 years before the date of the surveys. In absolute terms, nine countries show larger declines in under five mortality in the 1980s than in the 1970s and seven show lower. In relative terms, however, only two countries show lower declines in the eighties, Ghana and Peru, ten countries show larger declines and four show about the same level of decline. It appears that the 1980s economic crises have not slowed the pace of childhood mortality decline in most less developed countries.

A comparison is also made in table 2 with the most recent DHS-assisted survey for Colombia, where mortality has continued a rapid decline to now fairly low levels.

IV. Socio-Economic Differentials

Comparisons between countries involving socio-economic characteristics can not be as rigorous as we would perhaps like. Definitions and classifications vary among countries sometimes arbitrarily but usually for very good reasons since physical conditions and levels of development differ considerably. Table 3 presents under five mortality rates from the DHS according to type of area (urban or rural), mother's level of education and type of water supply.

Urban and Rural Areas

Criteria for classification of areas into urban or rural vary considerably among the countries in the DHS. The DHS classification is based on the sampling frame, which almost always uses the urban-rural designation of the last census. This is extremely useful for the country in question but complicates international comparison. Thus an area considered urban in one country might have been considered rural in others.

A glance at figure 4 reveals that the excess mortality of rural areas varies enormously from 100 deaths per 1000 births or over in Senegal and Mali to practically nothing in Kenya, Botswana, Sri Lanka, the Dominican Republic, and Paraguay. In Trinidad & Tobago the rural area has somewhat lower mortality than the urban area. The urban-rural difference does not appear to be related to region but does appear to be loosely related to overall level of mortality: the lower the level of mortality the lower the differential.

Mother's Education

Comparison of mortality patterns across countries according to level of education is also problematic. The number of years for completing primary education varies substantially from 5 to 8 years. One solution would be to group mothers by the number of years of education. This is what was done for the cross-national summaries of the WFS and what will most likely be repeated for the DHS comparative series. However, the number of years of education does not tell the whole story. Completing a level of education or entering secondary school is selective on many other characteristics so that there may be a much greater difference in mortality level between 5 and 6 years of education in a country where primary school is completed with 5 years than in a country where it takes 8 years to complete primary. A further complication for comparative analysis occurs for countries that do not span the full range of classification. Examples are Liberia, where very few women have any education, and Trinidad and Tobago at the other extreme, where few women have not completed primary school.

The mortality differentials in table 3 (shown graphically in figures 5a and 5b) are based on completed years of education. In almost all the countries there is a clear decrease in under five mortality with increasing level of education. The outstanding exception is in Trinidad and Tobago where children of women with seven or more years of education have a somewhat higher level of mortality than do children of women with four to six years. In Uganda, Ondo State of Nigeria, and Thailand women with no education have lower mortality than women with one to three years. These small reversals in the overall trends may be due to omission by the former group or sampling error among the latter group. Botswana and Ghana are the other two surveys where a slight reversal is seen between neighboring categories.

Comparing across countries for children of mothers with no education, in only six out of 26 with data have fewer than 10 percent died before age five. In three out of the 26 countries, more than 20 percent of the children have died before five, and Uganda almost reaches this level. Among children of mothers with seven or more years of education, in half of the 26 countries fewer than 5 percent fail to reach their fifth birthday. In only four countries, Mali, Liberia, Uganda, and Ghana, is survival quite difficult even for children of relatively well-educated mothers. On the whole, while the level of the mother's education accounts for a substantial portion of the differences of mortality level between countries, there is still a great deal of variation between countries within educational categories.

Water Supply

Information on differential mortality by water supply demonstrates the versatility of the DHS data, which allow for the investigation of many "non-standard" differentials. The results presented in table 3 come from a paper by Loaiza and Ekouevi for countries that have conducted both the DHS and the WFS surveys.[4] In eleven of the thirteen countries with data, children in households with a piped supply of water have lower mortality than those in households where water is obtained from wells or other sources. The exceptions are the Dominican Republic and Sri Lanka. Since type of water supply is usually linked to socio-economic status in general, the true effect of connecting a household to the piped supply will most likely be smaller than that indicated in the table.

V. Demographic Differentials

Although at first impression cross country comparison of differential mortality by demographic characteristics appears to be straight forward due to unambiguous definitions, differential fertility behavior by socio-economic status underlies categorizations by age at birth, birth order and even birth interval. For example, in one country mostly women of low socioeconomic status have seven or more children while in another women of all levels are likely to do so. Thus selectivity for other characteristics may be important and require multivariate methods to remove confounding factors. However, only univariate results will be presented here.

With the above cautions in mind, infant mortality rates by sex, age at birth, birth order and preceding birth interval can be reviewed from table 4 taken in part from the paper by Loaiza and Ekouevi[5]. I have added the data for the countries where only the DHS survey was done. Differentials are expressed as ratios (to the lowest expected value) in table 5.

Sex

Male infant mortality exceeds female in all countries except for the DHS survey in Trinidad and Tobago. However, the differences are very small in the North African countries for both the WFS and the DHS surveys. Botswana, Sri Lanka and Thailand have very high sex ratios of infant mortality.

Mother's Age at Birth

Children of young mothers (adolescents) and older mothers (40 and over) tend to have greater risks of dying than do children of mothers in the main childbearing period. In all DHS surveys except Botswana and Ecuador, the infant mortality of adolescent mothers is higher than that of mothers in their twenties. In seven countries children of teenage mothers are at a higher than 50% extra risk. On average the risk is 35% greater.

Children of women in their forties are also at greater risk, on average 47%

greater than women in their twenties. In only six countries is the increased risk under ten percent.

Birth Order

The effect of birth order on mortality is not great, except for seventh or higher order children, for whom there is an average of 50% higher mortality compared with second and third children. There is a considerable variation for first births, however. Six DHS surveys reveal lower mortality of first births than second or third and seven surveys show a greater than 20% excess mortality risk.

Birth Interval

All but two DHS surveys, Colombia and Paraguay, reveal greater than 50% excess risk to children born after short birth intervals (less than 2 years) compared with children born after normal length intervals (2 and 3 years). Indeed, eight of 27 DHS surveys reveal more than double the risk of infant death, and average the increased risk is 88 percent. On the other hand, children born after long intervals (4 or more years) have a reduced risk, 19 percent lower on average than children of normal intervals. Only two DHS surveys, Sri Lanka and Trinidad and Tobago, reveal higher risks for long interval births.

When countries are grouped according to the level of under five mortality, excess infant mortality appears to increase for children of women forty and over, and for birth orders four or higher, with decreasing overall level. The advantage of children coming after long birth intervals, however, appears to decline with decreasing level. The excess infant mortality of males, of first births, of children of adolescent mothers and of those born after short birth intervals do not appear to be related to the level of under five mortality (table 6).

Combined High-Risk Reproductive Characteristics

The high-risk reproductive characteristics of being born to a mother who was "too" young (under 18), or "too" old (35 or over), having a "too" high birth order (four or higher), and being born "too" soon after another child (less than 24 months) -- the "four toos", accentuates the risk of childhood death. These risk factors not only have deleterious effects separately, but combinations of risk factors are even worse. For the DHS surveys, Table 7 reveals the excess mortality attributable to combinations of adverse reproductive characteristics. A comparison is made between the proportion dead of children who were born in the five years preceding the surveys with none of the adverse characteristics to the proportion dead of those who were born with one or more such characteristics ("risk ratios"). The table presents means of the risk ratios for countries grouped by level of under-five mortality and for all countries. Certain combinations of characteristics are not shown because of small numbers of children included.

The analysis reveals that, overall, children with any adverse reproductive characteristic die almost twice a much as "low-risk" children. Children with only a single risk are fifty percent more likely to die and children with more than one risk factor are two and a half times more likely to die than "low-risk" children. Among children with only a single risk factor, being born to too young a mother is the characteristic that incurs the highest risk, twice that of children with none of the risk factors. However, children with the combination of too old a mother at birth, too high a birth order and too short a birth interval have almost four times the risk.

When the means of the risk ratios are calculated according to level of the overall under five mortality rate, it appears that at very high mortality levels the detrimental effects of adverse reproductive characteristics become overwhelmed by the general poor health conditions, and relative risks are attenuated.

VI. The Demographic and Health Survey Methodology

Over the years, demographers have developed several methods for measuring the level of infant and child mortality. The conventional approach, suitable for the more developed societies, uses data obtained from the vital registration of deaths and births. This approach breaks down in less developed societies where vital registration is incomplete. The other approaches make use of data gathered in censuses and surveys.

Indirect estimation methods based on the proportion of surviving children to women of differing ages have been used widely, principally using census information. A more recent development along these lines is the preceding birth technique, where a woman is asked about the survival status of her penultimate child at the time of her most recent birth. Though the indirect methods have several drawbacks, in part due to inappropriate assumptions and to likely errors in recorded data, they are useful where other direct methods cannot be used because of a lack of appropriate data.

The methodology adopted by the Demographic and Health Survey (DHS) program is based on information collected in a full birth history obtained from a nationally-representative sample of mothers between the ages of 15 and 49 years. The mothers are asked about the date of birth, sex, and survival status of each of their live-born children, and about the age at death if deceased.[6] Age at death is obtained in days if less than one month, months if one to 23 months and years if more than 23 months. In order to ensure completeness of reporting, before asking about each child each woman is asked whether they have ever borne a child or been pregnant and the number of children living with them, living away, and deceased, by sex. In addition, interviewers are instructed to probe birth intervals that exceed three years.

In the second phase of the DHS program, countries with high levels of contraceptive prevalence use a questionnaire which contains a reproductive calendar for the last five years in addition to the birth history. Since all pregnancy terminations are recorded in this calendar, it is possible to obtain perinatal mortality rates for the last five years as well as rates according to pregnancy interval, provided of course that the data

are of sufficient quality. Since the first such surveys has only recently finished fieldwork, the perinatal rates have not been tabulated.

Once the data have been collected in the birth history, mortality rates are calculated using a synthetic cohort procedure similar to that used for comparative analysis of the World Fertility Surveys (WFS).[7] Briefly, the procedure consists of calculating the probability of dying during a narrow age range among children surviving to the beginning of the range and limited to children who were exposed during a specific time period, taking account of incomplete exposure. The narrow age range probabilities are then combined into the conventional infant and child mortality rates. Narrow age ranges were chosen to allow for the age pattern of mortality. This procedure was chosen over the computationally simpler alternative of using real cohorts in order to take full advantage of the available information[8] and to give a preference to the relationship between mortality and the period of time instead of mortality and birth cohorts.

Another rejected alternative using the DHS data would have been to calculate mortality estimates using the indirect techniques available. Although these techniques are computationally simpler, they make less use of the available information (they disregard age at death), and do not allow for the determination of many of the mortality differentials of interest.[9] Additional drawbacks have been indicated above. With microcomputers widely available, there is no longer a need to be limited to "back of the envelope" procedures.

VII. Data Quality

Since the Demographic and Health Surveys uses direct techniques for estimating infant and child mortality, biases caused by poor quality of data can be due to four factors: omission of dead children (or with an equivalent effect, the misclassification of neonatal deaths as stillbirths), errors in reporting age at death, errors in reporting the date of birth of both living and dead children, and the lack of representativeness of the interviewed sample of mothers, due both to sampling and non-sampling errors.

A recent report by Sullivan, Rutstein and Bicego assessed the quality of DHS data for mortality estimation for twenty-two DHS surveys.[10] The results are briefly summarized here. Internal checks for omission involved checking the age pattern and sex, birth order, age at birth, birth interval, and maternal education differentials for anomalies. These internal checks indicate that there might have been some omission in the Botswana, Sri Lanka, Thailand, and Trinidad and Tobago surveys. External comparisons of under five mortality with WFS data reveal shortfalls in Indonesia (11%), Colombia (19%), Thailand (15%) and Sri Lanka (30%). Certain geographic areas of Sri Lanka were not covered in the DHS survey because of political unrest so that the surveys are not truly comparable. When the under five rate is broken down, the discrepancy between the results of the two surveys does not appear to be caused by omission of deaths at early ages, leading to speculation that it is the lack of representativeness of either the WFS or the DHS sample of women that is at fault.

Heaping of age at death on 12 months affects the distribution of mortality between the infant and child rates. Heaping on age at death is not likely to affect the under five mortality rate. Evidence from the assessment report indicates that while a substantial amount of heaping did occur at 12 months, most of this occurred because many deaths between ages 12 and 23 months were reported as "one year of age" rather than in terms of months. A redistribution of one-quarter of the heaped deaths would have increased estimates of infant mortality by about 5 percent in sub-Saharan Africa and 2 percent in the other surveys.

Displacement of dates of birth from the last five-year period into the preceding period occurred to a certain extent in a number of surveys, apparently due to both a desire by some interviewers to avoid asking certain sections of the questionnaire dedicated to children born in the last five years and in a few cases to faulty imputation of dates of birth when not reported. The report concludes that the impact of birth displacement appears to be minor, especially since there is a compensating effect between living and dead children. The largest effect, due to misimputation, occurs in Mali and raises the estimated infant mortality rate for the latest period from 108 to 118. Thailand also shows evidence of birth displacement due to misimputation but the effect is less than 2 deaths per thousand for the infant mortality rate.

To evaluate the quality of the data for estimating time trends, a comparison can be made between the DHS and the WFS surveys. To allow for the differing time periods between the two surveys, a rough average yearly change is shown in columns 8 and 9 of table 2. This average is based on the difference in the indicated years for the dates of the surveys. For three countries, Tunisia, the Dominican Republic and Colombia, the declines are just about the same whether only the DHS survey is used or using both the DHS and the WFS surveys.

In six of the countries, Egypt, Kenya, Indonesia, Thailand, Sri Lanka, and Peru, the decline estimated comparing the DHS and the WFS is higher than using the DHS data by themselves. This would be the case if the DHS omitted relatively more deaths in the period 10-14 years than the WFS did in the period 0-4 years. In five of the countries the discrepancy in decline is not very large and in two of the six countries, Indonesia and Sri Lanka, cover different portions of the population between the DHS and the WFS, but this fact does not appear to be the reason for the discrepancies in the declines in these countries. However, only the discrepancy for Kenya appears to be large.

In the remaining six countries, the decline comparing the WFS and the DHS is less than that indicated by the DHS data alone, indicating the WFS had a relatively high rate of omission of the 0-4 year period compared with the 10-14 year period of the DHS. Of these six countries, only in Ghana and Senegal are the discrepancies large, and especially so in Ghana, where an increase in mortality is indicated from the WFS-DHS comparison.

In sum, the evidence reviewed above indicates that the mortality rates from DHS and WFS programs for most countries appear to be reasonably accurate.

NOTES

1. Rutstein (1984), op. cit.

2. This classification was used to maintain consistency with the WFS, which did not report age at death in days.

3. From J. Cleland, G. Bicego, and G. Fegan, "Socio-Economic Inequalities in Childhood Mortality: From the 1970s to the 1980s", paper to be presented at the DHS World Conference, Washington, D.C., August, 1991.

4. E. Loaiza and K. Ekouevi, "Levels, Trends, and Differentials of Infant and Child Mortality from WFS and DHS Data", presented at the 1990 Annual Meeting of the Population Association of America, Toronto, Canada.

5. Op. cit.

6. In two surveys, El Salvador and Ondo State of Nigeria, a birth history truncated to the five years preceding the survey was asked.

7. For a more complete discussion of the procedure, see Rutstein, S.O., **Infant and Child Mortality: Levels, Trends and Demographic Differentials,** *WFS Comparative Studies* no. 24 (1983) or no. 43 (1984). Voorburg, Netherlands: International Statistical Institute.

8. In the real cohort computation information on children with incomplete exposure must be excluded, i.e. exclusion of children born in the year before the survey when calculating the infant mortality rate and more drastically children born in the last five years before the survey for the under five years mortality rate.

9. Differentials that apparently can be calculated using the indirect techniques, such as between urban and rural areas and between education categories suffer from differing amounts of bias according to category and so affect even the relative differences between categories.

10. J. M. Sullivan, S. O. Rutstein and G. T. Bicego, "Assessment of the Quality of DHS Data used in the Direct Estimation of Infant and Child Mortality" in Institute for Resource Development, **Assessment of DHS-I Data Quality**, Methodological Reports No. 1, Columbia, Maryland, 1990.

Table 1. Infant and Child Mortality Rates from DHS Surveys and Other Sources Since 1980 by Level of Under Five Mortality (DHS Rates are for the Five Years Preceding the Survey)

Country	Date of Survey	Neonatal	Infant	Child	Under Five
AFRICA					
Algeria	1983#		80		103
Egypt	1988	39	73	31	102
Morocco	1987	41	73	31	102
Tunisia	1988	28	50	16	65
Mali	1987	54	108	158	250
Liberia	1986	68	144	89	220
Rwanda	1983^		129		218
Senegal	1986	44	86	115	191
Uganda	1988—9	45	101	87	180
Togo	1988	43	81	84	158
Ghana	1988	44	77	84	155
Burundi	1987	35	75	84	152
Ondo	1986—7	26	56	55	108
Kenya	1989	27	60	31	89
Zimbabwe	1988—9	27	53	24	75
Botswana	1988	22	37	16	53
ASIA					
Bangladesh	1981^		130		208
India	1981-3#		107		165
Sri Lanka	1987	16	25	10	35
Indonesia	1987	30	70	33	101
Philippines	1984-5#		38		
China	1982^		35		51
Thailand	1987	20	35	10	45
Malaysia	1985-7#		16		
LATIN AMERICA					
Bolivia	1989	38	86	51	132
Honduras	1983^		84		119
Peru	1986	34	76	38	111
Guatemala*	1987	33	73	40	110
El Salvador	1985	29	71	29	98
Domin Rep	1986	39	67	23	88
Brazil*	1986	33	75	11	85
Ecuador	1987	35	58	25	82
Guyana	1986^		58		78
Mexico	1987	26	47	14	61
Paraguay	1990	19	34	9	43
Venezuela	1984-6#		34		
Colombia	1986	19	33	10	43
	1990	11	17	7	23
Argentina	1983#		30		
Uruguay	1985#		29		
Panama	1985-7#		27		
Trin & Tob	1987	21	26	3	30
Chile	1986#		19		
Costa Rica	1982-4#		19		
Guadeloupe	1985-6#		16		
Cuba	1985-6#		15		19
Puerto Rico	1985#		15		
Jamaica	1981-2#		14		
Martinique	1985-6#		13		

* Women 15-44 were eligible for interview.
na Not Available
Sources: Demographic and Health Survey Reports
United Nations, World Population Monitoring 1989, Population Studies No. 113, New York, 1990:
From civil registration data.
^ Non-DHS: Adjusted children surviving/children ever born.

Table 2. Trends in Under Five Mortality Rates from the Demographic and Health Surveys and World Fertility Surveys

Country	DHS			WFS			Absolute Change			Ave. Yearly Change		Relative Change		
	Date	0-4	10-14	Date	0-4	10-14	DHS	WFS	DHS-WFS	DHS	DHS-WFS	DHS	WFS	DHS-WFS
AFRICA														
Egypt	1988	102	203	1980	182	241	-81	-59	-80	-8.1	-10.0	-39%	-24%	-44%
Morocco	1987	132	166	1980	134	173	-64	-39	-32	-6.4	-4.6	-39%	-23%	-24%
Tunisia	1988	65	104	1978	102	138	-39	-36	-37	-3.9	-3.7	-38%	-26%	-36%
Mali	1987	250	358				-108			-10.8		-30%		
Liberia	1986	220	274				-54			-5.4		-20%		
Senegal	1986	191	286	1978	251	294	-95	-43	-60	-9.5	-6.9	-33%	-15%	-20%
Uganda	1988-9	180	187				-7			-0.7		- 4%		
Togo	1988	158	206				-48			-4.8		-23%		
Ghana	1988	155	187	1979	117	158	-32	-41	+38	-3.2	+4.2	-17%	-26%	+32%
Burundi	1987	152	224				-72			-7.2		-32%		
Kenya	1989	89	106	1977-8	135	157	-17	-22	-46	-1.7	-4.0	-16%	-14%	-34%
Zimbabwe	1988-9	75	92				-17			-1.7		-18%		
Botswana	1988	53	89				-36			-3.6		-40%		
ASIA														
Indonesia	1987	101	134	1976*	152	199	-33	-47	-42	-3.3	-3.8	-25%	-24%	-28%
Thailand	1987	45	67	1975	83	122	-22	-39	-38	-2.2	-3.2	-33%	-32%	-46%
Sri Lanka	1987**	35	58	1975	81	88	-23	- 7	-46	-2.3	-3.8	-40%	- 8%	-57%
LATIN AMERICA														
Bolivia	1989	132	160				-28			-2.8		-18%		
Peru	1986	111	140	1977-8	141	193	-29	-52	-30	-2.9	-3.5	-21%	-27%	-21%
Guatemala	1987	110	152				-42			-4.2		-28%		
Domin Rep	1986	88	118	1975	121	162	-30	-41	-33	-3.0	-3.0	-25%	-25%	-27%
Brazil	1986	85	124				-39			-3.9		-31%		
Ecuador	1987	82	134	1979-80	109	153	-52	-44	-27	-5.2	-3.6	-39%	-29%	-25%
Mexico	1987	61	91	1976-7	84	119	-30	-35	-23	-3.0	-2.2	-33%	-29%	-27%
Paraguay	1990	43	64	1979	85	77	-21	+ 8	-42	-2.1	-3.8	-33%	+10%	-50%
Colombia	1986	43	89	1976	90	117	-46	-27	-47	-4.6	-4.7	-52%	-23%	-52%
	1990	23	46				-23			-2.3		-50%		
Trin & Tob	1987	30	53	1977	41	46	-23	- 5	-11	-2.3	-1.1	-43%	-11%	-27%

Note: The change marked DHS and WFS are between periods 0-4 and 10-14 years preceding the each survey.
The change marked DHS-WFS compares the period 0-4 years preceding the DHS with 0-4 years preceding the WFS.

* Java and Bali only
** Excludes zones 4 and 5 of Sri Lanka WFS

Sources: Demographic and Health Survey Reports and S. O. Rutstein, op. cit.

Table 3. Under Five Mortality Rates by Type of Area and Mother's Education, in the Period 0-9 Years Preceding the Survey

Country	Date of Survey	Type of Area: Urban	Type of Area: Rural	Mother's Education: None	Mother's Education: 1 to 3 Years	Mother's Education: 4 to 6 Years	Mother's Education: 7 or more Years	Water Supply: Piped	Water Supply: Well	Water Supply: Other
AFRICA										
Egypt	1988	88	164	161	116	108	48			
Morocco	1987	81	137	125	76	66	50	72	91	152
Tunisia	1988	62	88	84	71	58	39	52	77	85
Mali	1987	203	303	290	244	214	112			
Liberia	1986	216	239	242	*	*	177			
Senegal	1986	135	250	226	179	123	75	156	213	238
Uganda	1988-9	164	191	195	222	173	144			
Togo	1988	131	169	170	163	131	89			
Ghana	1988	131	163	175	119	169	125	85	159	162
Burundi	1987	163	186	191	167	141	90			
Ondo	1986-7	100	115	110	141	103	96			
Kenya	1989	89	91	109	101	92	70	73	103	93
Zimbabwe	1988-9	55	98	120	94	83	60			
Botswana	1988	57	56	62	52	47	53			
ASIA										
Indonesia	1987	78	124	144	139	99	48	57	98	106
Thailand	1987	35	52	76	88	47	19	27	56	34
Sri Lanka	1987	40	43	72	47	41	35	43	34	31
LATIN AMERICA										
Bolivia	1989	114	168	180	166	141	70			
Peru	1986	74	153	169	147	113	53	73	169	138
Guatemala	1987	99	130	136	122	84	44			
Domin Rep	1986	69a	66a	136	100	96	66	93	53	83
Brazil	1986	88	121	136	137	70	40			
Ecuador	1987	63a	99a	159	121	74	49			
Mexico	1987	59b	104	112	91	54	29	29	56	102
Paraguay	1990	43	47	65c	51c	41c	27c			
Colombia	1986	48	58	78	65	40	25	36	65	64
	1990	35	32	74	——	36	——	26d		
Trin & Tob	1987	41	30	*	*	26	37	29	*	31

* Less than 500 children exposed
a Based on last 5 years
b Calculated from urban breakdown
c Paraguay education categories are 0-2 and 3-5 years, primary complete and secondary or higher
d Secondary only

Sources: Type of Area: DHS Survey Reports.
Mother's Education: Tabulated from DHS data.
Water Supply: E. Loaiza and K. Ekouevi, "Levels, Trends, and Differentials of Infant and Child Mortality from WFS and DHS Data", paper presented at the 1990 Annual Meeting of the Population Association of America, Toronto, Canada

Table 4. Demographic Differentials in Infant Mortality Rate (1q0) for 0-9 years preceding survey

Country	Date of Survey	Sex		Mother's Age at Birth				Birth Order				Months Since Preceding Birth		
		Male	Female	<20	20-29	30-39	40+	1st	2nd-3rd	4th-6th	7th+	<24	24-47	48+
AFRICA														
DHS Only														
Botswana	1988	48	32	35	42	39	NA	32	45	38	44	68	35	32
Burundi	1987	99	76	138	87	81a	69b	99	85	81	93	129	70	30
Liberia	1986	168	136	177	135c	136d	142e	157	147	146	172	203	124	72
Mali	1987	138	125	177	116	114a	142b	168	117	114	151	202	81	45
Ondo	1986f	59	53	93	51	51a	61b	78	48	51	63	80	47	45
Togo	1988	88	79	90	79	88	76	80	84	80	94	121	71	57
Uganda	1988-9	111	102	120	104	94	130	118	104	105	101	142	84	68
Zimbabwe	1988	65	50	78	48	62	67	64	53	49	75	79	48	43
WFS & DHS														
Ghana	1979-80	81	66	88	66	71	120	78	61	77	91	122	58	44
	1988	89	74	97	73	83	119	86	68	83	102	115	68	52
Kenya	1977-8	97	88	114	86	86	112	103	86	83	151	117	68	59
	1989	63	55	67	55	61	56	65	55	50	72	77	48	37
Senegal	1978	125	108	140	108	114	114	126	108	116	120	137	105	81
	1986	97	83	118	82	82	98	112	85	81	91	115	71	58
Egypt	1980	139	137	177	133	123	175	135	128	137	162	203	97	55
	1988	95	93	131	88	87	96	91	82	93	126	153	58	39
Morocco	1980	99	93	123	88	95	110	103	89	81	116	113	66	50
	1987	83	81	123	79	76	66	91	80	78	85	117	58	34
Tunisia	1978	78	77	97	74	73	111	75	70	61	117	122	49	24
	1988	58	56	69	56	52	110	61	44	60	76	84	32	28

Table 4 continued.

Country	Date of Survey	Sex		Mother's Age at Birth				Birth Order				Months Since Preceding Birth		
		Male	Female	<20	20-29	30-39	40+	1st	2nd-3rd	4th-6th	7th+	<24	24-47	48+
ASIA														
Indonesia	1976	109	84	125	88	89	120	108	93	86	112	138	77	56
	1987	84	66	99	68	74	71	78	70	71	94	109	62	51
Sri Lanka	1975	66	53	72	57	55	96	52	57	59	73	71	54	44
	1987	40	25	35	33	29	52	31	30	38	47	44	24	30
Thailand	1975	77	71	102	67	75	87	71	65	69	103	109	52	42
	1987	45	31	40	33	47	69	30	36	48	73	58	38	32
LATIN AMERICA														
DHS Only														
Bolivia	1989	106	86	101	94	93	140	80	88	101	124	154	77	43
Brazil	1986	82f	70f	103	77c	88d	88e	62	74	100	161	136	59	52
Guatemala	1987	90	68	98	72	77	166	84	70	78	98	120	52	51
WFS & DHS														
Colombia	1976	74	62	80	60	74	81	59	67	60	87	82	53	38
	1987	41	38	46	37	40	45	30	41	42	51	52	39	23
	1990	27	26	34	25	27	34	16	26	33	58	39	24	20
Dom. Rep.	1975	103	82	98	89	94	128	87	92	80	114	105	75	60
	1986	79	62	85	61	79	105	70	64	68	91	81	54	45
Ecuador	1979-80	88	72	96	71	87	106	62	76	79	106	107	64	58
	1987	70	60	62	63	63	141	59	52	69	104	90	52	44
Mexico	1976-7	83	66	87	67	80	98	70	65	77	88	88	57	64
	1987	60	52	63	53	57	74	42	50	60	88	81	45	43
Paraguay	1979	58	56	60	49	63	102	51	50	53	80	71	45	55
	1990	38	32	52	29	38	52	35	24	39	50	40	33	18
Peru	1977-8	105	100	109	95	105	141	80	90	102	137	137	87	55
	1986	84	75	100	68	86	104	62	63	89	115	121	64	34
Trinidad & Tobago	1977	47	39	50	37	54	21	36	35	38	77	53	28	36
	1987	29	34	43	28	26	92	29	26	33	73	41	15	26

a Ages 30-34 c Ages 20-24 e Ages 30+
b Ages 35+ d Ages 25-29 f Based on 0-4 years preceding survey * Women 15-44 were eligible for interview
Source: Demographic and Health Survey Reports and E. Loaiza and K. Ekouevi, op. cit.

Table 5. Relative Demographic Differentials in Infant Mortality Rate (1q0) for 0-9 years preceding survey

Country	Date of Survey	Sex		Mother's Age at Birth				Birth Order				Months Since Preceding Birth		
		Male	Female	<20	20-29	30-39	40+	1st	2nd-3rd	4th-6th	7th+	<24	24-47	48+
AFRICA														
DHS Only														
Botswana	1988	150	100	83	·100	93	NA	71	100	84	98	194	100	91
Burundi	1987	130	100	159	100	93a	79b	116	100	95	109	184	100	43
Liberia	1986	124	100	131	100c	101d	105e	107	100	99	117	164	100	58
Mali	1987	110	100	153	100	98a	122b	144	100	97	129	249	100	56
Ondo	1986f	111	100	182	100	100a	120b	163	100	106	131	170	100	96
Togo	1988	111	100	114	100	111	96	95	100	95	112	170	100	80
Uganda	1988-9	109	100	115	100	90	125	113	100	101	97	169	100	81
Zimbabwe	1988	130	100	163	100	129	140	121	100	92	142	165	100	90
WFS & DHS														
Ghana	1979-80	123	100	133	100	108	182	128	100	126	149	210	100	76
	1988	120	100	133	100	114	163	126	100	122	150	169	100	76
Kenya	1977-8	110	100	133	100	100	130	120	100	97	176	172	100	87
	1989	115	100	122	100	111	102	118	100	91	131	160	100	77
Senegal	1978	116	100	130	100	106	106	117	100	107	111	130	100	77
	1986	117	100	144	100	100	120	132	100	95	107	162	100	82
Egypt	1980	101	100	133	100	92	132	105	100	107	127	209	100	57
	1988	102	100	149	100	99	109	111	100	113	154	264	100	67
Morocco	1980	106	100	140	100	108	125	116	100	91	130	171	100	76
	1987	102	100	156	100	96	84	114	100	98	106	202	100	59
Tunisia	1978	101	100	131	100	99	150	107	100	87	167	249	100	49
	1988	104	100	123	100	93	196	139	100	136	173	263	100	88

Table 5 continued.

Country	Date of Survey	Sex		Mother's Age at Birth				Birth Order				Months Since Preceding Birth		
		Male	Female	<20	20-29	30-39	40+	1st	2nd-3rd	4th-6th	7th+	<24	24-47	48+
ASIA														
Indonesia	1976	130	100	142	100	101	136	116	100	92	120	179	100	73
	1987	127	100	146	100	109	104	111	100	101	134	176	100	82
Sri Lanka	1975	125	100	126	100	96	168	91	100	104	128	131	100	81
	1987	160	100	106	100	88	158	103	100	127	157	183	100	125
Thailand	1975	108	100	152	100	112	130	109	100	106	158	210	100	81
	1987	145	100	121	100	142	209	83	100	133	203	153	100	84
LATIN AMERICA														
DHS Only														
Bolivia	1989	123	100	107	100	99	149	91	100	115	141	200	100	56
Brazil*	1986	117f	100f	134	100e	114d	114e	84	100	135	218	231	100	88
Guatemala*	1987	132	100	136	100	107	231	120	100	111	140	231	100	98
WFS & DHS														
Colombia	1976	119	100	133	100	123	135	88	100	90	130	155	100	72
	1987	108	100	124	100	108	122	73	100	102	124	133	100	59
	1990	102	100	138	100	111	140	62	100	126	221	160	100	82
Dom. Rep.	1975	126	100	110	100	106	144	95	100	87	124	140	100	80
	1986	127	100	139	100	130	172	109	100	106	142	150	100	83
Ecuador	1979-80	122	100	135	100	123	149	82	100	104	139	167	100	91
	1987	117	100	98	100	100	224	113	100	133	200	173	100	85
Mexico	1976-7	126	100	130	100	119	146	108	100	118	135	154	100	112
	1987	115	100	119	100	108	140	84	100	120	176	180	100	96
Paraguay	1979	104	100	122	100	129	208	102	100	106	160	158	100	122
	1990	119	100	179	100	131	162	146	100	163	208	123	100	56
Peru	1977-8	105	100	115	100	111	148	89	100	113	152	157	100	63
	1986	112	100	147	100	126	153	98	100	141	183	189	100	53
Trinidad & Tobago	1977	121	100	135	100	146	57	103	100	109	220	189	100	129
	1987	85	100	154	100	93	329	112	100	127	281	273	100	173

a Ages 30-34 c Ages 20-24 e Ages 30+ * Women 15-44 were eligible for interview
b Ages 35+ d Ages 25-29 f Based on 0-4 years preceding survey

Table 6. Relative Demographic Differentials in Infant Mortality Rate (1q0) for 0-9 years preceding survey, according to level of under five mortality

Level of Under Five Mortality	Sex		Mother's Age at Birth				Birth Order				Months Since Preceding Birth		
	Male	Female	<20	20-29	30-39	40+	1st	2nd-3rd	4th-6th	7th+	<24	24-47	48+
175 or greater	115	100	136	100	97	118	124	100	98	113	186	100	69
125 to 174	121	100	128	100	104	122	107	100	107	128	181	100	64
100 to 124	115	100	153	100	106	133	120	100	112	141	205	100	76
75 to 99	121	100	131	100	117	150	109	100	111	166	176	100	85
Less than 75	123	100	126	100	107	188	101	100	124	177	188	100	97
All	119	100	135	100	107	147	111	100	113	150	188	100	81

Table 7. Mean Risk Ratios for High-Risk Fertility Behavior

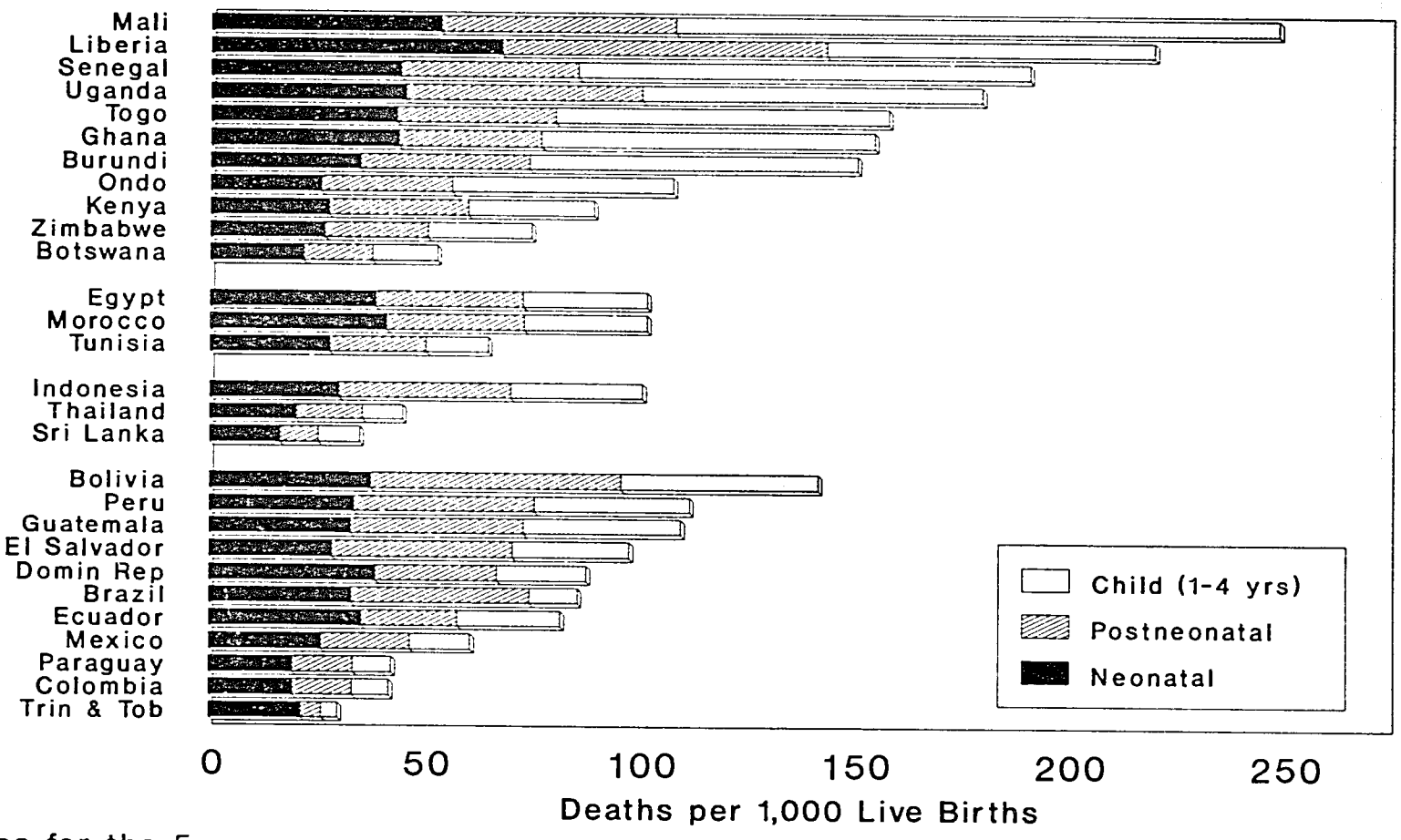
Under Five Mortality	Single Risk				Multiple Risks				Any High Risk
	A<18	I<24	O>3	Any Sing.	A>34 O>3	O>3 I<24	A>34 O>3 I<24	Any Mult.	
175 +	1.6	1.5	0.9	1.1	0.8	1.2	1.7	1.1	1.1
125-174	1.2	1.5	1.0	1.1	1.3	2.0	2.0	1.6	1.3
100-124	2.2	1.7	1.6	1.7	2.0	3.9	6.3	3.2	2.2
75-99	2.2	1.5	1.3	1.5	1.7	2.7	5.0	2.4	1.8
< 75	2.2	1.8	1.7	1.8	2.3	2.7	4.0	2.8	2.1
All	2.0	1.7	1.4	1.5	1.8	2.7	3.9	2.5	1.9

High Risk Categories:
A<18 Mother's age less than 18 years at birth
A>34 Mother's age over 34 years at birth
I<24 Preceding birth interval less than 24 months
O>3 Birth order higher than three

Note: Risk ratios are the ratios between the high-risk categories and children not in any high risk category for the proportions dead of children born in the five years preceding the surveys. Children not in any risk category are those born to mothers 19 to 34 years of age, of birth orders 1 to 3, and after a birth interval of 24 or more months.

Source: Demographic and Health Surveys.

Figure 1
Infant and Child Mortality Rates



Rates for the 5 years preceding survey.

Demographic and Health Surveys

Figure 2

Decline in Under Five Mortality Rates From 10-14 to 0-4 Years Prior to Survey

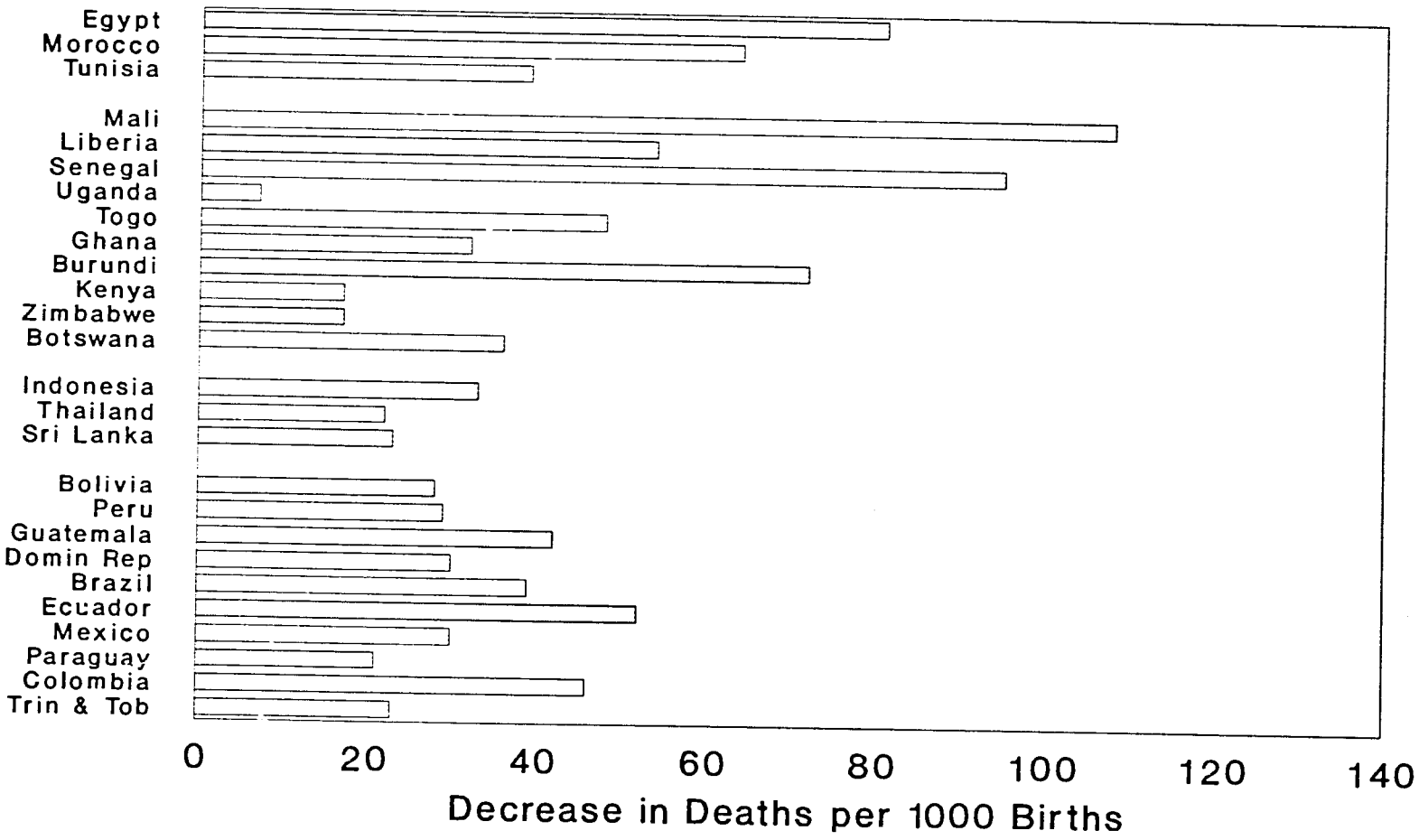


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Figure 3

Excess Under 5 Mortality of Rural Areas

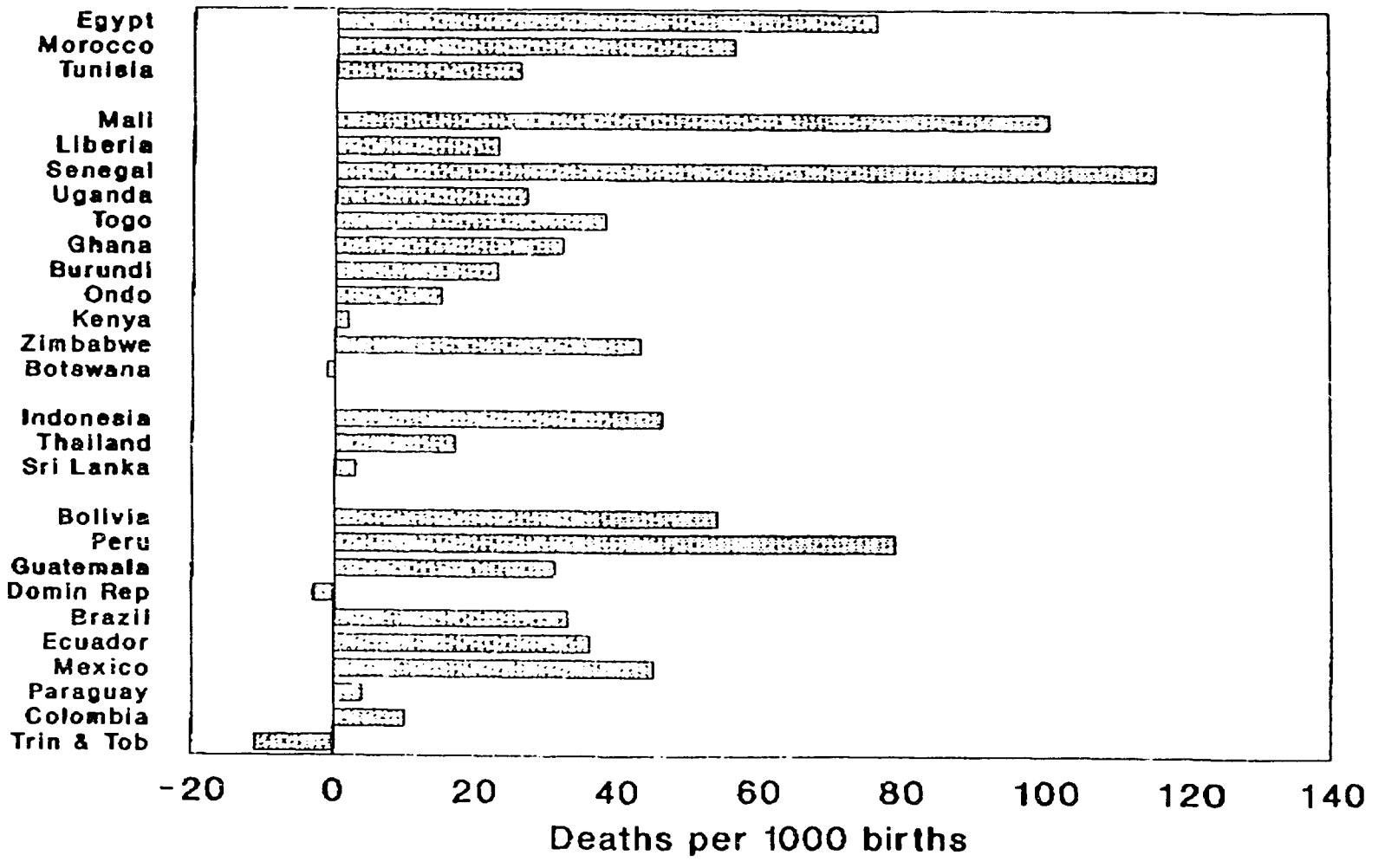

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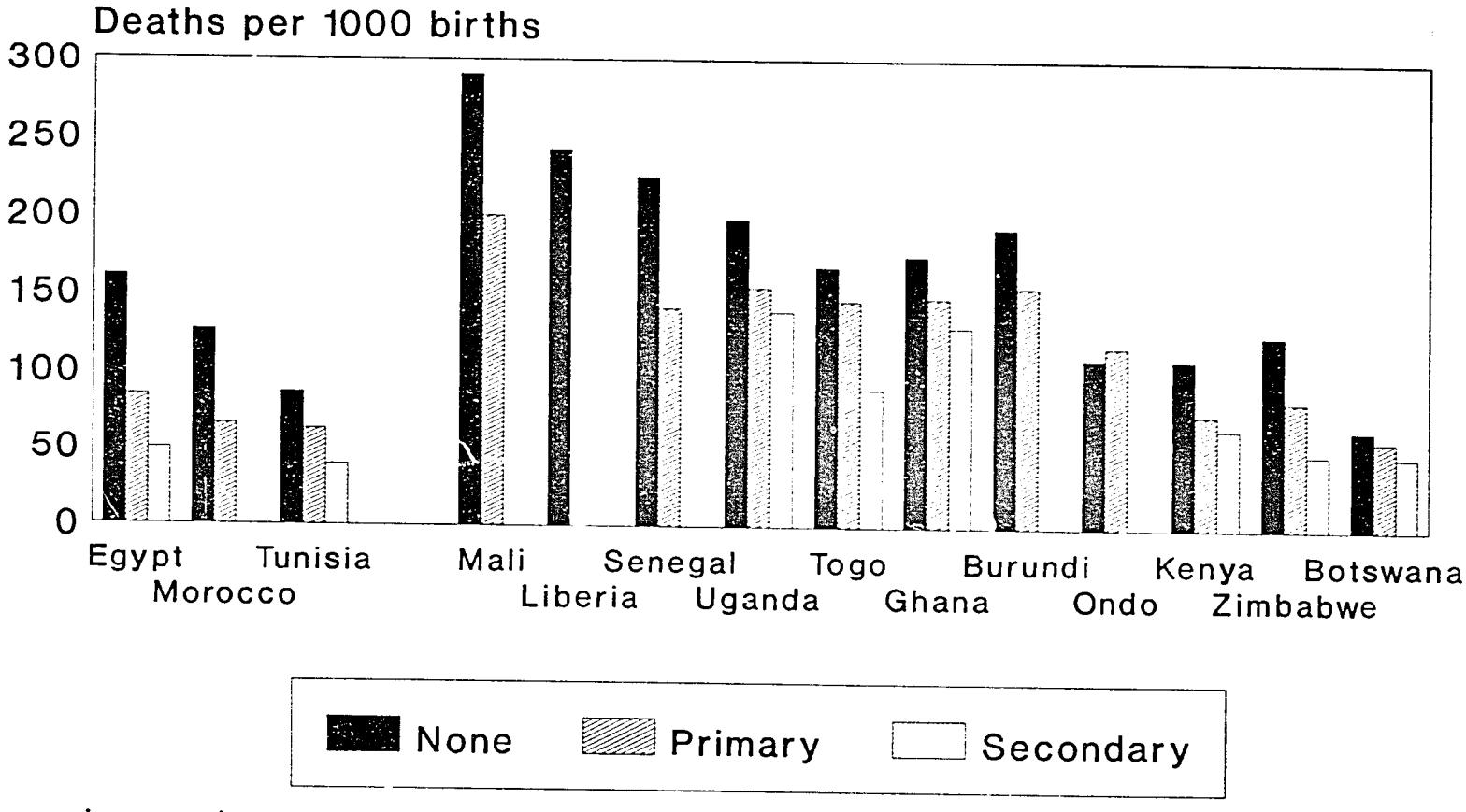
Figure 4a. Under 5 Mortality 0-9 Years Prior to Survey by Mother's Education AFRICA



Primary is complete where available
Secondary excludes higher where available

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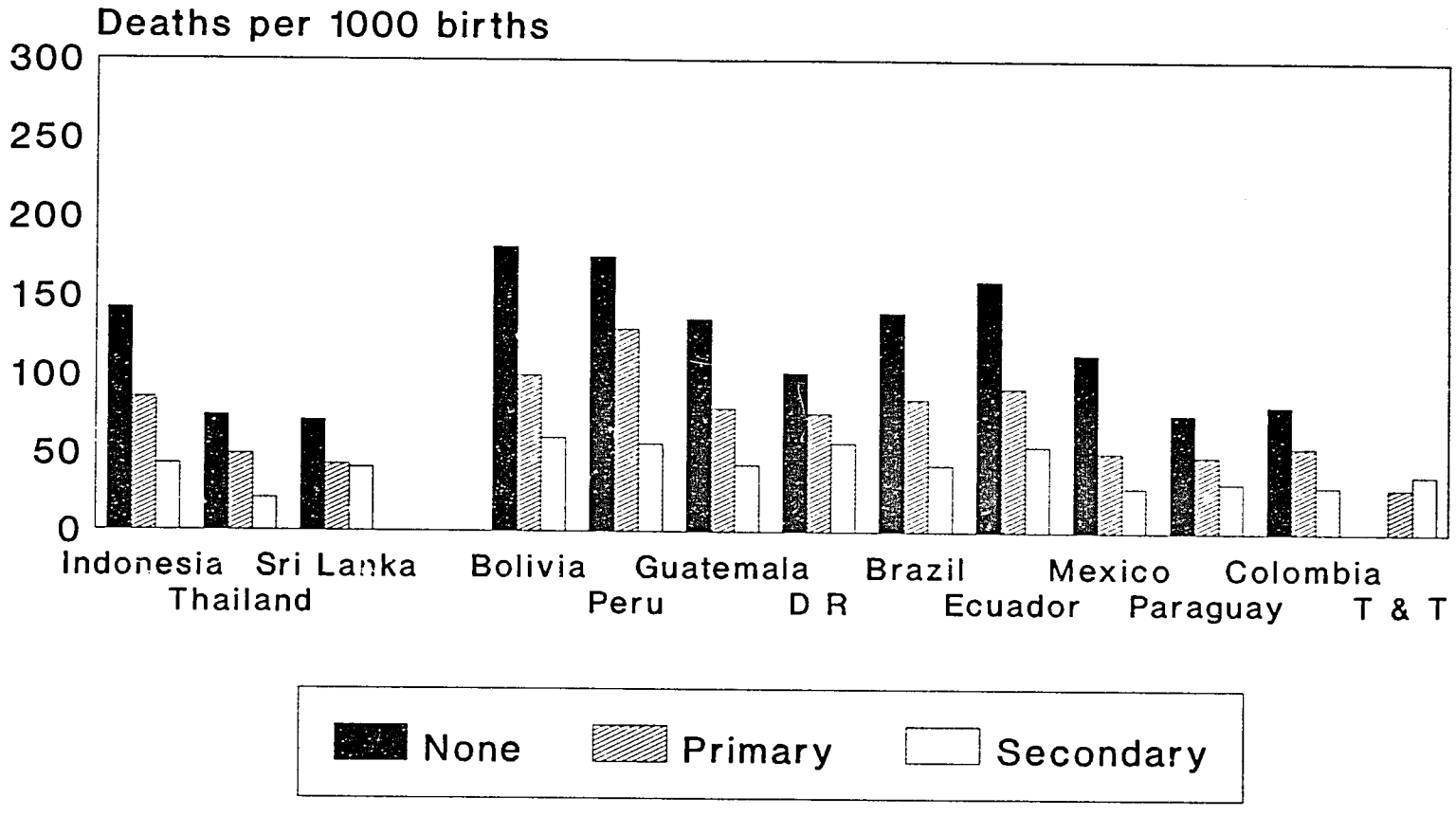
Figure 4b. Under 5 Mortality 0-9 Years Prior to Survey by Mother's Education ASIA & LATIN AMERICA



Primary is complete where available
Secondary excludes higher where available

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Figure 5a. Under 5 Mortality 0-9 Years Prior to Survey by Mother's Education AFRICA

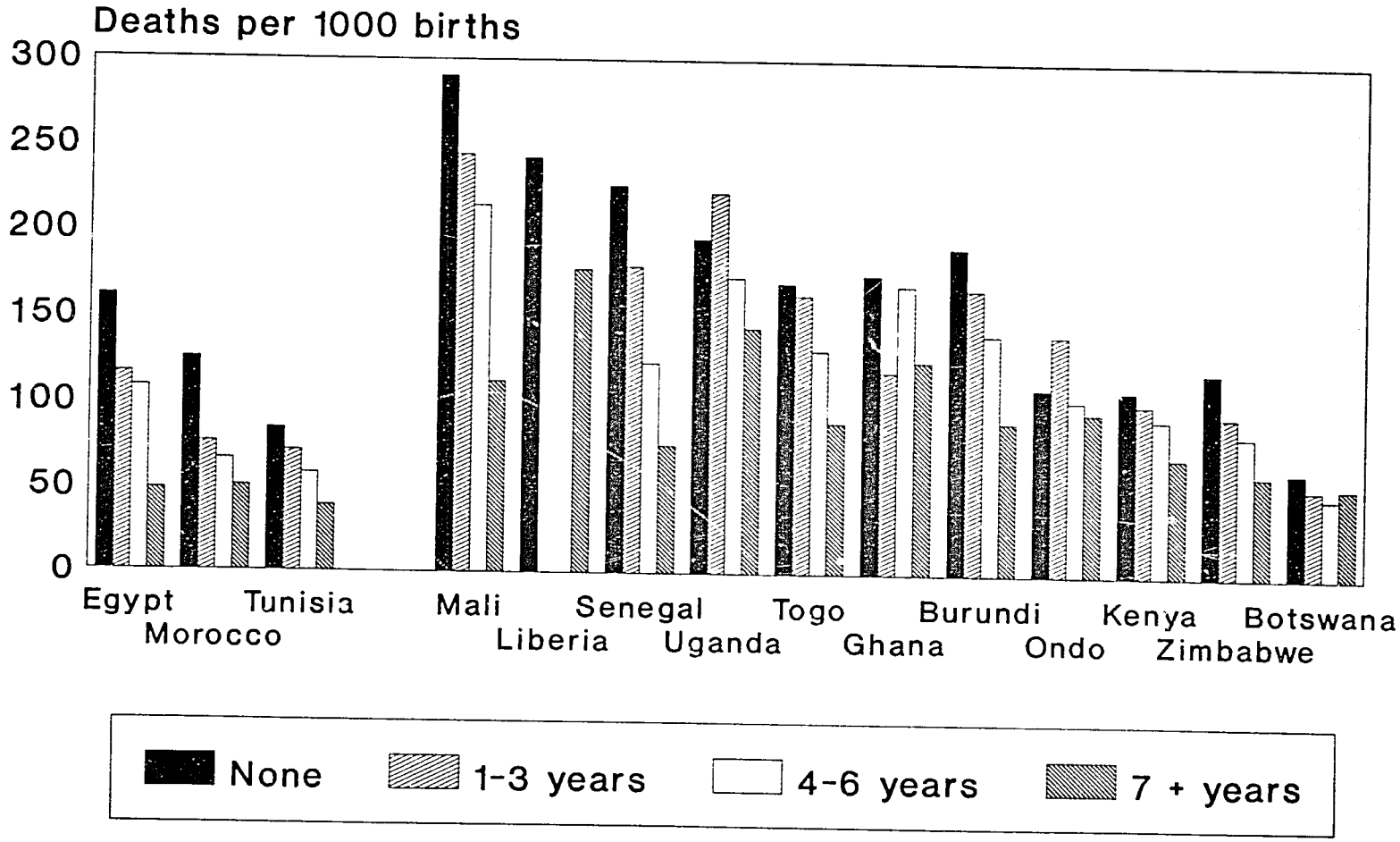
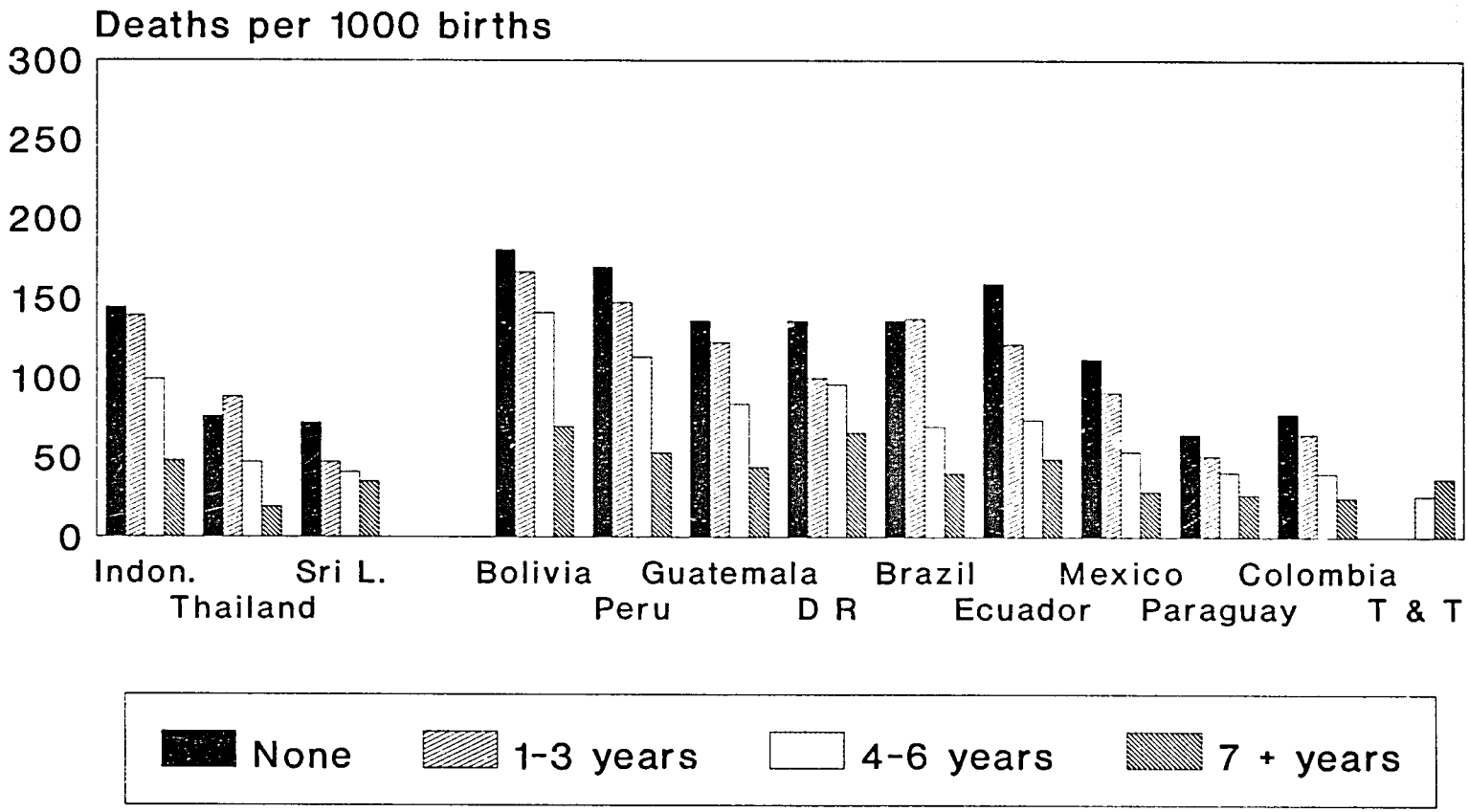


Figure 5b. Under 5 Mortality 0-9 Years Prior to Survey by Mother's Education ASIA & LATIN AMERICA



Demographic & Health Surveys

Mortality Reductions from Measles and Tetanus Immunization: A Review of the Evidence

Michael A. Koenig

Abstract

This paper reviews existing empirical evidence on the impact of measles and tetanus immunization upon reductions in mortality from the Matlab study area in Bangladesh and other developing countries. Pronounced effects of measles vaccination upon childhood mortality levels have been documented in all studies considered. The effects of vaccination upon mortality were also found to be sustained over time, with the greatest benefits accruing to the most disadvantaged children. These findings provide little support for the existence of a replacement mortality effect. Although our review of studies on maternal tetanus immunization also demonstrated consistent large reductions in neonatal mortality levels, considerable uncertainty persists regarding the number of doses required and the duration of resulting immunity. Recently available evidence raises the possibility that two doses of tetanus toxoid may confer significant levels of protection against neonatal tetanus death for 15 years or more. Evidence on the impact of a single dose remains more inconclusive. The findings from the studies reviewed indicate that tetanus and measles immunization programs have the potential to yield significant reductions in neonatal and 1-4 year mortality levels in many developing settings.

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In recent years, there has been increased recognition of the paramount importance of tetanus and measles as causes of childhood death in the developing world. It has been estimated that these diseases may together be responsible for more than 2.5 million childhood deaths annually. Considerable debate and uncertainty remains, however, concerning the actual reductions in childhood mortality which would result from the prevention of these diseases through immunization. Equally important, many unresolved questions remain regarding the most cost-effective and feasible operational strategies for measles and tetanus vaccination programs. The objective of this paper is to review existing empirical evidence on tetanus and measles immunization pertaining to these issues.

MEASLES IMMUNIZATION

Measles has been estimated to account annually for as many as two million deaths to children worldwide (WHO, 1985). The risk period for measles begins when protection conferred by maternal antibodies wanes, and continues throughout early childhood. The beginning of the risk period appears to vary considerably between settings and according to residence, with the onset of measles cases frequently reported as early as 4-6 months of life in many urban African settings, but generally later in other settings such as South Asia (Assaad, 1983).

Mortality Impact of Immunization

The main studies which have evaluated the impact of measles immunization upon reductions in childhood mortality are summarized in Table 1. In the following sections, the study design and analytical approaches taken by each of these studies, as well as their principal findings, are reviewed.

The Kasongo study in Zaire represents the earliest attempt to evaluate systematically the impact of measles vaccination upon child survival (The Kasongo Project Team, 1981). All children in one area born during or after September, 1974 were offered measles vaccination at 8 months of age. A total of 255 children in this area accepted measles vaccination during the period of the study, representing 83 percent of all eligible children. Three comparison groups of unvaccinated children were also identified: 1) children born during the same period from a neighboring area where vaccination had not been offered, 2) children from the same area who were born during an earlier period (1973- 1974), and 3) children from the neighboring area also born during this earlier period. Survival status of children was ascertained through a system of quarterly household morbidity and mortality surveillance, carried out from mid-1974 through the end of 1977.

The mortality experience of these cohorts of children during the age interval 7-35 months was compared using life table techniques. The results of this analysis demonstrated a pronounced impact of measles vaccination upon childhood mortality levels (Figure 1). Mortality among the cohort of vaccinated children was substantially lower than among the three control groups of unvaccinated children: 39 per 1000 vs. 69-95 per 1000 during the age period 7-35 months. This translates into mortality reductions

TABLE 1: SUMMARY OF MEASLES VACCINATION STUDIES

STUDY	LOCATION	STUDY PERIOD	STUDY POPULATION	MAIN FINDINGS
THE KASONGO PROJECT TEAM	ZAIRE	1974-1977	255 VACCINATED CHILDREN 3 CONTROL GROUPS OF UNVACCINATED CHILDREN	30-49% REDUCTION IN 7-35 MONTH MORTALITY
AABY, ET AL.	GUINEA-BISSAU	1980-1981	803 VACCINATED CHILDREN 193 UNVACCINATED CHILDREN	72% REDUCTION IN 6-35 MONTH MORTALITY
GARENNE AND CANTRELLE	SENEGAL	LATE 1960s	NA	31% REDUCTION IN 6 MO. - 3 YR. MORTALITY
CLEMENS, ET AL.	MATLAB, BANGLADESH	1982-1984	536 DEATHS 1072 AGE-SEX MATCHED CONTROLS	36% REDUCTION IN 10-60 MONTH MORTALITY
KOENIG, ET AL.	MATLAB, BANGLADESH	1982-1985	8135 VACCINATED CHILDREN 8135 MATCHED UNVACCINATED CHILDREN	UP TO 46% REDUCTION IN 9-60 MONTH MORTALITY

of between 44 to 59 percent among vaccinated children, depending upon the control group chosen. Differences between groups were most marked during ages 7-21 months, the period corresponding to the greatest risk of measles-related mortality.

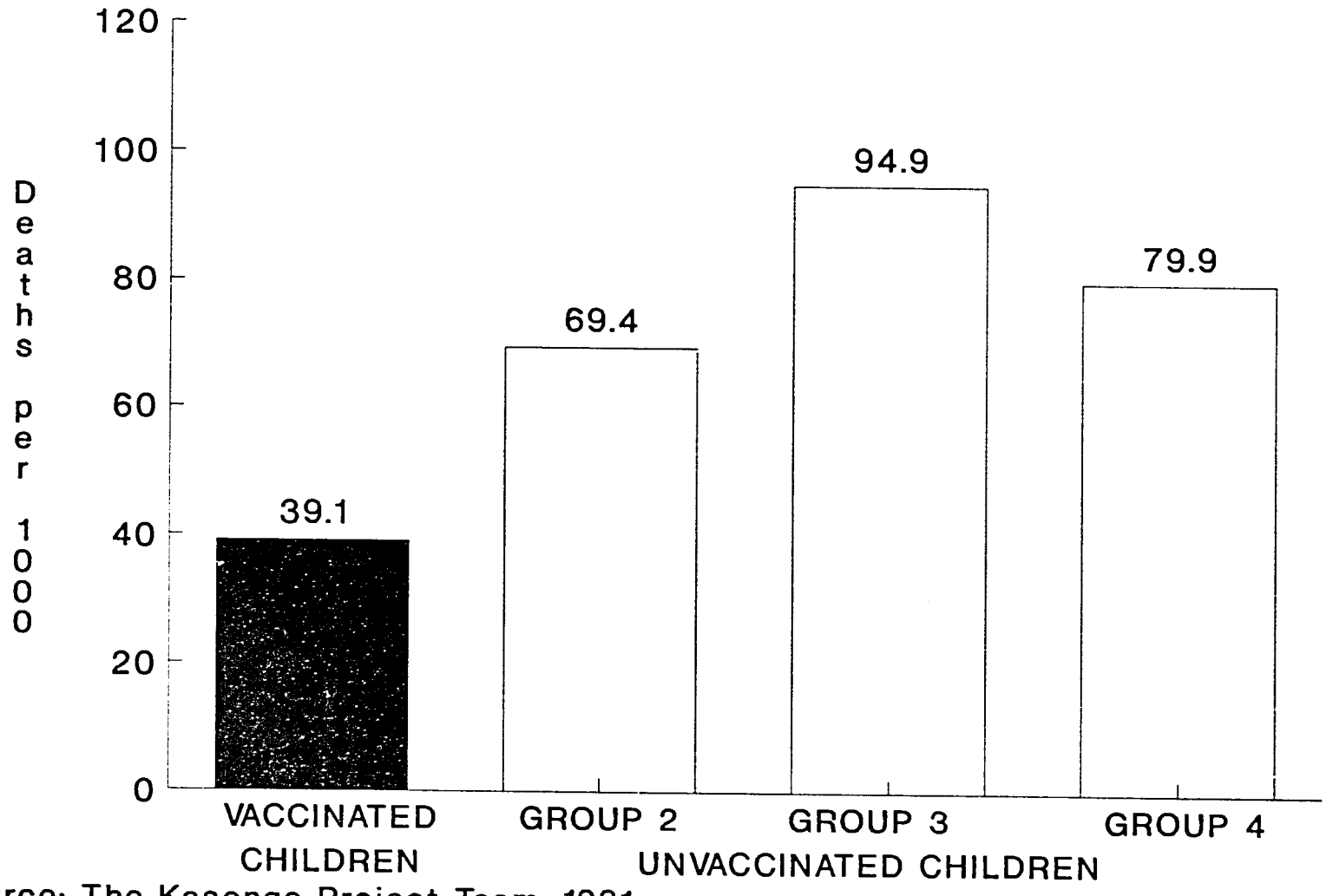
Two other studies from Africa merit consideration. A study in Guinea-Bissau compared the subsequent one year mortality experience of two groups of vaccinated children in 1980 and 1981 with two groups of children from the same area and periods who did not attend a measles campaign (Aaby, et al. 1984). Although the numbers in the study were comparatively small, especially the number of unvaccinated children (803 vaccinated and 193 unvaccinated children), the results indicated a markedly lower mortality level during the following year among immunized children--as much as 72 percent lower among children aged 6-35 months. In a second study, Garenne and Cantrelle (1986) analyzed the impact of two measles vaccination campaigns based on data from the Khombole area of Senegal over the 1965-68 period. The subsequent mortality experience of vaccinated children aged 6 months to 10 years in a set of villages selected for a measles vaccination program was compared with a control group of children from other villages where measles vaccination had not been offered. The findings of the study indicated a reduction in mortality among younger vaccinated children (6 months to 3 years) of 31 percent. The reduction in mortality among older children (3-10 years) was more modest (14 percent).

The two other major studies of mortality impact originate from a measles vaccination program in the Matlab study area of the International Centre for Diarrhoeal Disease Research (ICDDR,B) in rural Bangladesh. Since 1966, the ICDDR,B has maintained a system of continuous demographic surveillance in its rural field site in Matlab, consisting of the bi-weekly registration of vital events and periodic censuses. In 1982, the study area consisted of 149 villages with a total population of approximately 180,000. In 1978, half of the study area was designated as an intervention area for an experimental maternal and child health/ family planning program provided by the ICDDR,B; the other half remained a comparison area, with services limited to the less intensive government program. In early 1982, as part of a carefully phased expansion of services, measles vaccination was introduced into two of the four sub-areas of the intervention area (termed blocks); this service was expanded to the remaining two blocks in the fall of 1985. The fact that measles vaccination was introduced in this phased manner makes it possible to evaluate its impact upon subsequent mortality.

The first evaluation of the impact of the Matlab measles immunization program was a retrospective case-control study consisting of 536 deaths to children aged 10-60 months of age between early 1982 and the end of 1984 (Clemens, et al. 1988). These cases were randomly matched by age and sex with 1072 controls (i.e., children who survived) from the two blocks where vaccination was not offered, and compared in terms of their prior measles immunization status. Measles immunization was found to be associated with a child mortality rate which was 36 percent lower during the study period.

The second study based upon the Matlab measles vaccination program consisted of a longitudinal cohort analysis following children through late 1985 (Koenig, et al. 1990). All 9-60 month children in these two blocks who received measles vaccination during 1982-85 were eligible for inclusion in the study. These children were randomly matched with unvaccinated children of similar age from the other half of the intervention area, resulting in a final analysis cohort of 8135 vaccinated and 8135 unvaccinated children.

FIGURE 1. COMPARISON OF MORTALITY EXPERIENCES OF VACCINATED AND UNVACCINATED CHILDREN AGED 7-35 MONTHS: KASONGO, ZAIRE, 1974-77



Source: The Kasongo Project Team, 1981

Through a comparison of the relative mortality experiences of these two cohorts of children from the date of vaccination to the end of the observation (death, out-migration, exceeding five years of age, or the end of the study period, October, 1985), it was possible to evaluate the effect of measles vaccination upon short and longer-term survival. As Figure 2 shows, a striking differential in cumulative mortality risks according to vaccination status was evident. At 42 months from the date of vaccination, vaccinated children experienced mortality risks which were 40 percent lower than their unvaccinated counterparts.

Replacement Mortality

An issue of direct relevance to the impact of measles vaccination programs, but one which remains under considerable debate, is the replacement mortality hypothesis. According to this hypothesis, children 'saved' from death from a specific cause may continue to be at elevated risk of death from other unaddressed causes, resulting in little improvement in overall survival levels. While potentially relevant to many health interventions, this hypothesis has most commonly been applied to the issue of measles and measles immunization (see The Kasongo Project Team, 1981; Mosley, 1985). If substantiated, the contribution of measles vaccination would be largely to delay rather than prevent childhood mortality, calling into question the efficacy of this intervention as a means for improving child survival. The evidence on measles vaccination and replacement mortality is considered from two different perspectives in the following sections.

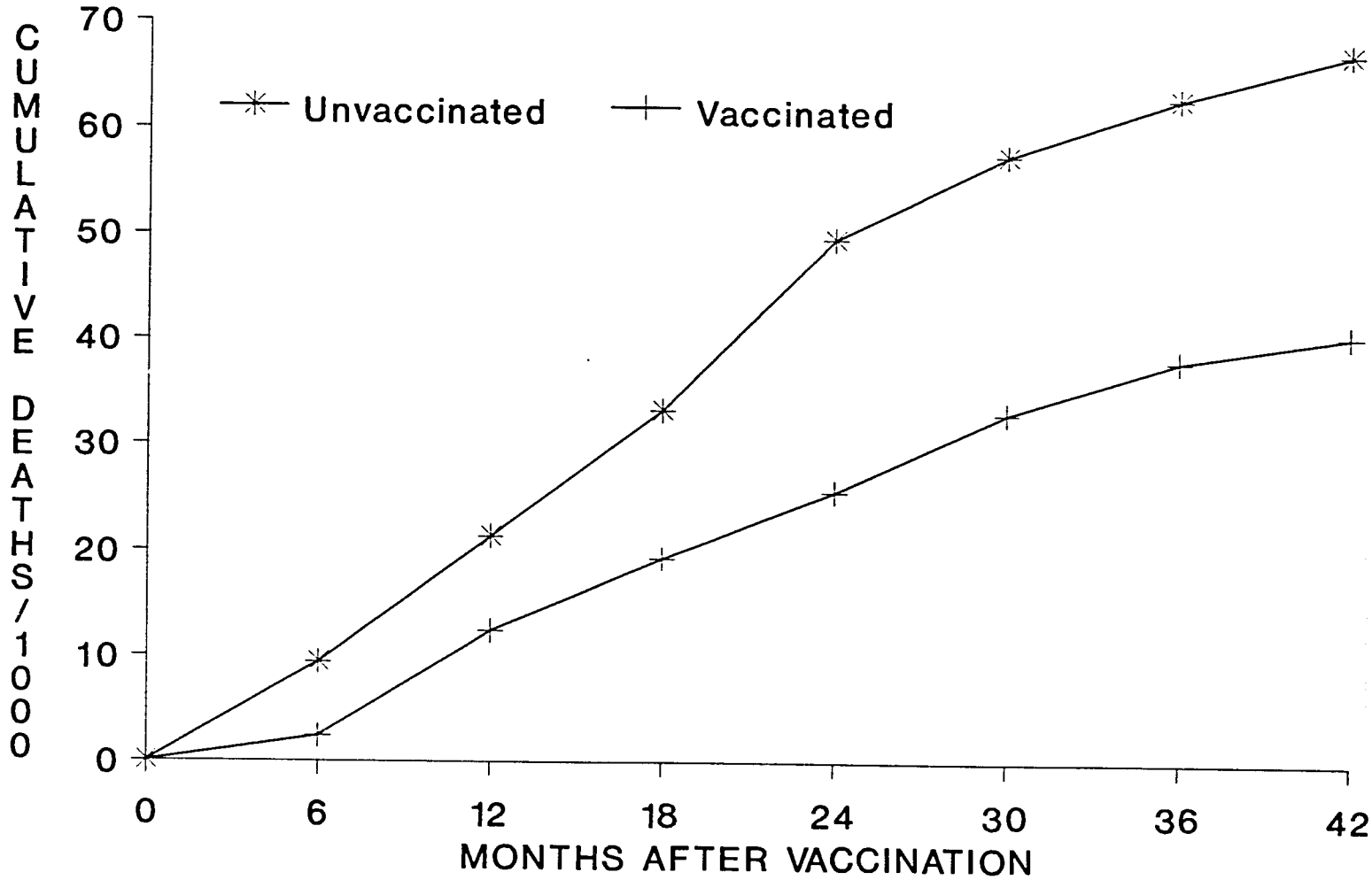
Convergence in Survival Over Time

If replacement mortality was evident, vaccinated children would be expected to experience improved survival in the short-run relative to unvaccinated children, but comparatively higher mortality levels in the longer run, as they would remain highly vulnerable to death from other causes. The result would be first a divergence followed by a convergence in survival probabilities over time between vaccinated and unvaccinated children.

The authors of the Kasongo study presented evidence which they interpreted as providing support for this hypothesis. Their analysis indicated that while vaccinated children had improved survival chances during the ages 7-21 months, the primary risk period for measles and measles-related mortality, the survival advantage of vaccinated children tended to diminish at later ages (22-35 months). However, as Aaby, et al. (1981) showed in a re-analysis of the Kasongo data, too few deaths occurred in this study population in this older age group to support the authors' original conclusions. Instead, the most salient finding of the study remains the marked reduction in mortality among vaccinated children throughout the entire age span, with reductions ranging from 44 to 59 percent among children aged 7-35 months.

The study by Clemens, et al. (1988) in Matlab also considered the issue of replacement mortality in detail. First, the authors examined whether the protective efficacy of measles vaccination for cases and controls selected during the second half of the year--corresponding to after the measles season in Bangladesh--might be negative, in

FIGURE 2. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS: MATLAB INTERVENTION AREA, 1982-85



contrast to cases and controls selected during or shortly after the primary measles season, when protective efficacy should be positive. The finding of a negative protective efficacy during the period after the measles season would reflect higher replacement mortality among vaccinated children. The results, however, did not provide support for a replacement mortality effect, since the protective efficacy of vaccination was positive and significant during both periods. Second, the authors evaluated whether among cases and controls selected in 1982, there was evidence of a reduction in mortality among vaccinated children in the initial year, followed by higher mortality rates relative to unvaccinated children in the ensuing two years (1983-84). The results provided no evidence of a decline in the effect of measles vaccination with increasing time from vaccination, once again failing to provide evidence of a replacement mortality effect.

Data from the Matlab cohort study by Koenig, et al. (1990) lead to similar conclusions. Among the cohort of children vaccinated at < 12 months of age and their matched controls, if replacement mortality were present, one would expect to see higher mortality among vaccinated children with increasing time from vaccination, leading to a partial or complete convergence in survival curves for the two groups. The results instead indicate that vaccinated children continue to experience relatively lower mortality at almost all subsequent age intervals. Moreover, the magnitude of reductions in mortality from measles vaccination reported in these two studies (between 36 and 46 percent) suggest that even if such an effect were present, its impact upon lessening the mortality gains resulting from measles vaccination would be quite minor. The studies from Matlab thus provide no support for the existence of a replacement mortality effect.

Impact Among High-Risk Children

If replacement mortality were present, it should also be expected that the most vulnerable children would benefit least from measles immunization, since it is these children who continue to remain most at risk of death from other unaddressed causes. Within the context of South Asia, high risk children would include females and those from the poorest households, both of which groups have been shown to experience significantly higher mortality risks during the early childhood period (D'Souza and Chen, 1980; D'Souza and Bhuiya, 1982). Data from the Matlab cohort study on measles immunization permit a more detailed investigation of this hypothesis.

Figure 3 shows life table results of the differential impact of measles vaccination upon mortality according to sex of child. If replacement mortality were present, little difference in the survival curves of female children according to vaccination status would be expected, since they would continue to be at high risk of death from other causes. The results of this figure do not provide support for the replacement mortality hypothesis, and in fact, indicate the opposite--that female children may benefit more from vaccination in terms of mortality reductions. Vaccinating a female child against measles provides her with roughly the same survival chances as an unvaccinated male child. These results are illustrated in greater detail in Figure 4. Although the relative reductions in mortality are not significantly different for male and female children (36 percent and 41 percent, respectively), because of the much higher mortality levels among female children during this age period, the absolute reduction in mortality for female children

FIGURE 3. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS AND BY SEX: MATLAB INTERVENTION AREA, 1982-85

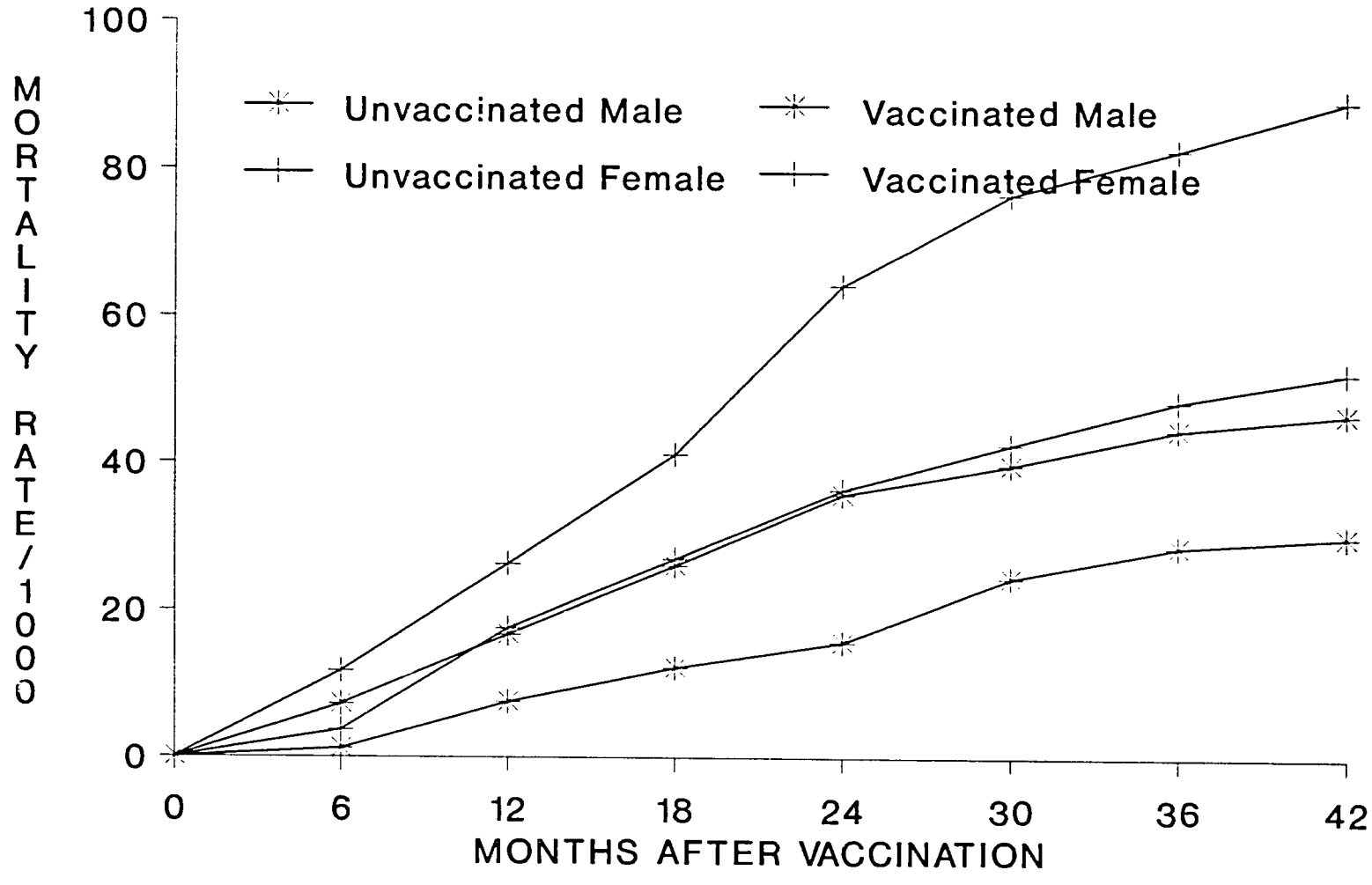
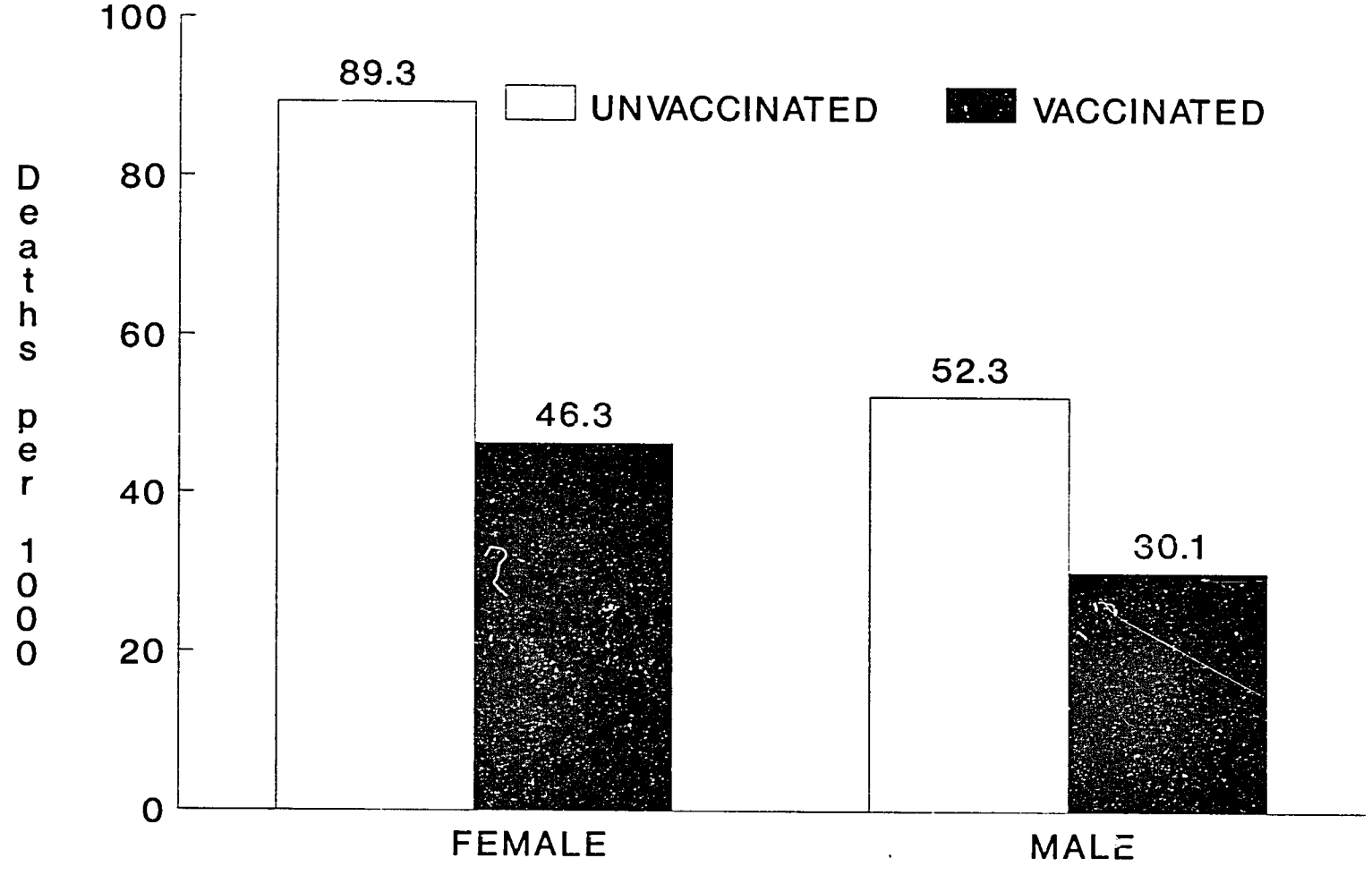


FIGURE 4. EXCESS FEMALE DEATHS BY MEASLES VACCINATION STATUS AMONG 9-60 MONTH CHILDREN: MATLAB INTERVENTION AREA, 1982-85



CUMULATIVE MORTALITY RATE 42 MONTHS AFTER VACCINATION

is more than twice that for male children (37 deaths vs. 17 deaths per 1000 live births at 42 months post-vaccination).

Similar results are evident in the relationship between measles vaccination, child mortality, and household area, a primary indicator of socioeconomic status among rural Bangladeshi families (Figure 5). While the presence of a child replacement effect would argue in favor of a much weaker effect of vaccination upon child survival among children from the poorest households (area of <200 sq ft), no such association is evident. The results indicate that children of all socioeconomic strata benefit from measles vaccination in terms of lower mortality risks. Although not as pronounced as in the case of sex, children in the poorest households benefit somewhat more from vaccination in terms of absolute reductions in mortality.

In conclusion, the evidence considered provides no direct or indirect support for the existence of a child replacement effect, which would diminish the contribution of measles vaccination to improved child survival. The available evidence instead indicates that the effect of measles vaccination is sustained over time, and that the greatest benefits from vaccination appear to be found among the most vulnerable children. As such, measles vaccination may reduce not only overall mortality levels but also inequalities between groups in their survival chances.

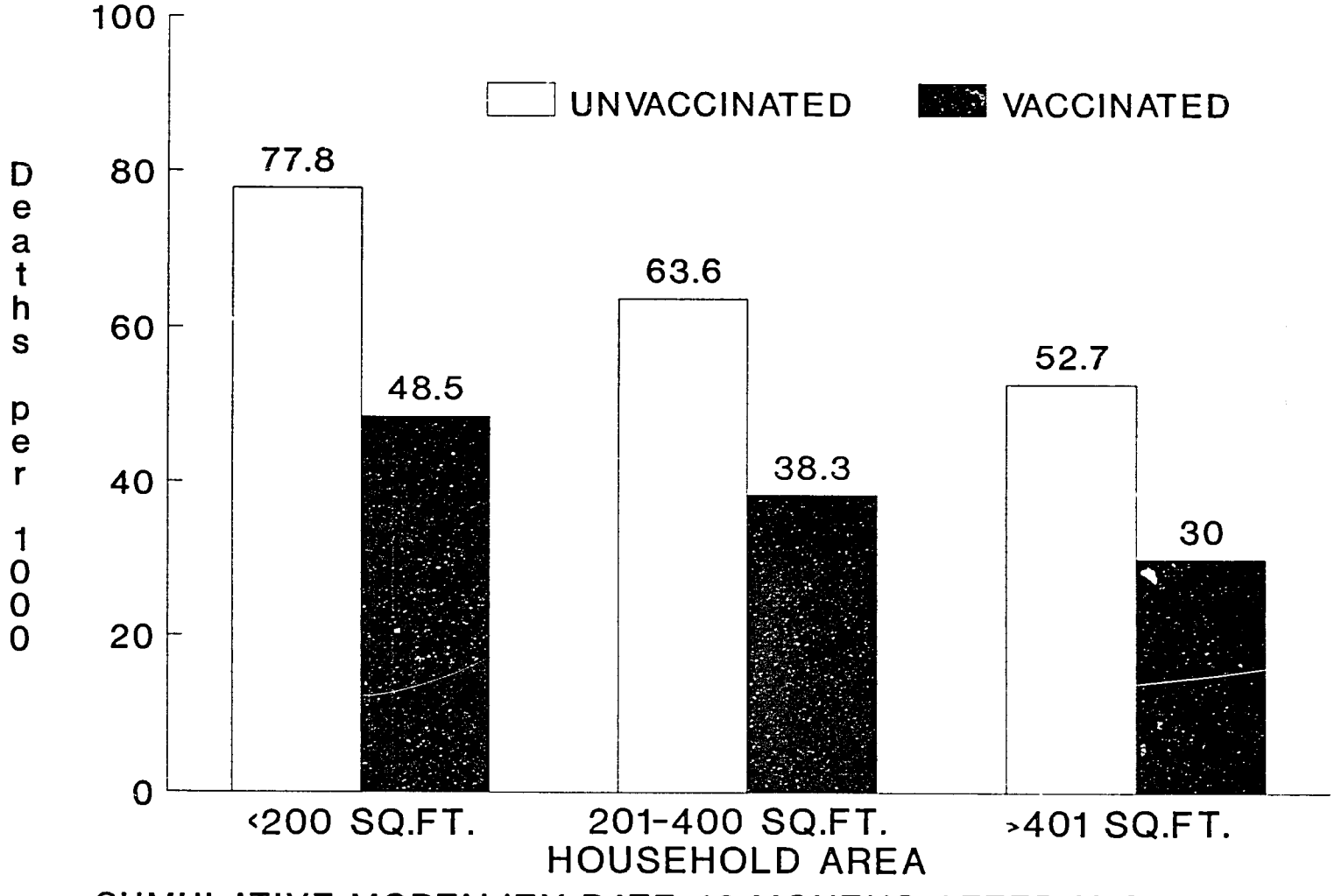
Potential Selection Bias

A primary issue of concern in all assessments of measles vaccination impact is that vaccinated children represent a special group of children who may have better health and survival prospects, even in the absence of measles vaccination. If this were the case, then the lower mortality risks observed may be due in large part to the special nature of vaccinated children, rather than to measles vaccination per se. The studies of measles vaccination impact have adopted a number of different approaches to dealing with the issue of potential selection bias.

The issue of potential selection bias was not directly addressed in the Kasongo study in Zaire. However, the authors presented survival data from the area where measles vaccination had been offered for both the 255 eligible children who were vaccinated as well as the 51 eligible children who were not; many of these latter children may have been self-selected for poorer survival outcomes. Analysis of the survival probabilities of all 306 children together takes into account any possible selection bias between vaccinated and unvaccinated children. The 7-35 month mortality rate for this group was 48.3 per 1000, an increase from the rate of 39.1 per 1000 for vaccinated children alone. However, this still translates into a reduction in mortality relative to the other three control groups of between 30 to 49 percent, indicating a sizeable impact of vaccination upon mortality even when possible selection bias is taken into account.

In both of the other African studies by Aaby, et al. (1984) and Garenne and Cantrelle (1986), control groups consisted of unvaccinated children from the same areas where measles vaccination was offered. As such, selection bias may represent an important confounding factor, with controls disproportionately comprised of children who face independently higher mortality risks. This may account in part for the extremely large reductions in mortality reported by the Aaby, et al. in the Guinea-Bissau study.

FIGURE 5. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS AND BY HOUSEHOLD AREA: MATLAB INTERVENTION AREA, 1982-85



CUMULATIVE MORTALITY RATE 42 MONTHS AFTER VACCINATION

In the case-control study by Clemens, et al. (1988) in Matlab, little or no effect of measles vaccination upon mortality would have been expected during the first year of the study, since the program was introduced at the end of the annual measles season, unless vaccination acceptors constituted a special group with lower overall mortality risks. The finding that there was no protective effect from measles vaccination during the first year of the study provides strong evidence that measles vaccines did not constitute a select group with better survival chances from the onset (WHO, 1987). In addition, the reported finding by the authors of a 36 percent mortality risk among vaccinated children was based upon multivariate analysis which controlled for the effects of a number of potentially confounding demographic and socioeconomic characteristics which might differentiate vaccinated from unvaccinated children.

The Matlab cohort study by Koenig, et al. (1990) also considered the issue of potential selection bias from several different perspectives. First, the study examined whether the families of vaccinated and unvaccinated children differed on other indicators of health behavior which might account for lower mortality among the former group of children. No difference between groups was evident with respect to one important indicator of health behavior--use of contraception. Second, the authors carried out multivariate analysis to control for the effects of a number of potentially confounding variables (birth order, sex, maternal education, and area of household) on which vaccinated and unvaccinated children might differ. The results indicated that even after controlling for these factors, vaccinated children still experienced mortality levels which were 46 percent lower. Lastly, the authors examined whether vaccinated children from the two blocks where measles vaccine was offered may have been self-selected for better survival--i.e., that a primary reason why children remained unvaccinated in these blocks was that they failed to live long enough to be vaccinated. To take this into account, they constructed a second data set which included all children--both vaccinated as well as unvaccinated--from the two blocks where measles vaccination had been offered, and randomly rematched with the pool of unvaccinated children from the other two blocks. These procedures resulted in 9871 children from each of the two areas. When re-analyzed, the results indicated a slightly reduced but still substantial effect of measles vaccination, with children from the area with measles vaccination still experiencing mortality risks which were 40 percent lower than unvaccinated controls. The authors viewed this figure as a minimum estimate of the effect of measles vaccination upon child mortality in this population.

Age at Immunization

A corollary issue of interest concerns the optimal upper and lower age boundaries for measles vaccination. Current WHO guidelines recommend 9 months of age as the optimal age for measles vaccination (WHO, 1982). The focus within immunization programs has generally been on reaching all children from 9 months to 2 years of age. One of the few studies to address this issue has been the study in Bangladesh by Koenig, et al. (1990). The results of life table analysis are summarized in Figure 6. Although the largest absolute reductions in mortality occurred among children who were vaccinated at <12 months of life, substantial and statistically significant reductions were also observed among children vaccinated during the 2nd and 3rd years of life. Although a

reduction in mortality was also observed for children vaccinated at above three years, this was not statistically significant, owing to the low mortality rate and small numbers of deaths at these older ages. These findings indicate that extending the priority target group for measles vaccination to all children under 3 years of age is likely to bring about significant further reductions in mortality in settings such as rural Bangladesh.

It has been recognized that in many settings, significant proportions of young children contract measles before nine months of age, frequently with resultant high case-fatality rates. This has spawned efforts toward the development of a new generation of measles vaccines which can be administered at earlier ages, 4-6 months of age (Markowitz, 1990). The incremental gains in mortality reduction from the introduction of these new vaccines will be contingent upon the following conditions:

1) The prevalence of measles infections among children <9 months of age.

2) The level of protective efficacy provided by these new vaccines.

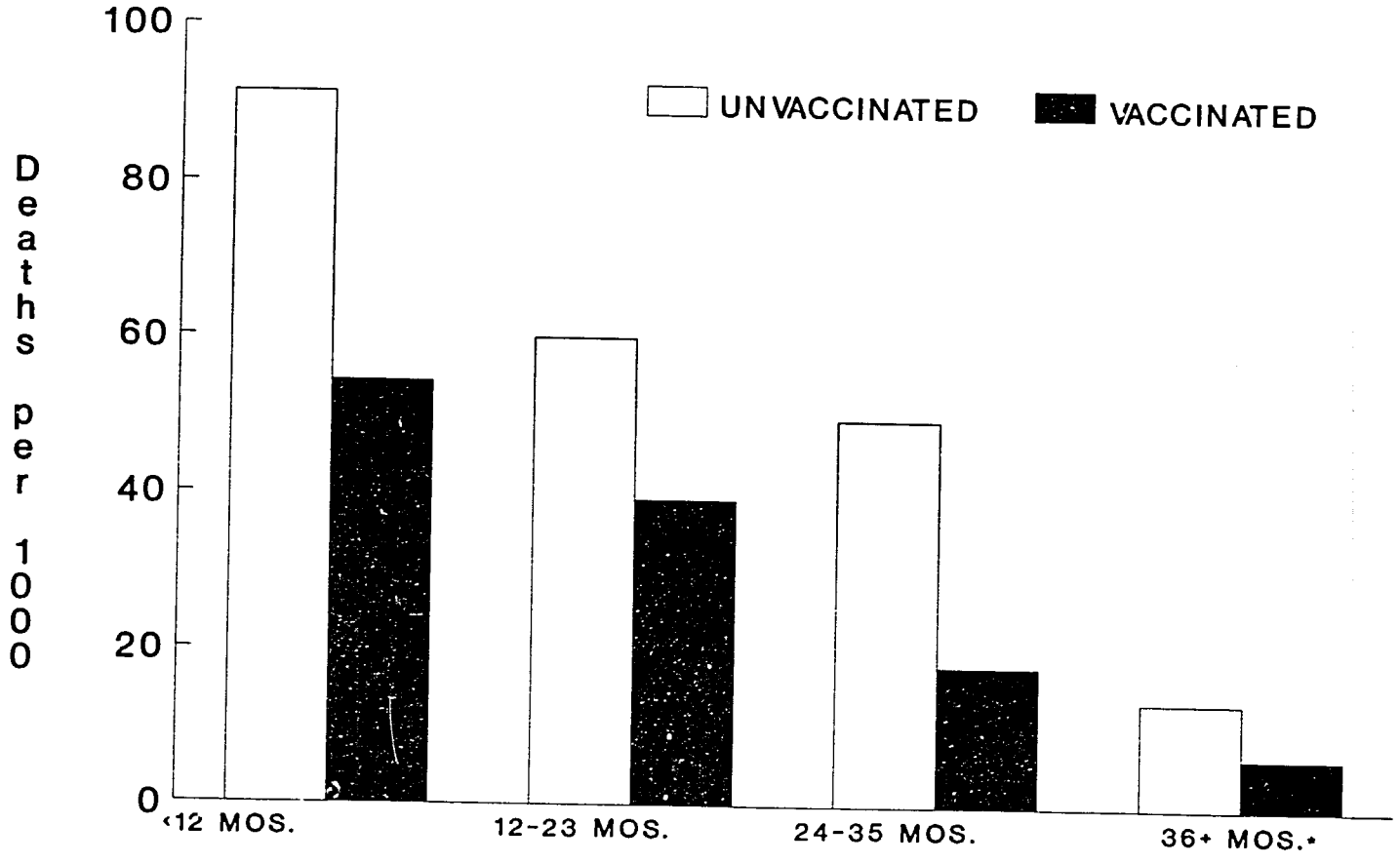
3) The extent to which existing measles vaccination programs (9+ months) may have already reduced such early measles cases through the elimination of the transmission mechanism through older children/siblings.

TETANUS IMMUNIZATION

Tetanus has been estimated to be responsible for at least 500,000 neonatal deaths annually (Stanfield and Galazka, 1984). Deaths due to neonatal tetanus result largely from the infection of the umbilical stump by Clostridium tetani. Tetanus deaths are extremely rare during the initial days of life, rise rapidly to a peak during the 7th to 8th day of life, then decline through the rest of the neonatal period. Neonatal tetanus is effectively prevented through the maintenance of hygienic conditions at the time of delivery, and/or through passive immunity through the immunization of the mother prior to or during pregnancy.

Tetanus immunization differs from immunization against other childhood diseases such as measles in an important way. Because protection is provided passively through immunization of the mother, the risks of neonatal tetanus and tetanus mortality persist undiminished throughout the mother's reproductive period. This contrasts with immunization against other childhood infectious diseases such as measles, with well-defined risk periods during which the risk of death generally steadily diminishes over time. Thus, in addition to the magnitude of neonatal mortality reductions resulting from maternal tetanus immunization, the issues of duration of immunity and the number of doses required to achieve this immunity become of paramount importance for immunization strategies. In the following sections, empirical evidence bearing on these issues is reviewed.

FIGURE 6. CUMULATIVE MORTALITY RATES BY MEASLES VACCINATION STATUS AND AGE AT VACCINATION: MATLAB INTERVENTION AREA, 1982-85



CUMULATIVE MORTALITY RATE 36 MONTHS AFTER VACCINATION

*Reflects rates to 24 months after vaccination

SOURCE: KOENIG, ET AL. 1990

An extensive literature has accumulated on the effect of tetanus toxoid immunization upon protective antibody levels (see Jones, 1983). However, the number of studies assessing the impact of maternal tetanus immunization upon neonatal mortality levels is much smaller (Table 2).

Reductions in Neonatal Deaths Due to Tetanus

One of the earliest studies from a developing country on the mortality impact of maternal tetanus immunization was a study by Schofield, et al. (1961) in New Guinea carried out during 1959-60. All women in an area where a system of health clinics had been established were offered tetanus toxoid during pregnancy. The size of the study population was relatively small: 234 births and 175 births to mothers who received 2 and 3 injections, respectively, and a control group of 160 births to mothers who received either 0 or 1 injections. Comparison of these three groups showed that two or more tetanus immunizations resulted in a significant reduction in mortality from neonatal tetanus; from 100 per 1000 live births in the control group to 34 per 1000 among births to women receiving two injections. Among births to women receiving three injections, only 1 neonatal tetanus case out of 175 births was reported, a rate of 6 per 1000 live births.

Further conclusive evidence on the efficacy of tetanus immunization in reducing neonatal tetanus deaths is found in the study by Newell, et al. (1966) in Colombia during the 1961-1966 period. This study consisted of a double-blind experiment in which all registered women were randomly assigned to one of two groups and offered either tetanus toxoid or influenza-virus vaccine. Subsequent births to these women during 1961-66, were then followed and deaths to these births and specific cause of death were identified. The results demonstrated no neonatal tetanus deaths during this period among births to women who had received 2-3 tetanus immunizations, compared to a rate of 78 per 1000 live births among the control group whose mothers received 2-3 injections of the influenza vaccine.

The Matlab study area is the source of much of the conclusive evidence on the effectiveness of maternal tetanus immunization in reducing mortality from neonatal tetanus. As part of a large-scale cholera vaccine trial in the Matlab study area in 1974, non-pregnant adult women and <5 year children received tetanus toxoid as a placebo. A total of 93,000 individuals participated in this trial, which was randomized on an individual basis, with participants receiving either 1 or 2 injections of cholera toxoid or 1 or 2 doses of tetanus toxoid, all on a double-blind basis. Black et al. (1980) analyzed the mortality impact of tetanus toxoid placebo in this trial upon two cohorts of children born during 1975-77 to mothers who participated in the 1974 vaccine trial. A recent study by Koenig, et al. (1991b) extended the original study through the 1975-89 period in the comparison area only, which has remained a population largely unimmunized against tetanus until recently. Finally, Rahman, et al. (1982) analyzed the mortality experience of children born during 1978-79 in the Matlab study area. Two groups of births to mothers immunized against tetanus were evaluated: those who had received tetanus toxoid while not pregnant as part of the 1974 vaccine trial described above, and those who received tetanus toxoid while pregnant in 1978-79, as part of the expanded MCH-family planning program introduced in half of the Matlab study area.

TABLE 2: SUMMARY OF MATERNAL TETANUS IMMUNIZATION STUDIES

STUDY	LOCATION	STUDY PERIOD	STUDY POPULATION	MORTALITY IMPACT	DURATION OF PROTECTION
SCHOFIELD, ET AL.	NEW GUINEAU	1959-1960	0 TT: 86 BIRTHS 1 TT: 74 BIRTHS 2 TT: 234 BIRTHS 3 TT: 175 BIRTHS	REDUCTION IN NEONATAL TETANUS DEATHS FROM 100 PER 1000 TO 34 PER 1000 WITH 2 TT DOSES AND TO 6 PER 1000 WITH 3 TT DOSES	< 12 MONTHS
NEWELL, ET AL.	COLOMBIA	1961-1966	0 TT: 270 AND 347 BIRTHS 1 TT: 224 BIRTHS 2-3 TT: 341 BIRTHS	REDUCTION IN NEONATAL TETANUS DEATHS FROM 78 TO 0 PER 1000 TO WOMEN WITH 2-3 TT DOSES	UP TO 4 YEARS
BLACK, ET AL.	MATLAB, BANGLADESH	1974-1977	0 TT: 4386 BIRTHS 1 TT: 1265 BIRTHS 2 TT: 2990 BIRTHS	33% REDUCTION IN NEONATAL MORTALITY WITH 2 TT DOSES DURING 1975-77 PERIOD	1 TT: UP TO 20 MOS. 2 TT: UP TO 32 MOS.
RAHMAN, ET AL.	MATLAB, BANGLADESH	1974-1979	0 TT: 7237 BIRTHS 1 TT: 486 BIRTHS 2 TT: 956 AND 934 BIRTHS	REDUCTIONS IN NEONATAL MORTALITY OF 18% AND 49% WITH 2 TT DOSES, DEPENDING ON DURATION	1 TT: NS 2 TT: UP TO 5 YEARS
KOENIG, ET AL.	MATLAB, BANGLADESH	1973-1989	0 TT: 10745 BIRTHS 1 TT: 2718 BIRTHS 2 TT 7891 BIRTHS	37% REDUCTION IN NEONATAL MORTALITY WITH 2 TT DOSES DURING 1975-79 PERIOD	1 TT: UP TO 4 YEARS 2 TT: UP TO 15 YRS.

In the absence of conclusive diagnosis of neonatal tetanus deaths, the Bangladesh studies used mortality during days 4-14 of life as a proxy for neonatal tetanus deaths. For the two birth cohorts combined, the study by Black, et al. showed that two injections of tetanus toxoid resulted in a reduction in 4-14 day mortality of 68 percent relative to the control group who received cholera vaccine (from 25 to 8 per 1000), a highly significant effect. The study by Rahman, et al. found that, relative to births to unimmunized mothers, two tetanus toxoid injections during pregnancy resulted in a statistically significant reduction in 4-14 day mortality of 69 percent; the effect of having received two tetanus toxoid injections through the vaccine trial an average of 4 1/2 years earlier also resulted in a substantially lower 4-14 day mortality rate (by 41 percent), although this difference was statistically significant in only one of the two areas.

Reductions in Neonatal Mortality

The considerable geographical variability in the importance of neonatal tetanus as a cause of death has long been recognized (Bytchenko, 1966). Data from retrospective surveys in a number of Asian and African countries indicated neonatal tetanus death rates ranging from 3 to 31 per 1000 live births, with tetanus accounting for from 8 to 60 percent of all neonatal deaths (Foster, 1984). In addition to true variability across settings in the importance of neonatal tetanus as a cause of death, these figures are also likely to reflect differences in both under- as well as over-reporting of tetanus as a cause of neonatal death.

The Matlab study area in rural Bangladesh has provided much of the reliable evidence on the actual or potential reductions in mortality resulting from tetanus immunization (Table 3). The study by Black, et al. showed that two injections of tetanus toxoid reduced neonatal mortality in subsequent births by 33 percent. Similar results are obtained from the data presented by Koenig, et al. in the extension of this study. Over the five year period following the vaccine trial (1975-79), two doses of tetanus toxoid were associated with a 37 percent reduction in neonatal mortality. The findings of Rahman, et al. were more variable, with reductions in neonatal mortality ranging as low as 18 percent among births to mothers who received two injections of tetanus toxoid an average of almost five years earlier as part of the cholera vaccine trial, to as high as 49 percent among births whose mothers had recently been immunized while pregnant with two tetanus toxoid injections, as part of the MCH-family planning intervention program.

Given the very high efficacy of two doses of tetanus toxoid in eliminating tetanus in at least the short-term, accurate data on diagnosed cause of neonatal death among unimmunized populations should also provide a reasonably precise picture of the potential reductions in neonatal mortality resulting from tetanus immunization programs. Table 3 also shows data from other studies in Bangladesh on the prevalence of neonatal tetanus death. Data presented by Koenig, et al. (1991a) on causes of death in the Matlab comparison area, when adjusted for the confounding effects of tetanus immunization delivered through the 1974 cholera vaccine trial described earlier, indicated that tetanus accounted for 27 percent of neonatal deaths in this area
during the 1986-87 period. An earlier study by Bhatia (1989) of 1982-83 infant deaths in the Matlab study area found that tetanus accounted for 20 percent of all neonatal deaths in the comparison area. However, the Bhatia study did not adjust for the effects

of the 1974 vaccine trial, so that tetanus deaths are likely to have been underestimated in this study.

It should also be emphasized that the earlier findings from Matlab, indicating reductions in neonatal mortality by one-third or more (Black, et al. 1980; Koenig, et al. 1991a) may not be inconsistent with the cause of death estimates of neonatal tetanus cited above. There is evidence of a steady decline in 4-14 day mortality in the Matlab study area since the late 1970s among births to unimmunized mothers (Koenig, et al. 1991b), although the factors which have contributed to this decline remain poorly understood. At the same time, a recent study in a separate area of rural Bangladesh, based upon one year retrospective survey data, reported somewhat higher levels of tetanus-related mortality (34 percent of reported neonatal deaths), raising questions about whether neonatal tetanus levels may be somewhat lower in the Matlab area than for Bangladesh as a whole (Hlady, et al. 1991).

Duration of Immunity

In the Colombian study, no neonatal tetanus deaths were reported among mothers who were immunized during pregnancy with 2 or 3 injections of tetanus toxoid and gave birth over the 1961-66 period (Newell, et al. 1966). This result provided evidence that the protection conferred by maternal tetanus immunization appeared to last for a period of at least four years. Black, et al. (1980) in their Matlab study found that two injections of tetanus toxoid resulted in significantly lower 4-14 day mortality levels through 21-32 months after immunization. The study by Rahman, et al. (1982) in Matlab also provided evidence of extended durations of protection through maternal tetanus immunization. Their findings showed that 1978-79 births to mothers immunized with two injections of tetanus toxoid during the 1974 cholera vaccine trial continued to experience significantly lower 4-14 day mortality rates than among the non-immunized group, indicating that two injections of tetanus toxoid may confer significant levels of protection against tetanus for a duration of as long as five years.

These upper bounds on the duration of immunity reported in all of the forementioned studies have been defined by the end of the respective study periods, rather than by a quantifiable diminution in protective immunity. The recent study by Koenig, et al. (1991b), which examined the duration of immunity conferred by tetanus immunization in the 1974 cholera vaccine trial over the 1975-89 period, provides the most conclusive evidence to date on long-term protection conferred by maternal tetanus immunization. Figure 7 shows three-year moving averages in 4-14 day mortality according to 1974 vaccination status for births to mothers residing in the Matlab comparison area. While mortality rates were comparable in the period prior to the vaccine trial (1973-74), a sharp differential in mortality by vaccination status is observed subsequent to the 1974 trial. Although some narrowing in mortality rates between groups is evident over time, the mortality rates for the different groups did not converge over time. Separate analysis by the authors indicated that, relative to the unimmunized group, the reduction in 4-14 day mortality among the group receiving two injections of tetanus toxoid was highly statistically significant ($p < .01$) for 8 years and remained significant ($p < .05$) through 1989 (with the exception of 1985-86), a period of 15 years. Thus, even in 1989, the 4-14

TABLE 3: SUMMARY OF FINDINGS FROM BANGLADESH IMMUNIZATION AND CAUSE OF DEATH STUDIES ON NEONATAL TETANUS

IMMUNIZATION STUDIES	NEONATAL MORTALITY RATE (PER 1000)		% REDUCTION IN NEONATAL MORTALITY
	0 TT	2 TT	
BLACK, ET AL. (1980): 1975-77 BIRTHS	59.7	39.8	33.3%
RAHMAN, ET AL. (1982):			
IMMUNIZED IN 1974	78.3	63.8	18.5%
IMMUNIZED IN 1978-79	78.3	42.8	48.8%
KOENIG, ET AL. (1991b): 1975-79 BIRTHS	78.2	49.5	36.7%

CAUSE OF DEATH STUDIES	NEONATAL TETANUS MORTALITY RATE (PER 1000)	% OF ALL NEONATAL DEATHS
BHATIA (1989): 1982-83 MATLAB COMPARISON AREA	13.7	20.4%
KOENIG, ET AL. (1991a): 1986-87 MATLAB COMPARISON AREA	18.6*	27.2%*
HLADY, ET AL. (1991): N. BANGLADESH DIVISION	18.2	33.9%

*Adjusted for the effects of the 1974 vaccine trial.

day mortality rate for the two injection group was 6 per 1000, compared to 23 per 1000 in the unimmunized group.

Number of Doses

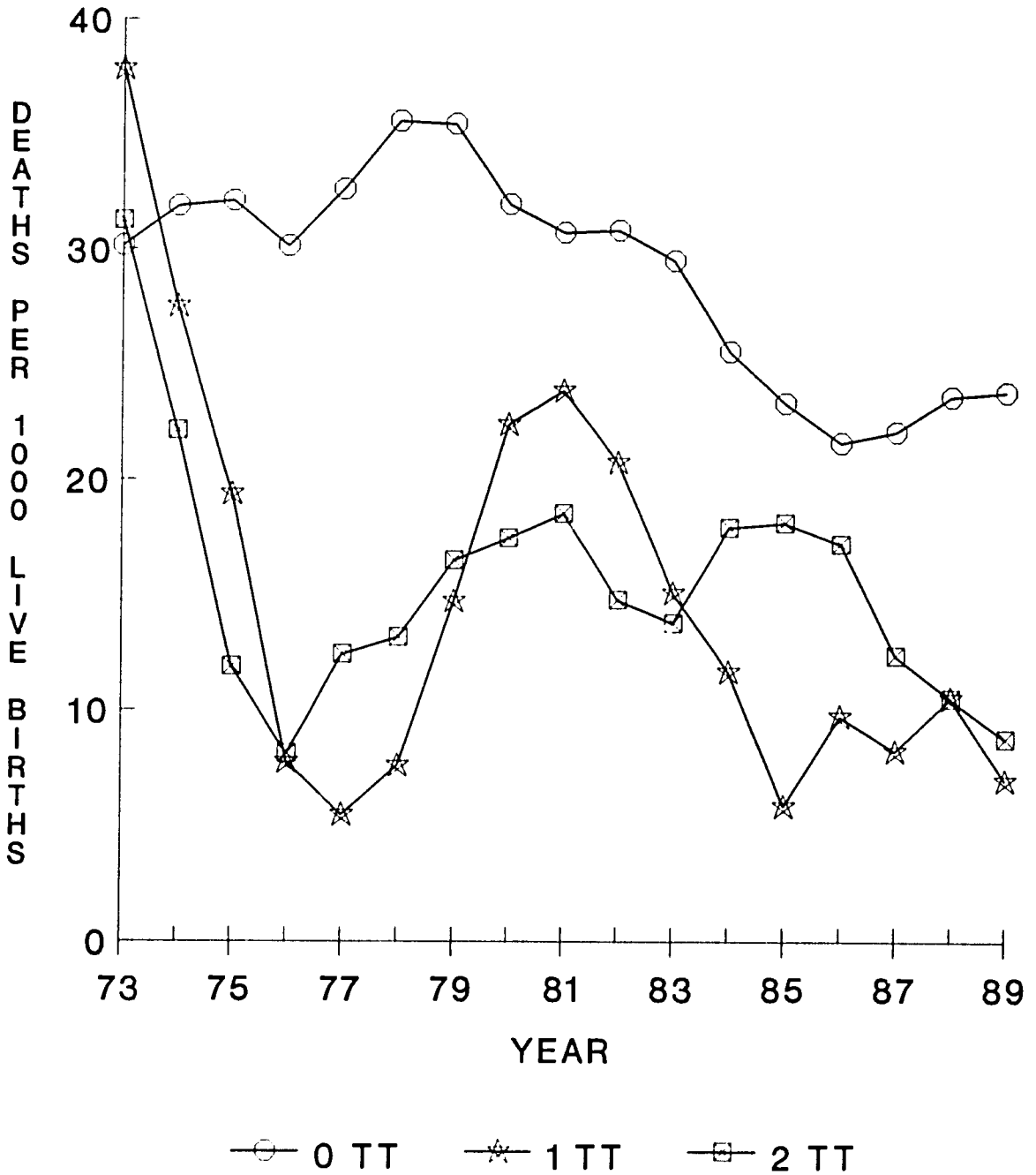
One Dose

Considerable interest has centered upon the degree of protection provided by one dose of tetanus toxoid, since an effective single dose would greatly simplify the delivery of maternal tetanus immunization. The findings on this issue with respect to mortality impact have been at best inconsistent, and not infrequently contradictory. For example, the New Guinea study found no differences in the neonatal tetanus rates between the small numbers of births to mothers with one injection vs. no injections, with both groups experiencing markedly higher neonatal tetanus rates than those who received 2 or 3 tetanus injections. The Colombian study, on the other hand, reported somewhat lower neonatal tetanus rates among births to mothers who received 1 vs. 0 tetanus toxoid injections, although this difference was not statistically significant and the rate for the 1 dose group was still considerably higher than the group who received 2-3 injections (40 vs. 0 per 1000). The small numbers of cases included in both of these studies, however, make definitive conclusions difficult.

Once again, the most persuasive evidence on the issue of a single tetanus toxoid dose comes from the Matlab study area. However, even within the Matlab study area, the findings on this issue have not been entirely consistent. The effect of one dose is closely linked to the issue of duration of protective immunity. As shown in Figure 8, the study by Black, et al. found that one injection of tetanus toxoid was associated with significantly lower 4-14 day mortality 9-20 months after immunization, with a mortality rate comparable to the two injection group. However, for the period 21-32 months post-immunization, the rate for this group was no longer significantly lower, but in fact substantially higher than for the two injection group, leading the authors to conclude that a single dose did not provide meaningful protection for longer than 20 months. The findings of the Matlab study by Rahman, et al. led them to conclude one injection of tetanus toxoid did not confer a meaningful level of protection. However, as Figure 8 shows, the results of their study indicated that among the small number of births to women who received only one injection of tetanus toxoid in the 1974 vaccine trial (N= 362), 4-14 day mortality rates were substantially lower than for the unimmunized group and only slightly higher than for the two dose group (34, 25, and 20 per 1000). However, 4-14 day mortality rates among the group who received only a single injection while pregnant through the 1978-79 immunization program were markedly higher than either of the two immunization groups, and twice as high as for the single injection group in the 1974 vaccine trial. This discrepant finding may be explained by the small numbers of births belonging to this group (N=124), as well as the highly selective nature of those who dropped out of the program after receiving only one injection (see subsequent discussion).

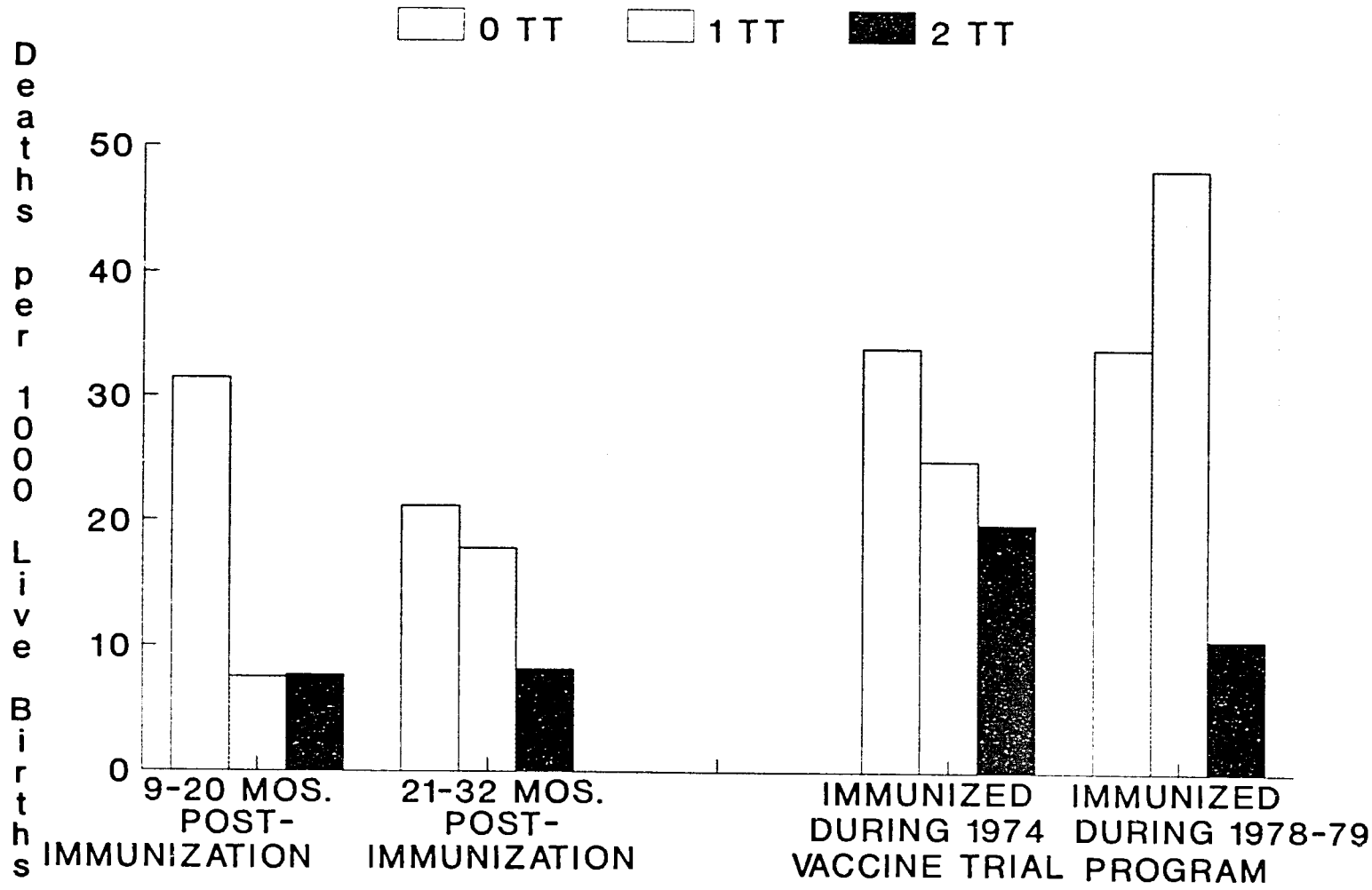
The recent Matlab study by Koenig and colleagues (1991b) provides additional and contrasting evidence on the effect of a single tetanus toxoid dose. As Figure 7 shows, 4-14 day mortality for the one tetanus toxoid injection group closely parallels that for the

FIGURE 7. DURATION OF PROTECTIVE IMMUNITY PROVIDED BY MATERNAL TETANUS TOXOID IMMUNIZATION AGAINST 4-14 DAY MORTALITY: MATLAB COMPARISON AREA, 1973-89



SOURCE: KOENIG, ET AL. (1991b)

FIGURE 8. SUMMARY OF MATLAB FINDINGS ON EFFECTS OF NUMBER OF TETANUS TOXOID DOSES UPON 4-14 DAY MORTALITY



SOURCE: BLACK, ET AL. (1980)

SOURCE: RAHMAN, ET AL. (1982)

two injection group not just in the short-run, but for the entire period of observation. The authors' analysis showed that relative to the group of births to unimmunized mothers, lower 4-14 day mortality among the one injection group was statistically significant through 1978-79; for a period of up to four years. At the same time, while not attaining statistical significance, mortality for the one injection group remained below one-half that for the unimmunized group in almost all subsequent years. For the 1975-89 period as a whole, 4-14 day mortality for the one injection group was 12.5 per 1000 live births, significantly lower than for the unimmunized group (28.4 per 1000) and even slightly below that for the two injection group (13.8 per 1000).

3+ Doses

Empirical evidence on the incremental mortality gains from more than two doses of tetanus toxoid is also slender and generally based upon very small study populations. The study in New Guinea found that three injections of tetanus toxoid during pregnancy conferred a higher level of protection against neonatal tetanus compared to two doses, with a reduction in neonatal tetanus mortality from 34.2 deaths per 1000 to 5.7 per 1000 (Schofield, et al. 1961). In contrast, the Colombian study found no difference in neonatal tetanus mortality rates between births whose mothers received 2 versus 3 tetanus injections; both groups experienced no recorded tetanus cases or deaths during the study period of more than four years (Newell, et al. 1966). Finally, data in the Matlab study by Rahman, et al. (1982) allow the comparison of the following 4-14 day mortality rates:

Tetanus Immunization Status	4-14 Day Mortality Rate (per 1000)	(N)
2 doses (1978-79)	10.7	(934)
2 doses (1978-79), 1 dose (1974)	15.6	(64)
2 doses (1978-79), 2 doses (1974)	7.0	(142)

Although the number of cases is small, the results provide no evidence of a consistent further reduction in 4-14 day mortality rates with either 3 or 4 doses of tetanus toxoid, relative to the group who received only two injections while pregnant in 1978-79, during the interval of the study period.

Further corroboration of the Matlab findings through serological studies would be desirable, particularly with respect to the effects of a single dose of tetanus toxoid, given the uncertainties which persist. One limitation common to all of these studies has been the use of 4-14 day mortality as an indicator of tetanus mortality. While most neonatal tetanus deaths are known to be clustered in this period, recent work in Matlab has shown that tetanus may account for only about half of all deaths during this age period (Koenig, et al. 1991a), leading to considerable imprecision in this measure as an indicator of tetanus-related mortality. It should also be recognized these studies demonstrate significant reductions in, but not necessarily the elimination of, neonatal deaths due to

tetanus--the stated objective of the Expanded Program on Immunization, and one which might lead to quite different immunization strategies. The recent findings from Matlab nevertheless provide strong evidence that current maternal tetanus immunization strategies may confer significant levels of protection for a much more extended period than has previously been believed. A single injection of tetanus toxoid may also confer a significant degree of protection against tetanus for at least several years, while two injections may provide significant protection throughout much of a woman's reproductive life.

Potential Selection Bias

The issue of potential selection bias among births to vaccinated and unvaccinated mothers has been less of a concern in the studies on the impact of tetanus immunization. One reason is that several of the major studies have been based upon controlled field experiments whose design effectively eliminated the possibility of such selection bias. The field trial by Newell, et al. in Colombia (1966), and the 1974 cholera vaccine trial in Matlab, on which the studies by Black, et al. (1980) and Koenig, et al. (1991b) were based, were both double-blind, controlled field trials. A second reason why selection bias may be of less concern with regard to neonatal immunization studies has been the absence of evidence suggesting that unimmunized mothers differ from immunized mothers in behavior (other than immunization) which predisposes the children of the former to higher risks of neonatal tetanus. A third and related factor has been the absence of evidence suggesting that children at risk of death from tetanus represent an especially vulnerable group who are also at much higher risk of death from other neonatal causes.

Nevertheless, in the studies considered which were not based upon controlled experiments, the possibility of potential selection bias cannot be ruled out. For example, in the study in New Guinea, a primary reason for non-immunization (86 cases) was that mothers came too late in pregnancy to be immunized. The possibility that such women constitute a highly selective group whose children are predisposed toward higher risks of tetanus cannot be ruled out, although the authors view this as unlikely.

Selection bias may have played a more important role in some of the Matlab findings reported by Rahman, et al. (1982). Although maternal tetanus coverage rates subsequently reached very high levels (when offered to all reproductive-aged women), at the time of this study, when made available only during pregnancy, only one-third of eligible women had accepted immunization. It could plausibly be argued that these women may represent a highly selective group who would face lower mortality risks--and unimmunized women conversely higher mortality risks--even in the absence of this program. (The dependent variable of 4-14 day mortality leaves open the possibility for selection bias with respect to both tetanus as well non-tetanus deaths, since this measure reflects both). This would help to explain the much larger reduction in neonatal mortality rates among births to mothers who received two injections during the 1978-79 program compared to the other studies from Matlab (49 percent lower). This might also partially account for the absence of a significant effect among the small one dose group, which may consist of a higher proportion of high risk mothers.

Mortality at Later Ages

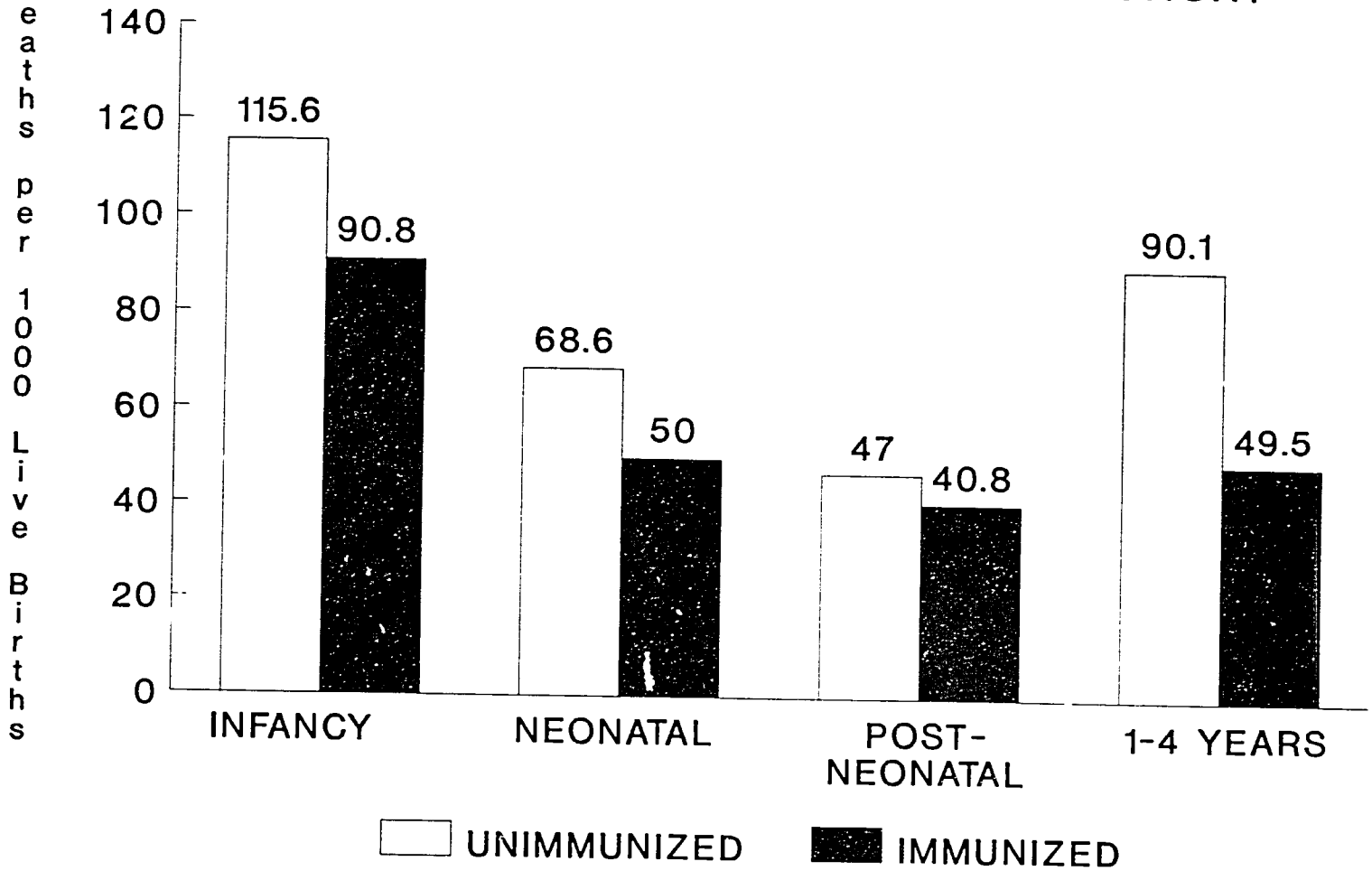
An additional argument advanced for tetanus immunization is the protection it provides against tetanus beyond the neonatal period. The available empirical evidence on this issue, however, suggests that the magnitude of this additional mortality effect may be quite modest. For example, a study of causes of childhood death in the Matlab comparison area during 1986-87--where tetanus immunization coverage levels were extremely low--indicated that tetanus accounted for only 3 percent of post-neonatal and less than 1 percent of 1-4 year deaths (Koenig, et al. 1991a). Similarly, a population-based study of 1037 deaths to adult women in the Matlab study area during 1976-85 found that only 6 were attributable to tetanus, representing less than 1 percent of all such deaths (Fauveau, et al. 1987). These findings indicate that from the standpoint of mortality impact, the benefits from tetanus immunization will derive largely from a reduction in neonatal tetanus mortality.

ESTIMATES OF POTENTIAL MORTALITY REDUCTIONS FROM MEASLES AND TETANUS IMMUNIZATION

The recent study by Koenig, et al. (1991a) allows the estimation of the mortality impact of measles and tetanus immunization for rural Bangladeshi children. In this study, the survival status of a cohort of 8161 births, representing all births within the Matlab comparison area during 1982-83, was followed through the end of 1987 to estimate under 5 year mortality levels in a largely unimmunized population. The authors then applied the previously reported findings from Matlab on cause of death and vaccination impact, in addition to data on the age distribution of mortality, applying the most liberal estimate of mortality reduction for each case, to estimate reductions in mortality based upon the elimination of deaths from these causes. The results of this exercise for measles and tetanus mortality are shown in Figure 9.

For this population of children, the elimination of tetanus and measles through immunization could be expected to reduce infant mortality levels from the previous level of 116 per 1000 live births to 91 per 1000 live births. It is apparent that most of this reduction would occur through a reduction in neonatal mortality levels (from 69 to 50 per 1000 live births) as a result of tetanus immunization; the reduction in post-neonatal mortality levels will be quite modest (from 47 to 41 per 1000 live births). A marked decline in 1-4 year mortality is also evident as a result of the large effect of measles vaccination, with mortality between these ages declining from 90 per 1000 to 50 per 1000 live births. Overall, the impact of eliminating measles and tetanus mortality through immunization would be to reduce under 5 year mortality from the baseline level of 206 per 1000 to 140 per 1000 live births, a reduction of 32 percent. Two caveats are in order. First, as the authors point out, a number of assumptions have been built into these estimates, with the result that the actual reductions in mortality could be either over- or underestimated by these figures. Second, these estimates are specific to one area in rural Bangladesh, and the likelihood exists that mortality reductions might vary considerably in other settings, or even in other parts of Bangladesh.

FIGURE 9. ESTIMATED REDUCTIONS IN INFANT AND CHILD MORTALITY FROM TETANUS AND MEASLES IMMUNIZATION: 1982-83 MATLAB COMPARISON AREA BIRTH COHORT



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Impact of Immunizations to Prevent Acute Respiratory Infections

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INTRODUCTION

It is becoming clear that control of mortality due to acute respiratory disease will be one of the major tasks of the 1990s. The decade of the 1980s has seen efforts to rationalize and improve case-management strategies to reduce mortality due to acute respiratory infections, and we will hear a summary of this data by Dr. R. Black later in this conference. In addition to case management, there is increasing interest in the use of vaccines which have the potential to reduce respiratory mortality. In this discussion, I will review data for currently available vaccines and assess their impact on mortality, as well as briefly discuss vaccines which will be available in the near future.

ACUTE RESPIRATORY MORTALITY

Respiratory deaths account for approximately one-third of all deaths in infants and under-five children in the developing world[1]. Most of this mortality occurs before 2 years of age, and includes deaths from many different microbial agents: pertussis, diphtheria, measles, as well as from pneumonias caused by a panoply of bacteria and viruses[2]. Each single vaccine will prevent disease and mortality due to only one organism. It is no easy task to distinguish the individual causes of pneumonia, so we will use estimates for organism-specific rates and proportions of disease. It may be difficult to directly measure the impact of a single vaccine without large field trials which include extensive diagnostic facilities. Nevertheless, the historical and field trial data are instructive, and allow us to estimate the impact of vaccines to prevent respiratory infections.

This discussion will focus first on the impact of the vaccines currently included in the W.H.O. Expanded Program of Immunization (EPI), followed by consideration of vaccines to prevent disease due to the bacteria H. influenzae type b and S. pneumoniae.

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Vaccines to prevent illness caused by these bacteria are not part of EPI, but they are licensed and used in the United States. These bacterial vaccines have the potential to reduce pneumonia mortality, and I will review estimates of their potential impact. Although respiratory viruses are important causes of respiratory disease and mortality, they will not be discussed here because effective vaccines are not currently available[3] A fuller discussion of the issues of prevention of pneumonia mortality has been recently published as the proceedings of a Bellagio Conference[4]

Diphtheria Toxoid Vaccine

Historically, diphtheria was the third most important cause of childhood mortality in the US and UK; this fact was the impetus for the development and use of diphtheria toxoid vaccine in the 1930s and 40s.[5] There were no well designed studies of efficacy before widespread use of diphtheria vaccine as part of Diphtheria Tetanus Pertussis (DTP) vaccine in Europe and North America. To be fair, the use of randomized controlled trials was in its infancy in the 1940s, and it was evident that the vaccine was safe and immunogenic. Although rates of diphtheria were declining before the use of the vaccine, the fact that diphtheria has virtually disappeared with the use of this vaccine is suggestive that the vaccine is effective.

There have been two recent studies of local epidemics of diphtheria which provide contemporary estimates of vaccine efficacy (Table 1). A school outbreak in Texas in 1970 provided an opportunity to retrospectively compare rates of disease in children with varying levels of immunization. In children who were fully immunized with three doses of DTP, the vaccine was 93% (95% confidence interval [C.I.]: 68 to 98) effective in preventing clinical diphtheria[6] A case-control analysis of DTP efficacy in an outbreak in Yemen in 1981 demonstrated an efficacy of 87% (95% C.I.: 32 to 99)[7] These studies, although not ideal, tend to confirm the impression of high efficacy associated with current diphtheria toxoid vaccine.

Measles Vaccine

The impact of measles vaccine on mortality has been extensively reviewed by Markowitz and Nieburg[8] and by Koenig[9,10] Although it is clear that measles vaccine has a substantial impact on overall infant and child mortality, there are also data suggesting it specifically reduces respiratory mortality. The case-control study by Clemens, et. al. from Matlab, Bangladesh showed the receipt of measles vaccine was associated with a 22% reduction (95 CI: -65 to 64) in putative respiratory deaths[11] There were only 45 deaths ascribed to respiratory causes, which limited the power of the study to assess the efficacy of measles vaccine.

Pertussis Vaccine (DTP)

Pertussis vaccine, as part of DTP, is currently the subject of intense scientific and policy interest. Most of the interest is focused on adverse effects of the whole-cell pertussis DTP vaccine and not on its efficacy. Fine and Clarkson published an extensive review of 44 published studies of the efficacy of pertussis vaccine[12]. They pointed out that the estimated efficacy of the vaccine is highly dependent on a variety of factors:

1. The individual vaccine products and the specific production lots of a single product;
2. The number of doses received;
3. The time from immunization to exposure to pertussis;
4. Pertussis disease ascertainment; and,
5. Clinical criteria for diagnosis of pertussis disease.

The range of efficacies was 4 to 91% in the cohort studies and from 0 to 97% in the case control studies they reviewed. An important study appeared after this review: a prospective Swedish study of the Wellcome whole-cell pertussis vaccine which reported an efficacy of 80% (C.I. 95% 58-90)[13]

I am not aware of any well designed prospective trial of the effect of pertussis vaccine in a developing region [14,15,16]. A single observational study with no control group from Kenya reported that 3 doses of DTP were marginally more effective than 2 doses against clinical pertussis. There was no placebo group included in this trial, so it is not possible to estimate overall efficacy of pertussis vaccine[17]. During an outbreak of pertussis in Indonesia, a case-control analysis of the efficacy of two doses of DTP vaccine showed 87% efficacy, with wide confidence limits (Table 2)[18]

In summary, although there is no single figure for the efficacy of pertussis vaccine, most authorities estimate a protective efficacy of DTP vaccine of 80 to 90%. Developed countries experienced a marked decrease of pertussis cases when universal DTP immunization was introduced[16]. Reverse or negative impact data are available for those countries in which DTP vaccine coverage has declined. The acceptance of vaccine decreased because of concern about adverse effects associated with the use of DTP. In Sweden, Japan, and England the decreased use of DTP was immediately followed by epidemics of clinical pertussis, which included deaths. In Britain and Japan the epidemics moderated after coverage rates of pertussis vaccine increased[19,20]. In Sweden, during the years when pertussis vaccine was not used, it was reported that 15% of all Swedish children developed clinical pertussis[21]. These patterns suggest that DTP vaccine is effective in preventing pertussis disease.

Acellular Pertussis Vaccines

Because of concern about the adverse effects of whole cell DTP vaccines, new acellular pertussis vaccines which contain purified antigens have been developed and tested, initially in Japan. Acellular vaccines containing pertussis toxin (PT) and filamentous hemagglutinin (FHA) have been used in Japan since 1976. Studies using household contact and case control methodology have demonstrated estimates of vaccine efficacy ranging from 77% to 95% after 3 doses in 2 year old children[22-24].

A Swedish trial of acellular vaccines compared 2 doses of PT alone, PT plus FHA, and a placebo in 1986. A total of 3,801 healthy infants were randomized to one of the three groups and received subcutaneous doses at 6 and 8 months of age. Using a broad case definition of any cough plus a positive culture for B. pertussis, the efficacy of the PT product was 54% over a 15 month period, and that of the PT-FHA vaccine was 69%[25]. However, an analysis using a more stringent case definition of more than 30 days of

cough or >8 spasms of coughing per day yielded efficacies of 95% and 91% for PT-FHA and PT, respectively[26]. Another calculation of efficacy derived from surveillance for up to 2 years after immunization indicated that efficacies against culture-proven pertussis disease were 83% (95% CI; 74 to 89) and 72% (95% CI; 59 to 81) with PT-FHA and PT, respectively[27]. Under NIH auspices, the Johns Hopkins Center for Immunization Research and 5 other vaccine evaluation groups have just completed a comparative immunogenicity assessment of 12 different acellular pertussis products, all of which were less reactogenic than whole cell DTP. Two or three of these acellular vaccines will be tested in a field trial of efficacy later this year. If efficacy is proven, one or more acellular pertussis vaccines will be licensed in the U.S.

We can assume that high coverage of pertussis vaccine (as DTP, which includes diphtheria toxoid) and measles vaccine will virtually eliminate respiratory mortality due to these 3 organisms. The impact on respiratory deaths is hard to estimate, since diphtheria does not appear to be common in most developing countries. It has been estimated that approximately 25% of respiratory deaths are caused by diphtheria, pertussis and measles[28], thus their elimination should result in a similar reduction in respiratory deaths, if one assumes no replacement mortality.

Other Vaccines

In order to consider the potential impact of other vaccines on acute respiratory mortality, I will use the assumption that the maximum potential impact of a single vaccine will depend on the following factors:

1. The proportion of all cases of pneumonia which are due to the specific agent;
2. The efficacy of the vaccine in preventing disease due to that agent; and
3. The immunization coverage achieved with the vaccine.

Table 3 illustrates how these assumptions are used to estimate the impact of a pneumococcal immunization program on pneumonia mortality. For purposes of illustration, this example ignores the effect of age on both incidence of disease and on the antibody response to the vaccine.

In 1987, the Institute of Medicine in its review of vaccine priorities assessed the distribution of causation of acute respiratory mortality[29]. Table 4 updates this assessment mainly with data available from the recent worldwide studies of pneumonia etiology carried out by the Institute of Medicine's Board of Science and Technology[30]. Most authorities agree that the leading bacterial agents of pneumonia mortality are the pneumococcus and Haemophilus influenzae type b[2].

Haemophilus influenzae type b

Vaccines to prevent Haemophilus influenzae type b disease were licensed at the end of 1990 for universal use in infants in the United States, to prevent the major cause of infant and childhood meningitis. Pneumonia caused by Haemophilus influenzae appears to be relatively rare in the United States, but seems common in certain developing countries. Among the 6 serotypes of Haemophilus influenzae, type b is usually the major cause of

pneumonia; however, the spectrum of Haemophilus serotypes varies from country to country[31]. It has been estimated in a recent review that approximately 30% of pneumonias are due to Haemophilus influenzae, and at least one-.hird of H. influenzae isolates from pneumonic disease are type b[31].

The current Haemophilus vaccines licensed in the U.S. are bacterial capsular polysaccharides chemically conjugated to a protein carrier to enhance their immunogenicity in infants. Table 5 summarizes the results of carefully executed prospective randomized trials of 3 Haemophilus influenzae type b conjugated vaccines[32-35]. All but the Alaska study showed very high efficacy against meningitis. These data led to the recent licensure of 2 of the vaccines for use in infancy in the United States. None of the studies evaluated efficacy against pneumonia.

Because of doubts regarding the magnitude of the potential effect of this vaccine on respiratory and invasive disease in developing countries, there has not been a move to incorporate this vaccine into national immunization programs. An estimate of the potential impact of H. influenzae type b conjugate vaccine is in Table 6. Given the wide variation in prevalence of H. influenzae pneumonia and in the proportion of pneumonia caused by type b, the estimated range of impact is wide. Although the potential impact is fairly low, the incremental cost of adding a safe, effective and licensed product to ongoing EPI programs is also relatively low. A detailed consideration of costs versus benefits will be essential before this vaccine can be considered for use in developing regions.

Issues which remain to be resolved include differences of response to H.influenzae vaccines which may be related to ethnic or geographic considerations[36,37]. The failure of the vaccine to prevent disease in a situation of high rates of illness in Alaska[33] indicates that variation in antibody response to the vaccine related to ethnic or geographic differences may be important. Increased data on the distribution of Haemophilus influenzae serotypes in various parts of the developing world will also be useful. If serotypes other than type b are found to cause a significant proportion of disease, new approaches to prevention by immunization will have to be initiated.

Pneumococcal vaccine

Pneumococci are the most common bacterial cause of pneumonia in childhood. There are 84 serotypes of pneumococci which cause invasive disease in man, and the current licensed vaccine includes the 23 most common serotypes. Table 7 summarizes the distribution of serotypes in pneumococcal childhood disease around the world[38-45]. It can be seen that from 66 to 95% of invasive disease is due to serotypes contained in the vaccine, depending on the region and age group. The currently available vaccine consists of several capsular polysaccharides which are not immunogenic in children under the age of two[46]. Table 8 summarizes the results of efficacy studies of the pneumococcal polysaccharide vaccine in adults and children in developing regions[47-50]. Studies of South African gold miners showed an efficacy of 80% to 90% in the reduction of bacteremic disease caused by vaccine serotypes. These studies led to the licensure of the polysaccharide vaccine in the U.S. Studies in U.S. adults show lower rates of efficacy,

which may be due to the poor response of older adults to this vaccine (reviewed in reference 51).

An important study of the impact of pneumococcal vaccine was reported from Papua New Guinea [50]. The authors carried out a randomized study of the pneumococcal polysaccharide vaccine in more than 4,000 children aged from 4 months to 59 months who received vaccine in vaccine campaigns. There were no bacteriologic diagnoses, and death was the outcome which was analyzed. A verbal autopsy procedure was used to classify the deaths; a history of rapid respiration identified pneumonia deaths. Pneumonia mortality rates were compared between the immunized and unimmunized and a 59% reduction of pneumonia mortality in the vaccinated group was reported (95% C.I. 19% to 79%); most of the effect was in older children (Figure 1). Overall mortality was 19% less in the vaccine group (95% C.I. -10% to 40%), although this difference was not significant. Given the relatively small sample of children, the wide confidence limits of the estimate of efficacy, the unique role of pneumococci in Papua New Guinea, and the evidence that there is limited immunogenicity of many pneumococcal serotypes before 2 years of age, further studies are needed to estimate the effect of this vaccine in other regions.

An interesting new development is the use of protein conjugation of the pneumococcal polysaccharides in order to render them immunogenic in infants[52-55]. This approach was successful in the development of Haemophilus conjugate vaccines, which have proven efficacy in infants. A trial of a bivalent conjugated pneumococcal polysaccharide vaccine will begin in the Johns Hopkins Center for Immunization Research in the summer of 1991. There are plans to produce a septavalent pneumococcal vaccine including serotypes 1, 5, 6A, 14, 18E, 19F, and 23F which are deemed most frequent in developing countries. Although it is anticipated that the polysaccharide-protein conjugate vaccines will be immunogenic in infants, this potential increased effectiveness may be counterbalanced by the fewer serotypes which it will be practical to include in a conjugate vaccine. Moreover, it is possible that 2 doses in infants will be needed before a vaccine is effective, which means that protection may not be achieved until 4 to 5 months of age.

We have developed a model to estimate vaccine reduction of age-specific respiratory disease mortality and to compare the potential impact of the pneumococcal polysaccharide vaccine given at 2 years of age compared to septavalent polysaccharide-protein conjugate vaccine given at 2, 4, and 6 months of age (Table 9). A summary of the model is presented here, as a full description will be published elsewhere. We made the following assumptions: 1) the 23-valent vaccine is 80% effective in preventing pneumococcal pneumonia mortality caused by the 23 included serotypes when given to children older than 2 years; the septavalent conjugate vaccine, when given at 2, 4, and 6 months, was assumed to be 100% effective after 5 months of age by analogy to the Hib conjugate vaccine experience (Table 5). 2) The 23-valent vaccine included 85% of invasive serotypes, while the septavalent vaccine included 75% of the invasive serotypes (Table 7). 3) Immunization coverage rates were assumed to be 80%. 4) Age-specific pneumonia mortality rates were calculated from data from Bangladesh[56] showing that of

all pneumonia deaths in children <5 years of age, 61% occur in infants under 6 months of age, 28% in 7-24 month old infants, and 11% in 24-60 month old children. 5) We assumed that 50% of pneumonia deaths were pneumococcal. 6) There will be no major changes in the spectrum of pneumococcal serotypes causing disease in a vaccinated population.

The 23-valent vaccine potentially could avert 25% of all pneumonia mortality in the 24-59 month age group. However, the impact on all childhood pneumonia mortality is a reduction of only 3%, because 89% of pneumonia mortality occurs before 23 months of age (see Figure 1). In contrast, the septavalent conjugate vaccine given at 2 months of age has a nearly 3 fold greater potential impact because it may prevent disease occurring at 6 months of age and older. Even though it protects against a smaller proportion of the serotypes than the 23 valent vaccine, the protection afforded during early infancy leads to a greater potential impact on overall mortality. Both vaccines are likely to reduce mortality due to meningitis and other invasive pneumococcal infections. The conservative estimates in Table 9 are crude and highly dependent on a series of assumptions, all of which need confirmation in developing country settings. The relative efficacy of these two vaccines may change as more data become available. Since the major portion of pneumonia and pneumococcal mortality is in early infancy, techniques which protect the young infant must be sought.

In addition to new vaccines, new strategies of vaccine use can increase the impact of existing vaccines. The "window of vulnerability" experienced by the newborn and infants less than 6 months of age could be closed by immunization of mothers. The antibody produced by mothers is passively transferred to the infant via the placenta with the potential of conferring protection for 2-4 months. This principle is the biological rationale for the immunization of pregnant women with tetanus toxoid, and has been demonstrated with H.influenzae type b and group B streptococcus polysaccharide vaccines in the U.S.[57,58]. Our preliminary estimates show maternal immunization with pneumococcal vaccine would cause an additional reduction of pneumonia mortality of 24% in the 0-5 month age group and would increase the estimated reduction in 0-60 month pneumonia mortality to 25%.

In summary, DTP and measles vaccines have the potential to prevent as much as 25% of pneumonia deaths. Currently available H. influenzae type b conjugate vaccines may avert 7% or more of these deaths. The current pneumococcal polysaccharide vaccine could prevent 3% of pneumonia deaths in children less than 5 years of age. Protein-conjugated pneumococcal vaccines under development have the potential to avert at least 9% of infant and childhood pneumonia deaths. Maternal immunization is a new strategy which may reduce early infant mortality caused by pneumococcal infections.

Given the success of EPI programs, with coverage rates of up to 80% for most vaccines, the consideration of adding vaccines to this efficient health delivery system is attractive. Costs of H. influenzae type b and pneumococcal vaccine will have to be reduced to levels which allow consideration for use in EPI programs. The marginal cost of adding 1 or 2 antigens to EPI programs is limited, and the potential impact is likely to be substantial.

Table 1

EFFICACY OF DTP IMMUNIZATION IN PREVENTION OF DIPHTHERIA

Outbreak	method	efficacy (95% C.I.)
Texas, 1970	retrospective comparison	93% (68 to 98)
Yemen, 1981	case-control	87% (32 to 99)

(from reference 6,7)

Table 2

EFFICACY OF DTP IMMUNIZATION AGAINST PERTUSSIS

North Sulewesi, Indonesia

Pertussis	DPT doses			
	0	1	2	totals
yes	49	12	1	62
no	19	1	9	29
totals	68	13	10	91

Efficacy of 2 doses = 87% (95% CI:14 to 99)
(from reference 18)

Table 3

IMPACT OF IMMUNIZATION ON PNEUMONIA DEATHS

Impact = reduction in mortality

factors	example
agent-specific etiology	50% pneumococcal
x vaccine efficacy	68% [a]
x proportion immunized	80% vaccine coverage
= impact	27% reduction

[a] assuming the vaccine includes 85% of invasive serotypes and 80% vaccine efficacy (0.85 x 0.80 = 0.68)

Table 4

ESTIMATED ETIOLOGY OF CHILDHOOD PNEUMONIA DEATHS

IN DEVELOPING COUNTRIES

S. pneumoniae	20 - 50%
H. influenzae type b	10 - 20%
other bacteria	5 - 20%
respiratory syncytial virus	20 - 30%
parainfluenza virus	5 - 10%
adenovirus	0 - 10%
influenza virus	0 - 10%

(adapted from references 2,30)

Table 5

EFFICACY OF Hib VACCINATION IN INFANCY

IN PREVENTION OF Hib INVASIVE DISEASE

vaccine	number	site	doses (ages)	% efficacy (95 CI)	reference
PRP-D[a)]	114,000	Finland	3 (3, 4, 6)	94 (83 to 98)	32
PRP-D[a)]	2,102	Alaska	3 (2, 4, 6)	35 (-57 to 73)	33
PRP-CRM[b)]	61,080	California	3 (2, 4, 6)	100 (64 to 100)	34
PRP-OMP[c)]	4,161	Navaho reservation	2 (2, 4)	93 (53 to 98)	35

[a)] ProHibit, (R), Connaught

[b)] HibTiter(R), Praxis/Lederle

[c)] PedVaxHib(R), Merck

Table 6

POTENTIAL IMPACT OF H. INFLUENZAE TYPE B CONJUGATE VACCINE ON PNEUMONIA MORTALITY

% fatal pneumonia which is caused by *Haemophilus influenzae* type b:	10 - 20%
efficacy of vaccine in infants:	90 - 100%
proportion immunized:	80%
potential pneumonia mortality reduction:	7% to 16%

Table 7

PROPORTION OF INVASIVE PNEUMOCOCCAL DISEASE CAUSED BY 23 VACCINE SEROTYPES OR BY THE TOP 7 SEROTYPES

Location	Number	Age	% vaccine serotypes	% top 7 serotypes	Reference
AFRICA	1304	all	94.6	75.0	
West Africa	1033	all	94.8	77.2	38
Nigeria	40	under 12	86.6	94.9	39
Gambia	29	all	89.6	82.7	40
South Africa	203	all	76.2	84.8	38
Egypt					
CSF	99	all	82.8	61.5	41
CSF	24	under 1	70.8	58.2	
CSF	16	1-4 yrs	93.8	94	
ASIA					
Thailand	55	under 15	89.1	74.7	42
Pakistan	87	under 5	71.3	97.6	43
Papua New Guinea					
Invasive	133	under 7	66.2	58.7	44
ALRI only	29	under 7	79.3	79.2	
NORTH AMERICA					
U.S (results of 5 surveys combined)	625	children	95.8	80.0	45

Table 8

PNEUMOCOCCAL POLYSACCHARIDE VACCINE

Prospective Efficacy Studies in Developing Countries

population	n	vaccine	efficacy	reference
S. African gold miners, 1975	1,675	12-valent	92%[a]	48
S. African gold miners, 1976	11,992	13-valent	82%[b]	47
Papua New Guinea adults, 1977	11,958	14-valent	84%[c]	49
Papua New Guinea children, 1980	4,862	14,23-valent	59%[d] 29%[e]	50

[a] reduction in vaccine serotype pneumococcal pneumonia.

[b] reduction in vaccine serotype pneumococcal bacteremia.

[c] reduction in vaccine serotype pneumococcal pneumonia. Pneumonia deaths were reduced by 44%.

[d] reduction in all pneumonia mortality.

[e] reduction in overall childhood mortality, not statistically significant.

Table 9

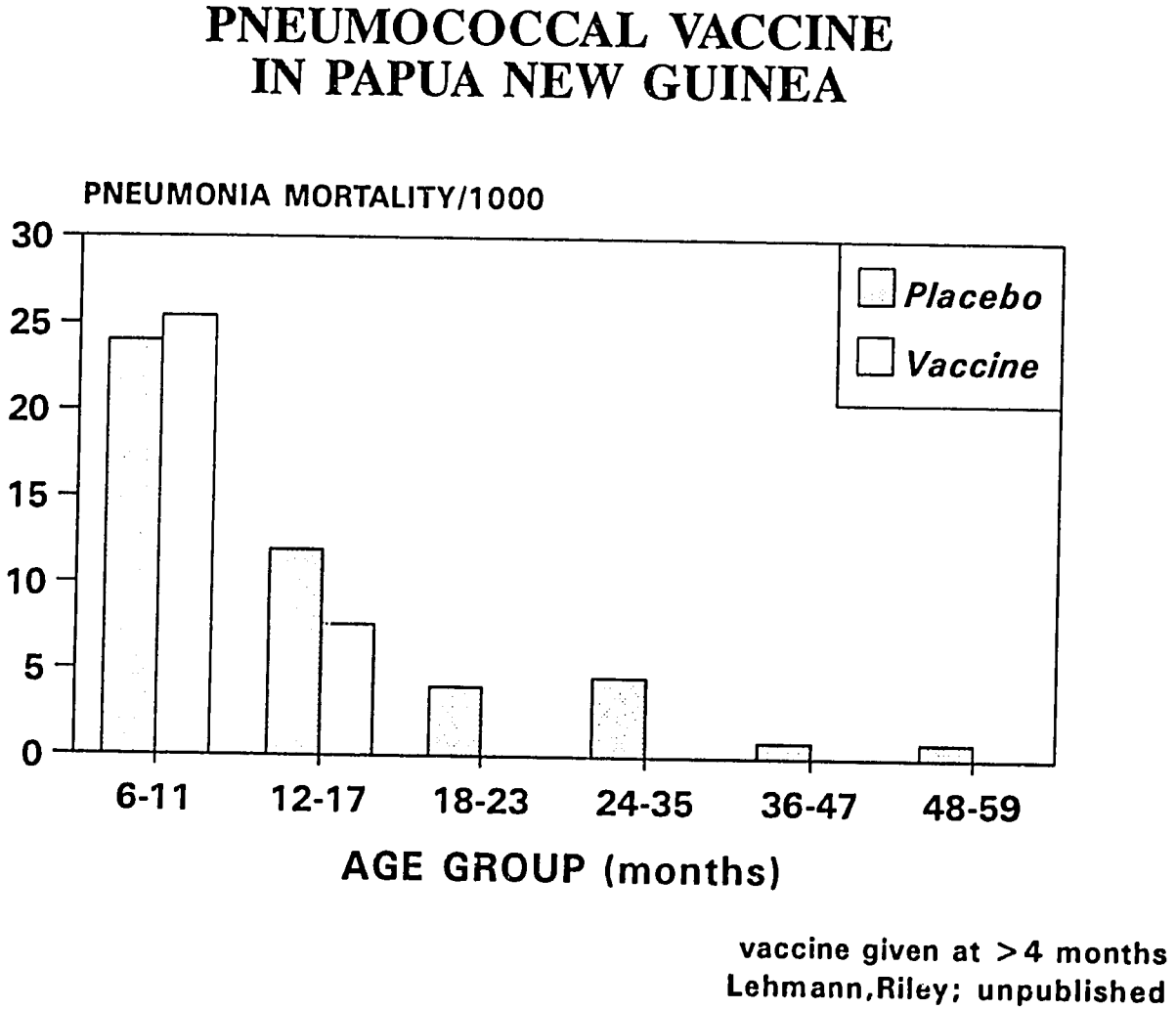
COMPARISON OF PNEUMOCOCCAL IMMUNIZATION STRATEGIES

FOR PREVENTION OF PNEUMONIA MORTALITY

	Strategy		Mortality reduction (%)				
	vaccine	age	0-5 mo.	6-23 mo.	24-60 mo.	overall	range
1.	23-v	24 months	0	0	25	**3%**	(1-4%)
2.	7-v	2, 4, 6 months	0	24	18	**9%**	(5-13%)

23-v = current 23 valent vaccine
7-v = proposed septavalent conjugate vaccine

Figure 1 Pneumonia mortality by age of death in children who received pneumococcal vaccine at 6-59 months of age.



(From reference 50 and personal communication from D. Lehman).

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Poliomyelitis and Hepatitis B: Impact of Immunization and Prospects for Eradication

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Part I. POLIOMYELITIS

Great strides have been made toward controlling poliomyelitis since the introduction of the two poliovaccines: inactivated poliovirus vaccine (IPV), which was licensed in 1954 and live, attenuated oral poliovaccine (OPV), in 1961. Today a large majority of physicians and other health care workers in industrialized countries never see a patient with paralytic poliomyelitis. Unfortunately, this is far from the situation in many developing countries, particularly in tropical and subtropical climates, where hundreds of thousands of children still become paralyzed victims, year in and year out.

It is rare that a serious disease has been controlled so quickly and dramatically as was poliomyelitis in many of the developed countries. In 1955, a total of more than 76,000 cases of poliomyelitis were reported from the United States, Canada, Australia, New Zealand, and 23 European countries plus the Soviet Union. By 1967, the number recorded in these same countries fell to 1013 cases -- a reduction of 99 percent. Numbers of poliomyelitis cases have continued to fall; in industrialized countries, poliomyelitis is now a rare disease.

In the United States, before the inactivated virus vaccine became available, there were 10,000 to 21,000 paralytic cases per year. The annual rates were between 5 and 10 per 100,000 population. Cases were far fewer after the inactivated vaccine came into use. In some years incidence rates fell tenfold, to as low as 0.5 per 100,000 population. Nevertheless, this meant that significant numbers of cases were still occurring; in 1960 there were more than 2500 paralytic patients. And some of these cases were fully vaccinated individuals. In a study of several thousand paralytic cases, 17 percent were in children who had received three injections of the inactivated vaccine. Some of the disappointing results were due to potency problems which have since been corrected, particularly in the few small countries that have used inactivated virus vaccines solely through most of the vaccine era.

After live attenuated vaccine was introduced and came into widespread use in the United States, the numbers of cases were reduced precipitously. In the 1980s, the annual number of cases was less than 10 per year. This translates into case rates as low as 0.001 per 100,000 population. [1]

For many years, the United States has relied almost completely on live poliovirus vaccine. It appears that there is no longer any endogenous reservoir of wild polioviruses

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within the country, and that a true break in the chain of infection has been achieved. Wild strains may continue to be introduced, but even such imported cases are sporadic and almost never result in secondary cases. The use of live poliovirus vaccine has achieved this result by establishing widespread intestinal resistance to the wild virus, thus reducing the pool of susceptible individuals below the level required for perpetuation of the virus in nature. Many other countries with extensive and continuing live vaccine programs are also reporting virtually no cases and few if any poliovirus isolates other than vaccine-like strains. [2,3,4]

In Sweden, Finland, and the Netherlands, where the inactivated poliovaccines have been used almost exclusively, good results also have been obtained. These are countries with relatively small populations (a total of 28 million persons), culturally homogeneous and socially advanced. They have excellent public health services, and inactivated virus vaccine has been administered in intensive and regularly maintained immunization programs, achieving vaccine coverage and boosting among children that has approached 100 percent.

But there can be important deficiencies in protection, even in well-vaccinated countries. This vulnerability was demonstrated in 1978 and 1979 by outbreaks of poliomyelitis among members of closely-knit, interconnected religious groups who refused vaccine on religious grounds. Imported into the Netherlands from the Middle East, a virulent type 1 strain spread through related religious groups in Canada and the United States. In none of the countries involved did paralytic cases occur beyond the unvaccinated members of these interconnected religious communities. However, subclinical infections with the epidemic virus did occur in significant numbers of IPV-vaccinated children: in nursery and primary schools in some of the affected Netherlands communities a large number (71 percent) of the nonvaccinated children excreted poliovirus, but 24 percent of those vaccinated with IPV were also observed to be excreting the epidemic virus. [5]

In Finland, where the use of standard IPV had produced 20 years of freedom from poliomyelitis, 10 cases occurred between August 1984 and January 1985. On the basis of virus isolations from healthy individuals and from sewage, it was estimated that at least 100,000 persons in the general population were infected. The 1984 epidemic strain was a wild type 3 variant that differed in both immunological and molecular properties from the type 3 vaccine strains. [6] Analysis of sera collected before the outbreak indicated that neutralizing antibodies against new type 3 isolates were much less prevalent in the population than antibodies to the type 3 strain (Saukett) used in the killed vaccine.

The precipitating factor in the outbreak was judged to be the appearance of the wild strain of poliovirus type 3 type that was sufficiently aberrant to break through the type 3 immunity of the population. However, immunization with the new enhanced IPV or with standard OPV induced high serum antibody titers against all known type 3 strains, including the Finnish epidemic type 3 strain. Thus, although differences among strains from various parts of the world have indeed been demonstrated for many years, the major neutralizing antigen of each poliovirus serotype is remarkably stable.

The study of the 1988 outbreak in Israel has also yielded pertinent information. Most cases occurred in young adults who had been given OPV during the first year of life but who had not received any booster doses. This suggested an age-related deficit

in immunity against the 1988 wild virus.

Neutralizing antibody assays of sera collected from healthy persons in Israel prior to the outbreak indicated high antibody levels against the Sabin strains in OPV, but very low levels against the wild virus. A booster dose of OPV in 1988 brought the antibodies to high levels against both the Sabin and the wild strains. Nonvaccinated adults over 30 years of age who had lived through the prevaccine period and who had been exposed to wild viruses as children were found to have high levels of antibody to both Sabin strains and wild virus in their pre-epidemic sera. After receiving a single dose of OPV in 1988 they also responded with an increase in antibody titer. [7] These findings indicate that a gap in immunity against wild polio may occur in persons who are OPV-vaccinated in the first months of life and who fail to be given boosters or who fail to be exposed to wild virus in the early years after vaccination when antibody levels are highest. This gap in immunity against wild strains can be overcome by a booster dose of OPV later in life.

While cases have almost vanished from the industrialized world, polio continues to be an urgent problem, particularly in developing nations in tropical and subtropical zones. WHO estimates that well over 200,000 cases of paralytic poliomyelitis are occurring each year. In India alone, more than 100,000 cases were reported annually throughout the 1980s. Of these cases, 98% were in children under 5 years of age; 42% of the patients were infants in the first year of life. As has been shown by surveys of lameness indicative of past paralytic poliomyelitis, in many developing countries the reported cases may represent no more than 10 percent of the actual number of cases that occurred. [8,9]

The worldwide magnitude of the problems that remain unresolved, as well as some encouraging trends, are illustrated in Figure 1, and in Tables 1 and 2. The figure depicts on a world map the incidence of paralytic poliomyelitis reported to WHO for 1985 from various areas. The tables give examples of the reported numbers of poliomyelitis cases since 1951 in two regions of the world, comparing countries which had controlled the disease by 1980 with countries in which control of poliomyelitis was incomplete at that time. [8-10]

Table 1 is based on data from representative countries of the Western Pacific Region. The top line of the table is based on data from countries that were experiencing a very high incidence in the years from 1951 to 1955, a period when they were in transition from the insidious endemic phase of poliomyelitis to the epidemic phase. With the availability and widespread use of OPV, these countries succeeded in controlling polio by 1980. For this entire "polio-controlled" group, which in 1985 had a total population of 162 million, there were only 10 cases in 1980, and only 1 to 7 cases each year since then -- an incidence of 0.003 to 0.004 per 100,000 population. The countries selected for this example are Australia, Japan, New Zealand, Singapore, Hong Kong and Malaysia. The first four of these countries accomplished control of polio very quickly, have had relatively few cases since 1966 and virtually none have been seen for many recent years. Hong Kong and Malaysia had a longer struggle, but have now succeeded in establishing control.

The data in the lower line of Table 1 illustrate a contrasting trend: countries were reporting relatively few cases in 1951 to 1955, at a time when wild polioviruses were circulating widely but infections were inapparent or unrecognized. Greatly increased numbers were then reported, with control still not established by 1980, and only now

beginning to be achieved. The totals shown are from China, Laos, Papua New Guinea, the Philippines, and Viet Nam. From an annual average of 221 cases reported during 1951-1955, cases in the Philippines increased to an annual average of 894 during 1976-1980; the annual average for the period 1981-1985 remained high -- almost 450 cases. The pattern in Viet Nam illustrates even more dramatically the shift from endemic to epidemic polio. After only 54 cases reported annually during 1951-1955, the numbers rose to more than 1700 in 1980. Since then, case numbers have ranged from 644 in 1981 to 1600 in 1985. China, with more than 7700 cases reported in 1982, reduced this number to 1537 cases reported for 1985, chiefly from rural areas.

Table 2 summarizes the data for 41 countries or areas in the American region. As in the Western Pacific, the 27 countries in the Americas that by 1980 had controlled polio were the same ones that reported huge numbers of cases in the prevaccine period: an annual average of more than 44,000 in 1951-55. With widespread use of vaccine, the incidence in these populations was greatly reduced over the decade, 1966-1975, and since 1971 in a number of areas there have been only a few cases or none at all. [11]

In contrast, the lower part of Table 2 shows that during 1951 to 1955 there was a relatively small number of cases reported from 14 countries where polio was endemic. By 1966 to 1970, the average annual number of cases reported had increased more than 6 times as the disease entered its epidemic phase. The number of cases remained high through 1980, in spite of the use of OPV. A large share of those cases came from only five countries (Bolivia, Brazil, Colombia, Honduras, and Mexico), several of which have had many of the problems that hinder adequate vaccination coverage, that is, a large geographical area, regions difficult to reach, and growing urban fringe populations. Since then, much progress has been made, and I shall come back to this topic after discussing the merits and problems associated with the use of inactivated and of live poliovirus vaccines. These are summarized in Tables 3 and 4. [12]

Inactivated poliovirus vaccine (IPV), if properly prepared and administered, can confer humoral immunity if sufficient doses of the new vaccine of enhanced potency are given. IPV can be incorporated into regular pediatric immunization along with other injectable vaccines (DPT). In certain tropical areas where live vaccine has failed to "take" in some young infants, IPV has proved useful. Since living virus is not present in IPV, its use excludes the possibility that the vaccine virus can revert toward virulence. Also for this reason it can be given safely to immunodeficient or immunosuppressed individuals and to the household contacts of these immunocompromised persons.

Problems with IPV are summarized in the lower part of Table 3. In the United States, the Soviet Union, and other countries, the low potency of the original IPV led to a disappointing record in the numbers of vaccinees developing antibodies after a full course of three doses. With the inactivated vaccines that were commercially available, repeated boosters were necessary to maintain detectable antibody levels. The need for repeated booster injections added to higher costs, and in developing countries also presented logistic problems of injecting several doses of vaccine at intervals into large numbers of infants and pre-school children. The immunity conferred by IPV, although it impedes pharyngeal and fecal shedding of virus to some extent, does not provide a high degree of intestinal immunity; therefore, when wild poliovirus is introduced, IPV vaccinees become infected, they excrete the wild virus and thus become a source of infection to others. Even in countries with highly developed health care systems and

populations very well-vaccinated with IPV, imported wild virus can circulate not only in unvaccinated sectors of the population but also through those who have been vaccinated.

The more concentrated and more potent inactivated poliovaccines prepared by the van Wezel procedure are proving to be more effective with fewer doses than the original Salk vaccine. Such vaccines are now being used in some west European countries, and selective field trials are being conducted elsewhere. Hopes have been high that newer, more potent IPV could provide long-lasting immunity after two doses. [13,14] However, the results in terms of resistance to the development of paralytic poliomyelitis have been somewhat disappointing in at least one field study in Africa. [15]

Live orally administered trivalent poliovirus vaccine (OPV) has been widely used, because of its ease of administration, its ability to induce not only serum antibodies but also intestinal resistance, and its rapid induction of an enduring immunity, similar to that induced by the natural infection (Table 4). OPV rapidly infects and preempts the alimentary tract of susceptibles, thus blocking spread of wild virus. Lower cost is an important factor for many countries: not only is the vaccine itself less expensive, but its administration does not require use of highly trained personnel, thus further reducing program costs, and continuing boosters are not required.

All living creatures undergo some degree of mutation, and polioviruses are no exception. Progeny virus particles produced during replication of OPV in vaccine recipients have reverted in very rare instances to increased neurovirulence sufficient to cause paralysis in vaccinees or their susceptible contacts.

The proven risks of paralytic polio associated with OPV are exceedingly small, and by the 1980s such cases had decreased to an almost vanishing number. Three sequential 5-year studies of polio cases have been conducted collaboratively among 12 to 15 nations, under the auspices of WHO. In these and other studies, live poliovirus vaccine has been judged repeatedly to be an extraordinarily safe vaccine, [16,17] with less than one reported case for every million babies vaccinated. These estimates were based on the maximum risk (the risk calculated as though every "vaccine-associated" case were indeed vaccine-caused). In a recent evaluation of cases in the United States, covering the period 1973-1984, it has been estimated [1] that the overall frequency of vaccine-associated poliomyelitis was one case per 2.6 million vaccine doses distributed. However, the associated frequency of paralysis was one case per 520,000 first doses, versus one case per 12.3 million subsequent doses. These rates include recipients with immune deficiencies.

In some tropical countries live vaccines have not induced antibody production in a satisfactorily high percentage of vaccinees. This lower rate of vaccine "take" has been ascribed to various factors such as interference from other enteroviruses already present in the intestinal tract, the presence of antibody in breast milk, the presence of cellular resistance in the intestinal tract due to previous exposure to wild polioviruses (or perhaps to related viruses), and the presence of an inhibitor in the alimentary tract (saliva) of infants that blocks multiplication of the vaccine virus. Some feel that this low response, especially for type 3, can be overcome by proper and repeated use of live vaccine. In addition, a significant improvement of seroconversion to type 3 has been obtained in a field trial in Brazil with a trivalent OPV containing a twofold increase in concentration of the type 3 vaccine strain. [18] The increased effectiveness of the latter, more expensive

vaccine might be due to an increased ratio of type 3 to the other types, rather than to the doubled concentration of type 3, form $10^{5.5}$ to $10^{5.8}$ $TCID_{50}$. The ratio of types 1, 2, 3 in the vaccine ordinarily used is 10:1:3, based on standard doses of 10^6, 10^5, $10^{5.5}$. In the Brazilian trial mentioned it was 10:1:6. An increase of type 3 in the ratio could also be achieved by lowering the concentration of the first two types, especially of the highly dominant type 2. The vaccine might consist of $10^{5.8}$, $10^{4.5}$, and $10^{5.5}$ $TCID_{50}$, for the three serotypes, or a ratio of 20:1:10. This increase in ratio can be attained, while simultaneously lessening the cost of the vaccine.

The problems of controlling paralytic polio by use of vaccine are often exacerbated by the fact that in some areas the newborn infant has only a short time in which to acquire protective immunity because exposure to wild viruses comes so early, in their first months of life. [19] Various plans have been proposed [20,21,22] and some are now being pursued in different developing and tropical countries.

WHO's EPI Global Advisory Group [23] has concluded that immunization of the newborn with OPV is a safe and effective means of improving protection against disease, and OPV may be administered simultaneously with BCG vaccine. Although the serological response to OPV in the first week is less than that observed after immunization of older infants, 70% or more of neonates benefit by developing local immunity in the intestinal tract. In addition, 30-50% of the infants develop serum antibodies to one or more poliovirus types. Many of the remaining infants have been immunologically primed and they respond promptly to additional doses later in life.

The EPI Advisory Group emphasizes that for those infants in many countries whose only encounter with preventive services is at the time of birth, this single dose of vaccine will offer some protection and they will be less likely to be a source of transmission of wild polioviruses during infancy and childhood. For the infants who receive only one or two additional doses of poliovirus vaccine, the initial dose at birth will help ensure higher levels of immunity. The EPI schedule designed to provide protection at the earliest possible age is: at birth, and then at 6, 10, and 14 weeks of age. If the vaccine is not given at those ages, it should be given as soon as possible afterwards. Intervals between doses greater than those listed do not require restarting the series.

Gradual incorporation into routine immunization schedules

OPV has been included in the regular childhood immunization programs without necessarily having prior mass vaccination campaigns. This has meant a gradual increase in vaccine coverage and an associated gradual decrease in polio incidence. In a number of countries using this approach, reported polio cases have significantly declined since the early 1970s.

An example of recent progress can be seen in special programs conducted in three areas in tropical Africa that were experiencing incidence rates (as estimated from lameness surveys) ranging from 25 to 62 per 100,000 population in the mid - to late 1970s. The programs emphasized intensive and carefully targeted schedules of routine vaccination. Programs were instituted [24] in Yaounde, Cameroon, in The Gambia, and in Abidjan, Ivory Coast. They included administration of three doses of OPV during the first year of life, one month apart starting at 2 to 3 months of age. The vaccine coverage

achieved was evaluated, [25] and surveillance of poliomyelitis was conducted both before and after the vaccination program. [26,27,28,29] Within a few years the proportion of the children who received 3 doses of the vaccine -- which had been virtually zero except for some (low) coverage in Abidjan -- was increased up to 50-70%. Even with this less-than-optimal vaccine coverage, the incidence of poliomyelitis decreased significantly. In Yaounde, among children 12-23 months of age only 35% received 3 doses of OPV, but the incidence of paralytic polio decreased by 85% [30].

Maintaining a routine immunization schedule that reaches virtually all of the target population requires a supply of viable vaccine constantly at the point of contact. This can be difficult in warm climates with limited cold-chain facilities, particularly if the vaccine has not been treated with a stabilizer equal or superior to molar $MgCl_2$. [31,32,33,34]

Sabin [20,21] advocated that paralytic poliomyelitis in tropical countries might best be eliminated by repeated mass administration of OPV. Annual campaigns should include all age groups in which cases are occurring. All children from birth to 3, 4, or 5 years of age (depending on the epidemiological situation in a given country) should be given two doses of OPV twice each year regardless of how many doses of live vaccine they may have received previously. This mass administration would reach those missed in previous campaigns and would avoid the problems of record-keeping which often has been a barrier to full coverage in administering the vaccine.

Mass campaigns with OPV have been conducted successfully in a number of countries, not only bypassing the need for constantly maintaining refrigeration as well as other logistic problems, but also providing a high level of coverage. These campaigns introduce massive quantities of live vaccine virus which colonizes the alimentary tracts of susceptible hosts, thus blocking wild virus circulation. In Cuba since 1962, all children from birth to three or five years (depending on concurrent serosurvey findings) regardless of individual immunization history have been given OPV on two Sundays, two months apart, each year. Serosurveys show almost universal immunity by the age of three, and since the end of the first campaign year, over a quarter of a century ago, only six cases have been reported. Czechoslovakia, using the same strategy, has had similar success, with the total disappearance of paralytic poliomyelitis. High levels of public cooperation, discipline, and dedication seem to be vital factors in these successes -- levels that may not necessarily be present in all situations.

This strategy of periodic mass campaigns, sometimes alone, sometimes combined with a regularly maintained schedule for immunizing infants, has been highly successful in some areas. Brazil in 1980 instituted such a program, entailing a huge national effort in which, regardless of any vaccine history, each child in the selected age groups is given a dose of live vaccine twice each year, with a two-month interval between doses. Some 90,000 vaccination stations (10 times the number of regular health stations) were established and 400,000 volunteers were mobilized. From several thousand cases annually in the late 1970s, polio cases in Brazil have been reduced dramatically, to an average of 80 annually during 1981 through 1984. [35,36] However, there was an increase to 461 cases in 1985 [9] and to 612 in 1986, which seems to have been a temporary setback due to low potency of the type 3 component of the vaccine. [11] This is being rectified by increasing the ratio of type 3 to the other types. [18]

Important questions relative to such a program have been raised: Would developing nations be able and willing to make such an annual repetitive mass

vaccination program? There also had been some misgivings as to whether the absence of record-keeping could be detrimental to the program and whether concentration on OPV could detract from other needed health services. In practice in Brazil and elsewhere, the annual polio program has led to an increased awareness of and activity for other immunizations.

Mexico likewise has had a long struggle to control polio through routine vaccinations, and still had an annual average of almost 700 cases during 1976-1980. In 1981, mass national immunization campaigns were instituted. [37] Monovalent type 1 vaccine -- the type that has long predominated in their paralytic cases -- was used for the first dose, followed by trivalent vaccine two months later. Much fuller vaccination coverage is being achieved (about 80% in 1982), and polio has been drastically reduced, to 186 cases in 1981, 80 cases in 1987, 25 in 1989, and almost to extinction in 1990. [3,11]

The effectiveness of OPV has been particularly striking in the Western Hemisphere as a result of the Expanded Programme on Immunization and the continuing surveillance for specific virus and antibody. Not only has the number of paralytic cases caused by wild polioviruses decreased but there also has been a precipitous decrease in the circulation of wild polioviruses. [38] Only 11 of the 2,456 cases of acute flaccid paralysis (AFP) reported in 1990 have been confirmed as polio. In addition, 57 of the AFP cases were regarded as compatible, 477 were still under investigation, and 1911 were categorized as nonpolio. In the few areas in the Americas where cases due to wild polioviruses occur, the EPI activities are focussing on mopping-up operations consisting of intensive use of OPV in these localities. It seems that the entire Western Hemisphere will soon be declared free of indigenously transmitted paralytic polio.

In India, despite many efforts at controlling poliomyelitis, thousands of cases still occur, the highest incidence being in infants 6 to 18 months old. [39] It is estimated that in the 1980s more than 200,000 cases occurred annually in that country alone. [39,40] To increase the level of immunity, "pulsed" mass vaccination has been proposed [40] -- OPV to be given to all the target children in each community at the same time, rather than following individual routine immunization schedules. This proposal recommends three doses of OPV before the first birthday, and three more between the 1st and 2nd birthdays; a village would be visited three times in the course of the year at intervals of 4 to 6 weeks, and then no more vaccine would be given over a nine-month period.

An innovative approach to obtain better delivery of vaccine -- not only of OPV but also of other pediatric immunizations -- has proven productive in one area of China (Gaoyi County, Shijiazhuang Prefecture, Hebei Province -- a county with a total population of 140,000 in 107 villages). To increase family cooperation in immunization programs and to encourage health staff members to enhance their preventive health efforts, the new plan, introduced in 1984, was expanded by early 1986 to include more than 12,000 children (62% of children under 7 years of age in the county). [41]

The average annual family income in Gaoyi is 438 yuan. The parents pay 10 yuan to the health center in the first year of their child's life, with a contract that "guarantees" that their child will not contact measles, pertussis, poliomyelitis, tetanus, or diphtheria if he or she receives the full recommended course of immunization. If the insured child suffers from measles or whooping cough, the parents receive an indemnity of 50 yuan; if poliomyelitis, diphtheria or tetanus, 300 yuan.

The insurance premiums received (nearly 100,000 yuan as of 1985) are distributed among the village doctors, county health centers, and the county epidemic station, which expends them for immunization equipment and education, reserving funds to compensate parents when an enlisted child contracts any of the designated diseases. In turn, the village doctor and the county agencies share the costs of compensation. Up to the end of January, 1986, a total of only 750 yuan had been paid in compensation, covering 15 cases of measles or whooping cough. There were no cases of poliomyelitis.

The advantages of the system have been described as follows [41]:

"1. It stimulates staff of health centres and village doctors to implement immunization activities.

2. Parents are enthusiastic to have their children immunized because they feel that they have paid a lot of money.

3. The primary health care setting has been strengthened because the staff can earn one-quarter to one-half more than their regular income.

4. Underreporting of cases has been reduced because parents are motivated to report a suspected case in order to receive compensation.

5. Wastage of vaccine has been minimized because the activities have been carried out strictly according to the schedule due to the enthusiasm of staff and parents."

Combined schedules using both live and killed poliovaccine

In some localities, it has been found advantageous to establish immunization schedules using both killed and live poliovirus vaccines. One type of situation in which this strategy has been successfully carried out has been the relatively recent addition of killed poliovaccine to supplement live poliovaccine immunization schedules, in some high-risk localities where there is very early and repeated exposure of infants to challenge by importations of wild virulent viruses. [19, 42, 43] In such high-risk areas, IPV alone has been inadequate, as in Israel in 1988. [44] The lessons of the 1988 outbreak in Israel are (i) that IPV alone does not interrupt the circulation of wild virus, which singles out susceptible contacts as targets; (ii) that OPV alone, administered in infancy, is not completely effective for life. A combined schedule [42,45,46] offers substantial benefit, with the optimal times of vaccination yet to be determined for different regions. For ease of administration, giving parenteral IPV and oral OPV simultaneously offers advantages. This procedure has been used regularly starting in 1978, in the West Bank and Gaza where some cases were occurring, particularly in infants, despite extensive campaigns of immunization with OPV. The combined schedule included administration of OPV (type 1 monovalent) during the first month of an infant's life; then at 2 1/2 months and again at 4 months of age trivalent OPV is given together with a quadruple vaccine consisting of DPT plus IPV; trivalent OPV is given at 5 1/2 months, and again at 12 months. The rationale for the combined schedule was that, under conditions of regular and heavy importation of virus resulting in frequent challenge from virulent wild polioviruses early in infancy, features of both types of vaccine are needed. OPV acts by inducing protective immunity both in the form of circulating humoral antibodies and in the form of intestinal immunity. Furthermore, the immunity that ensues is long-lasting, like that which follows the natural infection. IPV, on the other hand, provides an

immediate immunogenic stimulus that is not subject to the interfering or inhibiting factors described above, that may prevent live vaccine "takes" in some young infants. By administering both vaccines in a combined schedule, immediate protection can be provided in the critical first weeks or months of life, and long-lasting protection -- both humoral and intestinal -- also is provided.

Studies of the combined vaccine program described above indicate: (1) Protection provided by OPV alone was about 90 percent effective; that is, the case rate in those who received OPV alone was one-tenth the rate in those who were not vaccinated or who were incompletely vaccinated (receiving only part of the series of live vaccine feedings). (2) The children who were fully vaccinated with OPV and had IPV in addition were even more effectively protected; virtually 100 percent protection was seen in those who received both vaccines. Two serum surveys in children aged 9 to 36 months revealed high antibody levels, substantiating their protection. [45] Another type of combined program has been the addition of live poliovaccine in 1968 to supplement inactivated poliovirus vaccine (IPV) in Denmark where, despite extensive coverage with IPV alone, epidemics still occurred, and antibody prevalence was less than desired. [47] The combined IPV/OPV program has resulted in the elimination of poliomyelitis from Denmark, as well as from Israel, Gaza, and the West Bank. In earlier years the incidence of polio in the latter region had been one of the highest in the world, and today paralytic polio continues to be reported in the neighboring countries of the Middle East.

OPV is now in use in most countries and wherever it has been used, polio cases have decreased, but the frequency may vary in different areas. From the results to date, public health workers should take advantage of the assets of both IPV and OPV to bring the disease quickly under total control. The schedule shown in Table 5 is proposed as one which would be compatible with current EPI recommendations. This schedule should (1) introduce IPV into the current OPV immunization program so that in the first year of life both IPV and OPV are given to all infants; (2) in subsequent years, continue with the current EPI program which uses OPV alone for polio immunization.

For countries adopting mass campaigns, there would also be benefits from incorporating both IPV and OPV into the program for the first year. For subsequent years, the program with OPV alone would be sufficient to prevent wild poliovirus from colonizing the vaccinated population.

A note of caution has recently been raised. In a limited study of a small number of children, combining IPV and OPV immunization was highly effective in inducing both humoral and secretory antibodies, but virus excreted by children immunized with an IPV/OPV combination was found to possess a somewhat higher degree of reversion than virus excreted by children immunized by OPV alone. However, only 9 isolates in the OPV group and 12 in the IPV/OPV group were available for study. [48]

The questions of how and where eradication of poliomyelitis can be achieved will continue to be major objectives in the next few years. The World Health Organization Expanded Programme on Immunization was initiated with the aim of reducing morbidity and mortality rates from seven target diseases, including poliomyelitis, by providing immunization against them for every child in the world. The program depends heavily upon technical cooperation with and among developing countries, particularly those in tropical regions. Results are already being seen: increasing numbers of countries now participate in the EPI program or are otherwise enhancing their polio vaccination efforts.

Better and more complete surveillance programs have been implemented to detect and assess cases. [3] More information is being gathered on the epidemiology of poliomyelitis in specific regional and geographical settings, and better-informed and more determined national commitments to immunization are being made.

Eradication of polio is part of the EPI goal of universal immunization of children. There have been significant increases in coverage in recent years with regard to OPV -- from the situation at the beginning of 1986, when 45% of all children in the world received OPV in the first year of life, to that at the start of 1990, when this percentage had increased to 67%. The range at the beginning of 1990 varied from a high of 90% in the Western Pacific Region to a low of 45% in the Africa Region. Based on an expected polio incidence of 5 per 1000 surviving infants, the global OPV program is currently preventing at least 400,000 cases of paralytic disease per year.

Conclusions

The following is taken from the current chapter on Poliomyelitis by Jamison, Torres, Chen, and Melnick: [49]

" (1) Prior to the development and introduction of vaccines, over five out of every thousand children born would have been seriously affected by the disease, most typically with permanent lameness. ...

(2) The commitment to polio eradication by the year 2000, within the context of the EPI, deserves strong national and international financial and technical support. With such support, sustained over the coming decade, it is reasonable to hope that polio will be eradicated by the year 2000 of soon thereafter. ...

(3) There are now available, in OPV and IPV, two highly effective vaccines; the choice of OPV or IPV, or a schedule based on both, should rest on the epidemiological, economic, and logistic realities of each country. At present, schedules based on OPV are recommended by WHO as globally most desirable."

As for the ultimate goal of reducing the incidence of poliomyelitis to the vanishing point, it is too early to say "accomplished", but the coming years should bring significant progress.

Part II. HEPATITIS B*

The literature on hepatitis B (HB) has grown voluminously since the discovery of the virus marker antigens, readily detected in the serum of HBV-infected persons. HBV infections occur worldwide, but the patterns of transmission vary from a highly endemic disease transmitted perinatally at the time of birth or in childhood (East and Southeast Asia and sub Saharan Africa), to a disease of low endemicity transmitted primarily by blood and by sexual contact among adults (western Europe and North America).

Strategies for use of HB vaccine in different parts of the world differ according to the endemicity of disease. In areas of high HBV endemicity, prevention of perinatal and early childhood transmission is crucial, and universal immunization of infants should start at birth.

Valid data may come from serological studies done in the country under consideration or in nearby counties with similar populations. Hepatitis B prevalence differs markedly between North America and Africa, for example, but varies little between the countries of sub-Saharan Africa. All countries in sub-Saharan Africa and Asia east of Myanmar have hyperendemic levels of HBV transmission. All of these countries should now integrate HB vaccine into their immunization programs; lack of serologic survey data within a country should not be used as an excuse for inactivity.

The broad categories of endemicity as defined by studying adult populations are: (a) low prevalence, less than 1% positive for HBsAg and/or less than 15% with prior infection; (b) moderate prevalence, 2-7% positive for HBsAg and/or 15-40% with prior infection; (c) high prevalence, >8% HBsAg-positive and/or >45% with prior infection. Examples from different parts of the world are shown in Table 6.

Since the prevalence of HBsAg may be low (less than 10%), the study of very large populations is needed to differentiate small differences in endemicity. For example, to demonstrate low (1%) vs. moderate (4%) endemicity (with 95% confidence interval) requires a sample size of about 1200 persons. In contrast, the prevalence of prior HBV infection is usually much higher (10-70%), but still accurately reflects risk of HBV infection; it therefore can be used to discriminate low (10%) vs. moderate (40%) endemicity of prior infection with 95% confidence, in much smaller samples of about 100 persons.

Countries with diverse ethnic groups may have markedly different HBV prevalences in some of the groups. For example, even in Singapore with a fairly small

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* Much of the material in this section is taken from the excellent summaries on hepatitis B provided by the Expanded Programme on Immunization, WHO; by the Centers for Disease Control, US DHHS; and by the International Task Force on Hepatitis B Immunization and the Program for Appropriate Technology in Health (PATH). Other material is taken from chapters entitled Viral Hepatitis, by Hadler and Margolis, and Hepatocellular Carcinoma Caused by Hepatitis B Virus, by Melnick [in Viral Infections of Humans: Epidemiology and Control, 3rd Edition, 1989 (Evans AS, Editor)], and from presentation in the Proceedings of the 1990 International Symposium on Viral Hepatitis and Liver Disease (The 7th Triennial Congress) in press, 1991 (Hollinger FB, Margolis HS, and Lemon SM, Editors). Detailed reference to the hepatitis B literature is provided in these reviews.

and densely-packed population there are significant differences between the Indian, Chinese, and Malay populations.

The prevalence of HBsAg in pregnant women indicates the relative importance of mother-to-child transmission in the population. This information may be useful in deciding whether the first dose of hepatitis B vaccine is administered at birth, or with the first dose of DPT.

Hepatitis B vaccine (from CDC reports, 1990):

Two types of hepatitis B vaccines are currently licensed in the United States. Plasma-derived vaccine consists of a suspension of inactivated, alum-adsorbed, 22-nm, HBsAg particles that have been purified from human plasma by a combination of biophysical (ultracentrifugation) and biochemical procedures. Inactivation is a threefold process using 8M urea, pepsin at pH 2, and 1:4,000 formalin. These treatment steps have been shown to inactivate representatives of all classes of viruses found in human blood, including HIV. Plasma-derived vaccine is no longer being produced in the United States, and its use is now limited to hemodialysis patients, other immunocompromised hosts, and persons with known allergy to yeast.

Currently licensed recombinant hepatitis B vaccines are produced by Saccharomyces cerevisiae (common baker's yeast), into which a plasmid containing the gene for the HBsAg has been inserted. Purified HBsAg is obtained by lysing the yeast cells and separating HBsAg from yeast components by biochemical and biophysical techniques. These vaccines contain more than 95% HBsAg protein. Yeast-derived protein constitutes no more than 5% of the final product.

Hepatitis B vaccines are packaged to contain 10-30 ug HBsAg protein/ml and are adsorbed with aluminum hydroxide (0.5 mg/ml). Thimerosal (1:20,000 concentration) is added as a preservative. Vaccine should be shipped and stored at 2°C-8°C but not frozen, as freezing destroys the potency of the vaccine.

The recommended series of three intramuscular doses of hepatitis B vaccine induces an adequate antibody response ($\geq$ 10 milliInternational Units/ml, determined 1-6 months after completion of the vaccination schedule) in >90% of healthy adults and in >95% of infants, children, and adolescents from birth through 19 years of age. The deltoid (arm) is the recommended site for hepatitis B vaccination of adults and children; immunogenicity of vaccine for adults is substantially lower when injections are given in the buttock. Larger vaccine doses (two to four times normal adult dose) or an increased number of doses (four doses) are required to induce protective antibody in a high proportion of hemodialysis patients and may also be necessary for other immunocompromised persons (such as those on immunosuppressive drugs or with HIV infection).

Field trials of the vaccines licensed in the United States have shown 80%-95% efficacy in preventing infection or clinical hepatitis among susceptible persons. Protection against illness is virtually complete for persons who develop an adequate antibody response after vaccination. The duration of protection and need for booster doses are not yet fully defined. Between 30% and 50% of persons who develop adequate antibody after three doses of vaccine will lose detectable antibody within 7 years, but protection against viremic infection and clinical disease appears to persist.

Immunogenicity and efficacy of the licensed vaccines for hemodialysis patients are much lower than in normal adults. Protection in this group may last only as long as adequate antibody levels persist.

The primary vaccination schedule comprises three intramuscular doses of vaccine, with the second and third doses given 1 and 6 months, respectively, after the first. Adults and older children should be given a full 1.0 ml dose, while children less than 11 years of age should usually receive half (0.5 ml) of this dose. An alternative schedule of four doses of vaccine given at 0, 1, 2, and 12 months has been approved for more rapid induction of immunity. However, there is no clear evidence that this regimen provides greater protection than the standard three-dose series.

Hepatitis B vaccine, when given in the deltoid, produces protective antibody (anti-HBs) in >90% of healthy persons. Testing for immunity after vaccination is not recommended routinely but is advised for persons whose subsequent management depends on knowing their immune status (such as dialysis patients and staff).

Revaccination of persons who do not respond to the primary series (non-responders) induces adequate antibody in 15%-25% after one additional dose and in 30%-50% after three additional doses when the primary vaccination was given in the deltoid. Among persons who did not respond to the primary vaccine series given in the buttock, revaccination in the arm induced adequate antibody in more than 75%. Revaccination with one or more additional doses should be considered for persons who fail to respond to vaccination in the deltoid and is recommended for those who have failed to respond to vaccination in the buttock.

Vaccine-induced antibody levels decline steadily with time, and up to 50% of adult vaccinees who respond adequately to vaccine may have low or undetectable antibody levels by 7 years after vaccination. Nevertheless, both adults and children with detectable but declining antibody levels are still protected against hepatitis B disease. Current data also suggest excellent protection against disease for 5 years after vaccination, among infants born to hepatitis B carrier mothers. For adults and children with normal immune status, booster doses are not routinely recommended within 7 years after vaccination, nor is routine serologic testing to assess antibody levels necessary for vaccine recipients during this period. For infants born to hepatitis B carrier mothers, booster doses are not necessary within 5 years after vaccination.

For hemodialysis patients, for whom vaccine-induced protection is less complete and may persist only as long as antibody levels remain above 10 mIU/ml, the need for booster doses should be assessed by annual antibody testing, and booster doses should be given when antibody levels decline to < 10 mIU/ml.

Vaccine doses administered at longer intervals provide equally satisfactory protection, but optimal protection is not conferred until after the third dose. If the vaccine series is interrupted after the first dose, the second and third doses should be given separated by an interval of 3 to 5 months. Persons who are late for the third dose should be given this dose when convenient. Postvaccination testing is not considered necessary in either situation.

The immunogenicity of a series of three low doses (0.1 standard dose) of plasma-derived hepatitis B vaccine administered by the intradermal route has been assessed in several studies. The largest studies of adults show lower rates of developing adequate antibody (80%-90%) and twofold to fourfold lower antibody titers than with

intramuscular vaccination with recommended doses. Intradermal vaccination is not recommended, and particularly not advised for infants or children.

All hepatitis B vaccines are inactivated (noninfective) products, and there is no evidence of interference with other vaccines administered simultaneously. Because the vaccines contain only noninfectious HBsAg particles, there should be no risk to the developing fetus. In contrast, HBV infection of a pregnant woman may result in severe disease for the mother and chronic infection of the newborn. Therefore, pregnancy or lactation should not be considered a contraindication to the use of this vaccine for women who are otherwise eligible.

Hepatitis B vaccine produces neither therapeutic nor adverse effects for HBV carriers. Vaccination of individuals who possess antibodies against HBV from a previous infection is not necessary but will not cause adverse effects. Such individuals will have a postvaccination increase in their anti-HBs levels. Passively acquired antibody, whether acquired from administration of immune globulin (IG) or HBIG, or naturally via the transplacental route, will not interfere with active immunization.

Hepatitis B infection and control in the United States (from CDC reports, 1990):

Each year, an estimated 300,000 persons, primarily young adults, are infected with HBV. Of these, about 75,000 become ill with jaundice, more than 10,000 patients require hospitalization, and an average of 250 die of fulminant disease. The United States currently harbors between 750,000 and 1,000,000 infectious carriers. Approximately 25% of carriers develop chronic active hepatitis, which often progresses to cirrhosis. Furthermore, HBV carriers have a risk of developing primary liver cancer that is 12 to 300 times higher than that of other persons. An estimated 4,000 persons die each year from hepatitis B-related cirrhosis, and more than 800 die from hepatitis B-related liver cancer.

Serologic surveys demonstrate that, although HBV infection is uncommon among adults in the general population, it is highly prevalent in certain groups. Persons born in areas of high HBV endemicity and their immediate descendants remain at high risk of infection, as do certain populations in which HBV is highly endemic (Alaskan natives and Pacific islanders).

Certain lifestyles (e.g., homosexual activity, intravenous drug abuse) result in early acquisition of HBV infection and high rates of the infection. Persons who have heterosexual activity with multiple partners are also at high risk of infection. In addition, inmates of prisons are at high risk, usually because of parenteral drug abuse before or during imprisonment. Patients in custodial institutions for the developmentally disabled are also at increased risk, as are household contacts and sexual partners of HBV carriers, hemodialysis patients and recipients of certain plasma-derived products that have not been inactivated (e.g., antihemophilic factor). Those at occupational risk of HBV infection include medical and dental workers, related laboratory and support personnel, and public service employees who have contact with blood, as well as staff members in institutions or classrooms for the mentally retarded.

The incidence of reported acute hepatitis B cases increased steadily over the past decade and reached a peak in 1985 (12 cases/100,000/year), despite the introduction of hepatitis B vaccine 3 years previously. Incidence decreased but only slightly by 1988;

it still remains higher than it was when vaccine was introduced. This minimal impact of hepatitis B vaccine on disease incidence is attributable to several factors. The sources of infection for most cases include intravenous drug abuse (27%), heterosexual contact with infected persons or multiple partners (22%), and homosexual activity (9%). In addition, 30% of patients with hepatitis B deny any of the recognized risk factors for infection.

The present strategy for hepatitis B prevention is to vaccinate those individuals at high risk of infection. Most persons receiving vaccine as a result of this strategy have been persons at risk of acquiring HBV infection through occupational exposure, a group that accounts for approximately 4% of cases. The major deterrents to vaccinating the other high-risk groups include their lack of knowledge about the risk of disease and its consequences, the lack of public-sector programs, the cost of vaccine, and the absence of ready access to most of the high-risk populations.

For vaccine to have an impact on the incidence of hepatitis B, there must be a comprehensive strategy that will provide hepatitis B vaccine to persons before they engage in behaviors or occupations that place them at risk of infection. Universal HBsAg screening of pregnant women was recently recommended to prevent perinatal HBV transmission. The previous recommendations for selective screening failed to identify most HBsAg-positive pregnant women. As an alternative to vaccination of those in high-risk groups, universal vaccination of infants and adolescents must be the national policy to control the transmission of this disease.

Hepatitis B infection and control in developing countries (from reports of Task Force on Hepatitis B and EPI):

Over 2 billion persons in the world have been infected with HBV. Of these, more than 300 million people -- or about 5 percent of the world's population -- remain persistent carriers of the virus. In sub-Saharan Africa and Southeast Asia where HBV infection is highly endemic, up to 95% of the adult population has been infected with HBV, usually during infancy or childhood. About 10% become persistent carriers, and one-quarter of persistent carriers of HBV will eventually die of chronic liver disease, including liver cirrhosis and liver cancer.

Unlike other common infections of infancy and early childhood such as respiratory and diarrheal diseases that kill early in life, the deaths associated with hepatitis B occur in the prime of life, when individuals have become economically productive. These deaths result in family disruption and have an adverse impact on children. Approximately 3 out of every 100 babies born in countries where hepatitis B is highly endemic will die in adulthood from a complication of this infection. Thus, hepatitis B is now recognized as a major cause of overall mortality.

In the past three years, the cost of the vaccine for public-sector programs has decreased to about $1.00 per dose. Thus, the cost-effectiveness (cost per death prevented) of HBV immunization is now similar or superior to that of other vaccinations currently included in the EPI.

In areas of high endemicity, most HBV infections occur during childhood. They may occur around the time of birth as a result of perinatal transmission from an infected mother to her infant, or from one infected child to another. There is considerable

variation between areas, countries, and continents as to the age at which most transmission takes place. It is therefore important to know the local situation so that the immunization program can be tailored to provide the maximum impact.

Ways should be examined for introducing HB vaccine with minimal disruption to the existing immunization schedule. If perinatal transmission is found to contribute a significant proportion of childhood infections, the first dose of HB vaccine should be given as soon after birth as possible, as depicted in the top line of Table 7. It may be necessary to improve birth notification processes and strengthen immunization services so that they reach mother and child soon after birth. Health staff should be trained in reaching newborns and administering appropriate antigens including HBV, OPV, and BCG vaccines.

The PATH Task Force has often encountered the question: "What factors account for the geographic differences in rates of chronic carriage of the hepatitis B virus?" Their answer: The single most important factor that accounts for regional differences in chronic carrier rates is age of infection. In areas of the world where hepatitis B is hyperendemic and where chronic carriage rates are 5% or more, infection is predominantly in infancy and early childhood. Where endemicity of hepatitis B is low and rates of chronic carriage are below 1%, infection occurs chiefly in adult life. In these low endemicity areas, sexual transmission is the most important mechanism, in contrast to the high endemicity areas, where transmission from the carrier mother to her infant and transmission through close personal contact among young children predominate. The precise mechanism by which carrier rates are influenced by age is unknown, but probably relates to the effect of age on the immune system's ability to terminate a hepatitis B infection. The probability that an infant will become a chronic carrier if infected is about 90%. This probability is reduced to about 50% at 3 years of age, and 6% to 10% at 6 years of age. This last percentage is maintained from then on, and throughout adult life. Therefore, infections occurring at ages under 6 years result in a much higher proportion of carriers than infections occurring thereafter.

Model immunization programs

An important aspect of hepatitis B vaccination within the context of EPI is that the vaccine, especially in Asia, should be administered as soon as possible after birth, preferably within the first several days of life. Among the vaccines already included in EPI, BCG and poliovaccine also are recommended for administration at birth. In most rural areas of the developing world, where the large majority of births take place in the home and are attended by midwives, an infant's first encounter with the health-care system may not occur until three or four months after birth. Consequently, early administration of EPI vaccines is very difficult. While this delay is not necessarily critical for successful immunization with other EPI vaccines, delaying hepatitis B vaccination until several months after birth is undesirable, because with delay the risk of becoming a carrier is greatly increased.

The Task Force seeks to strengthen national EPI programs by developing strategies for early vaccination and improving birth notification systems. The model immunization programs are intended to demonstrate how national immunization programs can include hepatitis B vaccine while taking into account its different requirements for

delivery. The first model immunization program was launched in Indonesia in November 1987. Programs were subsequently established in China in March 1988 and in Thailand in August 1988. These were followed by programs in Cameroon and Kenya. Other programs for the control of hepatitis B vaccinating infants have begun in Singapore, Brazil, Gabon, Oman, Mongolia, and other countries, as part of WHO-sponsored programs.

The hepatitis B immunization program in Lombok, Indonesia, serves as an excellent model of what can be accomplished. The introduction of the hepatitis B vaccine stimulated the EPI program, leading to a marked increase in coverage of both polio and BCG vaccines following the introduction of hepatitis B vaccine. During the first year, HB immunization was begun in 18 villages. In each successive year of the project, HB vaccine coverage was expanded to additional villages. The model program has succeeded in protecting 75% of the target infants. The rate of HB carriage among children between 9 months and 2 years of age has been reduced from 6.7% to 1.7% within two years of project implementation.

Several key factors contributed to the program's success. The procurement and supply of an inexpensive vaccine was accomplished through an international tender and bid procedure. The cost was 0.95$ per dose and the vaccine was a plasma-derived alum adjuvanted vaccine which met WHO requirements. Government involvement included training of vaccinators and all personnel from ministry-level officials to master trainers at the provincial, district, and subdistrict levels. The vaccinators' schedule was also modified so that home visits were made within seven days after birth.

The Lombok project has extended EPI outbreak services to more than 20,000 newborns at the subvillage (hamlet) level. It has established an efficient and comprehensive system of birth notification, which is carried out at the village level. The volunteers are trained to conduct a census of pregnant women and newborns, and organize monthly mothers' club meetings to increase awareness. This birth notification system ensures that all births are reported through the hamlet chief to the government-appointed village leader within 48 hours. The village vaccinator from the public health centers then obtains the names of the newborns from the village leader and goes to the homes to administer the first dose of HB vaccine soon after the date of birth. With the establishment of a vital registration system and early identification of newborns, the HB model program allows for the introduction of other child survival interventions that can be delivered within a few days of birth in the home. By introducing other interventions in the same target areas, program delivery costs are shared, making each intervention more cost-effective.

For the first time in Indonesia, EPI delivery reaches the hamlet level. The example of Indonesia, where 85% of rural babies and 40% of urban babies are delivered at home by traditional birth attendants, demonstrates that community participation in vital registration and EPI outreach are important for achieving universal childhood immunization.

The Gambia's hepatitis B program began introducing hepatitis B vaccine into its Expanded Programme of Immunization in July 1986. Hepatitis B introduction occurred gradually, so that the vaccine's effects on carriage, cirrhosis, and liver cancer could be evaluated. During the introduction phase one additional team introduced the vaccine into its schedule every seven weeks, so that by February 1990 every team in the country was

delivering hepatitis B vaccine. Forty teams currently deliver vaccine throughout the country; each is based at a health center or hospital, and immunization sessions are conducted at these bases and at village clinics reached by vehicle.

A detailed record-keeping system was developed so that all immunized children can be followed over the next 30 years. A total of 126,000 children were studied, of whom 60,000 have received hepatitis B vaccine. The coverage obtained by the program has been found to be 97% for one dose, 95% for two doses, 91% for three doses, and 72% for four doses.

The program evaluation has three components. A group of the first 1000 representative children to receive hepatitis B vaccine has been followed for over three years with annual serological surveys to examine both primary vaccine response and decline in antibody with time. Only 2% of these children were non-responders. Through the third year of the study the decline in antibody appears similar to that which occurs in other populations. No clinical hepatitis cases and no carriers were reported after the first year of life, although 11 out of 711 children converted to core antibody at two years of age, indicating subclinical HBV infection. Two children became carriers perinatally from HBeAg-positive mothers; eight other children born to HBeAg-positive mothers did not become carriers, although none received their first dose of vaccine until the second week of life.

Overall, the study suggests that vaccine effectiveness against infection is 97%. This figure is for all children entering the EPI, including non-responders and those receiving less than the intended number of doses. The results so far suggest that the introduction of hepatitis B vaccine into EPI in Africa would control childhood hepatitis B infection.

The next steps in The Gambia are to identify donor support for supplies of vaccine (preferably in ten-dose vials to reduce wastage) and to implement a three-dose regimen. Trials will also be conducted with a combined DPT-hepatitis B vaccine in an effort to reduce the number of injections given to a child.

The Kenya hepatitis B program was begun in 1990, in Kiambu, a rural district with a population of about one million located just north of Nairobi. The model program represents, following the Gambia program, one of the first efforts within Africa to integrate childhood HB immunization into ongoing EPI systems.

Within Kenya the rate of the HB chronic carrier state varies widely from one area to another, with one area reporting a rate of 28% HBsAg prevalence, while other areas report lower rates, of 5% to 10%. Several small-scale surveys have shown that the HB infection rate is constant throughout early childhood, reaching a cumulative peak at around 20 years of age. Even when the mother was positive for HBeAg, only 30% of babies were found infected in the perinatal period, as compared to nearly 90% in Southeast Asia. Therefore, in contrast to the well-documented pattern of perinatal HBV transmission in Asia, the transmission in Kenya is mainly horizontal. Although significant exposure to infection occurs during infancy and early childhood (the ages at which the risk of converting to carrier status is the highest), exposure at birth does not play an important role in transmission.

Given the horizontal HB transmission pattern in Kenya (as in most parts of sub-Saharan Africa) and the probable availability of a combined DPT/HB vaccine in the near future, the model program was designed to link HB vaccine to the administration of DPT

at 6, 10, and 14 weeks rather than trying to give the first dose at or near birth as must be done in Asia. This approach could simplify considerably the logistics of introducing the HB vaccine and result in greatly reduced program costs. In addition to the goal of introducing HB vaccine in a cost-effective manner, the model program hopes to strengthen EPI generally by improving community understanding of the need to complete multi-dose courses of vaccine (thus reducing dropout rates), reinforcing the training of health workers with regard to immunization practices, and improving record-keeping.

Linking HB vaccination to routine DPT represents a highly efficient way to introduce an important new vaccine into childhood immunization programs. The model program will provide the opportunity to gather systematic data on the protective effect of HB vaccine given according to this schedule of doses and to identify and constraints on this strategy.

EPI has identified three factors which would markedly contribute to a wider use of HB vaccine: (1) Further decrease in vaccine cost. (2) Development of a combined vaccine such as DPT-HB. Such a combined vaccine would reduce additional storage and delivery costs and would spare the recipients several additional injections. (3) Development of a slow-release product that can provide solid long-lasting immunity with only one injection. Various controlled-release systems include biodegradable synthetic polymers, liposomes, and microsponges. Under study is a slow-release tetanus toxoid incorporated into injectable and biodegradable polymers (microspheres) to release the antigen at predetermined intervals over a long period of time, thus mimicking repeated injections. The concept of a slow-release product may apply, in general, to any vaccine that requires more than one injection, including HB vaccine.

Conclusions

1. The epidemiology of hepatitis B has become clarified from studies made possible by the relatively recent recognition of the antigens associated with the virus. Programs can now be planned to bring the disease under control.
2. Vaccines have been prepared either from viral antigen in plasma of human carriers or from viral antigen grown in yeast cells by recombinant techniques. The vaccine prepared from either source material has proven to be safe and effective Its cost to public health agencies has been reduced to less than one dollar per dose. This makes possible its worldwide use -- essential if this common infection is to be suppressed.
3. For effective control of hepatitis, universal vaccination of infants and adolescents is recommended. In many regions, vaccine will have to be administered soon after birth, to prevent perinatal infection and the resulting high prevalence of the virus carrier state.
4. Since there is only a single immunotype and there are no known animal carriers of the virus, the incorporation of available hepatitis B vaccines into the EPI mission should lead to the eradication of diseases caused by hepatitis B virus -- acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma.

Figure 1. Poliomyelitis incidence per 100,000 population, as reported to WHO for 1985. [9]

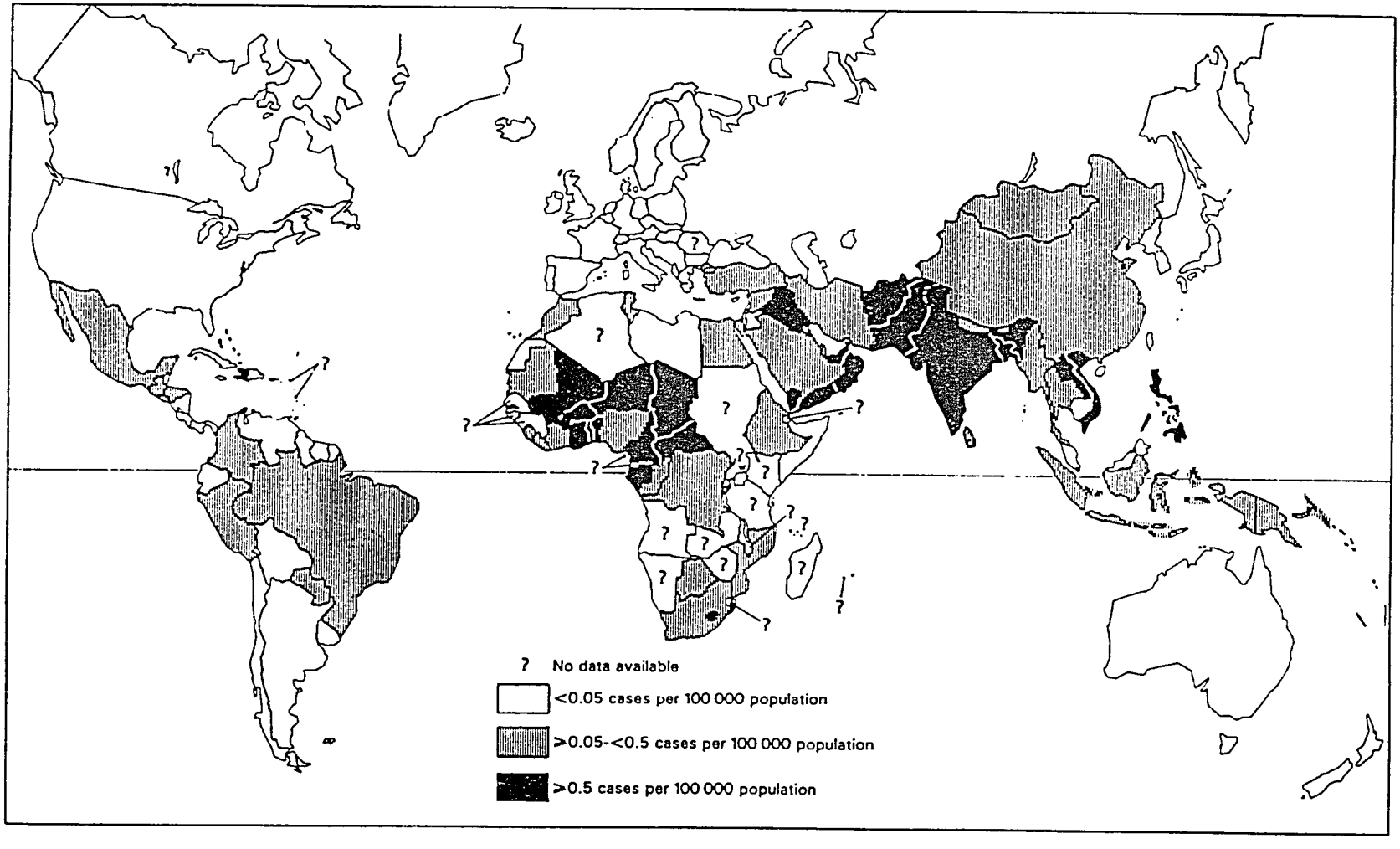

Table 1. Poliomyelitis in the Western Pacific Region: Comparison of countries in which the disease was brought under control and those in which it was incompletely controlled as of 1985.

	Population (millions) (est. 1985)	Average Annual Number of Cases				Annual Number of Cases				
		1951-1955	1966-1970	1971-1975	1976-1980	1981	1982	1983	1984	1985
Polio controlled:										
TOTALS	162	5233	142	359	37	7	7	5	6	6
Polio incompletely controlled:										
TOTALS	1180	276	746	1092	9920	5640	8958	4792	3555	3729

The totals of populations and cases include only those countries selected as examples (listed below).

"Polio controlled" countries included: Australia, Hong Kong, Japan, Malaysia, New Zealand, Singapore.

"Polio incompletely controlled" countries included: China, Laos, Papua New Guinea, Philippines, Viet Nam.

Table 2. Polio in American Region through 1985: Progress in countries in which the disease was brought under control, and those in which it was incompletely controlled as of 1985.

Population (millions) (est. 1985)	Average Annual Number of Cases				Annual Number of Cases				
	1951-1955	1966-1970	1971-1975	1976-1980	1981	1982	1983	1984	1985
Polio controlled:									
(317)	44391	470	221	34	9	79	39	9	10
Polio incompletely controlled:									
(332)	2202	14453	10249	3837	1538	884	881	526	855

The totals of population and cases include only those countries selected as examples (listed below).

"Polio controlled" countries included here are: Argentina, Canada, Cuba, United States,

"Incompletely controlled" countries included here are: Brazil, Colombia, Mexico, Peru, and others.

Table 3. Inactivated Poliovirus Vaccine (IPV): Advantages and Problems*

Advantages:

- Confers humoral immunity in vaccinees if sufficient doses of potent vaccine are given.
- Can be incorporated into regular pediatric immunization, with other injectable vaccines (DPT).
- Absence of living virus excludes potential for mutation and reversion to virulence.
- Absence of living virus permits its use in immunodeficient or immunosuppressed individuals and their households.
- Has greatly reduced the spread of polioviruses in small countries where it has been properly used (wide and frequent coverage).
- Beneficial in certain tropical areas where live vaccine has failed to "take" in some young infants.

Disadvantages:

- Early studies indicated a disappointing record in percentage of vaccinees developing antibodies after three doses, but more immunopotent antigens are now produced.
- Generally, with the vaccines that have been commercially available, repeated boosters have been required to maintain detectable antibody levels.
- Does not induce sufficient local intestinal immunity in the vaccinee to block transmission of wild polioviruses by the fecal-oral route.
- More expensive than live vaccine.
- Growing scarcity of monkeys for kidney tissue substrate was a problem but has been overcome by use of continuous-passage monkey cells (Vero) for vaccine production.
- Use of virulent polioviruses as vaccine seed creates potential for tragedy if a single failure in virus inactivation were to occur in a batch of released vaccine. This risk is somewhat increased since monkey neurovirulence tests are no longer required before release of inactivated vaccine. However, this problem is being overcome by use of attenuated strains for production.

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* Modified from reference 12.

Table 4. Live Poliovirus Vaccine (OPV): Advantages and Problems *

Advantages:

Confers both humoral and intestinal immunity, like the natural infection.
Oral administration is more acceptable to vaccinees than injection and is easier to accomplish.
Induces antibody very quickly in a large proportion of vaccinees.
Under epidemic conditions, it not only induces antibody quickly but also rapidly infects the alimentary tract, blocking spread of the epidemic virus.
Is relatively inexpensive, both to produce and to administer.
When properly stabilized, it can retain potency under difficult field conditions with less refrigeration and without freezing.

Disadvantages:

Vaccine viruses may mutate, and in very rare instances (about 1 per million) have reverted toward neurovirulence sufficient to cause paralytic polio in recipients or their contacts.
Vaccine virus also spreads to household and community contacts (Some people consider this spread to be an advantage, but the progeny virus excreted and spread by vaccinees often is a mutated virus and obviously cannot be a safety-tested vaccine, licensed for use in the general population.)
In certain tropical countries, induction of antibodies in a satisfactorily high proportion of vaccinees has been difficult to accomplish.
Contraindicated in those with immunodeficiency diseases, and in their household associates, as well as in persons undergoing immunosuppressive therapy, and their households.
Requires monkeys for safety testing. However, the new molecular techniques that monitor any change in the nucleotide sequence of the attenuated poliovirus genome may supplant the monkey test.

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* Modified from reference 12.

Table 5. A combined vaccination schedule proposed for EPI

Age	Vaccine Doses *
At birth	BCG / OPV
6 weeks	DPT1 / OPV1
10 weeks	DPT2-IPV1 / OPV2
14 weeks	DPT3-IPV2 / OPV3
6 - 12 months	Measles

* The first, second, and third doses are indicated by the numbers. A nonscheduled dose is also recommended at birth when the infant is readily available. After the circulation of wild poliovirus in the community is sharply reduced by the above schedule, progress toward eradication can be achieved by use of OPV alone.

Table 6. Examples of studies in different countries showing varying levels of HBV markers and their significance (WHO summary)

Prevalence of HBV markers				Interpretation		
				Likely importance of transmission		
Area/group studied	HBsAg	HBeAg*	Prior HBV infection	Perinatal	Childhood	Adult
Chile, Argentina	< 1%	20%	5-15%	Moderate (accounts for 15% of HBV carriers)	Minimal	Moderate
Venezuela, NE Brazil	1-3%	20%	5-15%	Moderate (as above)	Moderate	Moderate
Africa	7-15%	15%	15-45%	Moderate (accounts for 10% of HBV carriers)	High	Low
Southeast Asia	7-15%	40%	70-90%	High (accounts for 30% of HBV carriers)	High	Low

* Percent of HBsAg-positive individuals who are also HBeAg-positive.

Table 7. Examples of vaccination schedules which use HBV.

Age	Example 1	Example 2
At birth	BCG / OPV / HBV1	BCG / OPV
6 weeks	DPT1 / OPV1 / HBV2	DPT1 / OPV1 / HBV1
10 weeks	DPT2 / OPV2	DPT2 / OPV2 / HBV2
14 weeks	DPT3 / OPV3	DPT3 / OPV3 / HBV2
6 - 12 months	Measles / HBV3	Measles / HBV3

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Interventions to Reduce Childhood Morbidity and Mortality From Tuberculosis[1]

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Abstract

Some 8 million of new cases of tuberculosis emerge globally each year, 10 to 20 percent of which are among children. The root of the failure of tuberculosis programs in many resource-poor countries lies with the failure to properly diagnose and treat adults with infectious tuberculosis. To tackle the tuberculosis problem in children in resource-poor countries, two independent strategies must simultaneously be put into work.

On the short and long term most important is an aggressive approach to the cure of newly diagnosed tuberculosis patients with infectious forms of the disease. By curing these patients, the chain of transmission can be cut, and thereby exert both a direct and indirect impact on the tuberculosis situation in the community. Each cured case of tuberculosis is prevented from spreading the organism to the most susceptible, previously uninfected segment of the population. This will result in a proportional decrease in tuberculosis in children. Epidemiologically more important is the effect of the reduction in infection risk in the community. Whenever the risk of infection with M. tuberculosis is constantly being reduced, the cumulative pool of persons with tuberculous infection (from which future cases will arise) will continuously be depleted by the succession of cohorts with less and less infection.

Second, BCG must remain an important cornerstone of the Expanded Programme of Immunization that must extend further and further. This will help to immediately reduce the number of deaths from tuberculosis in children. The main effect of BCG is in children who rarely develop infectious forms of tuberculosis. Because it is these infectious cases that not only result from, but also determine the epidemiologic situation in a community and not cases among children, vaccination can be expected to have little impact on the course of the tuberculosis epidemic.

Additionally, preventive therapy of newly discovered infected contacts has proved to be efficacious. Whenever manpower and financial resources are available, small children who are household contacts of newly discovered infectious, sputum smear-positive cases should always benefit from preventive therapy, irrespective of their BCG vaccination status.

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Magnitude of the problem

Several analyses from the past few years on estimates of the global burden of tuberculosis permit the conclusions that tuberculosis is a problem of a tremendous magnitude and that little progress has been made in those parts of the world where health resources are limited and the tuberculosis burden is particularly heavy [1-3]. Although available interventions against tuberculosis, in particular effective treatment of infectious cases, are being considered to be among the most cost-effective [2, 4], these tools have not come properly into use in resource-poor countries. In contrast, in most industrialized countries, tuberculosis has ceased to be a major public health problem. However, even among the latter, tuberculosis continues to be an important, and sometimes increasing, health problem among certain population segments [5, 6].

While children are themselves relatively unimportant sources of infection, they acquire their infection from undiagnosed and untreated sources of infection in the community. Several surveys indicate that between 10 and 20 percent of all tuberculosis cases in resource-poor countries occur among children [7-9]. Although in most cases, tuberculosis in children is a relatively benign, self-limiting disease, serious complications of hematogenous dissemination, such as miliary disease and meningitis, occur more frequently in children than in adults, and their outcome is usually fatal, if left undiagnosed and untreated [10-12].

It is the purpose of this paper to summarize the merits and roles of available tuberculosis intervention strategies in resource-poor countries that aim at both reducing unnecessary morbidity and mortality from tuberculosis in children directly and indirectly by targeting scarce resources most efficiently to reduce the problem immediately and on a long-term basis.

Pathogenesis of tuberculosis and intervention opportunities

According to current understanding, it appears that the risk of becoming infected is determined primarily by factors exogenous to the susceptible host, while the subsequent risk of progression from latent infection to clinically active disease appears, in contrast, to be determined primarily by endogenous factors [13]. In this respect, the distinctly two-stage character of tuberculosis etiology has been likened by analogy to the two-hit theory of cancer pathogenesis, infection with *Mycobacterium tuberculosis* being the necessary cause, and a breach of cellular immunity the independent sufficient cause [14]. A simplified sketch summarizes the pathogenesis of tuberculosis with exposure, infection, disease, and death with possible opportunities for intervention (figure). Vaccination with Bacille Calmette-Guérin (BCG) does not prevent infection [15], and must, to prevent tuberculosis following infection, be given before infection has occurred. Preventive therapy is the treatment of subclinical infection with *M. tuberculosis* and its target population are persons who are identified with a positive tuberculin skin test and are considered to be at an increased risk of progression to active disease. Chemotherapy of new cases reduces the risk of dying from tuberculosis and, epidemiologically most important, cuts the period of transmissibility of potentially infectious cases.

An emerging consensus in industrialized countries puts early diagnosis and adequate chemotherapy of new cases, coupled with proper contact examination, followed by

preventive therapy for those found to be recently infected at the top of priorities for the elimination of tuberculosis [16, 17]. Preventive therapy for groups recognized to have an increased risk of progression from latent, subclinical infection with *M. tuberculosis* to clinical tuberculosis [13] must also play a major role in eliminating tuberculosis from industrialized countries. Vaccination with BCG has never been widely used in some, and is losing its importance in other industrialized countries [17]. In resource-poor countries, this list of priorities must be reviewed and, where necessary, be adapted to the epidemiologic situation and availability of resources.

Efficacy of intervention strategies

BCG vaccination

Several controlled clinical trials and case-control studies have not provided any clear answer as to the protective efficacy of BCG vaccination. Protection in these trials has ranged from nil to 80 percent and even more, in some studies on tuberculous meningitis [18-20].

Preventive therapy

Numerous clinical trials of the efficacy of preventive chemotherapy among household contacts, persons with long-standing infection with *M. tuberculosis*, documented recent converters, and persons with fibrotic lesions all have shown that preventive therapy can reduce the risk of subsequent development of tuberculosis [21, 22]. A major constraint and impediment in exploiting the full possible protective efficacy in these trials has been non-adherence of patients to the prescribed regimen [22, 23].

Case-finding and treatment

So-called 100-percent efficacious regimens [24] have been developed as early as in the early 1950s, when streptomycin, para-aminosalicylic acid, and isoniazid had all become available. With the introduction of rifampicin and pyrazinamide into modern chemotherapy, powerful, so-called short-course regimens of six to nine months duration have been developed [25]. The considerable costs for the necessary drugs have left the World Health Organization reluctant for years to recommend these regimens for resource-poor countries [24]. More recently, experiences in Mutual Assistance Programmes of the IUATLD [26] and analyses by the World Bank [2, 4] have brought about a change in the World Health Organization's recommendations for preferred treatment regimens in resource-poor countries [3].

Role and operational efficiency of intervention strategies

BCG vaccination

Vaccination with BCG has become one of the most widely provided vaccines in the world [20]. BCG is generally well tolerated and serious adverse reactions are uncommon

[27]. Because its usefulness in reducing serious hematogenous complications of childhood tuberculosis, such as miliary tuberculosis and tuberculous meningitis has been uncontested [28], tuberculosis should remain an integral part of the Expanded Programme of Immunization, whenever the tuberculosis problem is considerable and provision of health care and diagnostic capabilities are limited [29]. In industrialized countries, where the risk of infection with *M. tuberculosis* has become very low, and where an excellent health infrastructure provides ample opportunities to conduct appropriate contact tracing around newly occurring cases, BCG plays an increasingly insignificant role. This is further emphasized by the need to preserve the tuberculin skin test as a screening tool for such investigations as the test becomes more difficult to interpret after BCG vaccination [30]. Furthermore, in low-incidence countries the rare serious complications of BCG vaccination may begin to outweigh the potential benefits of vaccination [31].

Preventive therapy

As efficacious as preventive therapy may be, its operational efficiency is unsatisfactory low [32, 33]. Because not more than 10 percent of persons infected with *M. tuberculosis* ever develop tuberculosis, ten positive tuberculin reactors would have to be treated to prevent a single case. Given toxicity of isoniazid preventive therapy, as low as it may be [34], the benefit for low-risk tuberculin reactors has been debated fiercely [35-38]. A strategy to enhance the efficiency of preventive therapy must clearly rest on the selection of individuals eligible for preventive therapy who are at particularly high risk of progression from latent infection to overt disease. Numerous risk factors have been identified to increase this risk [13]. Few of them are important, because they either increase the risk manyfold and/or are highly prevalent in the community. Weighing all the strength of the association, prevalence of the condition, and opportunity for identification, the three most important conditions which are generally agreed to identify those in need of preventive treatment include 1) co-infection with the human immunodeficiency virus (HIV), 2) fibrotic lesion, and 3) recent tuberculous infection. Nevertheless, while there should be little impediment to build consensus in industrialized countries that patients with these three risk factors should benefit from preventive therapy whenever identified, the logistic hurdles to overcome are enormous in most resource-poor countries. Still now, it is not uncommon to find that in many of the latter countries resources are insufficient even to treat patients with tuberculosis.

Case-finding and treatment

Case-finding and treatment are the cornerstones of any tuberculosis control program [24]. While a not unusual lag in medicine postponed their acceptance into general medical practice, it appears that by the 1960s such regimens became fully to the benefit of the individual patient and the community in most industrialized countries [39]. In contrast, in resource-poor countries the product of case-finding (not uncommonly only 30 percent) times case-holding (commonly below 50 percent) times regimen efficacy (often only 85 percent due to increasing drug resistance) amounts until today often to an overall impact of such a national program of about 10 percent [40]. Recently it has been demonstrated that low cure rates may even be detrimental to tuberculosis control efforts,

as patients may survive and become chronic transmitters of tubercle bacilli in the community [41]. It becomes now more and more accepted that the emphasis of tuberculosis control must shift to achieving the highest possible cure rate of infectious tuberculosis cases, if an impact on the epidemiologic situation is to be expected [2, 3].

Direct and indirect impact of various interventions on reduction of childhood morbidity and mortality

A case of tuberculosis in a child is virtually always a reflection of a failure in the health care system [42]. Tuberculosis in children almost always results from recent, unrecognized transmission from an infectious case that has usually been in close proximity to the child. In industrialized countries it should be expected that each new case of tuberculosis is properly diagnosed and treated, contact identification and tracing been carried out and that those found to be infected be placed on preventive therapy. Before the advent of chemotherapy, when BCG was first introduced in Europe, the objective of vaccination was to reduce serious complications and death from then unpreventable childhood tuberculosis. While this direct effect of BCG vaccination on childhood morbidity and mortality from tuberculosis still holds and is a clear indication for the continuation of BCG vaccination in countries where the infrastructure for case identification and treatment coupled with contact identification and tracing is insufficient [43], it may not be expected that BCG also exerts a considerable indirect effect, i.e., reducing the occurrence of adult type infectious forms of tuberculosis [44]. Where such health structures exist, and BCG is continued, vaccination should be supplemented with preventive therapy of children (at least of those under age 5 years) found in close contact with a newly discovered infectious case [45].

Tuberculosis in children is merely a reflection of the overall epidemiologic situation of tuberculosis in a community. The epidemiologic objective of tuberculosis control in a community must thus be to reduce immediately and lasting transmission and to reduce the pool of persons infected with *M. tuberculosis* in the community over time. In the pre-chemotherapy era, fatality from untreated sputum smear-positive tuberculosis reached 50 and more percent within 5 years [46, 47]. Before death, cases continued to spread tubercle bacilli in the community. Early case finding followed by curative treatment of new cases not only reduces morbidity and fatality of an individual case, it cuts, more importantly from a public health point of view, into the chain of transmission. Taking into account patient's and doctor's delay, the remaining span of infectiousness has, on average in industrialized countries, been reduced to some three to four months [48]. Treatment of newly discovered cases has reduced case fatality even under poor conditions to some 5 to 10 percent [49-51]. Reduction of case fatality is, however, far from being synonymous with bacteriologic cure. The keeping alive of potentially infectious cases with partial chemotherapy may, in contrast, add to the burden of transmission in a community rather than to alleviate the problem [41, 49]. The lack of the expected large impact of chemotherapy on risk of infection with *M. tuberculosis* [1] must be explained partially by this phenomenon. Because the major drawback in chemotherapy of tuberculosis is the length of treatment, patients tend to abscond once their health has improved over the pre-treatment status [52]. A larger proportion of patients who are diagnosed must thus be cured before they abscond than is the practice in many resource-

poor countries at this point in time [41]. The development of new short-course regimens has allowed for a powerful action of drug combinations within the first few weeks of treatment [25]. Although all short-course regimens are more expensive (rifampin and pyrazinamide cost) than 12-month regimens, many of the former are more cost-effective [2, 4]. To reduce the drug costs, regimens have been developed which utilize the most expensive drugs only during an initial period of two months [2 53]. These regimens have been successfully implemented in Mutual Assistance Programmes of the IUATLD [3, 54-55]. These programs utilize the initial period when the patients are still subjectively ill to enforce adherence to the prescribed regimen. As a rule, every single dose of the first two months must be taken fully supervised. This may be accomplished through ambulatory treatment or hospitalization of patients where infrastructures have not been developed to observe treatment on a daily ambulatory basis. Patients who complete successfully these first two months have a very high probability of being cured [22]. After this period, a cheaper drug combination is taken self-administered by the patient who is provided with 1-month supplies for another 6 months. Those patients who comply have a near-100-percent probability of cure, while some of the others may experience relapse with usually fully susceptible strains.

The impact of a higher frequency of cures is not immediately amenable to quantification, because the incidence of new cases is largely contributed to by the cases which continue to emanate from the pool of infected persons. A continued reduction in person-time of infectiousness through case-finding and cure will impact directly on the risk of infection in the community. Gradually, generations will be replaced by cohorts with less and less infection.

As a direct effect of an efficient chemotherapy program, the number of children infected each year will also become smaller to the extent that transmission is cut. Thereby the number of complications of primary tuberculosis among children and reinfection tuberculosis among adults can be reduced. If such a program is supplemented by a good coverage with BCG vaccination and preventive therapy for those most susceptible, the prospects for a reduction of the tuberculosis problem would look brighter than they do now. This prioritized tuberculosis control strategy is even more urgent in the light of the HIV pandemic which, in terms of tuberculosis control, capitalizes on every year that is lost in reducing the pool of young adults who are infected with *M. tuberculosis*.

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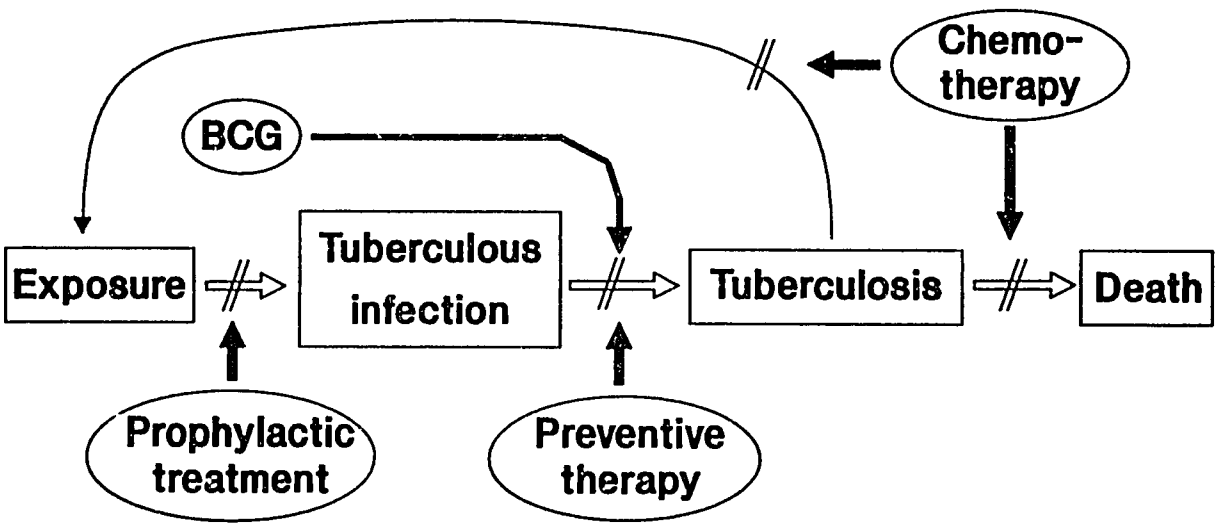
Figure 1. Pathogenesis of tuberculosis and opportunities for intervention.



The Mortality Impact of Oral Rehydration Therapy in Egypt: Re-appraisal of Evidence

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Introduction

Oral rehydration therapy (ORT) is the key low cost health intervention included in primary health care packages in many developing countries to deal with their high toll of diarrheal morbidity. The existence of a low cost, highly efficacious technological fix (oral rehydration salts) for dehydration consequent upon diarrhea provided a strong rationale for making ORT a cornerstone of diarrheal disease control programs. The large scale implementation of this therapy in different communities highlighted the need to differentiate between the efficacy of an intervention in clinical settings and its effectiveness in actual applications.[1, 2]

The importance of the socio-political, cultural and economic barriers to reaching the full potential of this treatment suggests that the impact of such therapy is less than initially envisaged. However, very few studies have actually examined the mortality impact of ORT interventions in large community settings[3-8]. The Egyptian ORT program appears to provide the strongest support for the significant role played by ORT in reducing infant and child mortality and is quoted as having the most spectacular success[9].

The success or otherwise of the Egyptian program has important implications for the strategy of health improvements, not just within Egypt but also for other developing countries. Thus, it is crucial to examine the evidence that has been presented in support of a causal link between the program and declines in infant and child mortality, and to decide whether it is adequate for such an important inference. This paper attempts to reappraise the previous evaluation attempts through making use of new sets of information and following closely the basic steps for impact evaluations.

Review of the Egyptian Program and Previous Studies

The National Control of Diarrheal Diseases Project (NCDDP) was launched in Egypt in 1983. In its first year efforts were concentrated in only one of the country's 26 governorates. This pilot program was followed by national promotion starting in February 1984. The NCDDP's aim was to increase the use of oral rehydration therapy (ORT) in episodes of diarrhea. The program activities covered training of health workers, national production of oral rehydration salts, establishment of special medical units for treatment of diarrheal disease, and conduct of a large media campaign. The objectives of this media campaign were to increase knowledge of dehydration signs and of the use of oral rehydration salts to treat dehydration, and to change certain behaviors,

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such as stimulating use of ORS at the onset of diarrheal attacks and continuing breastfeeding during episodes.

NCDDP had been preceded by other activities. The Ministry of Health introduced a national program for provision of ORT through its clinics in September 1977. In spite of possible small contributions, the general consensus is that prior to 1984, no marked changes occurred in either utilization of ORS or the outcome measure of mortality.[5, 6, 7]

Two controlled field trials[10] of oral rehydration therapy in rural villages of two governorates in Lower Egypt (Menoufia, Dakahlia) were conducted around 1980. The impact of each of these trials was evaluated. The two evaluations reported dramatically different findings. The Menoufia study concluded that the ORT intervention efforts did not reduce diarrheal mortality among children. The Dakahlia study indicated around 50 percent less diarrheal mortality and 40 percent less overall mortality among children aged one month to five years for certain configurations of program interventions. Tekce (1982)[7] suggested that the difference in results could have been due to different intervention strategies. The Dakahlia trial had better elements (for example, periodic home visits, health personnel education, more reliance on nurses with higher credibility among mothers) than the Menoufia trial. These elements may have achieved fuller cooperation as well as provided better support for the mothers in utilizing the new therapy. The importance of these two impact studies for the national evaluation attempted here is that they provide needed baseline information (prior to NCDDP) on the clinical epidemiology and management of diarrheal episodes. Another source of information is a diarrhea surveillance study[11] in children under 3 years of age conducted in 6 sentinel communities.

As early as 1985[12], opinions were being expressed on the positive demographic impact of NCDDP activities. However, some observers were questioning the validity of conclusions drawn about causality. A detailed review was performed of the available sets of data[13], concluding that the causality statements required firmer substantiation. Major concerns of the study were the reliability of the available data and their inadequacy for supporting more positive statements of impact.

Making use of more up to date information, several recent studies[5, 6] have attributed a substantial portion of recent child mortality declines in Egypt to ORT activities. The basic rationale of, and pieces of evidence presented in, these studies are summarized below. The studies start by presuming that the successful application of ORT would result in a significant reduction in child mortality. This presumption rested upon three considerations. First, at least half of the infant and child deaths in Egypt prior to the 1980s were diarrhea-associated. This figure is supported by the civil registration statistics summarized in Table 1. Second, prior to the project, there was poor case management of diarrheal episodes. Third, the theoretical efficacy of ORS was well established.

The studies provide ample evidence that basic project input goals such as production and accessibility of oral rehydration salts, training of physicians and annual public education campaigns via the media were satisfied. Concerning the actual outputs of the project, the studies refer to greater knowledge of ORT and of the dangers of diarrheal episodes. They also report that the required changes in the management of acute

Table 1. Proportion of diarrheal associated deaths
to all infant deaths and to
post-neo infant deaths
(1965-1988)

YEAR	PROPORTION OF DIARRHEAL ASSOCIATED DEATHS	
	TO ALL DEATHS 0-11 MONTHS	TO DEATH 1-11 MONTHS
1965	52.79	62.85
1966	55.12	65.05
1967	55.65	66.15
1968	58.21	67.30
1969	61.25	71.35
1970	48.91	56.90
1971	40.51	47.18
1972	45.82	52.24
1973	49.22	56.88
1974	52.44	59.89
1975	48.37	55.41
1976	52.98	60.66
1977	50.81	57.37
1978	51.88	59.36
1979	52.49	59.38
1980	51.56	60.17
1981	51.24	58.79
1982	47.06	55.93
1983	45.35	52.14
1984	41.81	48.51
1985	36.92	44.24
1986	33.95	42.75
1987	32.53	40.86
1988	28.77	36.66

Source: Annual Vital Statistics Reports published by Central Agency for Public Mobilization and Statistics, Egypt.

diarrhea had occurred. The evidence on which such statements were based is summarized in Table 2, which is derived from three publications[5, 6, 14]. The data are drawn from three sets of studies. The first is a series of national Knowledge, Attitude and Practice (KAP) surveys commissioned by NCDDP and conducted annually since 1984. The study universe covered Cairo and eight other governorates (four in Lower Egypt and four in Upper Egypt). The other two studies are a 1986 follow-up of the Dakahlia 1980 control study and a 1988 follow-up of the Menoufia 1979-80 control study.

The inference concerning a causal connection between the program and reduced child mortality was based on the sharp decrease in infant and childhood mortality, particularly diarrhea-associated mortality, that followed the ORT intervention. Table 3 summarizes the evidence presented.

Before accepting the evidence of a change in diarrhea-associated mortality, it is necessary to make sure that the decline in diarrheal mortality is a true change rather than a change in the tendency to misclassify cause of death. Such a change in misclassification could result from the program itself, as a result of the extra attention and the large media campaign focussed on diarrhea. Seasonal trends, which do not have the same potential for misclassification, were used as an alternative indicator of trends in cause of death. The reduction in the proportion of deaths occurring in the summer season (the high season of diarrhea) from around 45% prior to 1983 to around 33% in 1987 was used as an indicator of true changes in diarrheal deaths. Another test for bias arising from misclassification of cause of death was performed by checking whether the decrease in the number of diarrhea-associated deaths had been offset by an increase in the number of deaths from other causes, either from replacement mortality or classification bias. No offsetting effect was detected in the data.

Accepting a substantial change in mortality, the investigators dismissed the contributions of factors other than NCDDP to this change by noting "the immediate determinants of diarrheal mortality may be classified as curative care, incidence, and host resistance; other factors must operate through one or more of these determinants. There was no major change in the incidence of diarrhea or nutritional status during the course of the project. We cannot exclude changes in the severity of illness (eg, subtle changes in the virulence of microbes causing diarrhea) but ORT together with continued feeding reduces duration of diarrhea".[5]

Table 2. Summary of evidence in studies supporting positive impact of NCDDP

	before NCDDP (most around 1980)	84	85	86	87	88
% ever used ORS						
National Data (b)	27 (a)	50	64	68	66	
Menoufia (c)						80
% of mothers who can mix correctly						
National Data (b)	12 (d)	53	73	81	88	
Menoufia (c)						86
Dakahlia (e)				90		
% use of ORT in Last episode						
Menoufia (c)	39 (f)					52
Dakahlia (e)				81		
% of children being breastfed with breastfeeding continuing through episode						
National Data (b)	42 (g)	68	83	86		83
Menoufia (c)						93
Dakahlia (e)				72		

Source: references: 5, 6, 14

a. Dakahlia control group (n=105)
b. NCDDP commissioned KAP household cluster survey (n=1500)
c. Menoufia follow-up study 1988
d. Dakahlia control group (n=410)
e. first round Dakahlia follow up study (control and outreach)
f. first round Dakahlia 1980 study (control and outreach)
g. 3 surveys in Menoufia governorate, pooled (n-1062 episodes)

Table 3. Infant and Childhood Mortality, 1970-1987

	INFANT MORTALITY*		CHILDHOOD MORTALITY	
YEAR	DIARRHEAL	OTHER	DIARRHEAL	OTHER
1970	65.9	50.0	17.0	15.2
1971	48.6	54.4	11.6	15.4
1972	60.8	55.6	14.4	16.4
1973	55.8	42.2	11.6	12.0
1974	59.6	41.4	11.8	10.0
1975	49.3	39.7	10.3	11.2
1976	52.8	34.2	9.6	8.5
1977	49.0	36.3	9.7	9.1
DECLINE 1970-77:	4.2	4.6	8.0	7.3
1978	43.7	29.8	6.7	6.3
1979	42.3	34.1	9.5	7.6
1980	39.2	36.8	5.7	5.5
1981	36.0	34.3	4.9	6.3
1982	33.2	37.3	5.9	7.7
DECLINE 1977-82:	7.8	-0.5	9.9	3.3
1983	29.1	35.6	4.0	6.0
1984	25.8	36.3	4.0	6.4
1985	15.3	33.9	2.7	6.9
1986	15.2	32.0	2.6	5.2
1987	12.3	32.8	2.3	5.5
DECLINE 1982-87:	19.9	2.6	18.8	6.7

Source: Figures in table (3) for 1982 to 1987 were based on detailed tabulations prepared specially for NCDDP by the civil registration authority.

* Figures reported here are different from the ones reported in table 6, particularly for 1985 and 1987. Table (6) used the published official data not the special tabulations. The difference can be explained as follows: Diarrheal rates in table (3) excluded some diseases of digestive system. The official reports that are the basis of table (6) included these diseases and excluded Cholera and Typhoid fever. The difference in infant mortality rate for 1987 resulted from using preliminary data which seem to have included births occurring to Egyptians abroad in the denominator of table (3).

Examination of Evidence

The basic steps of the impact evaluations examined in this study are the specification of a conceptual framework, the actual implementation of the project and the attribution of causality. The present analysis emphasizes the importance of the first two steps (conceptualization, implementation) of impact evaluation. It turns out that both the anticipation of a large decline in mortality as a result of ORT use and the statements concerning proper management of episodes were based on very weak information. The paper then presents a new analysis of changing mortality trends using a regression discontinuity analysis which avoids biased inferences due to choices of specific starting or ending years.

1. Conceptualization

Conceptualization refers to a spelling out of causal mechanisms. Specifying in detail the course of actions through which program activities lead to envisaged effects is important because it allows a sound choice of suitable outcome measures and plausible theoretical quantification of potential impact.

In general, ORT (with all its elements of ORS, nutrition and hygienic practices) has the potential for reducing case fatality of acute watery diarrhea (ORS and nutrition provides replacement of fluid and electrolytes to combat dehydration). The therapy reduces case fatality of all types of diarrhea and indeed of other diseases also (through its effect on nutritional status that in turn influences host resistance) and even reduces the incidence rates of diseases (improved nutritional status alters immuno-competence and better hygienic practices reduce exposure risks).

In the Egyptian program, the early messages focused on ORS and the evidence that has been cited suggests no change in either nutritional status or incidence rates. Thus, one route of impact is specified: The reduction of case fatality of acute watery diarrhea due to better palliative case management of episodes. The proper outcome variable is deaths due to dehydration and the theoretical quantification is strongly related to that.

The first step in the analysis examines the possible theoretical impact of eradicating all dehydration deaths in Egypt. Two points need to be considered:

- Cause of death statistics in Egypt are known to be inaccurate. The 50 % level of diarrhea associated deaths may be too high. This in itself may be overstating the potential impact of the ORT program.
- Dehydration deaths represent only some proportion of all diarrhea associated deaths. There is a need to quantify this proportion better to avoid another possible source of overestimation of potential impact.

To discuss these two points, we need better information on the cause of death structure in Egypt and an estimate of what proportion dehydration deaths are of all diarrheal deaths. The objective here is to reach a plausible estimate of dehydration mortality in Egypt, which in turn will set the upper ceiling of maximum possible impact of the program.

It is unfortunate that detailed base line epidemiological studies are not available for Egypt. Most of the available evidence comes from a few small area studies. A

study[11] of diarrheal morbidity (but not mortality) conducted around 1983 in several Egyptian communities suggests a high toll of such morbidity. On average, young children were found to have diarrhea for 11 percent of the time (varying from 13 percent in the under ones to about seven percent in the 2 to 3 year olds), and nearly two-thirds of this diarrhea was watery. The 1980 Menoufia controlled field trial[7] conducted careful retrospective medical interviews, discussions and consultations to determine the most probable primary cause of reported deaths. The data showed that diarrheal deaths constituted some 48% and 55% of infant and childhood deaths respectively. The scanty information available does not support the notion that diarrheal deaths are overstated in the civil registers.

Information on deaths due to dehydration are even more difficult to come by and little is known for Egypt. Black (1984)[15] states that acute diarrheal deaths usually constitute 50-60 percent of all diarrheal deaths. If this figure applies to Egypt, a potential impact of ORS is around 50% of diarrhea associated deaths and 25% of infant deaths. The few studies[16, 17] that have examined closely the contribution of acute watery diarrhea, the type most likely to respond to ORS, to overall mortality come up with much lower estimates. These studies are based on the Matlab field project in Bangladesh. They estimate that acute watery diarrhea deaths accounted for 11% of all deaths in 1 to 11 months old[16] and only 5.5% of all infant deaths[17].

The few and quite different estimates available for the share in mortality of dehydration deaths caused by episodes of acute watery diarrhea, and the fact that the role of ORS in preventing death from dysenteric or chronic diarrhea is limited, suggest the need for greater caution in estimating the potential of ORS.

Another point of concern is the role of ORS in influencing the health status of those cured from dehydration. Mosley and Becker[18] point out that children not dying from dehydration are more frail and more predisposed to further infection with increased risk of dying. This attenuates the mortality-reducing potential of curative interventions. Others maintain that ORS may reduce the severity and duration of subsequent sickness episodes through its role in limiting the nutritional damage during an acute watery diarrhea episode. No scientific evidence is available to support either claim.

2. Implementation

When examining the evidence presented in Table 2, there is a need to pay attention to the reliability and validity of the reported information. Some of the data may not be of high quality. Also, it is well known that the methodology adopted to obtain the specific pieces of data can have important implications for the validity of results. Further, Menoufia, in particular, had intensive presence of activities prior to the NCDDP -- and it is likely that successes reported there cannot be used as a basis for national generalization. Bearing these caveats in mind, a closer look at the evidence presented in Table 2 is carried out below. The quality of information is not investigated here and all surveys are assumed to be of reasonable quality.

All evidence on ORT utilization before NCDDP is derived from the two control trials in small areas. It seems reasonable to assume that the data related to ORS practice would hold nationally. However, the percentage of ORT use prior to NCDDP may be inflated by the fact that the first round of the Dakahlia 1980 control trial started a few

months after the ORT promotion activities. The data on continuation of feeding during episodes could have benefitted from other supportive evidence, but the case made for weak management of episodes seems reasonable. For the period after the initiation of the NCDDP, the percentage of ever use of ORS differs between the National (66%) and the Menoufia (80%) surveys, despite the fact that both surveys collected information concerning children less than 2 years of age. The difference in utilization may be attributed to the concentration of efforts in Menoufia that started before NCDDP. The evidence suggests that two out of three mothers (with young children) have at least once used ORS and that most women (over 85% of respondents) can mix it properly. The proper mixing was actually observed by interviewer.

To sum up, most available studies and reviews are in agreement that the NCDDP has succeeded in improving knowledge and general use of oral rehydration salts. The percentage of ORS use in recent episodes and the quality of such use are two key pieces of information for inferences about impact.

a) *ORS Use in Recent Episodes*

It is surprising to note that data on ORS use have not been presented on a national basis to support causality inference. A probable explanation is the fact that the reference periods of the last episodes in the national KAP studies (prior to 1988) were almost open ended. The question referred to the experience of diarrhea since the previous Ramadan (the month of fasting in Egypt which occurred several months before the survey). For each child experiencing diarrhea in the reference period, questions were asked about use of ORS in the most recent episode. The rate obtained from the 1988 national KAP for this rather long reference period is 51%, which is almost identical to the Menoufia rate of 52% (the Menoufia study suffers from the same problem of long reference period). It is strongly suspected that this methodology tends to overstate percentage utilization. The Dakahlia evidence refers to children under the age of five and the recall period was 2 weeks prior to the survey. The level of utilization reported (81%) is impressive and deserves a closer look to determine its validity for national inference.

In a critical assessment of the utilization of ORS use rates as an ORT program indicator, Larson and Mitra (1990) [19] refer to 4 national surveys taken in Bangladesh during the 1980s that gave use rates ranging from 14 to 80 percent. The authors discuss three methodological issues to which use rates are sensitive: "The terms used to describe a diarrheal episode, the reference period of the episode for which treatment information is collected and the prompting sequence regarding treatment". We add to these issues the type of diarrhea. Severe diarrhea episodes may have a higher use rate of ORS than milder ones. Thus in Egypt, data collected for younger children during the summer season are likely to show higher rates. To obtain more valid and consistent information on use rates, an attempt is made to reduce methodological biases by standardizing for reference period and age of children. Also, newer evidence is presented[20, 21, 22, 23, 24]. A summary of information is presented in Table 4. It is obvious that, even after standardization, a wide range of estimates of ORS use in last episodes is provided by different sources of data. In what follows, an attempt is made to reach a single plausible estimate.

The use rate provided by the Menoufia KAP survey is identical to the

September/October use rate of the 1990/91 Menoufia Child Survival in Rural Egypt survey. Menoufia use rates are much higher than the national rates, though the difference is reduced by comparing Menoufia to Lower Egypt. The higher use rates for Menoufia may be explained by one or more of the following: the two week reference period may favor recollection of severe cases with higher than average utilization of ORS; and the special history of Menoufia[25] may have resulted in ORS utilization rates above the national average.

The expectation that the conduct of the Egypt Demographic and Health Survey (EDHS) in winter would underestimate the ORS use rate is not supported by data from Menoufia classified by survey dates, since these data show little variation in use rate per episode by season (see Table 4). The EDHS national estimate of utilization of around 30% seems the most reasonable, but to avoid any underestimate of utilization of ORS an average (using both EDHS and Menoufia Child Survival Survey) level of ORS utilization is around 42%, 44% and 37% for ages less than 1 year, 2 years and 5 years respectively.

The NCDDP encouraged use of ORS at the onset of diarrheal attacks. Nevertheless, the available evidence (unfortunately EDHS estimates are not available yet) strongly suggests differential treatments by type of episode, as is shown in Table 5. Allowing a ratio of 3:1 (a higher ratio than implied by actual data) for use of ORS in severe to non severe cases, and a distribution of diarrhea by mild and severe of 2:1, would provide an estimate of ORS utilization in severe cases of around 75%. This is of course a very rough estimate but it is as good as the available information permits.

We can now put an upper bound on impact. Assuming proper utilization and that half of all diarrheal deaths are due to dehydration (both quite generous assumptions), the maximum expected reduction in diarrhea associated mortality is 37.5% (.5 X .75) and in infant mortality 19% (.5 X .5 X .75).

b) *Quality of Use*

The anticipated reductions in diarrheal and overall infant mortality assume 100% efficacy of ORS. Efficacy of ORS is well established in clinical settings. In community settings, the social constraints that resulted in high incidence rates of diarrhea are the same constraints that are likely to impede the proper utilization of ORS.

Table 4. SUMMARY OF EVIDENCE ON USE OF ORS DURING LAST DIARRHEAL EPISODE BY RECALL PERIOD, AGE OF CHILD AND SEASON OF SURVEY

SURVEY	SEASON	YEAR	RECALL PERIOD					
			LAST WEEK			LAST 2 WEEKS		
			<1 YEAR	<2 YEARS	<5 YEARS	<1 YEAR	<2 YEARS	<5 YEARS
EDHS	WINTER	1988						
EGYPT			29.9	32.6	28.7			
LOWER EGYPT					36.0			
NATIONAL KAP	WINTER	1988		14.3			16.1	
MENOUFIA KAP	WINTER	1988					45.0	
MENOUFIA C.S.	ALL YEAR	1990				54.1	55.2	45.1
	JULY/AUG							40.1
	SEPT/OCT							45.9
	NOV/DEC							48.4

Source: The data are drawn from the first country report of Egypt Demographic Health Survey [24], a draft report[21] on the base line round of a Menoufia child survival study underway under Johns Hopkins / AUC auspices, and recent national and Menoufia KAP impact studies[22, 23] conducted by SPAAC in Egypt.

Table 5. Use of ORS(%) by type of diarrhea

"Severe" vs. "mild" diarrhea

	NATIONAL KAP 1988	MENOUFIA KAP 1988	MENOUFIA CS 1990
SEVERE	69.7	71.6	66.2
MILD	25.2	38.7	36.8
"Dehydrated" vs."not dehydrated"			
	MENOUFIA KAP 1988	MENOUFIA CS 1990	
DEHYDRATED	83.4	89.2	
NOT DEHYDRATED	32.8	32.7	

Source: references 22, 23, 21.

Ethnographic methods are clearly superior to cross-sectional surveys in reporting actual case management of diarrhea, as the latter may tend to obtain answers that reflect the ideal behavior supported by media messages. The results of an ethnographic study[26] conducted in 6 communities with 56 cases of diarrhea followed daily strongly suggest improper utilization of ORS. Such improper use would, in turn, greatly reduce the expected impact on both diarrhea associated and infant mortality.

3. Investigation of Causality

The two previous steps dealing with theoretical quantification and implementation analysis provide some sobering insights. The first relates to the complex mechanisms through which ORT may exert its impact on mortality. The simplest curative mechanism that is implied by the early focus of the program and data on incidence and nutritional status has a lower theoretical potential than that implied by the more complex mechanism passing through health status. The implementation data -- particularly ORS utilization and quality of use -- further reduces the expected demographic impact of ORT.

This section investigates mortality trends and attempts to answer the question: is the pace of change after 1984 significantly different from the pace of change prior to the project period? A regression discontinuity analysis is adopted[27]. This procedure examines time series data involving a one group pre test - post test design in which data are available for a number of times before and after program implementation. The trend in the series is examined as a function of time, which is used as a surrogate for other causal factors. A dummy variable is added to the model to capture post-project activities. Tests are performed to check whether the amount and speed of change in the outcome measure (following project activities) could have occurred by chance or are too

large for this conclusion to be drawn. The advantage of adopting a regression methodology is in avoiding inferences shaped by particular choices of specific starting and ending dates for the series. However, the methodology does have pitfalls. First, there is an implicit assumption that the previously exhibited trend would have prevailed in the absence of NCDDP activities. This assumption can never be substantiated given the lack of controls and the complex interactive processes governing mortality change. Nevertheless, the assumption of continuation of prior trends seems the most reasonable one in the absence of information to the contrary. Second, a decision on significant deviations from prior trend is closely related to the type of models chosen for the fit. The assumption of a constant yearly magnitude of decline implied by the linear trend may be unsuitable for dealing with mortality change since improvements in mortality become more difficult to achieve with lower bases and relative declines gain more importance. However, the linear trend is justified by the almost perfect fit to the existing data, the short span of time considered and, more importantly, the fact that a significant linear change would imply a significant relative change with higher confidence. Significance will also depend on the selected starting point of the series and on the date from which a deviation in trend is expected.

The model is specified as:

$$y_i = a + b\,t_i + c\,p_i \qquad (1)$$

where y, the dependent variable, is the IMR or the post-neonatal mortality rate or the diarrhea associated post-neonatal mortality rate; t is time, with the starting year taken as equal to 1; and p is a dummy variable representing project activities, equal to 0 prior to the project and equal to 1 after project initiation. The parameter c measures the change in intercept following project activities. Standard methods are applied to test whether the parameter c is significantly different from zero, that is, to test whether the change in intercept could reasonably have happened by chance.

A second model can test for the possibility that the program might have changed the speed of decline in mortality (whether a change in intercept occurred or not). This hypothesis is investigated by introducing a time-project interaction into the model as follows:

$$y_i = a + bt_i + cp_i + d\,(t_i\,p_i) \qquad (2)$$

It is important for the analysis to choose an appropriate starting point for the time series, and also to choose an appropriate date, given program characteristics, from which a deviation in trend is expected (allowing a preliminary period for the project to reach its full potential). Table 6 and Figure 1 summarize relevant information on infant mortality and diarrhea associated mortality from which these choices can be made.

Registered IMR in Egypt portrays a picture of wide fluctuations up to the mid-seventies, after which a smoother, more systematic trend is established. It should be emphasized that these rates are believed to suffer from under-registration, but the available studies do not point to recent improvements in registration completeness. Adjusted rates for Egypt [28] portray trends similar to those of the registration data from

Table 6. Infant and diarrheal associated mortality*, yearly absolute and relative percentage change

YEAR	IMR	DIARRHEAL ASSOCIATED MORTALITY	ABSOLUTE CHANGE		PERCENTAGE CHANGE	
			IMR	DAM	IMR	DAM
1965	113.15	59.60				
1966	127.05	70.03	13.9	10.07	12.28	16.79
1967	116.09	64.60	-10.96	-5.43	-8.63	-7.75
1968	131.27	67.42	15.18	2.82	13.08	4.37
1969	114.60	70.20	-16.67	2.78	-12.70	4.12
1970	116.28	56.88	1.68	-13.32	1.47	-18.97
1971	103.27	41.83	-13.01	-15.05	-11.19	-26.46
1972	115.97	53.24	12.70	11.31	12.30	27.04
1973	97.96	48.21	-18.01	-4.93	-15.53	-9.28
1974	101.26	53.10	3.30	4.89	3.37	10.14
1975	89.17	43.13	-12.09	-9.97	-11.94	-18.78
1976	87.49	46.35	-1.68	3.22	-1.88	7.47
1977	85.29	43.33	-2.20	-3.02	-2.51	-6.52
1978	73.46	38.11	-11.83	-5.22	-13.87	-12.05
1979	76.43	40.12	2.97	2.01	4.04	5.27
1980	76.02	39.20	-0.41	-0.92	-0.54	-2.29
1981	70.29	36.02	-5.73	-3.18	-7.54	-8.11
1982	70.49	33.17	0.20	2.85	0.28	-7.91
1983	64.64	29.32	-5.85	-3.85	-8.30	-11.61
1984	62.10	25.96	-2.54	-3.36	-3.93	-11.46
1985	49.28	18.19	-12.82	-7.77	-20.64	-29.93
1986	47.14	16.00	-2.14	-2.19	-4.34	-12.04
1987	49.43	16.08	2.29	0.08	4.86	0.01
1988	42.83	12.32	-6.60	-3.76	-13.35	-23.38

Source: Annual Vital Statistics Reports published by Central Agency for Public Mobilization and Statistics, Egypt.

1970 onwards (but of course at a higher level). A starting date for the series of 1975 seems reasonable in view of the smaller erratic variations that occur thereafter, while at the same time providing a time series of adequate length. The NCDDP started nationally in 1984, but it seems reasonable to allow one year for the program to get underway before expecting effects. Figure 1 also suggests a break in the series in 1985. Thus 1985 is taken as the beginning of post project period, and p_i is set equal to zero up to 1984, and equal to one for 1985 onwards.

A quick inspection of the data suggests that the magnitude of absolute decline in IMR (13 per thousand) between 1984 and 1985 had been surpassed in earlier periods, though large absolute changes in earlier periods occurred before a firm declining trend was established. If we focus on relative decline, the 20 percent change in IMR between 1984 and 1985 is unparalleled for the period considered. The same points hold when we focus on diarrhea associated mortality. The magnitude of absolute change has been surpassed in earlier periods, though the magnitude of the 1984-85 change is the largest from 1975 onwards. The relative change in diarrhea associated mortality is higher between 1984-85 than for any other one year period in the series. Diarrheal mortality change contributed to 61% of the decline in mortality between 1984-85. It should be emphasized that the share of diarrheal decline in the overall change in mortality has surpassed 61% in several earlier years. With the exception of the changes from 1974 to 1975 and from 1982 to 1983 (in which periods diarrhea mortality change was responsible for 82% and 66% of the overall change, respectively), the decline in diarrheal mortality was accompanied by an increase in mortality from other causes. A graphical inspection suggests a change in intercept starting in 1985 and continuing up to 1988, with no change in the speed of decline.

The results of regression discontinuity analysis at the national level are presented in Tables 7 to 9 for different dependent variables (IMR, post-neonatal mortality, diarrhea associated infant mortality) and for both models (1) and (2), using a forward selection technique. In all applications the regression discontinuity analysis rejects the hypothesis of no change in intercept and does not reject the hypothesis of no change in slope. Thus it seems that, from 1985 onwards, infant mortality rates in Egypt moved to a lower base (a change in the constant in the models) keeping the same rate of annual change (no change in the slopes of the relationships) in operation since 1975. The analysis estimates an average decline in IMR, post-neonatal mortality and diarrhea associated infant mortality following NCDDP activities of around eight, nine and seven percent respectively. The change is significantly different from what could have occurred by chance based on time series information from 1975 up to 1984. Table 10 summarizes the expected level of mortality (based on earlier trends) and the estimated new level after smoothing out erratic variations.

The analysis so far has revealed that from 1985 onwards a certain unexpected absolute decline has occurred in infant mortality, particularly diarrhea associated mortality. The level of the decline is consistent with what would have been expected given the levels of current ORS utilization in Egypt, if the use were of very high quality (general high level and efficient utilization of ORS, at least insofar as utilization for children who would otherwise have died is concerned). However, the estimated impact is much higher than what would have been anticipated based on the few available pieces of information on quality of use.

Table 7

MODEL 1: IMR = a + bt + cp					
VARIABLES IN THE EQUATION					
VARIABLE	B	SE B	Beta	T	Sig T
PROJECT (p)	-8.18560	2.61282	-.24814	-3.133	.0095
TIME (t)	-2.88320	.29281	-.77991	-9.847	.0000
(CONSTANT)	91.39560	1.82859		49.981	.0000

MODEL 2: IMR = a + bt +cp + d(pt)					
VARIABLES IN THE EQUATION					
VARIABLE	B	SE B	Beta	T	Sig T
INTERACTION (pt)	1.24855	1.26277	.47575	.989	.3461
TIME (t)	-2.95455	.30186	-.79921	-9.788	.0000
PROJECT (p)	-23.29300	15.50170	-.70611	-1.503	.1638
(CONSTANT)	91.78800	1.87298		49.006	.0000

t: time, 1975 = 1, 1976 = 2, ... 1988 = 14
p: project effect
less or equal 1984 = 0
1985 onwards = 1

Table 8

MODEL 1: POST NEO MORTALITY = a + bt + cp					
VARIABLES IN THE EQUATION					
VARIABLE	B	SE B	Beta	T	Sig T
PROJECT (p)	-9.21440	2.21068	-.29523	-4.168	.0016
TIME (t)	-2.59051	.24774	-.74064	-10.456	.0000
(CONSTANT)	76.07583	1.54715		49.171	.0000

MODEL 2: POST NEW MORTALITY = a + bt +cp + d(pt)					
VARIABLES IN THE EQUATION					
VARIABLE	B	SE B	Beta	T	Sig T
INTERACTION (pt)	.61145	1.10260	.24626	.555	.5914
TIME (t)	-2.62545	.26357	-.75063	-9.961	.0000
PROJECT (p)	-16.61300	13.53545	-.53229	-1.227	.2478
(CONSTANT)	76.26800	1.63541		46.635	.0000

t: time, 1975 = 1, 1976 = 2, ... 1988 = 14
p: project effect
less or equal 1984 = 0
1985 onwards = 1

Table 9

MODEL 1: DIARRHEAL ASSOCIATED INFANT MORTALITY = a + bt + cp					
VARIABLES IN THE EQUATION					
VARIABLE	B	SE B	Beta	T	Sig T
PROJECT (p)	-7.35421	1.70230	-.33425	-4.320	.0025
TIME (t)	-2.07489	.22777	-.70481	-9.110	.0000
(CONSTANT)	48.93786	1.62204		30.171	.0000

MODEL 2: DIARRHEAL ASSOCIATED INFANT MORTALITY = a + bt + cp					
VARIABLES IN THE EQUATION					
VARIABLE	B	SE B	Beta	T	Sig T
INTERACTION (pt)	.35562	.82008	.20331	.434	.6776
TIME (t)	-2.10862	.25257	-.71627	-8.349	.0000
PROJECT (p)	-11.59952	9.95318	-.52720	-1.165	.2820
(CONSTANT)	49.15952	1.78592		27.526	.0000

t: time, 1975 = 1, 1976 = 2, ... 1988 = 14
p: project effect
less or equal 1984 = 0
1985 onwards = 1

Table 10. Summary of expected (based on earlier trends) and estimated (based on fitted model) measures of mortality

	Year	Expected	Estimated	Relative Difference %	Absolute Difference
INFANT MORTALITY					
	1985	59.68	51.50	13.70	8.18
	1986	56.79	48.61	14.40	
	1987	53.91	45.73	15.10	
	1988	51.03	42.85	16.00	
DIARRHEA ASSOCIATED INFANT MORTALITY	1985	26.11	18.76	28.15	7.35
	1986	24.05	16.68	30.57	
	1987	21.96	14.61	33.46	
	1988	19.89	12.54	36.95	
POST-NEONATAL MORTALITY	1985	47.58	38.37	19.37	9.21
	1986	44.99	35.78	20.48	
	1987	42.40	33.18	21.73	
	1988	39.81	30.59	23.15	

The question then arises of whether this unexpectedly large change can be attributed to NCDDP activities. Detailed information on changes in other macro factors operating in Egypt are unavailable to us at the moment. The general feeling is that, apart from other health campaigns, no sudden major change occurred in determining forces. Other health campaigns, particularly the Expanded Program for Immunization (EPI) program, are believed to have considerably improved immunization[29] practices in Egypt. However, immunization campaigns did not start before 1986, and the benefits of measles vaccination (as one component of EPI) are expected at ages beyond nine months. Following 1986, the change in mortality might have occurred due to the interaction of a multitude of determining forces.

The fact that the decline in mortality occurred in 1985 is the only piece of evidence in favor of NCDDP. The trend post 1985 is quite puzzling: the lack of increase in the speed of decline implies either that increased vaccination levels did not translate into mortality reductions or that NCDDP effects are decreasing over time. However, in the absence of reasonable justification for the change in mortality between 1984 and 1985, and in spite of lack of convincing evidence of the mechanisms operating, there is no basis to refute the claim that NCDDP activities are responsible for such a change. Thus the final conclusion drawn is that an average decline of around eight per thousand in infant mortality can be attributed to NCDDP activities.

The fact that the logic of disproof rather than proof is the basis of our conclusions in favour of NCDDP strongly indicates the need to perform more analysis attempting to document clearly with supporting evidence the mechanisms that are operating.

Summary and Discussion

The previous analysis illustrated that, in spite of the seemingly simple conceptualization of the role of ORT in reducing mortality, a great deal of complexity is involved in attempting to estimate the potential demographic impact of ORT. This complexity arises in part from the different combinations of actions that may constitute an ORT program. The potential of an ORT intervention is strongly linked to the configuration of treatments adopted which in turn influence the resulting health status of individuals. The implicit curative conceptualization of the ORT intervention in Egypt, the weak state of information on the epidemiology of diarrhea, and the lack of supportive evidence on changes in health status of children cured from dehydration suggest the need for greater care in anticipating the potential of ORT. An upper ceiling for the potential impact of ORT in Egypt is a 25% reduction in IMR.

Despite marked improvements in knowledge, data on ORT practice suggest that the full potential of NCDDP, even in its simplest curative route, has not been achieved. The national estimate of ORS utilization during last episode is only around 30%. Assuming a higher level of ORS utilization (42%) and allowing for differential treatments by type of episodes, the maximum expected reduction in infant mortality is reduced to 19%. Furthermore, the available ethnographic studies suggest a low quality of utilization which, in turn, greatly reduces the expected mortality impact of ORS. The infant mortality and diarrhea associated mortality following the project are lower by around eight and seven per thousand respectively than the level expected to prevail assuming the continuation of the mortality trend that existed prior to the project. Following the

project, the mortality measures exhibit the same speed of decline as before the project, but at a new, lower level. The sizes of the changes in infant mortality between pre- and post- project periods are statistically significant (unlikely to have occurred by random chance). The changes are also larger than would be expected from the data on quality of use. Other routes of impact may be operating, particularly in relation to feeding during diarrheal episodes, but available data do not allow this point to be investigated.

There is no evidence that major changes in macro forces -- other than NCDDP activities -- occurred during 1985. However, from 1986 onwards other health campaigns have operated and the Expanded Program for Immunization reported marked increases in immunization coverage[29].

Within the limitations of current information, NCDDP activities appear to be responsible for the change in mortality from 1984 to 1985. Post 1985, as other large scale interventions have come into existence, the attribution of causality is more complex. The fact that the causality attribution is largely based on the change in mortality in one time period (1984-85) and the weak conceptualization of and information on the implementation side indicate the need for more supportive evidence of the positive role of NCDDP.

In discussing the success of ORT intervention in Egypt, it is important to keep in mind the level of change in mortality and that there is still unmet potential for this program. A better appreciation of the constraints involved in effective use of the technology and a wise choice of configuration of actions adopted by the intervention could greatly enhance its impact. There is also a need realistically to decide the potential of other interventions, on the basis of their cost effectiveness. In doing so, it is important to remember that the utilization of infant or child mortality as outcome measures biases the conclusions drawn. Measures of healthy life must be brought to the forefront.

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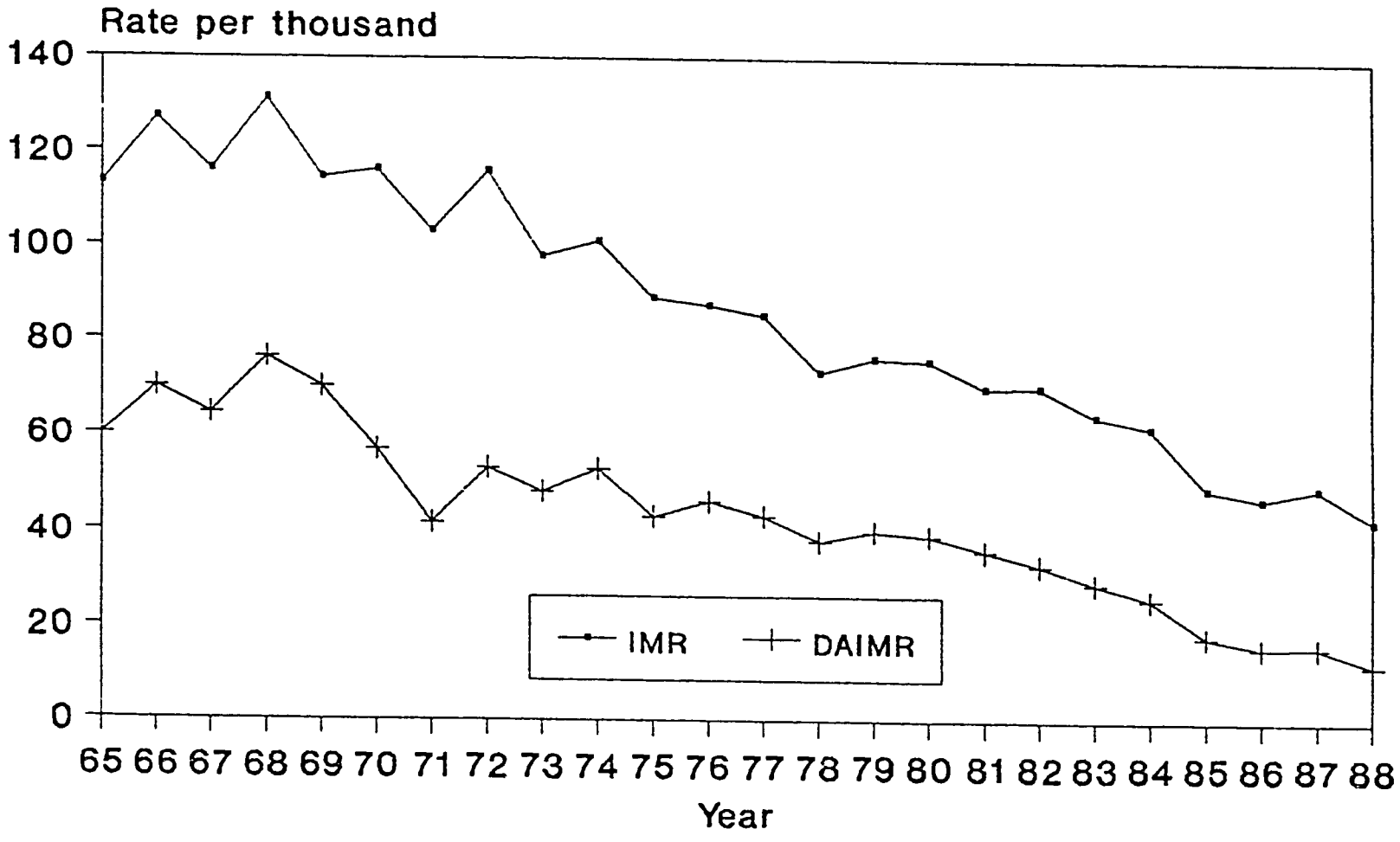
Fig 1 :REGISTERED IMR & DAIMR
EGYPT (1965-1988)



Impact of Community-based Case Management of Pneumonia on Infant and Child Mortality: A Meta-analysis of Six Intervention Trials

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ABSTRACT

In order to reappraise the effectiveness of the pneumonia case management strategy, proposed by the World Health Organization as a child survival intervention to reduce under five mortality, and to quantitatively assess the expected reduction in child mortality with this strategy, we performed a meta-analysis of the published intervention trails. All intervention trials evaluating the case management strategy were identified in consultation with the WHO and using computerized searches. Of the nine studies conducted so far, seven have been published or accepted for publication. Six of these were used for the meta-analysis, as the data from the seventh study could not be abstracted. The results of that study and the two unpublished studies were also reviewed to ascertain any bias affecting interpretations.

A detailed study quality assessment protocol was applied to all the selected studies, which were then ranked by the quality score both in terms of overall methodological quality and extent of co-intervention in the studies. There was no clear trend relating magnitude of impact and methodological quality. The data for mortality events and child years at risk were abstracted from the studies. The study-specific and summary mortality rate reductions and 95% confidence intervals were estimated using the DerSimonian and Laird method. The analyses were separately performed by age category and study design for both total mortality and ALRI-specific mortality.

The pooled overall impact on the infant mortality (deaths/1000 live births) was 15.9 (95% CI 10.6-21.1), while the effect on the ALRI-specific infant mortality was 10.7 (95% CI 4.8-16.7). The pooled impact on the total mortality 1-4 year old children was 5.1 (95% CI 4.1.-6.1). The impact on ALRI specific mortality in this age group was 1.1 (95% CI 0.3-1.8). From these results it could be estimated that pneumonia case management may reduce cumulative under five mortality by at least 36 deaths per 1000 births. Using the lower bound of confidence limits, we can be 95% confident that this reduction is going to be at least 27 deaths during the first five years per 1000 births. In terms of proportionate reduction, the pooled estimates of relative risk are consistent with a 20% reduction in the infant mortality and a 25% reduction in under 5 mortality. Using the 95% confidence limits of the relative risk, this reduction is expected to be at least 15% and 21% respectively.

The consistency of findings across the studies, regardless of the methodological scores, suggests that in spite of the methodological short comings of the individual studies, there is evidence that the case management strategy can have impact on mortality in infant and under five year old children, at least in settings with infant mortality rates of 90 or more. The implications

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of these results are that countries with high childhood mortality need to develop ARI control programs with an emphasis on pneumonia case management. Resources and efforts need to be directed towards research to ascertain the most efficient ways of implementing this strategy and integrating it into primary health care.

Respiratory tract infections, specifically pneumonia, are the commonest cause of childhood mortality accounting for 25-33% of all childhood deaths in developing countries, a total of 4-5 million deaths per year (1,2). With estimated mortality rates of 10-30/1000 infants and 1.6-4.0/1000 children 1-4 years (3), it is evident that any strategy to improve child survival in developing countries needs to consider management of pneumonia. The case management approach proposed by the World Health Organization is based on the assumptions that i) a high proportion of the fatal pneumonia in developing countries is caused by *Streptococcus pneumoniae* and *Hemophilus influenzae* (4), ii) antibiotic therapy of these bacterial infections can reduce case fatality (5), iii) a simple algorithm based on a respiratory rate of greater than 50 per min is a reliable basis for diagnosis of pneumonia in children with cough (6), and finally iv) health workers can recognize these illnesses based on simple criteria and correctly provide the antibiotic treatment.

In order to test the effectiveness and feasibility of reducing pneumonia mortality through the case management strategy, six intervention studies were initiated and completed with WHO support; four of these have been published (7-10). Three additional studies have since been performed and published (11-13). The evidence for mortality reduction from these interventions needs to be evaluated. Preliminary results were reviewed by an ad hoc technical group convened by WHO (14). At that time, however, some of studies were still in progress and data were incomplete. Furthermore, data from additional studies are now available. We therefore performed a meta-analysis of published case management intervention trials to evaluate the impact of the case management intervention on overall and ALRI mortality in children.

Meta-analysis entails critically reviewing and statistically combining the results of independent studies (15-17). The objective of such analysis is to obtain a stable estimate of the intervention effect, examine variability among trials, and resolve the uncertainty of possibly conflicting results (16). In the context of pneumonia case management intervention trials, our objective was to meaningfully synthesize the evidence to provide a framework to guide decision makers both for developing further research and for planning control programs. We asked the following questions: a) What are the methodological characteristics or shortcomings of the case management intervention studies. b) What inferences can be made about the impact of the case-management approach on reduction of infant and under five mortality from these studies. Even with the diversity of the intervention packages, varying local conditions and methodological limitations in these studies, meta-analysis provides useful information by examining the impact of each study and consistencies and trends across the studies, in addition to summary estimates of the treatment impact.

METHODS

Selection of trials

We attempted to locate all published reports of the case-management intervention trials. The WHO ARI control program, which has been involved in implementing many of these trials, was contacted for information on published and unpublished studies. We however also used MEDLINE, SCISEARCH and Current Contents computerized bibliographic data-bases to locate any published research. It is unlikely that an intervention study would have been missed by this assessment. Nine intervention studies that have been undertaken were identified (7-13,18,19). Of these five were published (7-11), two were accepted for publication (one of which was published during the compilation of this review) (12,13), while two are not yet published (18,19). For this analysis, data from only six of the seven published trials were used. One of the published trials (13) did not present sufficient information to permit its inclusion in the meta-analysis although its results are discussed where possible for comparison. We did obtain a copy of the results of two unpublished trials as provided to WHO or presented at scientific meetings in order to assess the possibility of a publication bias that could affect our interpretations.

Abstraction of data

Only data provided in the publications were considered; no attempt was made to contact the authors for the missing information. From each of the trial publications, data were abstracted by S.S. and reviewed by R.E.B.; any disagreements were resolved by consensus after again reviewing the paper together. We created 12 strata (six intervention and six control group) based on three age group categories i) infants, ii) 1-4 years, and iii) 0-4 years and two mortality categories i) all deaths and ii) ALRI-specific deaths. A further distinction was made based on the study design as having a concurrent control group or a before/after design. The data were separately abstracted for the concurrent and the before/after design part of the studies when intervention was introduced in a phased manner in the control group. Also, for studies with two years of intervention, attempt was made to abstract data for each year separately. The information provided in the paper was used to abstract and/or calculate for each study the number of events (all deaths; ALRI-specific deaths) and child years of follow up in each of the strata. ALRI deaths were used rather than pneumonia deaths since this is what the papers provided, but it is likely that nearly all these deaths were related to pneumonia. ALRI case fatality was not included in the analysis because it was not provided by all studies and when provided the methods of its ascertainment were not the same in all studies. The data from the Tanzania study (9) could only be used for the 0-4 year of age analysis as data for infants and 1-4 years of age were not given in the paper. The data for the before/after component of the Bangladesh study (12) could not be abstracted by year as data by year were not provided.

Review of methodological soundness

Based on methodological requirements for the intervention trials (20,21) and specific issues of concern in the ALRI case management interventions, we developed a comprehensive evaluation framework to facilitate the assessment of the design and methodology of these studies (appendix 1). The framework and scoring system were discussed before using them to ensure consistency of approach. Each of the studies was evaluated and scored independently on a separate scoring sheet (appendix 2) by two authors who were blinded to each others responses. Any disagreement in the scores was resolved by discussion and review of the paper.

Analytical strategy and statistical methods

For the impact assessment in this paper we used the absolute difference scale in preference to the ratio scale. Although a ratio scale is useful for exploration of causal associations, the rate difference provides a more useful assessment of the potential public health impact of a treatment (22-24), which is the primary objective of this exploration.

The rate difference (rate in control group minus the rate in the intervention group) was calculated for each study and study design (concurrent, before/after), in each of the twelve strata of analysis based on mortality (all causes, ALRI-specific), age category (infants, 1-4 years, 0-4 years). We calculated confidence limits for the rate difference of each study (or part thereof) and summary estimates within strata. As there did not seem to be a significant difference in impact between the effects in concurrent and before/after designs, we estimated combined summary estimates for concurrent and before/after designs. This analysis was then a summary estimation across studies stratified by study design.

In the analysis of rate differences for concurrent studies, data from the total period of the study were used. For before/after designs the first year of the intervention was compared with the last pre-intervention year. This was done to ensure consistency in analytical strategy among studies and also because it provided a conservative assessment of impact.

In order to evaluate the impact by duration of intervention on infant mortality and ALRI mortality in infants, we selected three studies (Bangladesh (12), Pakistan (7) and Nepal (10)) that had two years of intervention, the first two being with a concurrent design and the third one with a before/after design. We estimated rate reductions and 95% confidence intervals for each year of each study and summary estimates by year. For the concurrent design studies, contemporaneous intervention and control groups were used. For the before/after design, the last pre-intervention year was used as the control group for both years of intervention.

Within each of the strata, we used DerSimonian and Laird modified Cocharan method (D&L method) for estimation of confidence limits for the risk differences (22). The D&L method was also used for summary estimation of the impact and its confidence

interval across studies. This method produces a weighted average of the rate differences, where weights are given by the inverse of a combination of within-study variation and among-study variation. Choice of weights has at least two implications. First, the standard error of the D&L estimate incorporates an among-study component of variance and so is a more conservative testing procedure. Second, as the among-study variance gets larger this term will dominate the D&L weights and will tend to weight all studies (large and small) about equally. Third, being based on the random effect model philosophically it leads to inferences about all studies in the hypothetical population of studies rather than the particular studies assembled as is done by fixed effect models (22,25). Under the conditions of heterogeneity across studies the D&L method provides more appropriate confidence limits.

The homogeneity of intervention impact across the studies was evaluated with Cocharan's Q test (22,26). The association of impact with co-intervention in these studies was investigated using estimated odds ratios and 95% confidence limits, as well as summary odds ratios with 95% confidence limits using exact conditional maximum likelihood estimate (27). In this analysis homogeneity was evaluated by the Breslow and Day method (28). If there was heterogeneity among the stratum specific estimates, the results were confirmed using the Miettinen method for estimation of summary odds ratio and its confidence limits using three different weights (29,30). This method does not assume homogeneity for its derivation. We selected the most conservative of these estimates. In this analysis mortality satisfies the rare event assumptions and hence the odds ratio approximates to relative risk. The pooled estimates of the relative risk were thus used for estimation of percent reduction of mortality associated with intervention.

RESULTS

Study descriptions

A brief description of study design, case detection and management of pneumonia in the six included studies is presented in Table 1. It is evident that these studies had appreciable differences in study design and methods. The studies by Datta et al (8) in India and Pandey et al in Nepal (10) had very small numbers of children and the study in Pakistan (7) had a small control group. Five of the six studies had a concurrent control group, while one study was purely a before and after design. In three of the studies (Bangladesh (12), Pakistan (7) and Tanzania (9)), there is a before and after comparison available in addition to the concurrent comparison. Only in one study was the intervention and control group allocation random. In the Bangladesh study (12) the ARI intervention was superimposed on a primary health care program resulting in a high degree of co-intervention in comparison to the non-intervention comparison area. Thus, the before/after portion of this study may provide a more direct estimate of the isolated ARI case management intervention effect. The study in India (8) only included infants with low birth weight.

In order to evaluate in detail the methodological variability of these studies which

could have affected the results we applied to each of the studies a methodological evaluation protocol. A brief description of methodological score, types of co-intervention and study population characteristics is presented in Table 2. The papers provided little data on population characteristics and few details about the types or levels of co-intervention. Nevertheless it is clear that some studies had substantial co-interventions, e.g childhood immunization, diarrheal disease control activities, which necessitated a specific analysis of possible effects on mortality rate reductions in the studies. A summary of the scoring and ranking of studies is presented in table 3, while the detailed evaluation protocol and scoring are provided as annexure 1 and 2, respectively.

Impact on mortality within each study and summary estimates

The results of the ARI case management intervention effect on infant mortality (ALRI-specific and total) are presented in figure 1a and 1b, in descending order of methodological evaluation score. The studies were consistent in that all had a positive point estimate of impact. The reduction of infant mortality ranged from 13.6 to 69.8 in the concurrent studies, while it ranged from 14.4 to 52.3 in the before/after design. In two of the four concurrent studies and two of the three of before/after studies, the 95% confidence interval crossed zero. There was no clear trend in the intervention effect in the trials related to the methodological standard of the trials. The pooled rate difference for concurrent studies was 17.9 deaths/1000 live births and that for before and after studies was 20.0 deaths /1000 live births. We calculated a pooled rate difference treating the seven studies as separate strata. The pooled overall estimate of impact on infant mortality was 15.9 (95% CI 10.6-21.1). The effect on the ALRI mortality varied from 5.7 to 40.3 in the concurrent studies and 4.7 to 32.6 in the before/after studies. The overall pooled estimate of rate difference was 10.7 (95%CI 4.8-16.7). Using the pooled odds ratio estimate and its confidence interval, this difference is consistent with a 20% reduction in total infant mortality, with the minimum expected reduction using lower bound of the 95% confidence interval being 15%. The reduction in the ALRI-specific infant mortality was 35% with a minimum expectation of 26%.

The statistical tests for homogeneity (Cochran's Q and Breslow-Day) for intervention effect indicated lack of homogeneity across the studies for infant mortality while the variation of ALRI-specific infant mortality across the studies was consistent with random variation alone ($p=0.32$). The estimates for two study designs combined were similar to concurrent and before/after designs separately. We used the D&L method for estimation of pooled estimates, which adjusts the estimate for such heterogeneity. For the odds ratios we estimated the Miettinen standardized estimates using treatment, control and both as the weights. The estimates using the Miettinen method were similar to those derived using exact conditional maximum likelihood estimates, and did not change the inference in any of the analysis.

Among the 1-4 years old children, the intervention effect on ALRI-specific and total mortality is presented in Figure 2a and 2b. The intervention effect on 1-4 year mortality varied from 2.9 to 7.8 in concurrent studies and 4.2 to 15.5 in before/after studies. The results of the study in Bangladesh and the concurrent portion in Pakistan

were statistically significant. Other studies had wide confidence intervals, but the consistency of the point estimates in these studies suggests that this was due to an inadequate sample size to detect a small difference in this age group. The pooled estimate of reduction in total mortality (deaths /1000 child years) was 5.1(95% CI 4.1-6.1). The difference in ALRI-specific reduction in the 1-4 years group ranged from 0.8 to 4.9 in the concurrent studies and 0.6 to [illegible] in the before/after studies. The combined pooled estimate of ALRI-specific mortality difference was 1.1 (95% CI 0.3-1.8). The statistical tests for homogeneity (Cochran's Q and Breslow-Day) for intervention effect indicated lack of homogeneity across the studies both for total and ALRI-specific mortality.

The total and ALRI-specific mortality in under five years old children is presented in figure 3a and 3b. These data need to be interpreted with caution given the differences in the impact between infants and 1-4 years. The combined pooled rate difference in total mortality (/1000 child years) was 7.9 (95%CI 6.3-9.4), while for the ALRI-specific mortality it was 3.6 (95% CI 2.0-5.2). This would result in an estimated reduction in cumulative under five mortality of [illegible]9.5/1000 births and of ALRI mortality of 18/1000.

The impact on infant and 1-4 mortality can also be used to estimate the cumulative reduction in the mortality in the first five years of life. The mortality reduction in the infants must be added to the reduction in each of the next four years of life. Using the overall pooled estimate of mortality reduction, the cumulative reduction would be 36 deaths/1000 births. Using the lower confidence limits, we could with 95% confidence say that this estimate of mortality reduction would be at the least 27 deaths/1000 births. The pooled odds ratio estimates are consistent with a reduction of 35% in total mortality in 1-4 years old children and a 25% reduction in the overall under five mortality. The ALRI-specific mortality reduction in the 1-4 years and under five age groups was 53% and 35% respectively.

There was no consistent association of the methodological score with the risk difference. The summary estimates of the risk difference comparing the overall mortality and the ALRI-specific mortality are presented in figure 4. For infants, the gap between the total mortality and ALRI-specific mortality impact was less in the concurrent than in the before/after study design. In 1-4 year olds, the difference between total and ALRI mortality rate reductions is small.

Difference in total and ALRI-specific mortality impact by co-intervention

In order to evaluate if the difference in the total mortality and ALRI-specific mortality was related to the other interventions provided in some of these trials, we evaluated the rate differences by the co-intervention scores. There did not seem to be any consistent trend. The impact in each trial both on the additive scale (risk difference) and multiplicative scale (odds ratio) with 95% confidence interval of both by study design and co-intervention score is provided in Table 4.

Intervention effect related to baseline IMR

The intervention effect on total infant mortality and ALRI-specific infant mortality, both as rate difference and percent rate reduction related to the baseline infant mortality in these studies is presented in figure 5a and 5b. The rate difference in both total and ALRI-specific infant mortality increases with increasing IMR. The gap between the actual rate difference in total mortality and ALRI mortality also increases with increasing infant mortality. Percent reduction in infant mortality levels off after an IMR of 100; there are not enough data to comment about trends below 100, as studies in lower infant mortality areas have not been published. The percentage reduction in total mortality is less than the ALRI-specific mortality and the gap appears to be the same regardless of the baseline infant mortality.

Intervention effect by duration of intervention

Comparison of the intervention effect on infant mortality and ALRI-specific infant mortality by year of intervention in the three studies that had two years of intervention is presented in figure 6a and 6b. The effect upon total mortality was higher in the second year in all three studies. In these studies, a summary estimate of the infant mortality rate difference (deaths/1000 births) for the first year was 9.3 (95% CI 0.3 - 18.2), while for the second year it was 19.9 (95% CI 11.5-28.4). The effect on ALRI-specific infant mortality was also consistently higher in the second year than in the first. The summary estimate of the ALRI-specific infant mortality for the first year was 9.9 (95% CI -5.4-25.3) and for the second year was 19.9 (95% CI 2.4-37.3).

Other studies:

Data from the three studies not included in the analysis were also reviewed to evaluate a possible bias in the effect on impact assessed in this meta-analysis. Two of the three studies report an impact on mortality and the third showed a trend which did not reach significance.

The study by Pandey et al in Jumla, Nepal (13) has reported a 28% reduction in the risk of death in under five year old children by third year of intervention. They evaluated impact in terms of relative risk for mortality; the overall relative risk for all mortality in children under five years was 0.72 (95% CI 0.63-0.82), for infants 0-6 days was 0.8 (95% CI 0.59-1.10), for infants 7 days to 5 months old was 0.74 (95% CI 0.58-0.94) and for 6-11 months old infants was 0.36 (95% CI 0.24-0.55), while the relative risk for 1-4 years children was 0.89 (95% CI 0.73-1.09). The under five pneumonia-related relative risk of death was presented as 0.7 (95% CI 0.5-0.97). The relative risks for infant mortality or ALRI-specific infant mortality were not presented, nor could they be computed from the data presented. Relative risk for overall under five years mortality was 0.87 (95% CI 0.73-1.03) and 0.76 (95% CI 0.66-0.87) for first and second years respectively. The pneumonia-specific relative risk of death was 0.88 (95% CI 0.59-1.08) and 0.80 (95% CI 0.59-1.08) for first and second year of intervention respectively. The infant mortality in the area was 189/1000 live births and the 1-4 mortality was 52/1000

child years.

The study by Roesin et al in Kediri, Indonesia (18) in the last report of data available upto June, 1989 reported a ALRI mortality reduction in under 5 (deaths/1000 child years) from 11.92 (86-87) to 4.27 (88-89) ($p<0.001$), and a reduction of total mortality from 43.1 (86-87) to 25.8 (88-89) ($p<0.001$). The report does not provide data for infants separately.

For the study by Lucero et al at Bohol, The Philippines, only preliminary data are available (19). At the time of the WHO meeting, in April 1988, the study did not report a significant impact of the intervention, which was a limited one consisting of training the health staff without community illness surveillance or education. The data presented in the report of this meeting do not allow computation of rates of mortality and hence the magnitude of effect can not be assessed (14).

DISCUSSION

Magnitude of the impact on mortality

The results of this analysis suggest that ARI case management strategy has a significant impact on infant mortality. In meta-analysis of the selected 6 trials, the summary estimate of the magnitude of this impact was 15.9 deaths / 1000 live births, which is consistent with a 20% reduction in infant mortality in these studies. The magnitude of impact in terms of rate difference on mortality in 1-4 year old children, though seemingly small in absolute terms, is no less important for two reasons. First, the overall mortality in this age group is low and second, the rate difference applies to each of four years of life. The summary impact of 5.1 deaths /1000 child years in 1-4 year old children is consistent with a 35% reduction in the total 1-4 mortality. Impact on under five mortality estimated by the meta-analysis as 25% is consistent with the 28% reduction reported in the Jumla study (13), which was not included in this meta-analysis.

It is not possible to totally isolate the impact of the pneumonia case management intervention in this analysis because the earlier studies included immunization as a part of ARI intervention and some studies also included other health inputs. However, the consistency of findings in the studies in Bangladesh (12) before/after component, India (11), Nepal (13) and Pakistan (7) where case management and related education was the only health intervention, favors the interpretation that the case management was responsible for a substantial part of the observed impact.

To determine the policy implications, this demonstrated impact of the ARI case management intervention needs to be compared to the expected impact of other direct child survival interventions, e.g oral rehydration therapy programs or expanded immunization programs. The limited evidence for impact of oral rehydration therapy programs is suggestive of a 1-8% reduction in infant mortality and 4-14% reduction in mortality among 1-4 years old children (31,32), although greater reductions have been

reported for Egypt (33,34). The impact of an oral rehydration therapy program may vary depending on the proportion of deaths in a given setting that are associated with acute dehydrating diarrhea, which may be averted by ORT, rather than as invasive or persistent diarrhea that require other interventions. We could not find any valid data on estimates of mortality reduction from DPT vaccination; however, the impact of measles immunization on childhood mortality has been demonstrated in several countries (35-39). In the best documented studies of impact (Matlab, Bangladesh), a reduction of 22% in deaths among children under five years old has been reported (39). It is evident from these comparisons that pneumonia case management should rank high on the list of child survival interventions because of its high impact on mortality.

The consistent findings in these studies that the total mortality was reduced, and that the absolute reduction in total mortality was larger than the reduction in ALRI-specific mortality, is suggestive that with ALRI-case management, "replacement mortality" does not seem to be taking place. In addition to the direct effect on mortality, an effect on other causes of mortality by interrupting the ARI-malnutrition cycle has been hypothesized (13). There are no data available to document this effect and it is also difficult from the results of these trails to separate the possible indirect effects of treatment from the effects due to health education or other aspects of the health intervention.

Factors determining the size of effect

The magnitude of the effect expected from the case management intervention would seem to be dependant upon the importance of ALRI as a cause of death in the respective settings. There are few data provided in these trial reports regarding the ALRI mortality in the settings where the trials have been undertaken. Using the control group ALRI-specific mortality as an indicator, it seems the ALRI-specific mortality increases with increasing IMR. The absolute impact on ALRI mortality increases with increasing IMR, but the percent reduction in ALRI-specific mortality levels off at about 50 percent. This could imply that only a certain proportion of deaths due to ALRI would respond to the case management strategy, possibly due to the proportion of pneumonia cases caused by *H.influenzae* and *S.pneumoniae* or to bacterial resistance to the antibiotics used in the trials. However, this incomplete effect may be a function of the quality of intervention; more effective community education and access to appropriate diagnosis and antibiotic therapy may actually increase the proportional impact. The results of the Jumla study where the degree of self-referral and promptness of care-seeking was improved with the period of intervention, as was the mortality impact, would support this hypothesis. It is evident that a higher IMR would imply a more deprived population in terms of access to health care and less well developed capabilities in the family for recognition of illness and care seeking. This setting may require more intensive education and a longer period of intervention for improvement in utilization of health services early in the course of serious ALRI. It is of interest that all three studies that provided relevant data showed greater effects on both ALRI and total mortality in the second year of intervention, suggesting that the mortality impact of a more mature ARI program could be greater than that estimated in this meta-analysis using predominantly results on the first year.

There is very little description in the studies of the intensity and quality of the intervention itself. Although active case finding every two weeks does have the advantage of identifying at least a minimum number of cases, many children with severe pneumonia die within days and would be missed. Furthermore even fortnightly household visiting is too expensive and logistically impractical for a program to implement. The effect on the magnitude of impact of not including active surveillance cannot be inferred with certainty from the available data. However, the results of the study from India (11) and possibly findings of the Jumla study (13) suggest that self referral through education is a feasible approach and may ultimately be found to have a higher impact on mortality due to reduction in lagtime before treatment.

The setting of the studies differed widely in terms of the malnutrition, female literacy and other socio-economic indicators. Insufficient data are available in the trial reports for these indicators, but if we consider IMR to be a surrogate for these variables, it is evident that the absolute impact increases with the increase in the IMR, and that the percent reduction of IMR does not change much across the settings with increasing IMR. This suggests that the results of these studies may be generalized to other settings with high childhood mortality. We could not in this analysis determine the impact in low mortality settings, but one may speculate that the impact could be less due to changes in the patterns of illness accompanying the epidemiological transition. The present evidence for impact of the pneumonia case-management suggests intervention should only be applied to places with IMR of 90 and above.

Potential limitations of this study

In the interpretation of the results of the present review some of the limitations that could have affected our results need to be considered.

The results of a meta-analysis are affected by the quality of the studies that are included. The intervention studies did have important methodological lacunae which potentially could have affected the results. We did however rank the studies according to the methodological quality and this did not seem to be related to the magnitude of the impact. Further, the consistency of the direction of impact in these studies favors validity of the results. The ascertainment of cause of death by verbal autopsy, used by all studies, is a method of limited accuracy, but it needs to considered that other than bias on part of the investigator to not assign deaths to ALRI in the intervention area, all other errors of verbal autopsy including increased maternal reporting with increasing eduction, should actually bias the results toward the null. Hence the estimates should be conservative if anything.

In the initial study designs childhood immunizations were considered part of the ARI intervention which seems logical in the program context, but this has made it difficult to ascertain the effect of the pneumonia case management strategy by itself. Some of the studies had other health interventions as well. The ideal design would be to add case management to an existing primary health care program or to an EPI program and evaluate the impact. The before/after comparison of the Bangladesh study in that

sense provides a good measure of impact (12). The consistency of findings in this study and also the observation that co-intervention scores were not related to the impact or the difference between ALRI-specific and total mortality suggests that although a potential limitation co-intervention does not seem to have significantly affected the results of these studies.

We have based our analysis on published information which has two potential limitations. First is the possibility of a publication bias, which we tried to evaluate by examining the results of unpublished studies. The similarity of results for overall under five mortality impact in Jumla (13) and our analysis, and a similar direction of effect in the Kediri study (18), are suggestive that this limitation may not have affected the results in any significant way. Second we were limited to the information provided in the papers which may have affected our interpretation of the results.

With the differences in the settings and nature of the interventions, one may expect some variation in the magnitude of the impact, so the pooled estimate resulting from meta-analysis needs to be interpreted with caution. We did use conservative methods both for rate difference and odds ratio estimation which do not require the assumptions of homogeneity. Consequently, the pooled estimates of this analysis should be conservative. Yet it may be more appropriate to take the variations in the setting into account. If the relationships of the magnitude of impact to population characteristics like baseline IMR or ALRI-specific mortality, are confirmed in subsequent analyses, it may be more appropriate to use impact estimates applicable for a specific setting rather than an overall pooled estimate to predict the expected impact in another similar setting.

The selection of study populations and settings may have implications for the external validity of these results; however the consistency of the results in the varied settings and populations of these studies in fact favors the external validity of the findings. The intensity of the intervention and active case finding approach used are impractical in an actual program, but there is suggestion from these studies that community education and self referral could be at least as effective. Additional evaluation of the effectiveness of actual ARI control programs are needed.

CONCLUSION

The strength and consistency of findings across studies with varying methodological and co-intervention characteristics suggests that pneumonia case management is an effective intervention for reduction of childhood mortality. In terms of magnitude it may have more impact than an oral rehydration therapy program, and would have at least as much impact as expected from measles vaccination.

The implication of these findings is that countries with high childhood mortality should develop ARI control programs with emphasis on improvement in case management and education to recognize and seek treatment for pneumonia. Further studies should now focus on evaluation of the most efficient ways to implement the case-

management approach and to integrate it with other interventions for control of childhood mortality and for ALRI prevention.

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ANNEXURE 1

Methodological evaluation of the published research on ARI intervention studies : empiric framework for scoring.

A. Population description [3]

- Adequate population description was provided [3]
- Some population description was provided [1]
- No population description [0]

B. Project design [10]

- Randomized controlled trial [10]
- Concurrent controlled trial, the selection into intervention and control groups, based on non-random but matched allocation [7]
- Concurrent controlled trial, allocation to intervention and control groups not randomized or matched [3]
- Before and after design [1]

C. Data collection [24]

C.1. Blinding [5]

- Mortality data collection workers blinded to the group allocation [5]
- Mortality data collected by separate team without blinding [3]
- Mortality data collected by health care team without blinding [0]

C.2. Mortality data collection method [5]

- Mortality data collection planned, data collected prospectively with active surveillance[5]
- Mortality data computed from records [2]

C.3. Morbidity data collection method [5]

- Morbidity data collection planned, collected prospectively on sample with active surveillance; sample representative and selected randomly [5]
- Morbidity data collection planned, collected prospectively on sample with active surveillance; sample not selected randomly, representativeness questionable [4]
- Morbidity data collected retrospectively on a representative sample of population [3]
- Morbidity data collected retrospectively on a subset of population, representativeness uncertain [1]
- Morbidity data not collected [0]

C.4. Mortality cause assessment [5]

- Determined by independent investigator [5]
- Determined by a team including principal investigator [2]
- Determination not explained [1]
- Cause not determined [0]

C.5. Cause verification [4]
- Verified by autopsy in a subset [4]
- Verified with records in a subset [2]
- No verification [0]

D. Training and supervision of field workers [10]

D.1 Training [5]
- Data collectors trained adequately, training explained, and adequacy of training documented [5]
- Data collector training seems adequate, training explained but adequacy not documented [4]
- Data collector training adequacy unknown, but no apparent bias [3]
- No description of training given [0]

D.2. Supervision [5]
- Data collectors' supervision adequate, explained and adequacy evaluated [5]
- Data collectors supervision seems adequate, explained, but adequacy not evaluated [4]
- Data collector supervision adequacy unknown, but no apparent bias [3]
- No description of supervision given [0]

E. Selection of the subjects [8]
- Selection of the sample explained ; yes [2] no [0].
- Details of clustering by group and family described; yes [2] no [0].
- Data for shift, addition, exclusion in study population explained; yes [2] no [0].
- Mechanism of enrollment described; yes [2] no [0]

F. Baseline group differences [30]

F.a. For the concurrent studies or phases of study.

Fa.1. For mortality; prospective collection [5], retrospective data [3], nil [0].

Fa.2. For morbidity prevalence; prospective collection [5], retrospective data [3], nil [0].

Fa.3. For SES; yes [5], some [3], given not comparable [1], nil [0].

Fa.4. For health service access; yes [5], some [3], given not comparable [1], nil [0].

Fa.5. For Immunization coverage; yes [5], some [3], given not comparable [1], nil [0].

Fa.6. Group differences limit the interpretability of the study; no [5], may be [3], yes [0].

F.b. For the before and after design, both for mortality and morbidity, the data collection in the pre-group was:
- For at least 1 year [5],
- Greater than 6 and less than 12 months [3],
- Less than 6 months [0].

G. Sample size determination [4]

G.1. Magnitude of worthwhile difference specified prior to the study and pre-trial sample size determined; yes [2] no [0]

G.2. Issues of clustering effect taken into consideration in sample size; yes [2], no [0].

H. Suitability and similarity of study subjects [20]

H.1. Referral pattern in both intervention and control area
- Yes, was similar [5]
- Yes, was dissimilar [1]
- Not given [0]

H.2. Mechanism of enrolment
- Given, was unbiased [5]
- Given, was biased [1]
- Not given [0]

H.3. Antibiotic availability or its surrogates
- Antibiotic was not made availability or provided for other diseases than respiratory disease (directly or indirectly by the study) [5]
- Antibiotic was made availability or provided for other diseases than respiratory disease (directly or indirectly by the study), but distribution mechanisms suggest it was unbiased [3]
- Antibiotic for conditions other than respiratory disease given, and distribution seems to have been biased [1]
- Description regarding antibiotic usage or distribution was not provided [0]

I. Co-intervention (differential application in intervention group) [35]

I.1. Diarrhea management education was imparted [5]
- No [5]
- Yes, some co-intervention [3]
- Yes, strong co-intervention [1]
- Not described [0]

I.2. ORS and/or drugs were provided for the diarrheal management [5]
- No [5]
- Yes, some co-intervention [3]
- Yes, strong co-intervention [1]
- Not described [0]

I.3. Differential measles vaccination was provided between intervention and control groups [10]
- No [10]
- Yes, some co-intervention [5]
- Yes, extensive co-intervention [1]
- Not described [0]

I.4. Other EPI vaccinations were provided differently in the intervention and control group [8]
- No [8]
- Yes, some co-intervention [5]
- Yes, extensive co-intervention [1]
- Not described [0]

I.5. The antenatal and birth care practices were explained [4]
- Yes, no co-intervention [4]
- Yes, some co-intervention [2]
- Yes, extensive co-intervention [1]
- Not described [0]

I.6. Other health education given was explained [3]
- Yes, no co-intervention [3]
- Yes, some co-intervention [2]
- Yes, extensive co-intervention [1]
- Not described [0]

J. Evaluation and presentation of outcome measures [27]

J.1. Total mortality; yes [5] no [0]
J.2. Infant mortality; [5], no [0]
J.3. 0-4 or 1-4 mortality; yes [5], no [0]
J.4. Disease-specific mortality; yes [5] no [0]
J.5. Respiratory disease deaths separated from deaths with diarrhea as a cause as well; yes [2] no [0]
J.9. Measles-related mortality considered; yes [5], no [0]

K. Treatment compliance [5]
- Assessed and good [5]
- Assessed and not good [3]
- Not assessed [0]

L. Analysis of data, statistical and clinical significance [20]

L.1. All comparisons involve same number of subjects [5]
- Same numbers [5]
- Discrepancy is explained and unbiased [4]
- Discrepancy is explained and biased [1]
- Not explained [0]

L.2. Confidence limits given, yes [2] no [0]

L.3. Statistical tests used to test differences [5]
- Yes, appropriate [5],
- Inappropriate [2],
- Not used [0]

L.4. Power in case of negative results given; yes [5], no [0]

L.5. Clustering effect was taken into account; yes [3], no [0]

ANNEXURE 2 : Table for scoring of the studies (for description refer to the details).

Description of the feature	(max points)	Study 1 Bangladesh Bef/aft	Concu	Study 2 India (B)	Study 3 India (K)	Study 4 Pakistan Bef/aft	Concu	Study 5 Nepal	Study 6 Tanzania Bef/aft	Concu
A. Population description	[3]	1	1	3	1	1	1	1	1	1
A. Population Description	*(3)*	1.00	1.00	3.00	1.00	1.00	1.00	1.00	1.00	1.00
B. Project design	[10]	1	2	2	2	1	7	1	1	10
B. Project Design	*(10)*	1.00	2.00	2.00	2.00	1.00	7.00	1.00	1.00	10.00
C.1. Blinding	[5]	0	0	0	0	0	0	0	0	0
C.2. Mortality Data collection method	[5]	5	5	5	5	5	5	5	5	5
C.3. Morbidity Data collection method	[5]	0	0	4	5	0	0	0	0	0
C.4. Mortality cause assessment	[5]	5	5	2	1	5	5	5	1	1
C.5. Cause verification	[4]	0	0	0	0	0	0	0	0	0
C. Data collection	*(24)*	10.00	10.00	11.00	11.00	10.00	10.00	10.00	6.00	6.00
D.1. Training	[5]	4	4	3	3	0	0	3	3	3
D.2. Supervision	[5]	4	4	4	3	3	3	3	3	3
D. Training and supervision of Field staff	*(10)*	8.00	8.00	7.00	6.00	3.00	3.00	6.00	6.00	6.00
E.1. Selection of sample	[2]	2	2	2	2	2	2	2	2	2
E.2. Details of clustering by group and family	[2]	0	0	0	0	0	0	0	0	0
E.3. Bookkeeping Data for Population	[2]	0	0	0	0	0	0	0	0	0
E.4. Mechanism of enrollment	[2]	2	2	2	2	2	2	2	2	2
E. Selection of Subjects	*(8)*	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
F.1. For mortality assessment	[5]	5	5	0	0	5	0	0	5	0
F.2. For morbidity prevalence	[5]	0	0	0	0	0	0	0	0	0
F.3. For SES comparison	[5]	0	0	3	5	0	0	0	0	0
F.4. For health service access comparison	[5]	5	1	0	3	0	0	1	0	5
F.5. For Immunization coverage	[5]	5	1	0	0	3	3	0	0	0
F.6. Group differences and study interpretability	[5]	5	3	5	5	5	5	3	5	5
F. Baseline Group Differences	*(30)*	20.00	10.00	8.00	13.00	13.00	8.00	4.00	10.00	10.00
G.1. Magnitude of worthwhile diff specified	[2]	0	0	2	0	0	0	2	0	0
G.2.Clustering effect taken into consideration	[2]	0	0	0	0	0	0	0	0	0
G. Sample size determinations	*(4)*	0.00	0.00	2.00	0.00	0.00	0.00	2.00	0.00	0.00
H.1. Referral pattern comparison	[5]	1	5	0	5	0	0	0	0	0
H.2. Mechanism of enrolment	[5]	5	5	5	5	5	5	5	5	5
H.3. Antibiotic availability or its surrogates	[5]	5	5	5	5	5	5	5	5	5
H. Suitability and similarity of subjects	*(20)*	11.00	15.00	10.00	15.00	10.00	10.00	10.00	10.00	10.00
I.1. Diarrhea management education imparted	[5]	5	0	5	1	3	3	0	1	1
I.2. ORS, drugs for diarrhea magement	[10]	5	1	5	3	1	1	1	3	3
I.3. Differential measles vaccination	[10]	10	1	10	10	10	10	1	5	5
I.4. Other EPI vaccinations provided differently	[8]	8	0	8	5	8	8	0	1	1
I.5. The antinatal birthcare practices explained	[4]	2	1	1	4	4	4	4	4	4
I.6. Other health education given was explained	[3]	3	2	1	3	3	3	1	1	1
I. Co-intervention (differential intervention)	*(35)*	33.00	5.00	30.00	26.00	29.00	29.00	7.00	15.00	15.00
J 1. Total mortality yes	[5]	5	5	5	0	5	5	5	5	5
J.2. Infant mortality	[5]	5	5	5	5	5	5	5	0	0
J.3. 0-4 or 1-4 mortality yes	[5]	5	5	5	0	5	5	5	0	0
J.4. Disease specific mortality yes	[5]	5	5	5	5	5	5	5	5	5
J.5. Resp deaths separated from diarr deaths	[2]	0	0	5	0	5	5	5	5	5
J.6. Measles mortality considered/accounted	[5]	5	5	5	0	5	5	0	0	0
J. Evaluation and presentation of outcome measures	*(27)*	25.00	25.00	30.00	10.00	30.00	30.00	25.00	15.00	15.00
K. Treatment compliance	*(5)*	0	0	0	0	0	0	0	0	0
K. Treatment compliance	(5)	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
L.1. All comparisons, same number of subjects	[5]	5	5	5	5	5	5	5	5	5
L.2. 95% CI and clinical significance given	[2]	0	0	0	0	0	0	0	0	0
L.3. Statistical tests used to test differences	[5]	5	5	5	0	5	5	5	5	5
L.4. Power in case of negative results given yes	[5]	0	0	0	0	0	0	0	0	0
L.5. Clustering effect was taken into account	[3]	0	0	0	0	0	0	0	0	3
L.Analysis of data, statistical and clinical significance	*(20)*	10.00	10.00	10.00	5.00	10.00	10.00	10.00	10.00	13.00
TOTAL POINTS		123.00	90.00	117.00	93.00	111.00	112.00	80.00	78.00	90.00

Table 1 : Published ARI case management intervention studies : Study designs, case detection and pneumonia management methods.

Location Author Years	Number of child years studied		Study design	Case - detection		Pneumonia treatment		
	Infants Intervention/ control	1-4 years Intervention/ Control		Case - finding	ARI education on need for treatment	Location of primary treatment	Antibiotic used	Referral care
Bangladesh Fauveau et al (1986-89)	Concurrent 13,136/15,592 Before/after 6,700/6,436	Concurrent 45,800/50,650 Before/after 23,300/22,500	Concurrent control group with pre-post within each group	Active monthly	Unknown	CHW 50% other 50 % at subcenter	Inj Penicillin Oral Ampicillin	Good
Pakistan Khan et al (1985-87)	Concurrent 1,977/677 Before/after 400/351	Concurrent 7407/1706 Before/after 823/893	Concurrent control group with phased intervention in control area.	Active Every 10-14 days	Yes	CHW or supervising team (in community) or at clinic	Co-trimoxazole	Poor access to hospital (clinic available)
India Bang et al (1987-89)	Concurrent 1,533/1,059	Concurrent 4812/3042	Concurrent control group	Active only in subset, figures extrapolated	Yes	CHW, TBA	Co-trimoxazole	Unknown
India Datta et al (1982-84)	Concurrent 195/211	Not studied	Concurrent control group	Active every week	No	CHW	Penicillin oral	Unknown
Nepal Pandey et al (1984-87)	Before/after 200/228	Before/after 947/987	Before and after design	Active every 2 weeks	Yes	CHW	Ampicillin	Limited
Tanzania Mtango et al (1983-86)	Only data for 0-4 years	Concurrent 8,028/8,098 Before/after 9,915/8,098	Concurrent control group with intervention in control group	Passive	Yes	Clinic (mainly) some CHW	Co-trimoxazole	Yes

Table 2 : Published ARI case management intervention studies : Co-interventions and study population characteristics.

Location	Methodology score. (Differential co-intervention score)	Interventions in addition to ARI case management			Study population characteristics				
		Immunization	CDD Program	TBA, TT and others	Baseline ALRI mortality infants (0-4yr)	IMR (/1000 live births)	Measles immunization coverage	Literacy	Malnutrition
Bangladesh Fauveau et al (1986-89)	Before/after 123 (33) Concurrent 90 (5)	High coverage in intervention area but no change in study period	No change, CDD implemented in intervention area	No change	20.1 (2.0)	90.6 (85-93)	Intervention area 5,13%; control area 69,89%	NA	NA 74% malnour. in 6-47 mo age group
Pakistan Khan et al (1985-87)	Before/after 111 (29) Concurrent 112 (29)	Increased in both areas	Started in both areas	NA	32.5 (7.4)	93.1 (90-100)	Low (6%)	NA	NA
India Bang et al (1987-89)	Concurrent 117 (30)	Similar in both areas	Similar in both areas	Yes, TBA trained	55.7 (3.3)	121	NA	Female 26%	14-16% 3rd degree
India Datta et al (1982-84)	Concurrent 93 (26)	DPT/ BCG Intervention area higher coverage	Similar	No change	71.1 (--)	106 LBW 210-275	Nil	Male 60%	9-13% (12 mo)
Nepal Pandey et al (1984-87)	Before/after 80 (7)	Immunization introduced in intervention	CDD introduced in intervention	Some change	52.6 (10.5)	162	11% but it increased during study	Female 6%	7% Severe
Tanzania Mtango et al (1983-86)	Before/after 78 (15) Concurrent 90 (15)	Similar in both groups	Similar in both groups	Similar	-- (14.3)	137	53%	Female 67%	7% Severe 35% Mod

Table 3: Scoring and ranking of intervention studies for ARI, evaluating methodological strengths from the reported methods in the published papers.

Description of the methodological feature	[max points]	Study 1 Bangladesh Before/after	Study 1 Bangladesh Concurrent	Study 2 India (B) Concurrent	Study 3 India (K) Concurrent	Study 4 Pakistan Before/after	Study 4 Pakistan Concurrent	Study 5 Nepal Before/after	Study 6 Tanzania Before/after	Study 6 Tanzania Concurrent
A. Population description	[03]	1	1	3	1	1	1	1	1	1
B. Project design	[10]	1	2	2	2	1	7	1	1	10
C. Data collection	[24]	10	10	11	11	10	10	10	6	6
D. Training and supervision of field workers	[10]	8	8	7	6	3	3	6	6	6
E. Selection of subjects	[08]	4	4	4	4	4	4	4	4	4
F. Baseline group differences	[30]	20	10	8	13	13	8	4	10	10
G. Sample size determination	[04]	0	0	2	0	0	0	2	0	0
H. Suitability and similarity of study subjects	[20]	11	15	10	15	10	10	10	10	10
I. Differential co-intervention	[35]	33	5	30	26	29	29	7	15	15
J. Evaluation and presentation of outcome measures	[27]	25	25	30	10	30	30	25	15	15
K. Treatment compliance	[05]	0	0	0	0	0	0	0	0	0
L. Analysis of data, statistical and clinical significance	[20]	10	10	10	5	10	10	10	10	13
TOTAL POINTS	[196]	123.00	90.00	117.00	93.00	111.00	112.00	80.00	78.00	90.00
Ranking among concurrent controlled studies		--	IV	I	III	--	II	--	--	IV
Ranking among the before and after studies		I	--	--	--	II	--	III	IV	--

Table 4: The impact both as odds ratio and risk reduction in relation to the co-intervention scores by study design and age category.

Study	Co-intervention score	Difference in total ALRI specific Mortality	Mortality due to ALRI		Overall mortality	
			OR (95% CI)	Risk Diff (95%CI)	OR (95% CI)	Risk Diff (95%CI)
Infants concurrent studies :						
India (Bang)	30	3.3	2.1 (1.4-3.1)	27.9 (11.5-44.2)	1.4 (1.1-1.9)	31.2 (7.0-55.4)
Pakistan	29	28.0	2.5 (1.4-4.6)	17.0 (2.8-31.1)	1.3 (0.96-1.8)	45.0 (21.2-68.8)
India (Datta)	26	29.5	2.3 (0.9-5.5)	40.3 (-2.0-82.6)	1.5 (0.9-2.3)	69.8 (-13.0-152.5)
Bangladesh	5	13.1	1.4 (1.2-1.7)	5.7 (2.6-8.6)	1.3 (1.1-1.5)	13.6 (7.2-20.0)
Infants before and after studies :						
Bangladesh	33	9.7	1.4 (1.0-1.9)	4.7 (0.6-8.8)	1.2 (1.1-1.4)	14.4 (5.2-23.5)
Pakistan	29	22.8	1.9 (0.7-5.2)	13.5 (-7.6-34.6)	1.7 (1.0-3.0)	36.2 (-1.3-73.7)
Nepal	7	13.1	2.5 (0.9-6.7)	32.6 (-2.2-67.5)	1.5 (0.9-2.7)	52.3 (-12.3-11.7)
Children 1-4 years concurrent studies :						
India (Bang)	30	2.1	1.3 (0.6-3.1)	0.8 (-1.7-3.3)	1.4 (0.9-2.2)	2.9 (-1.7-7.4)
Pakistan	29	-10.0	4.0 (1.7-9.7)	4.9 (0.7-9.1)	0.8 (0.6-1.1)	-5.1 (-12.4-2.1)
Bangladesh	5	4.5	2.1 (1.6-3.0)	1.1 (0.7-1.6)	1.6 (1.4-1.8)	5.6 (4.3-7.0)
Children 1-4 years before after studies :						
Bangladesh	33	3.6	2.0 (1.1-3.6)	0.6 (0.0-1.2)	1.6 (1.3-2.0)	4.2 (2.5-5.9)
Pakistan	29	-2.0	3.1(0.9-10.7)	6.5 (-0.5-13.6)	1.3 (0.6-2.7)	4.5 (-7.7-16.6)
Nepal	7	10.2	1.9 (0.6-6.0)	5.2 (-3.8-14.1)	1.8 (1.0-3.3)	15.5 (-1.1-32.1)

+ The odds ratio and 95% CI is presented as control verses intervention, while the rate difference is presented as control minus intervention.

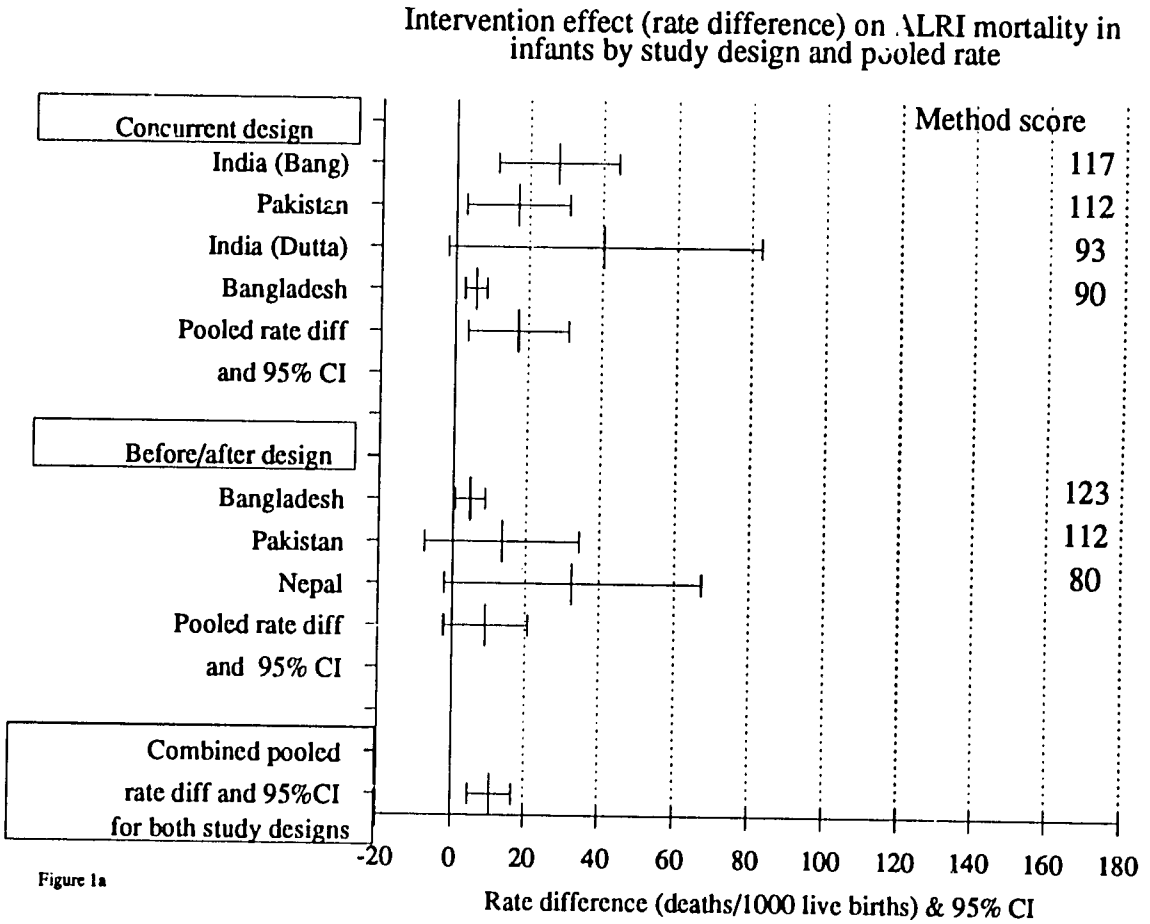

Figure 1a

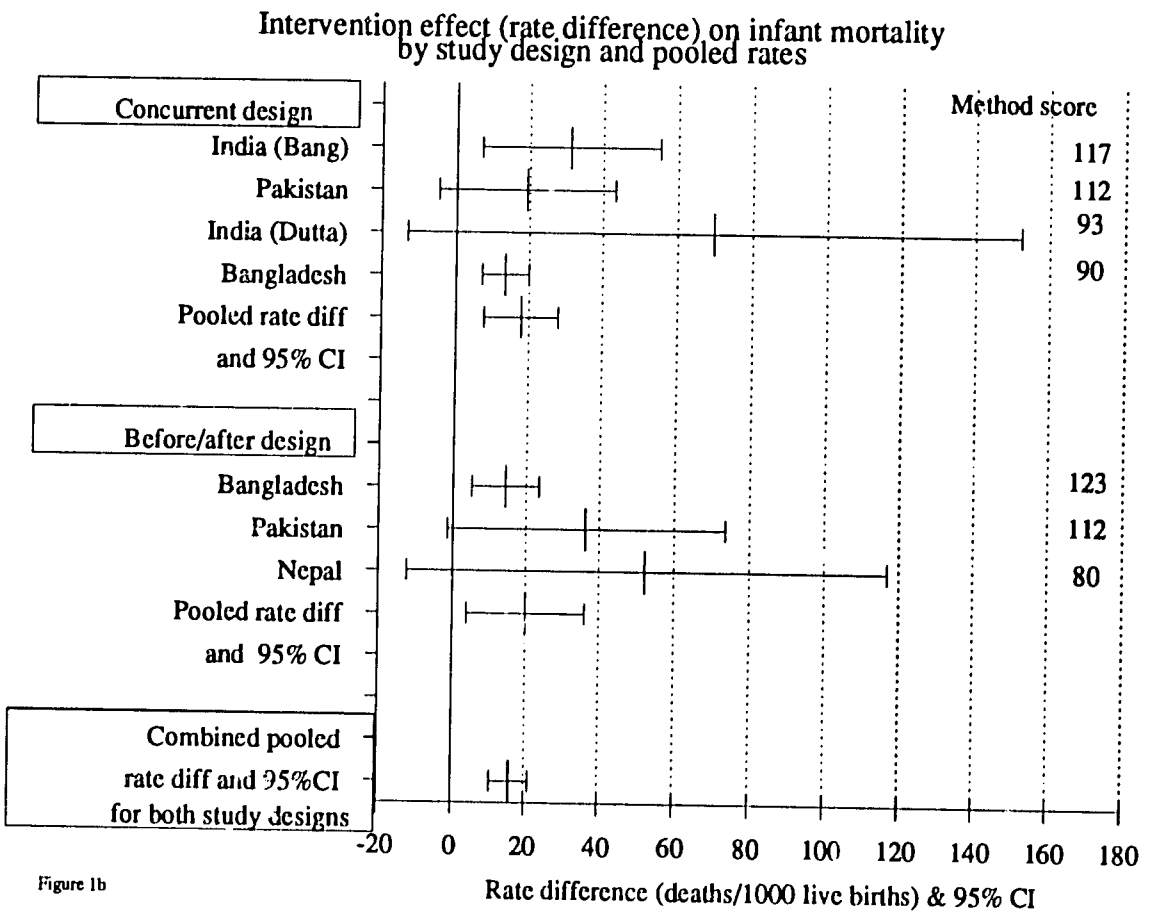

Figure 1b

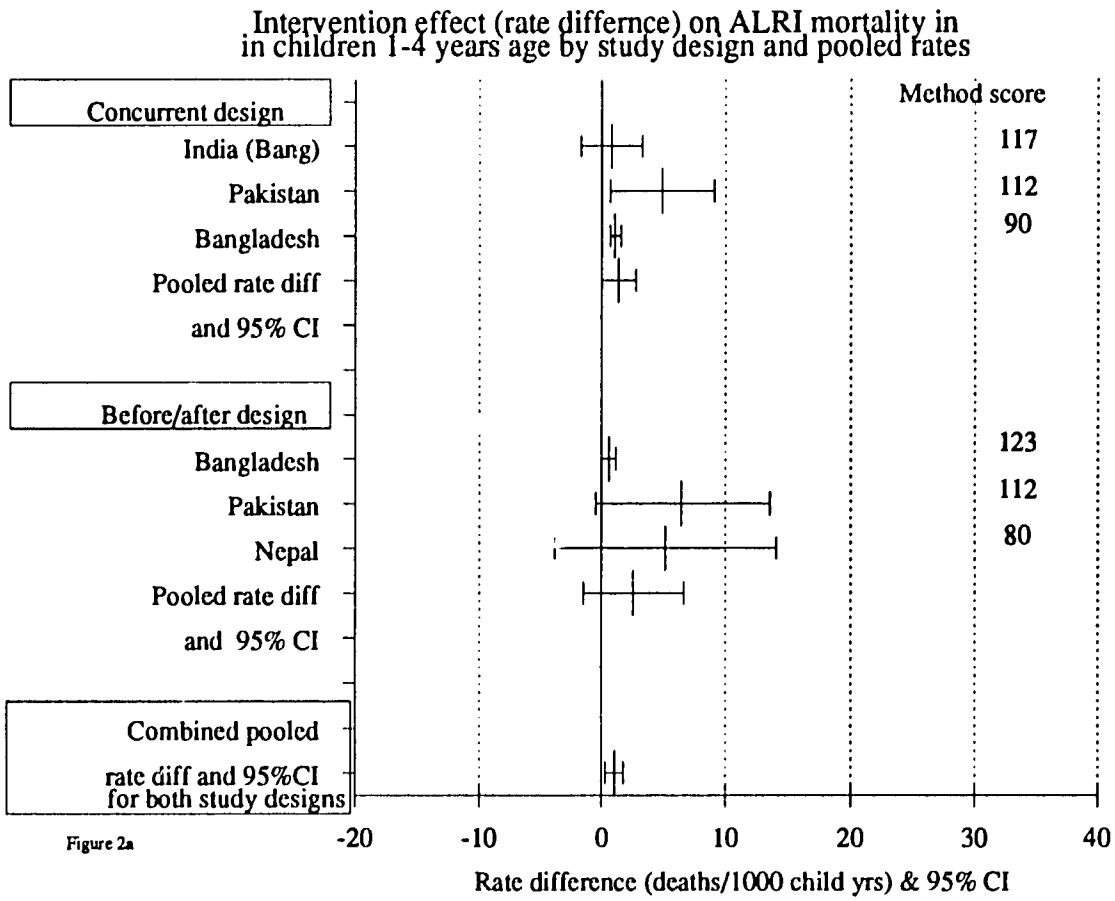

Figure 2a

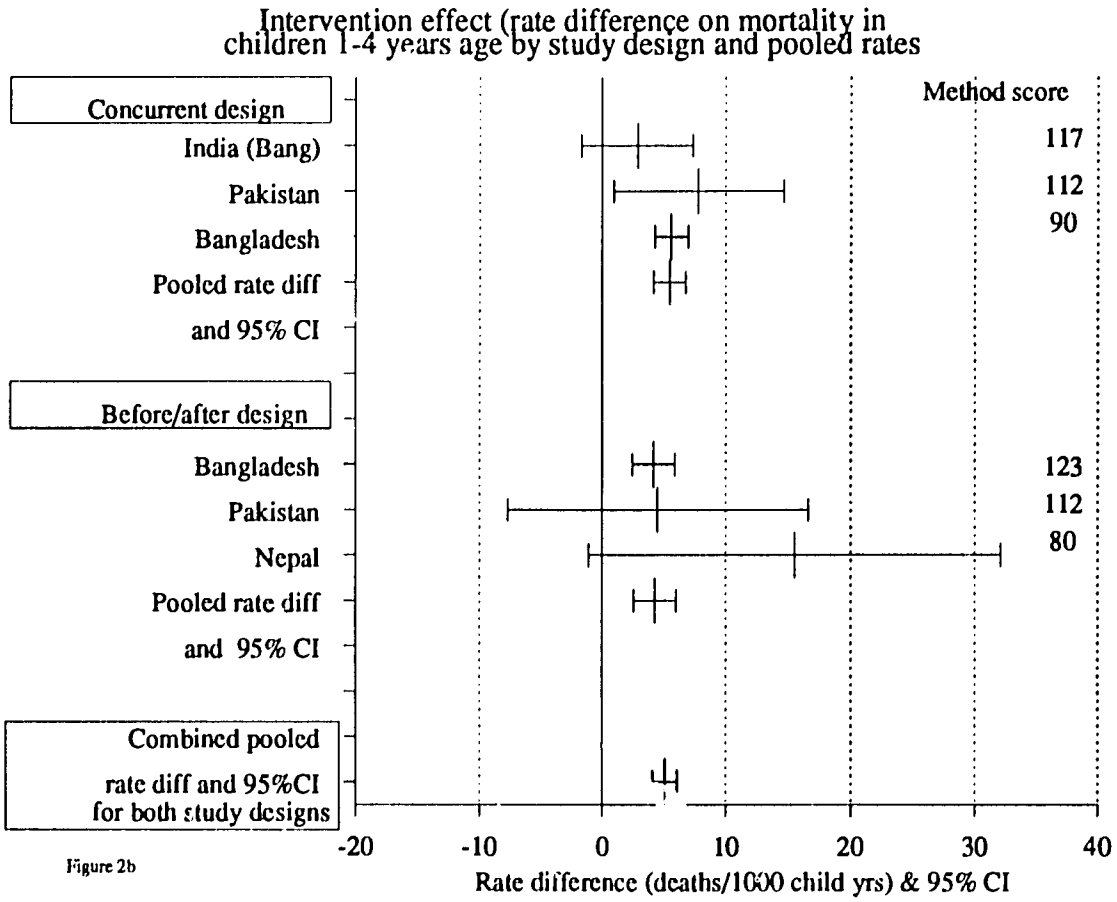

Figure 2b

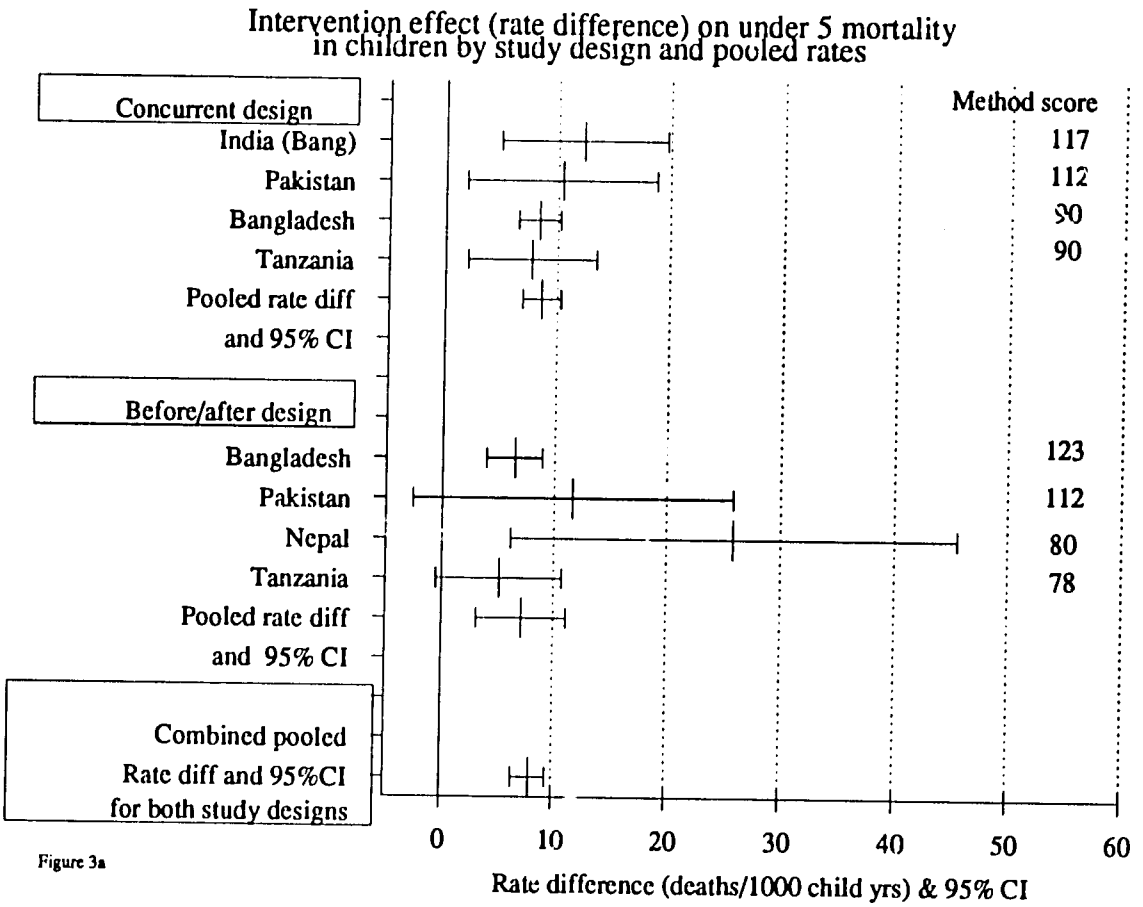

Figure 3a

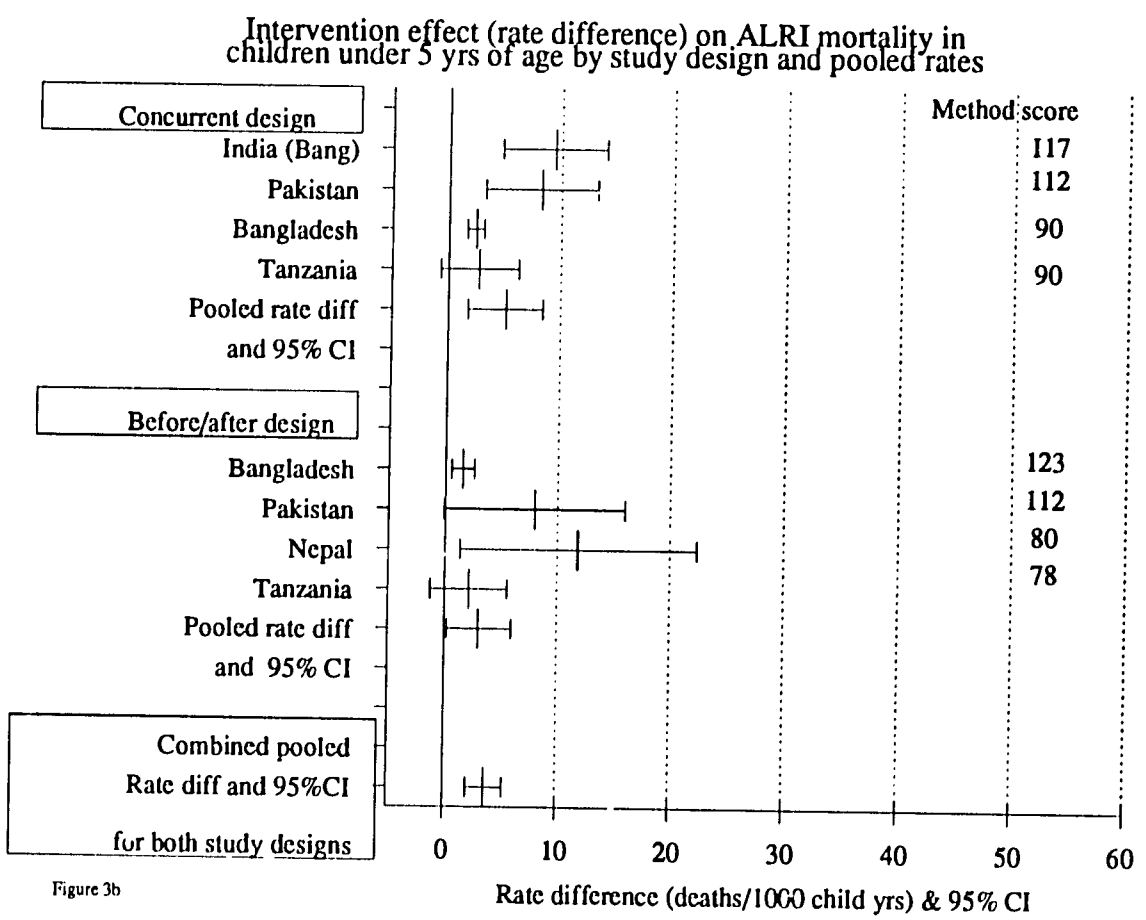

Figure 3b

Comparison of the impact on all deaths and ALRI deaths in infants and children 1-4 years, overall and by study design

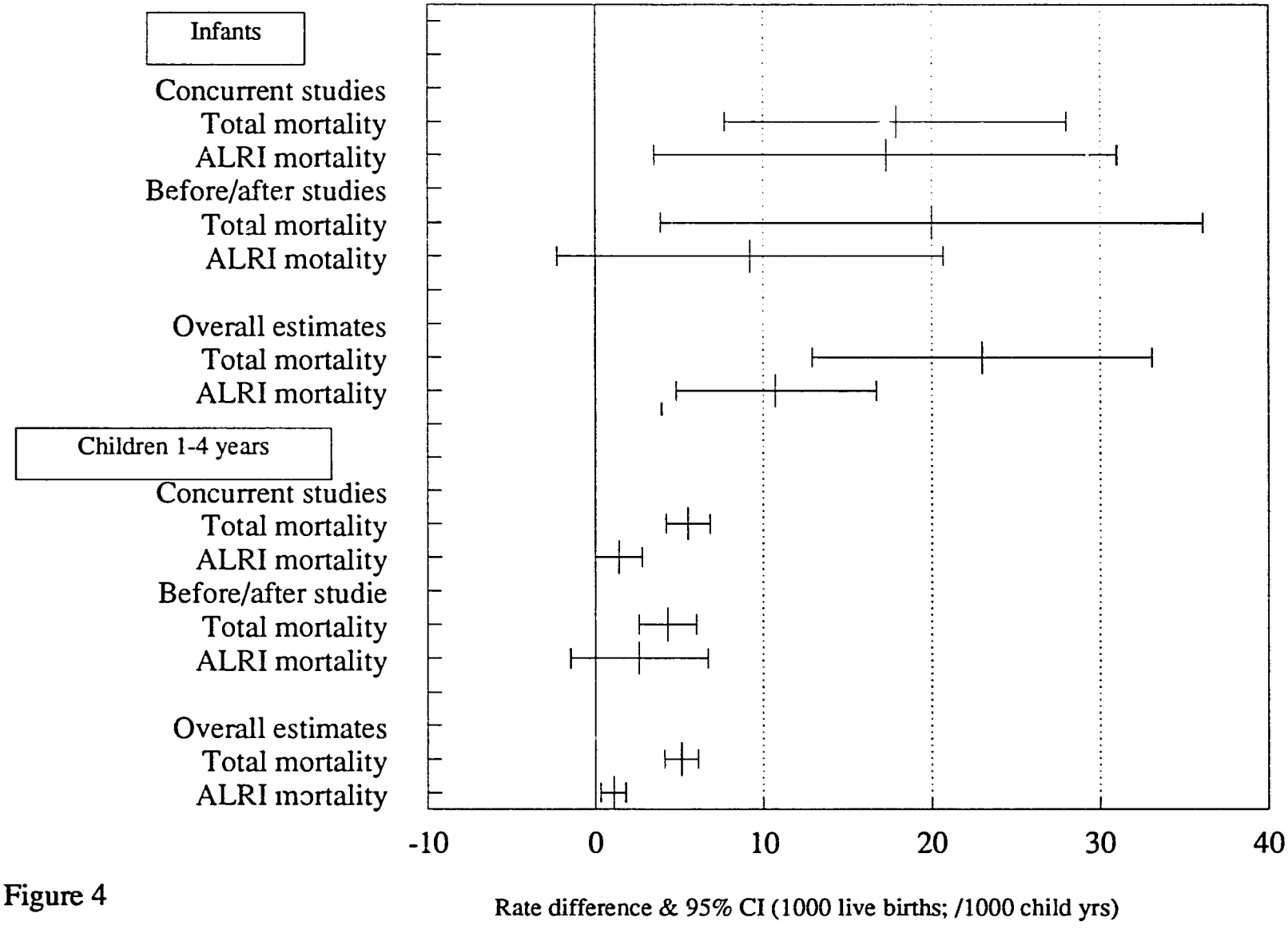

Figure 4

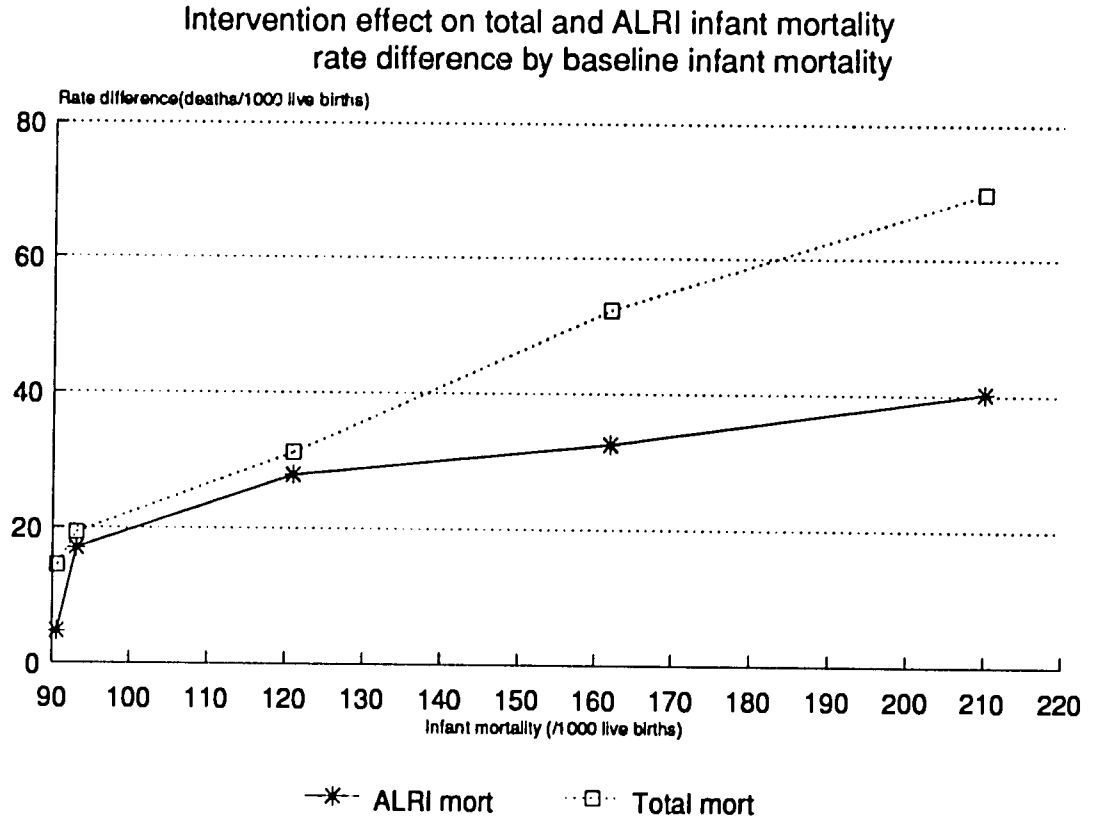

Figure 5a

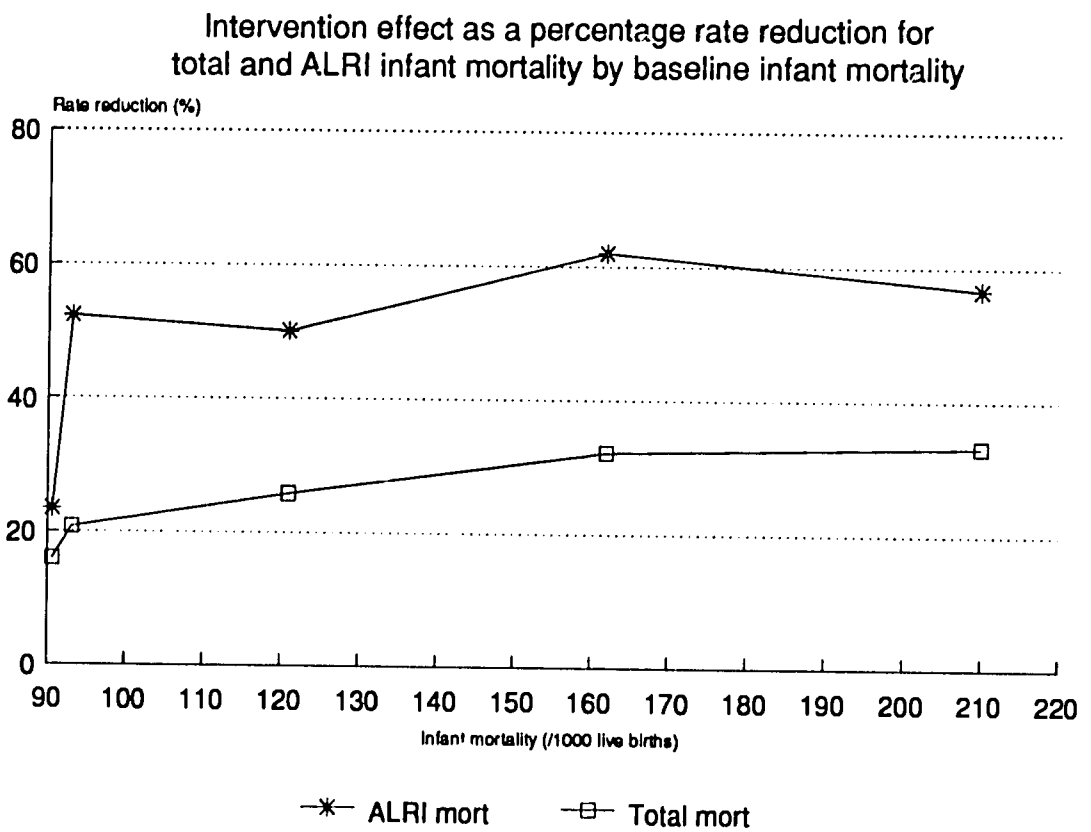

Figure 5b

Intervention effect (rate difference)
on infant mortality by intervention year
in studies with 2 years of intervention.

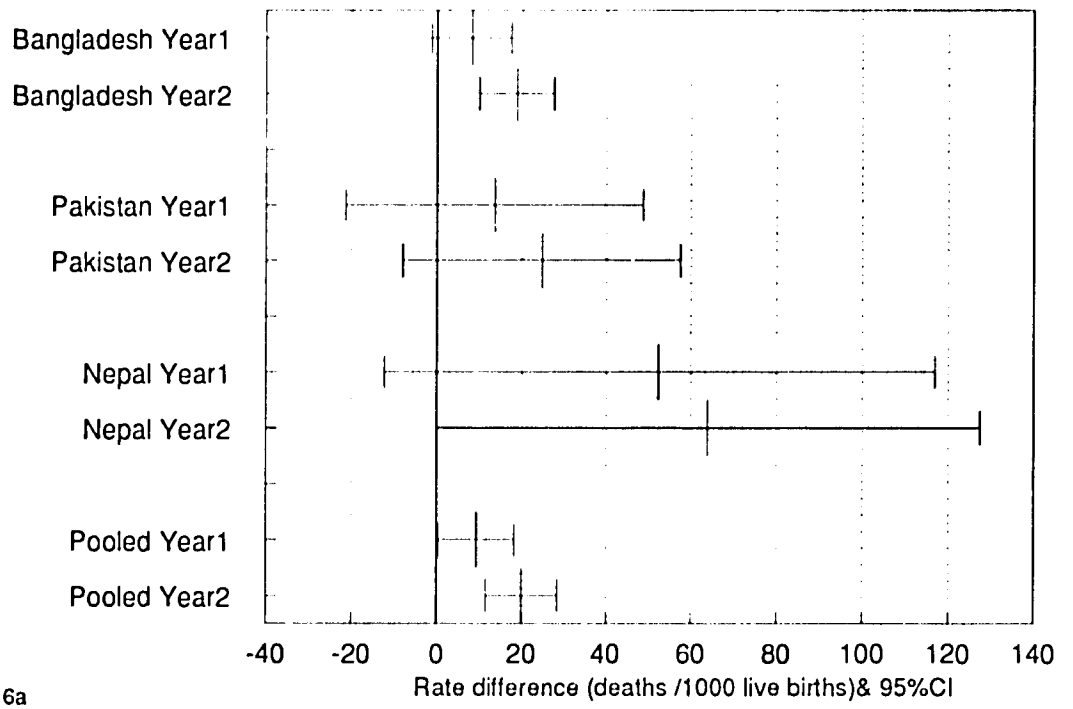

Figure 6a

Intervention effect (rate difference) on
ALRI infant mortality by intervention Yr
in studies with 2 years of intervention

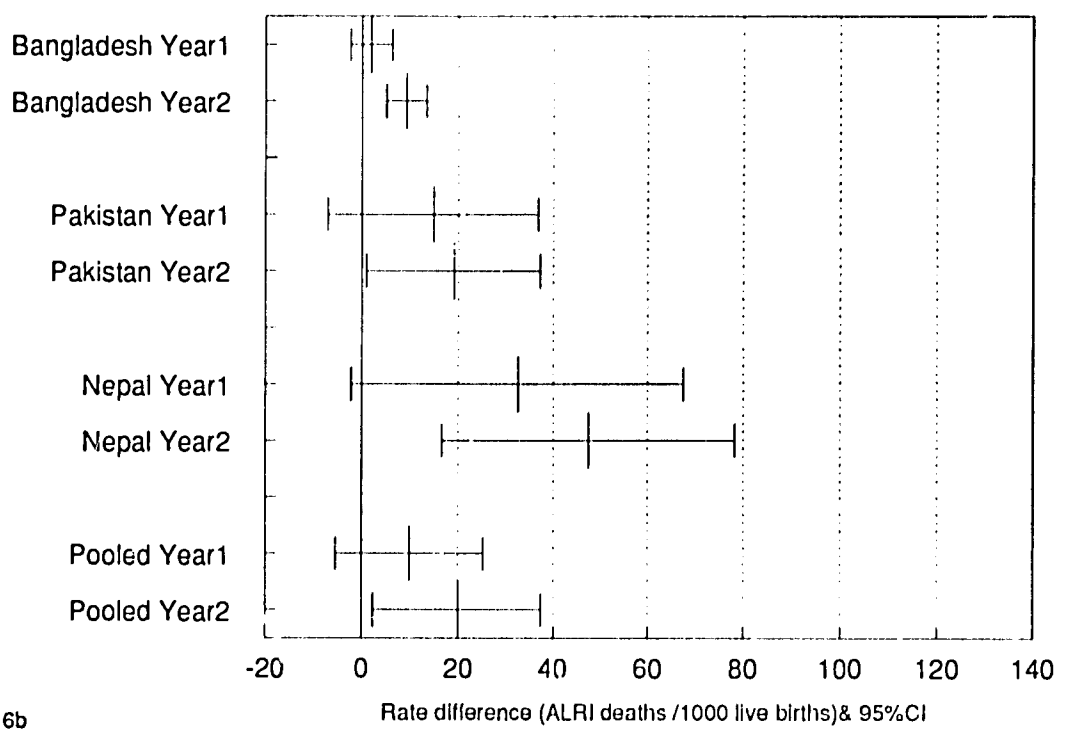

Figure 6b

The Impact of Protein-Energy Supplementation Interventions On Child Morbidity and Mortality[1]

Donald Rose[2] and Reynaldo Martorell[3]

Abstract

The literature on the impact of protein-energy supplementation interventions on child morbidity and mortality is reviewed. Indirect evidence for an effect of nutrition on mortality is available from studies which indicate positive effects of food interventions on physical growth and from investigations which show that better physical growth predicts lower mortality rates. Although improved nutrition does not lower the incidence of infections, it does appear to lower severity. Some study designs permit direct assessment through the impact of isolated food supplementation interventions; results indicate decreases in infant mortality rates (IMR) of 23 to 64% in comparison to controls. Studies of combined nutrition and health care interventions have reported IMR decreases of between 25 to 77% relative to controls. In spite of some weaknesses in individual studies, the overall evidence shows that food supplementation programs can make a significant and positive impact on the reduction of childhood morbidity and mortality. It follows that other types of interventions that are equally effective in improving nutrition in children also would lead to similar benefits.

Introduction

What is the impact of protein-energy supplementation interventions on child morbidity and mortality? Some aspects of this question have been considered by nutritionists, physicians, economists, and psychologists, as well as by planners and policy-makers from national and international agencies (Beaton and Ghassemi, 1982; Scrimshaw et al., 1967; Knudsen, 1981; Pollitt, 1987; Berg, 1987; and Chidambaram, 1989).

This is an important question because large numbers of malnourished people in the world call attention to the need for nutrition interventions. As of the mid-1980s, an estimated 348 million people in developing countries had inadequate energy intakes (ACC/SCN, 1987) and approximately 165 million of the world's preschool children were

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[1] Paper presented at the workshop on Child Health Priorities for the 1990s, Johns Hopkins Institute for International Programs/World Bank joint seminar; June 20-22, 1991; Baltimore.

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underweight (Kates et al., 1988). The continued need for such interventions comes exactly at a time when the economic crisis in the developing world and associated austerity efforts is creating increased concern about how well these programs actually work.

The prevailing view is that early child nutrition plays a central role in the promotion of health and the prevention of disease. Figure 1, adapted from Martorell and Sharma (1985) and Edmonston and Martorell (1984), displays the linkages between programs/interventions and child health outcomes. Improved birthweight and postnatal nutritional status are depicted as playing a key role in the reduction of child mortality and increased food and nutrient availability is shown as a factor for improving children's nutrition either directly or through effects on maternal nutritional status.

This paper reviews recent as well as classic studies on the impact of food supplementation on child morbidity and mortality. Some study designs permit the assessment of the specific contribution of supplemental food interventions, and these are discussed in the first section below. Evaluations of this sort are relatively rare because there has been an increasing trend to integrate nutrition interventions into the primary health care setting. In line with this development, researchers have tended to analyze the effects of combined food supplement/health care programs. A brief review of some of these studies is given in the second section below.

Since there is a complex set of intervening factors between a food intervention and a decreased mortality rate (see Figure 1), one strategy suggested by Feachem (1983) for estimating the impact of the former on the latter is to break the problem into more manageable parts. For example, if it can be shown that food supplement programs improve nutritional status and that an improved nutritional status lowers the risk of mortality, then one can argue that there is indirect evidence for the effectiveness of supplementation in lowering mortality. The third section below addresses the impact of food supplement programs on child nutritional status. Following that section is a discussion of the impact on birth weight of supplemental foods received during pregnancy. Finally, two sections review the evidence for the relationship between child nutritional status and morbidity and mortality.

A few of the terms used in this paper need to be defined. Supplementation interventions are here referred to as programs with on-site feeding or take home foods. Nutrition rehabilitation centers, or therapeutic feeding, though important in case management of the severely malnourished, are not considered here. Protein-energy supplements will be referred to as food supplements and include any foods whether specially prepared as in the "atole" used in studies conducted by the Institute of Nutrition of Central America and Panama (INCAP) in Guatemala, or raw foods such as oil or dry milk used in the CARE interventions. Childhood mortality encompasses both infant mortality (less than one year) and child mortality (one to four years). Childhood morbidity refers to illness, most frequently diarrheal, but also includes acute respiratory infections, fever, and other illnesses for the same age group.

Direct Evidence for the Impact of Exclusive Food Supplement Programs on Childhood Mortality

There are very few studies which have evaluated the direct impact of food

supplementation on mortality rates. Table 1 summarizes the results of three studies which have attempted to do this. In 1959, INCAP began a five year study addressing the question of the relative importance of food supplementation vs. health care in childhood mortality. One community received only food supplements at a local center, a second community received health care and the third community acted as a control. Only the values for the food supplement and the control communities are shown in Table 1. The village which received the food supplement had an infant mortality rate (IMR) of 146 deaths per thousand live births compared to the control community rate of 191 (Ascoli et al., 1967). Perhaps even more significantly, the Guatemala study compared the rates during the study in each of the communities to rates for the nine years previous to the study. The IMR in the community with the food supplement dropped 19% (from 182 to 146) whereas the control community stayed about the same (186 to 191).

There is other evidence concerning the beneficial effects of food supplementation on mortality rates. Baertl and coauthors (1970) found that Peruvian villages with a take-home food supplement program had an average infant mortality rate of 48, far lower than the average for the control communities of 134.[4] In one classic study from India, the Narangwal Nutrition Project, three villages treated exclusively with on-site food supplementation had an infant mortality rate of 89 compared to 129 for two control communities (Kielmann et al., 1978).

In a study in Colombia, Mora et al. (1978) gave protein-calorie supplements to 226 low-income pregnant women and compared mortality rates of their newborns with those of an unsupplemented control group of 230 women. On average, the take-home supplements resulted in an increased intake of 150 kcal and 20.6 grams of protein for the women, despite the fact that 856 kcal and 38.4 grams of protein were actually supplied to the families. Stillbirth, neonatal and perinatal mortality rates were lower in the supplemented group. The stillbirth rate was one fourth and neonatal and perinatal mortality rates were about one-half the rate in the control group. Differences between supplemented and control groups were statistically significant when stillbirth and neonatal deaths were combined.

Results from these studies present a positive picture of the benefits of supplemental food programs, but due to methodological limitations, the results should not be considered in isolation. A criticism of the Narangwal and Peruvian studies is that villages were not allocated at random to treatment and control groups and the Guatemalan study only had a single village per intervention--too small a sample size to analyze the effects properly. The study in Colombia was a randomized trial. It was not principally designed to study mortality and, therefore, its results are based on very small sample sizes. Nevertheless, the results were statistically and epidemiologically significant.

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[4] Values for the food supplement villages are averages of populations III (which received 250 kcal and 7.5 g of protein) and IV (250 kcal and 12.5 g of protein). Values for control communities combine populations I (which received only occasional medical assistance) and II (which participated in a feeding program targeted to children 6-30 months old in the last two years of the study). See Baertl et al. (1970) for further details.

Direct Evidence for the Impact of Integrated Food Supplement- Health Care Programs on Childhood Mortality

In addition to pointing to the importance of food supplements, the early studies discussed above were also suggestive of the importance of health care. Health care alone was associated with infant mortality declines in Guatemala (Ascoli et al., 1967) and India (Kielmann et al., 1978). Over the years, in a number of both research and applied programs, food supplementation has been combined with health care. Such integrated programs were endorsed at the Alma Ata Conference on Primary Health Care (WHO, 1978) and continue to be an important element in the battle against child mortality. Though evaluation of the effects of these programs cannot point to the sole importance of food supplementation, they add weight to the mounting evidence in support of including nutrition interventions in primary health care programs.

INCAP undertook such an intervention from 1969-1977, in order to identify the relative importance of energy and protein for early childhood growth and mental development. Two communities received a non-protein, low calorie drink known as Fresco, and two received a high protein-energy drink called Atole. Both drinks contained vitamins and minerals (Lechtig et al., 1975). Three villages served as comparison communities and were selected in a follow-up study of this original intervention (Martorell and Rivera, in press). Additional details about the design of the study are presented in Table 2.

Analyses of data from the INCAP follow-up study show that village level infant mortality rates were significantly lower in the Atole villages than in the comparison communities after controlling for pre-intervention rates (Table 3). Infant and childhood mortality rates declined by 66 and 68%, respectively, in the villages receiving the high nutritive beverage (Atole) in comparison to corresponding declines in the villages receiving the very low nutritive beverage (Fresco) of 19% and 33% and of 24% and 34% in the control villages (Rose, Martorell and Rivera, in press). Using the village as the unit of analysis, the decline in Fresco villages ($n=2$), which received the same type of medical care as Atole villages ($n=2$), was not significantly different from that observed in control villages ($n=3$). On the other hand, differences in IMR trends between the Atole and control villages, were statistically ($P < .05$) and epidemiologically significant. Also, IMR trends between Atole villages ($n=2$) and Fresco and control villages ($n=5$) were statistically significant ($p<.05$). Since the only difference in the programs implemented in Atole and Fresco villages was the nutrition content of the beverages, it would appear that the cause of the decline in infant mortality was nutritional.

There are other integrated health programs in which the effect of the food supplement cannot be differentiated from the medical intervention. They have shown lower infant mortality rates in treatment populations than in comparison groups. Table 4 displays the results of three such studies. In Haiti, treatment communities had an IMR of 34 and a child mortality rate of 6 compared to national averages of 150 and 23, respectively (Berggren et al., 1981). A project in Jamkhed, India found the IMR in treatment areas to be 57% lower than in control areas (Gwatkin et al., 1980). The large-scale Integrated Child Development Services Program (ICDS) in India found treated areas to have an IMR of 86 compared to the national average of 114 (Tandon et al., 1984). Another large scale project in India, the Tamil Nadu Integrated Nutrition Project (TINP),

compared infant mortality rates at baseline with those at a final evaluation in four geographic districts of the state serviced by the Project. Infant mortality declined in all four districts and ranged from 12.5% to 29.1% below baseline levels (Chidambaram, 1989). All of the projects mentioned here included immunizations, prenatal care, and health education in the health care package along with food supplementation.

The Impact of Food Supplement Programs on Anthropometric Indicators of Nutritional Status

Apart from studies assessing impact on mortality, food supplementation experiments have also demonstrated significant improvements in nutritional status as measured by child growth anthropometry. Some of these studies provide insights about the interaction of illness and diet on nutrition which are useful in interpreting mortality data.

Lutter and colleagues (1989) found that food supplementation had positive effects in overcoming growth faltering due to diarrheal illness and that the effect varied with age. Analyses of the Atole/Fresco Guatemalan project also suggest that diarrheal diseases cease to have an effect on growth among children whose dietary intakes are improved through supplementation (Martorell et al., 1990).

Other studies on the impact of supplementation on anthropometry address the issue of effectiveness of broad-scale feeding programs. Ten years ago the evidence for improvements in nutritional status due to broad-scale routine feeding programs was not convincing. In their oft-cited review of over 200 reports on supplemental food programs, Beaton and Ghassemi (1982) find that "close scrutiny of the results of the total experience suggested that anthropometric improvement was surprisingly small". They attribute this in part to the relatively low levels of net supplementation.

In a study of supplemental food programs sponsored by CARE, Anderson et al. (1981) compared the heights and weights of participants and non-participants in five countries -Colombia, Dominican Republic, Costa Rica, India, and Pakistan. Rates of stunting (less than 90% of the reference height-for-age) and wasting (less than 90% of the reference weight-for-height) were examined. There was a significantly lower percentage of stunting among participants in the India project and a significantly lower percentage of wasting among participants in the Dominican Republic, but the rest of the countries showed no significant differences when comparing participants and non-participants. Among other explanations, Anderson and coauthors attribute the lack of effect to the fact that the programs were not adequately targeted to malnourished children.

More recent broad-scale feeding trials have been much more effective. The Tamil Nadu Integrated Nutrition Project (TNIP), funded by the World Bank, is one of the largest nutrition education/targeted supplementary feeding programs in the world. Begun in 1980, it serviced 9000 villages in the late 1980s and had as an objective the reduction of malnutrition by 50% in children under five years of age (Chidambaram, 1989). The project had remarkable effectiveness in combating severe malnutrition (as measured by weight-for-age less than 60% of Indian reference standards). It has been estimated that TNIP reduced severe malnutrition among children 6 to 24 months old by a third to a half and that together with another state-run nutrition program contributed to the reduction

of half of the severe malnutrition in children from 24 to 60 months of age (World Bank, 1990).

An innovative grass-roots health and nutrition program was undertaken in Iringa, Tanzania under the auspices of the Joint WHO/UNICEF Nutrition Support Program (1989). The program integrated a number of components including maternal and child health, water and environmental sanitation, household food security, and child care. Community participation in all phases of project design and implementation was a key aspect. This included growth monitoring and the local provision of foods for supplementary feeding of infants and young children at community-run day care centers. From the third quarter of 1984 to the third quarter of 1987, there was a steady drop in the prevalence of severely underweight children from 4.7% to 1.7%. This 64% decline in prevalence is based on measurements in 168 villages of 26,922 (1984) and 37,054 (1987) children. Measurements of all children in the 442 villages outside the program area in 1987 showed a prevalence of severe malnutrition similar to that in the program area in 1984, i.e. at the start of the program. The dramatic drop in cases of malnourished children in the project areas is impressive, especially given the deteriorating trend in the rest of Africa during the 1980s (WHO/UNICEF, 1989).

A recent review of maternal and child health supplementary feeding programs found that evidence of nutritional impact was found in other broad-scale programs undertaken in the Philippines, India, Morocco, Haiti, and Sri Lanka (Mora et al., 1990). For example, in Morocco the program resulted in a 69% reduction in moderate and severe malnutrition of program participants. In India, an evaluation of the Integrated Child Development Services (ICDS) program found that severe malnutrition was reduced by 5% in severe drought areas and by 37% in areas less affected by drought.

In summary, supplementary food programs in a controlled research environment have been able to significantly improve nutritional status as measured by anthropometry. This effect is now also seen in broad-scale public health interventions, probably because of recent program advances, including extensive growth monitoring, improved targeting of benefits, and increasing the size of the benefit package.

The Impact of Food Supplement Programs During Pregnancy on Birth Weight

The relationship between low birth weight and infant mortality has long been recognized (Chase, 1969). Strategies to reduce infant mortality rates have therefore focused attention on prenatal nutrition. The impact of supplementation during pregnancy on birth weight has been studied in several countries and is reviewed selectively in this section.

The INCAP study discussed above, was one of the first well-designed studies to examine the impact of prenatal supplementation on birth weight in developing countries. The average birth weight for infants born to women receiving high-energy Atole supplements was 115 grams greater than for those born to women who received the low-energy Fresco supplements (Lechtig et al., 1975). The data were also analyzed according to level of supplement intake. Average birth weight for infants born to women who consumed greater than 20,000 calories of supplement during their pregnancy was 3,105 grams, compared to 2,994 grams for those consuming less than this level. Differences in both analyses were statistically significant with a p-value of less than .025.

The previously-mentioned Colombia study on prenatal supplementation also demonstrated significant differences in birth weight. Full term newborns from supplemented mothers weighed on average 63 grams more than their counterparts from the control group (Mora et al., 1983). The Bacon Chow study undertaken in Taiwan demonstrated a 55 gram differential in birth weight of males between high and low supplemented mothers (Adair and Pollitt, 1985). The difference in female birth weight between the two groups was 32 grams. Mothers in the high supplement group consumed an average of 444 calories and 27 grams of protein per day more than mothers in the low supplement group. A study in Gambia found that birth weights of newborns after the start of a food supplementation program were an average of 99 grams greater than before the program began (Prentice et al., 1987). On average mothers consumed an additional 431 calories after supplementation began. On the other hand, a controlled randomized trial in three villages in Madura, East Java found similar mean birthweights in women who consumed a high energy supplement during pregnancy (465 kcal/day) as in women who consumed a low energy supplement (52 kcal/day) (Kardjati et al., 1988). However, the nutrition of these women was better than that of the women in comparable studies elsewhere.

Some information exists about impact from broad-scale supplementation trials. Anderson (1989) has provided results from the ICDS project in India. She found the adjusted mean weight at 1 month of infants whose mothers were supplemented during pregnancy to be 230 grams greater than that for infants from unsupplemented mothers. In addition, the prevalence of low weight-for-age was 24% in supplemented infants compared with 50% in the controls.

The Link Between Anthropometric Indicators of Nutritional Status and Morbidity

Most of the studies of supplemental food programs have not evaluated the impact on morbidity. Beaton and Ghassemi (1982) point out that of the 200 programs that they reviewed only eight included information on morbidity outcomes. If supplementation does improve nutritional status, can it be assumed that such improved nutritional status will result in lower morbidity rates in the target population?

There is clear evidence that malnutrition impairs the immune response, but the effect varies with the particular component of the immune system. The reduction of cellular immunity is the most well-documented effect. Summarizing the literature in this area, Martorell and Ho (1984) point out that effects at the cellular level include atrophy of tissues involved in T-cell maturation, reduction of the number of T-lymphocytes, interference with lymphocyte transformation, and reduction or absence of the delayed hypersensitivity reaction. Non-specific immunity can also be adversely affected in malnutrition. For example, gastric acidity is decreased in children with marasmus and kwashiorkor (Gracey et al., 1977).

The humoral immune system appears to be least affected by malnutrition. Earlier, Kielmann et al. (1976) showed that specific antibody response to tetanus immunization as well as IgG and IgM levels were unrelated to nutritional status as measured by weight-for-age. Responses to immunization appear satisfactory even for children with marasmus or kwashiorkor (Tomkins and Watson, 1989).

The weight of evidence argues strongly for the importance of nutritional status in

determining immune response. However, as several authors have pointed out, the functional significance of changes in the immune response with regards to disease incidence and duration remains unmeasured (Martorell and Ho, 1984; McMurray et al., 1981).

A number of researchers have related anthropometric measures of nutritional status to the incidence and duration of diarrhea. Table 5, adapted from Tomkins and Watson (1989), summarizes this information. None of the studies indicate that poor growth, as measured by height-for-age, is predictive of an increased incidence in diarrhea. Only a minority of the studies indicate weight-for-height as a predictor of incidence. The panorama changes, however, when considering duration of illness; the majority of studies indicate that poor anthropometric status is predictive of an increased duration of diarrheal illness.

Information on morbidity from the INCAP study described earlier (Table 2) has been reanalyzed for this paper. Unfortunately, the data have been summarized in the computer files as percent of time ill (i.e., incidence x duration as a percentage of days at risk). This precludes examination of specific relationships between supplement intake and incidence or duration. Table 6 presents linear regression results from an analysis of the determinants of percent of time ill with diarrhea from 6 to 18 months of age. This age range was selected because previous analyses indicated that this was the period in early childhood with the highest prevalence of diarrheal diseases (Martorell et al., 1975). After controlling for the effects of sex, birth year, length at six months of age, household socio-economic status (as proxied by an index of the characteristics of the home) and type of supplement received, energy intake from supplemental food was not significant in predicting the percent of time ill with diarrhea. The only significant predictor was the housing scale: children from poorer homes had significantly more diarrhea. Supplement type was not significant in models which omitted the variable "energy intake from the supplements" (i.e., a test of Atole vs. Fresco). The mean unadjusted percent of time ill with diarrhea was 13.8 ($\pm$ 13.0) in Atole villages and 12.6 ($\pm$ 14.2) in Fresco villages. In addition, energy supplement intake was non-significant in analyses carried out separately for Atole and Fresco villages. Results for the period 18 to 30 months of age also indicated a lack of association between supplementation and percent of time ill with diarrhea. In this study therefore, supplement intake was found to be unrelated to percent of time ill, a measure which combines incidence and duration.

In summary, can it be expected that food supplementation will result in lower morbidity in the target population? Clearly, the evidence necessary to answer this question is limited but some speculation is possible. Food supplements, as noted above, improve nutritional status as measured by anthropometric indicators. From the studies to date one would expect that food supplementation programs, by virtue of their effect on nutritional status, would lead to reduced severity of infections and reduced case fatality rates.

The Link Between Anthropometric Indicators of Nutritional Status and Mortality

There is a growing body of literature which addresses the relationship between anthropometric measures of nutritional status and subsequent risk of mortality. Some of the first to study the question on a large scale were Sommer and Lowenstein (1975), who

measured height and mid-arm circumference in 8,292 children aged one to nine years in Matlab, Bangladesh. Using arm circumference-to-height standards constructed for that population, they found that children below the tenth percentile had a 3.4 times greater risk of dying within 18 months than those above the 50th percentile. The risk was 1.5 times greater for children between the 10th and 50th percentiles.

Kielmann and McCord (1978) evaluated the relationship between weight-for-age and the risk of subsequent mortality in 2,808 children aged one to three years in Narangwal, India. They found the increase in mortality with decreasing weight-for-age category to be a linear relationship. This contrasts with the threshold effect found by Chen and coauthors (1980) in their study of 2,019 one to two years old Bangladeshi children. In the two years following measurement, severely malnourished children, as measured by weight-for-age below 60% of the Harvard standard, were 3.1 times more likely to die than children greater than 75% of the standard.

More recent studies on physical measurement and the subsequent risk of mortality confirm the direction of the relationship found in these early studies, that is, that the risk of death increases with decreasing nutritional status. What remains less clear is the nature of this relationship. Is there a threshold effect with the risk of death greater only for those who are severely malnourished, or is the effect a gradual one in which the mild and moderately malnourished are also at risk?

Heywood (1986) found a threshold-like relationship for children below 85% of the height-for-age standard in his study of 1,232 Papua New Guinea children aged 6-30 months. But measurements of weight-for-age and weight-for-height in the same children revealed a more gradual relationship between mortality and growth. Bagenholm and Nasher (1989) found the opposite in their study of 2,071 Yemeni children. That is, the threshold effect occurred in the weight-for-height variable, whereas height-for-age was not significantly related to subsequent deaths.

The most recent and comprehensive review of the subject has been prepared by Pelletier (1991), who studied the results of 15 community-based prospective studies from Asia and Africa. The accumulated findings suggest that even anthropometric status consistent with a classification of mild to moderate malnutrition is associated with an elevated risk of death. The finding is an important one, since there are far greater numbers of children in this category. The implication is that even a small increased risk among those with mild to moderate degrees of poor anthropometric status will account for a considerable number of increased deaths. Pelletier (1991) calculates that anywhere from 33 to 80 percent of nutrition-related deaths in a given population will be associated with mild to moderate growth failure rather than with the type of growth failure associated with severe malnutrition.

In summary, there seems to be universal agreement that an increased risk of mortality is associated with poor nutritional status as measured by poor physical growth. There is also a growing consensus that some amount of increased risk exists at all levels of growth impairment.

Summary and Conclusions

A number of investigations have assessed the impact of isolated food supplement interventions on mortality rates. These studies have reported decreases in infant

mortality by anywhere from 23% to 64% below rates for comparison populations. Studies of combined nutrition and health care interventions have reported infant mortality declines in treatment groups ranging from 25% to 77% below those of the comparison groups. Certainly there are methodological flaws in these studies, and the results do vary widely, but all of the work points in the direction of a positive impact of food supplement interventions in reducing childhood mortality.

Another way of viewing the impact of supplemental food programs is to piece together more specific relationships. Small-scale research projects have documented increased weight and height gains in young children as a result of supplementation. Increased birth weight due to prenatal supplementation has been well documented by a number of research studies. While many of the broad-scale food supplement interventions of the 1970s could not document significant improvements in nutritional anthropometry, more recent studies have demonstrated an impact on growth.

The connection between nutrition and morbidity and mortality is more complex. The importance of nutritional status for immune response has been verified. But the functional consequence of this with respect to protection from illness is less certain. However, there is general consensus that nutritional status affects the severity of illness, including duration of episodes, but not its incidence. The severely malnourished are the most likely to suffer drastic consequences of illness when it does occur and this has been shown in a number of studies which have related anthropometric status to subsequent risk of death. Those less retarded in growth are also at increased risk of mortality.

In summary, nutritional status is an important element of child health and improvement of it will result in decreased severity of infections and lower mortality. Food supplement programs clearly have the potential to improve child nutrition and that potential has been demonstrated in many of the studies reviewed here. Taken together, all of the evidence presented above supports the assertion that supplemental food programs can make a significant and positive impact on the reduction of childhood morbidity and mortality.

Perhaps it is time to stop asking about the impact of food supplement interventions, in general, and focus on more specific questions. For example, under what specific environmental and programmatic conditions will supplemental food interventions produce desired results? This is not an original idea. A number of authors have reviewed successful elements of food supplement programs (Anderson et al., 1981; Beaton and Ghassemi, 1982; Kennedy and Knudsen, 1985; Mora et al., 1990). Some of the suggestions, such as to improve targeting or to increase the size of the benefit package or to focus on prenatal nutrition, have already been implemented in various projects with successful results.

Given the important role that nutrition plays in childhood morbidity and mortality, it is worth addressing attention to a second and related question. Under what specific conditions would alternative nutrition interventions be more likely to produce a desired impact? Despite the generally beneficial role of food supplement interventions, few would agree that they are panacea. In fact, several authors have cautioned against potential deleterious effects, such as increasing the dependence of community members on local power structures or outside assistance (Gwatkin et al., 1980; Pacey and Payne, 1985). Since the conditions which foster malnutrition are rooted in the socio-economic aspects of development and since those aspects vary so much from place to place, it

makes sense that different types of interventions or even combinations of interventions would be needed. Table 7, adapted from the WHO/UNICEF publication (1989) on the Iringa project in Tanzania, demonstrates how defining the local causes of a particular nutrition problem can suggest specific program interventions. A more expanded list of alternative interventions to promote nutritional improvement has been adapted from an FAO publication (1983) and is presented in Table 8.

While the question posed above regarding the relative merits of alternative nutrition interventions is a difficult one and will take much time to answer, there is reason for optimism on two accounts. First, a number of authors have already begun work on this question (Kennedy and Pinstrup-Anderson, 1983; FAO, 1983; Pinstrup-Anderson, 1986; Kennedy and Alderman, 1987). Second and more importantly, it opens the door to exploring a wide range of projects which can be tailored to the demands of local conditions, a strategy which holds much promise for the future.

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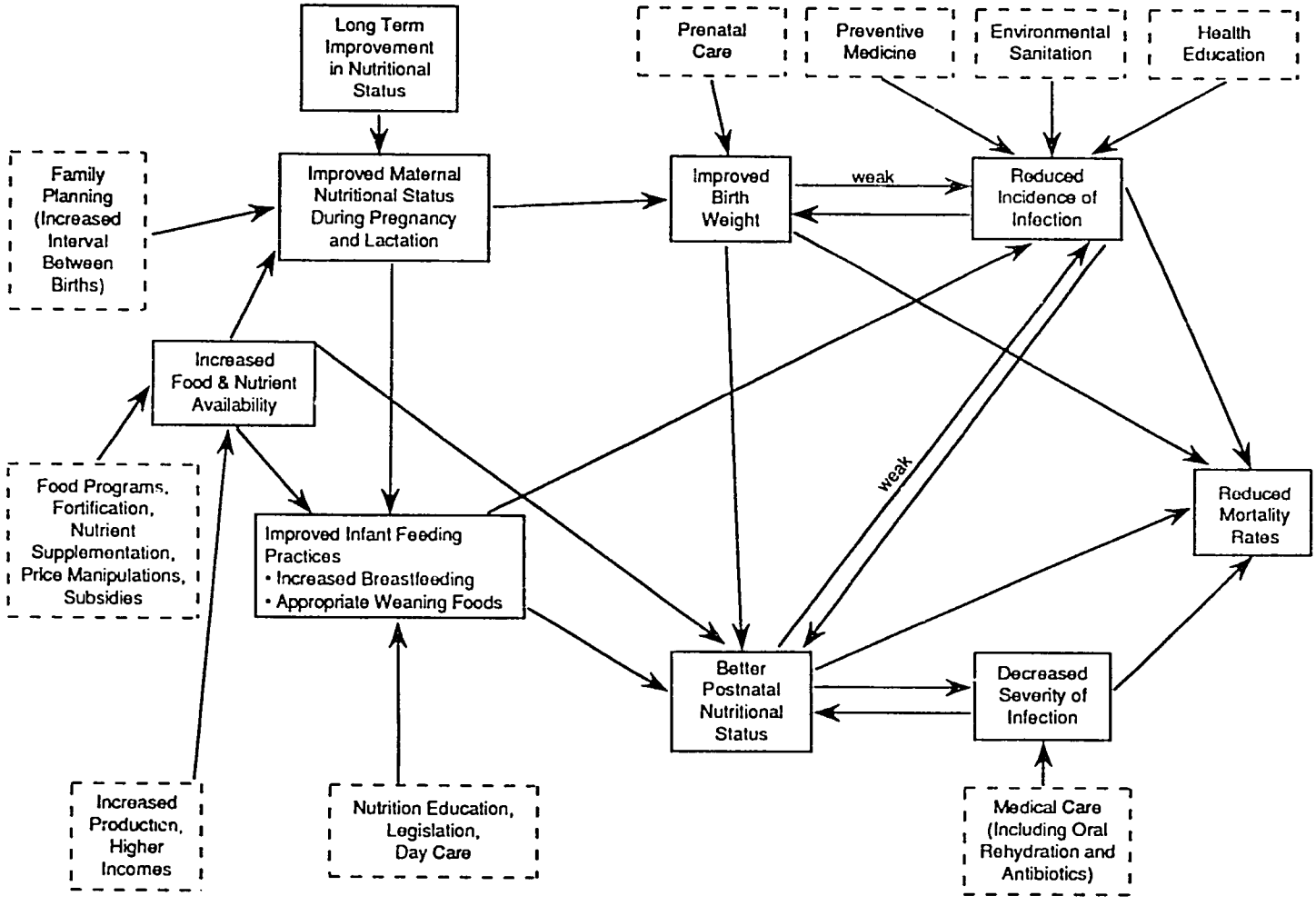

Figure 1. Relationship of Child Nutritional Status, Health, and Survival. Solid Boxes are Intermediate Variables or Outcomes and Dotted Boxes are Points of Intervention.

Table 1 - Mortality rates in studies of exclusive food supplementation interventions.*

Project	Type of Feeding**	Infant Mortality Rates		Child Mortality Rates	
		Treatment	Control	Treatment	Control
Guatemala 1959-64	On-site 350 kcal 15g prot	146	191	24	50
Peru 1962-67	Take-home 250 kcal 7.5 g/12.5 g prot	48	134	21	40
Narangwal, India 1970-73	On-site 400 kcal 11g prot	89	129	10	19

* SOURCES: Ascoli et al., 1967; Baertl et al., 1970; Kielmann et al., 1978;
** Energy and protein values refer to portions provided to participants

Table 2 - Description of the INCAP Intervention

DATES:	1969-1977
SUPPLEMENTS:	Provided at no cost, ad libitum consumption
	FRESCO non-protein, low calorie drink 59 kcal, 0 grams protein per 180 ml
	ATOLE high protein-energy drink 163 kcal, 11.5 grams protein per 180 ml
MEDICAL SERVICES:	Prenatal care, tetanus immunization, neonatal and infant assessments
DESIGN:	Randomized study in which 2 villages received ATOLE + medical services and 2 villages received FRESCO + medical services.
	3 villages received neither (comparison group selected for follow-up study in 1988; not randomized).
DATA COLLECTION:	SUPPLEMENT INTAKE amount consumed at feeding site measured on all occasions to nearest 10 ml
	HOME DIET 1-day and 3-day recall by mother every 3 months throughout study period
	MORBIDITY home interview of mothers every 2 weeks from July, 1970 - February, 1977
	MORTALITY life history survey of mother during follow-up study in 1988

Table 3 - Average Infant and Child Mortality Rates by Type of Intervention Before (1949-1968) and During (1969-1977) the INCAP Intervention*.

		1949-1968	1969-1977	% Decline
INFANT (0-12 months)				
	Control	140	113	-19.3
	Fresco	120	91	-24.2
	Atole	176	60**	-65.9
CHILD (1-4 years)				
	Control	50	33	-34.0
	Fresco	42	28	-33.3
	Atole	79	25	-68.4

* SOURCE: Rose, Martorell and Rivera, in press.
** Change from baseline values significantly different from that in control villages, $\alpha = 0.05$, 1-tail. There were no other significant differences in infant mortality rates.

Table 4 - Mortality rates from integrated supplementary food/health care programs.*

Project	Health Services Provided	Infant Mortality Rates	
		Treatment	Control
Haiti 1968-72	Immunizations Deworming ORT Prenatal care Nutrition education Take-home supplemental foods	34	150
Jamkhed, India 1971-79	Immunizations Prenatal care Health education Vitamin A supplementation On-site supplemental foods	39	90
ICDS, India 1982-83	Immunizations Prenatal care Diarrhea management Vitamin A supplementation On-site supplmental foods	86	114

* SOURCES: Berggren et al., 1981; Gwatkin et al., 1980; Tandon et al., 1984.

Table 5 - The relationship between poor growth status, as assessed by various anthropometric indices, and subsequent diarrheal disease incidence and duration.

Author	Country	Anthropometric Index	Diarrheal Disease	
			Incidence	Duration
James 1972	Costa Rica	Weight/Age	Increased	Increased
Palmer et al., 1976	Bangladesh	Weight/Height		Increased
Tomkins, 1981	Nigeria	Weight/Age	-	Increased
		Height/Age	-	Increased
		Weight/Height	Increased	Increased
Chen, 1981	Bangladesh	Weight/Age	-	
		Height/Age	-	
		Weight/Height	-	
Delgado et al., 1983	Guatemala	Weight/Age	Increased	-
		Height/Age	-	Increased
		Weight/Height	Increased	-
Black et al., 1984	Bangladesh	Weight/Age	-	Increased
		Height/Age	-	Increased
		Weight/Height	-	Increased
Mathur et al., 1985	India	Weight/Age	-	-
		Height/Age	-	-
		Weight/Height	-	-
Bhan et al., 1986	India	Weight/Age	-	
		Height/Age	-	
		Weight/Height	-	

Note: "Increased" means that disease incidence (or duration) was increased among those with inadequate growth as measured by this index. "-" means there was no difference in disease incidence (or duration) between those with normal and inadequate growth using this index. A blank means the relationship was not tested.

Adapted from: Tomkins and Watson, 1989.

Table 6 - Linear Regression Analysis of the Effect of Supplemental Energy on Percent of Time Ill with Diarrhea from 6 to 18 Months of Age.

DEPENDENT VARIABLE:	Percent of time ill with diarrhea	
MODEL STATISTICS:	N = 731	
	F = 2.80, p-value = 0.11	
	R^2 = 0.023	
INDEPENDENT VARIABLES:	t-statistic	p-value
Sex[+]	- 0.95	0.343
Birth year	- 0.77	0.441
Length at 6 months	0.80	0.424
Housing scale	- 3.29	0.001
Intervention type[++]	- 0.40	0.691
Energy intake from supplements	1.58	0.115

[+] Males = 1, Females = 0.

[++] Atole = 1, Fresco = 0.

Table 7 - Selected food security program interventions from the Iringa Nutrition Project, Tanzania*.

Problem	Possible Causes	Program Intervention
Inadequate food in households (most severe a few months before harvest)	Lack of household planning	Training of trainers on household food planning
	Choice of wrong crops, poor crop management, shortage of inputs	Promotion of drought-resistant crops such as sorghum, sunflower, cowpea and especially cassava
	Failure of rains	
	Storage losses	Improved storage
	Lack of income to buy food	
Inadequate nutrient intake (especially in children)	Poor economic resources	Promotion of income-generating activities
	Nutritionally poor diet	Nutrition education especially to mother through health workers
	Shortage of fuelwood	Training and inputs for village afforestation and home gardening
	Shortage of fruits and vegetables	Training and inputs for small animal keeping
	Scarcity of meat	Promotion of grain milling and appropriate technology
	Scarcity of beans and other legumes	
	Too much workload for mother	
Lack of awareness of good weaning practices	Lack of awareness of children's nutrient needs	Provide weaning recipes based on local foods
	Inadequate feeding frequency	Mobilize communities to provide extra food at child care post
	Scarcity of energy-dense foods such as groundnuts and cooking oil	Campaign on use of Kimea (power flour)
	Dietary bulk	

* SOURCE: WHO/UNICEF, 1989

Table 8 - Selected list of interventions for nutritional improvement

1. FACE-TO-FACE NUTRITIONAL COMMUNICATION
2. ON-FARM AND COMMUNITY FOOD STORAGE
3. HOME AND VILLAGE WEANING FOODS
4. NUTRITION INTEGRATED INTO HEALTH CARE
5. NUTRITIONAL COMMUNICATION VIA MASS MEDIA
6. NUTRITIONAL REHABILITATION
7. SUPPLEMENTARY FEEDING OF PRESCHOOL CHILDREN
8. SUPPLEMENTARY FEEDING OF PREGNANT/LACTATING WOMEN
9. SCHOOL FEEDING
10. HOME AND COMMUNITY GARDENS
11. SMALL LIVESTOCK PRODUCTION
12. APPROPRIATE TECHNOLOGY IN FOOD PRESERVATION/PREPARATION
13. DISTRIBUTION OF SPECIFIC NUTRIENTS
14. PROMOTION OF BREASTFEEDING
15. FOOD FOR WORK

SOURCE: FAO, 1983

Discussion:

Mortality, Malnutrition and Synergies: Determinants and Interventions

Jean-Pierre Habicht

Rose and Martorell (1992) present estimates of the impact on childhood mortality that have been associated with improvements in protein-energy nutrition in pregnant women and in their offspring. Our calculations show that this improvement in nutrition is cost-effective in reducing childhood mortality, especially if done during pregnancy (Pinstrup-Andersen 1992).

One might also be able to reduce childhood mortality through improving protein-energy nutrition of malnourished lactating mothers. However, the cost-effectiveness of such an intervention is unknown, because no appropriate supplementation trials have yet been done. A first randomized control trial supplementing otherwise malnourished lactating women has too small a sample size to examine the impact on mortality. However, a preliminary report from this study describes a clear effect on milk volume and on the duration of full breast feeding, both of which should effect the health and mortality of the suckling infant (Gonzalez-Cossio et al. 1991).

The information presented by Rose and Martorell comes from populations otherwise malnourished in protein and energy, and excludes the negative evidence from similar interventions in populations that were well nourished. This is appropriate and important in a review of the mortality effects of improving nutrition--because the issue of importance here is the effect on mortality of ameliorating or preventing malnutrition. One would not expect any effect on childhood mortality from increasing the ingestion of proteins and energy in the absence of protein-energy malnutrition. Some reviews have not made this differentiation.

The usefulness of the discussion by Rose and Martorell and that by Kjolhede (1992) dealing with vitamin A in this seminar is in the scientific demonstration that improving nutrition decreases child mortality. The demonstration of a marked association between childhood malnutrition and mortality has been available since 1973. Data on this subject have been thoughtfully discussed by many of the participants in this meeting for over a decade. However, except for protein-energy malnutrition in pregnant women in Colombia (Mora et al. 1983) and in preschool children in the Guatemala study analyzed by Rose and Martorell, and for the recent studies reviewed by Kjolhede for vitamin A, this association could have been due to other factors such as poverty. This is because poverty both kills and deprives; therefore the association of death and malnutrition does not necessarily mean that malnutrition causes death.

The only way to take these other factors into account in the statistical hypothesis testing of causality is through randomized control trials with appropriate safeguards against biased responses and measurements. We feel that such trials are essential before major resources are poured into interventions. All other methods only give statistical inferences about association and not about causality, and we have had bad experiences in the past in making inferences from such studies.

Other presentations at this symposium consider less careful studies as sufficient evidence for effective interventions against non-nutritional illnesses. Perhaps the reason that nutrition interventions seem less effective than others is because the criteria for judging impact are based on more rigorously designed studies than are interventions in other areas.

Another reason the benefits of nutrition interventions are not immediately apparent is that deaths due to malnutrition are often obscured because mortality is reported by the most proximal cause of death (e.g., from diarrhea, sepsis or pneumonia). This is because few children die from severe malnutrition compared to those who die from these proximal causes. Malnutrition thus appears to be unimportant as a cause of death. How then can one explain the important improvements in survival in the studies in which all other contributions to health are held constant across better nourished and control groups except for improved nutrition? The answer comes from a review of the relationship of malnutrition to mortality across six studies that presented sufficient evidence to make comparisons (Pelletier D, 1991).

We were disappointed to find that the absolute differences in mortality rates (attributable risk) associated with malnutrition varied markedly across these populations. Absolute mortality rates were expressed as deaths per thousand child years, and malnutrition was estimated by anthropometry standardized to age by using weight-for-age.

However, on closer inspection it appeared that the attributable risk depended upon the mortality rates of the better nourished in these populations. In fact there is a remarkable constancy of impact from malnutrition if one looks at proportional changes in mortality (relative risk) instead of looking at the attributable risk. Infant and childhood mortality increases at a compounded rate of 7.6% for every one percent deterioration in weight-for-age. This compounded increase is constant over the whole range of severe (i.e., 55% weight for age) to mild malnutrition (i.e., 85% weight for age) (Pelletier et al. submitted). The result of this synergism is that at 55% weight-for-age the death rate is 11 times, at 65% three times and at 75% twice the mortality rates of the better nourished children. Statistical tests show this relative risk model, a synergistic model, to be a much more appropriate description of the data than is the attributable risk model, an additive model. These findings provide empirical evidence for the existence of "frailty" hypothesized to be a major determinant of mortality (Mosley and Becker 1991). These results also show that protein-calorie malnutrition is a more important contributor to frailty than is indicated by Mosley and Becker who do not consider it in the calculations of their paper.

The most sensible interpretation for our findings is that the case fatality rate for the same common killer diseases is higher among malnourished children. Supporting this argument are the findings by Garenne (1987) in Senegal of a synergistic effect of malnutrition on the disease specific mortality of the most common killer diseases-

-diarrhea and pneumonia (but, interestingly, not at all in malaria). The scientific literature shows that another explanation, an increase in the incidence of disease, appears not to occur except in the most severe degrees of malnutrition. Finally the explanation that weight-for-age is a better proxy for socioeconomic status than for increased risk of case fatality is unlikely given the consistency of the synergism. This consistency argues more for a direct biological effect than one mediated through socioeconomic variables.

We also found that there is no threshold with decreasing malnutrition beyond which this synergism ceases its pernicious effect on mortality, because the synergistic effect of malnutrition on mortality holds true even at rather mild degrees of malnutrition.

There are two major implications from our findings:

1) Trying to count deaths due to malnutrition is impossible because malnutrition kills in synergy with other diseases. Estimating universally-valid, disease-specific mortality rates is also impossible. The higher the overall levels of disease, the more deaths will be caused by the same severity of malnutrition. Of course, the same can be said for counting the mortality impacts of diarrhea or pneumonia because they depend to a large degree on the prevalences of different degrees of malnutrition.

2) The <u>number</u> of children who die because of the synergy of malnutrition with infection is much greater at milder degrees of malnutrition than at more severe degrees of malnutrition because the prevalence of mild to moderate malnutrition is so much higher even though their death rate is much lower. Therefore concentrating interventions on those with severe malnutrition will have a minor impact on mortality due to malnutrition.

Given the above synergisms one can calculate whether reducing the incidence of diseases such as diarrhea and acute respiratory infections is more cost-effective than reducing malnutrition because of the trade offs involved in a synergy. Both strategies will result in fewer deaths from both malnutrition and the other diseases. However, such calculations neglect the other effects of malnutrition on child well-being, learning capabilities and subsequent productivity. This means that these other benefits need to be taken into account to place cost-effectiveness calculations of reducing malnutrition into a more realistic context relative to social weal and economic productivity. This is in contrast to those killer diseases that cause no permanent harm among the survivors, especially if those diseases, such as tetanus, kill swiftly.

In the Rose and Martorell and in the Kjolhede reviews, proof that malnutrition increased mortality was attained through food supplementation trials. These findings do not mean that feeding programs are necessary or even desirable. Any method of improving protein-energy nutrition should have the same effect: improving the purchasing power for appropriate foods, or improving appropriate breast feeding, or improving the efficiency of food acquisition, preparation and distribution in the household to best meet the family's nutritional needs, may all contribute. However, the best, most cost-effective way to improve nutrition will be different according to the circumstances of the population. Where purchasing power is adequate, nutrition education can do the trick-

-where it is not, purchasing power must also be increased. This is because there is a synergism between purchasing power and nutrition knowledge in their impact on malnutrition (Ruel et al. in press)

The scientific challenge of the 1990's is how to collect observational data, conduct intervention trials and develop information that gives meaningful guidance for cost-effective policies and programs in the real world of synergisms and multiple outcomes.

The practical challenge is how to do good by applying what we think we know without doing harm by dogmatically insisting that we have identified the best interventions for all circumstances. The synergies of malnutrition and disease that sicken, maim and kill, and the synergies that heal and protect through increased income for food and better nutrition knowledge mean that no single universal set of most cost-effective interventions can ever be identified even with perfect knowledge. I expect this insight will lead to new imaginative initiatives in promoting not just survival but also health and well-being.

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Vitamin A Nutriture and Child Health

Chris Kjolhede, MD, MPH

I. Introduction

The most important nutritional problem faced by populations worldwide is that of protein and energy malnutrition. This age old, recurrent problem is altogether too familiar to too many children around the world. Efforts to impact on this serious problem are costly, logistically problematic and are often hampered by politics and war. Macronutrient interventions will undoubtedly still be used in limited situations such as for populations afflicted by natural calamities and war, but such interventions are extremely difficult to sustain over the long term. More amenable to intervention are some of the conditions related to micronutrient deficiencies such as nutritional anemia, goiter and cretinism, and nutritional blindness or xerophthalmia.

Micronutrients, as their name implies, are required in the diet in small quantities. This minute requirement, plus the fact that many can be stored in the body, make micronutrient interventions more feasible means of impacting on child health than any effort attacking problems of macronutrient deficiencies. There are well known methods for alleviating micronutrient deficiencies; indeed, many food products in developed countries are fortified with not one but multiple micronutrients. Additionally, periodic supplementations of certain micronutrients has been a successful intervention in several settings. When populations with micronutrient deficiencies are identified in the developing world, they go wanting not for a lack of means for addressing these important nutritional problems.

There are many micronutrients which play a role in normal development and in child survival. It is beyond the scope of this paper to discuss all of these important micronutrient deficiency states, the extent to which they occur in the developing world and the means for dealing with these problems. Clearly, there have been, and are, ongoing investigations of the relationships between various micronutrients and their impact on various degrees of health and disease. These studies often entail expanding the definitions of various micronutrient deficiency states beyond the classical descriptions and establishing the relationship between the more broadly defined condition and child health. Among these important micronutrients are vitamins C and E, and iron, iodine, folate and zinc. This paper, however, will only highlight vitamin A, in part due to findings from important research reported recently which indicates a potential significant impact of vitamin A on child survival.

II. Vitamin A

Nutrition of Vitamin A

Vitamin A is an essential vitamin for normal physiologic processes including cell differentiation, membrane integrity, vision, immunologic responses and growth. Vitamin

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A is present as retinol (preformed vitamin A) in animal products, for example, liver, milk, butter, and eggs, and as carotene (provitamin A) in vegetables such as carrots, cassava leaves and spinach, and in yellow-colored, non-citrus fruits such as mangoes and papayas. The biological activity of carotenes is only a fraction of that of retinol, and intestinal absorption of the former is influenced by the presence or absence of fat in the diet. Multiple factors affect vitamin A status in the individual; two of the most important are availability and adequacy of intake and absorption. Populations at risk of developing xerophthalmia (clinical vitamin A deficiency) appear to receive most, if not all, of their vitamin A from carotene-rich fruits and vegetables. Such foods tend to be seasonal, necessitating intake at many times the normal daily requirement in order to ensure that there are adequate liver stores which are needed to cover those periods when availability and consumption are low. Because their diets lack sufficient vitamin A, one million preschool age children worldwide may develop severe eye disease (xerophthalmia) each year. Of those children who develop corneal disease, as many as 85% may die[1].

Epidemiology of Vitamin A Deficiency

'Xerophthalmia' applies to all the ocular manifestations of vitamin A deficiency. These include the structural changes affecting the conjunctiva and cornea, and the physiological disorders of retinal rod functions attributable to vitamin A deficiency. The classification adopted by the World Health Organization (WHO) lists these clinical signs in order of severity, as follows:

Night blindness (XN)
Conjunctival xerosis (X1A)
Bitôt's spots (X1B)
Corneal xerosis (X2)
Corneal ulceration (X3).

The WHO has published prevalence criteria for determining the public health significance of vitamin A deficiency that use clinical signs and symptoms and serum retinol levels[2]. A problem of vitamin A deficiency of public health significance is felt to exist for a population when the prevalence for one or more of the following conditions exceeds that listed below:

Night blindness (XN) in >1%
Bitôt's spot (X1B) in >0.5%
Active corneal disease (X2/X3A/X3B) in >0.01%
Corneal scar (XS) in >0.05%
Plasma vitamin A of <0.35 umol/l (10μg/dl) in >5%

The true prevalence of vitamin A deficiency is very difficult to ascertain[3]. Case definitions must be consistent in order to compare rates both within and among populations and sampling methods must consider some of the epidemiological problems associated with assessing vitamin A deficiency, eg. clustering, seasonality and spontaneous reversibility of signs and symptoms. Although guidelines for assessing vitamin A status have been outlined by the International Vitamin A Consultative Group

(IVACG)[4], the various methods of assessments by which prevalence rates of vitamin A deficiency are established may describe different portions of the vitamin A deficiency spectrum which make comparisons difficult.

Surveys have been conducted in numerous countries or regions that have added to the understanding of the extent of the problem of vitamin A deficiency. Xerophthalmia, or clinical vitamin A deficiency, is often associated with rice based diets in Asia. Investigators from several Asian countries have reported results of surveys that indicate that vitamin A deficiency is a problem in all or part of their country. These countries include Indonesia, the Philippines, India, Bangladesh, Nepal and Thailand[1,5,6,7,8,9]. Other countries have not benefitted from such rigorous surveys but anecdotal reports of xerophthalmia suggest that a more extensive problem may exist. Several countries in Indochina fall into this category.

The extent of the problem of vitamin A deficiency in Africa is not accurately known. Few methodologically rigorous surveys have been conducted recently, although many case reports and hospital- or clinic-based data are available. No country-wide survey has been completed in Africa but several at-risk locales have been surveyed and the results published. Among those countries with known regional problems of vitamin A deficiency are Kenya, Malawi, and Ethiopia[10,11,12]. Much of the population living in the Sahel is suspected to be periodically suffering from nutritional deficiencies including vitamin A deficiency.

Historically there have been reports of vitamin A deficiency from diverse settings in Central and South America including Brazil, Bolivia, El Salvador, Guatemala and Haiti[13]. Recent reports of the extent of vitamin A deficiency are limited and often from surveys from at-risk subpopulations[14]. Political unrest and the poor economy in the region over the last ten years may have exacerbated the conditions that were related to the levels of vitamin A deficiency previously reported.

In summary, there are problems in establishing the prevalence of vitamin A deficiency, which include as yet inconsistent case definitions, the rarity of the clinical manifestations, clustering and seasonality of the condition, and the expertise and resources required for accurately determining vitamin A status. The problem has been best studied in Asia but even in Asia, and certainly elsewhere in the world, data from previous surveys are becoming outdated.

III. Vitamin A and Child Health

Vitamin A Deficiency and Eye Disease

Young children are at the greatest risk of developing xerophthalmia. Children are at high risk because their vitamin A requirements are proportionately higher than adults due to growth and because they frequently experience infections which, in general, increase their need for the nutrient and, in the case of diarrhea, decrease its absorption. As a result of increased needs and decreased absorption, severe, blinding corneal destruction is most frequently observed in children between the ages of six months and six years. Vitamin A deficiency is, in fact the single most frequent cause of blindness among preschool children in developing countries. The younger the child and the more severe the disease, the higher the risk that corneal destruction will be followed by death.

A significant percentage of all untreated cases of corneal xerophthalmia will result in death within weeks to months of the onset of blindness[15].

Vitamin A Deficiency and Diarrhea

Various researchers have looked at the relationship between vitamin A deficiency and diarrhea. Extensive work has been done in Indonesia that focused interest on the possible degree and direction of this relationship. In a prospective study of rural Indonesian children, an increased risk of diarrheal disease (RR=2.7) was noted among those children with preexisting vitamin A deficiency[16] and in a subsequent analysis it was reported that there was an increased risk of xerophthalmia following diarrhea[17]. However, the study showing this association between diarrheal disease and vitamin A deficiency could not confirm a causal relationship between the two conditions.

Numerous other studies, some much less rigorous than the above, have found associations between vitamin A deficiency and diarrhea. Eighty-six percent of the cases of xerophthalmia in a study in Matlab, Bangladesh gave a history of diarrhea or dysentery[7]; however, there was no control group. In another Bangladeshi study, children who were aged 1-10 years and hospitalized for diarrheal disease and who had night blindness were more likely to have dysentery (especially Shigella and E. hystolytica) (RR=1.68)[18]. Another study conducted in Bangladesh demonstrated that "protracted" diarrhea (greater than 14 days) was also found to be associated with mild vitamin A deficiency defined as X1A and/or X1B[19]. From the Nepal Blindness Survey[20], the authors report that diarrhea preceded xerophthalmia in a high proportion of cases. Investigators from Ethiopia report an association between diarrhea and vitamin A deficiency but the one-year recall period is rather a long interval[12].

Other investigators have reported no significant association between vitamin A deficiency and diarrhea. Indian researchers could not show an association between mild xerophthalmia and the incidence of diarrhea[21]. In the Philippines, diarrhea was not positively correlated with xerophthalmia[5]. And from a prevalence survey conducted in the lower Shire valley in Malawi, a history of diarrhea was not found to be associated with xerophthalmia[11].

A recent review of the issues addresses the relationship between vitamin A deficiency and diarrhea[22]. Models for the relationship between vitamin A deficiency and diarrhea are suggested, introducing the possibility of confounding by "unspecified poverty-related factors" as an explanation for some of the confusing reports.

Vitamin A Deficiency and ARI

A relationship between vitamin A deficiency and acute respiratory illness (ARI) has been suspected for some time. Studies have described keratinization of the larynx and trachea in several species of laboratory animals that were made vitamin A deficient[23]. Certain viral infections reportedly produce keratinization of nasal mucous epithelium in vitamin A deficient chicks but not in normal chicks[24]. Studies of tracheal tissue have more recently demonstrated preferential depletion of mucous secreting cells due to decreased mitotic rate[25]. Compromise of this mucociliary lining of the respiratory tract during vitamin A deficiency could be one way to specifically link

respiratory infection and vitamin A deficiency in a causal chain. The degree of vitamin A deficiency necessary to precipitate this respiratory dysfunction remains in question and has yet to be documented in humans.

Associations between vitamin A deficiency and respiratory disease have been reported by many investigators. These reports are difficult to compare, however, given the varying definitions of both vitamin A deficiency and respiratory disease and the differing study designs. An increased risk of respiratory disease (RR=1.8) was reported for children with mild vitamin A deficiency (defined as XN and X1B) in a longitudinal observational study in Indonesia[16]. In a similarly designed study of children in India, mild vitamin A deficiency was associated with a comparably increased risk of respiratory disease (RR=2.0)[21]. In a prevalence survey conducted in the Philippines, active xerophthalmia was positively correlated with having had pulmonary tuberculosis (diagnosed by x-ray) or recent whooping cough[5]. In a prevalence survey of xerophthalmia in Malawi, children with active xerophthalmia were more likely to have had a history of cough and fever during the previous week than those without xerophthalmia[11]. In southern Ethiopia, children with severe xerophthalmia or Bitôt's spots were found to have had a higher prevalence of respiratory disease over the preceding year[12].

Recent clinical trials have examined the impact of vitamin A on respiratory disease outcomes in children: two were conducted among vitamin A replete Australian children[26,27], one among preterm U.S. infants with respiratory distress syndrome[28], and another intervention trial was conducted in Thailand[29]. The Australian group initially looked at 1-4 year olds with a history of respiratory disease. These children were randomized into vitamin A and placebo groups. Over the ensuing 11 months, the supplemented group had 19% ($p<0.05$) fewer episodes of respiratory infection symptomatology than the placebo group. In a follow up study, children aged 2-7 years who had a history of bronchiolitis during infancy were randomized into a controlled trial of vitamin A supplementation. This treatment did not raise retinol levels nor did it affect respiratory morbidity over the 12 months of observation, thus contradicting the original study. The third clinical trial involved 40 very low birth weight infants with premature lungs, a noninfectious condition, and examined the duration of mechanical ventilation. Over the 28 days of supplementation, the vitamin A supplemented group demonstrated higher mean retinol levels, less bronchopulmonary dysplasia (BPD, lung scarring) and shorter required ventilation time than the placebo group. The intervention trial in Thailand involving 166 children aged 1-5 years noted lower rates of respiratory infections among the vitamin A treated children compared to the controls. These differences were not always statistically significant. Limitations of this study include that it was not randomized, nor masked, and the outcomes were based on 2-3 month recall.

The associations between vitamin A deficiency and ARI reported from the epidemiologic studies above do not confirm a cause and effect relationship. None of the reports of the trials in children mentioned above present a convincing argument for vitamin A impacting on ARI. The role of vitamin A in the incidence and severity of respiratory disease during childhood remains somewhat unclear. Several studies which were specifically designed to look at this relationship are underway and should help clarify the issue. The role of vitamin A in measles has been better characterized and is discussed below.

CLINICAL TRIALS OF VITAMIN A FOR ACUTE RESPIRATORY TRACT INFECTIONS

Author, Year and Country	Design and Sample Size	Main Results	Comments
Pinnock CB, et al, 1986, Australia	Randomized, placebo controlled; 147 children 1-4 years followed for 11 months.	Vitamin A group had 19% fewer episodes of ARI symptoms ($p<0.05$).	ARI not clearly defined, ultimate dose unknown, outcomes reported by parents.
Pinnock CB, et al, 1988, Australia	Randomized, double masked, placebo controlled; 206 children aged 2-7 years followed for 12 months.	No difference between vitamin A group and controls.	Weekly dosing scheme; addressed some of the shortcomings of the previous trial.
Shenai JP, et al, 1987, U.S.A.	Double masked, controlled trial of vitamin A among premature infants; 40 infants followed for 28 days.	Vitamin A infants required shorter ventilation times and had less BPD.	Unclear importance with respect to undernourished children in LDCs, does suggest a role for vitamin A in epithelial tissue repair.
Bloem M, et al, 1990, Thailand	Controlled trial of vitamin A (200,000 IU); 166 children aged 1-5 years.	Higher incidence (>2 times) of respiratory infections among controls.	Significance not universal to all sub-groups, not randomized, nor masked, outcomes based on 2-3 month recall.

Vitamin A and Measles

Measles is a particularly unusual childhood morbidity. Its effects on the immune system and on epithelial tissues in some ways parallels what is known about vitamin A deficiency from animal studies. There are reports from at least three areas of research which suggest an association between vitamin A deficiency and undesirable measles outcomes. These reports relate to post-measles blindness, low retinol blood levels during measles, and reduction of measles' associated morbidity and mortality with vitamin A supplementation.

Many reports from Africa document that eye disease is a serious complication of measles and that this keratoconjunctivitis can lead to blindness. Vitamin A deficiency appears to be an associated factor, perhaps weakening the conjunctiva of the eye and making it more susceptible to invasion by pathogens such as herpes simplex or other viral infections[30]. In India, however, researchers studied children with measles and age-sex matched healthy controls to determine the underlying mechanism leading to eye complications[31]. The mean serum vitamin A levels in children with corneal lesions were similar to those in children without lesions. Also, the presence of fine lesions had no significant association with severity of vitamin A deficiency.

Various studies have observed that during measles, as well as during other infections, especially febrile conditions, serum retinol levels decrease. Speculative mechanisms have been suggested including:

i-reduction of food intake due to anorexia during infection;

ii-decreased absorption of pre-formed and pro-vitamin A due to diarrhea;

iii- increased demand and utilization of retinol to maintain and to repair injured tissue (eg. mucosal lining of the trachea and/or gut);

iv- fever, which depresses the mobilization of retinol from liver.

The adjuvant effect of vitamin A in cases of severe measles has been reported from several sites. In the 1930s, Ellison reported a lower mortality rate among children in the United Kingdom with severe measles who were treated with a vitamin cocktail containing large amounts of vitamin A[32]. In Tanzania[33], children admitted to hospital with severe measles were randomly allocated to receive routine treatment alone or treatment with additional 200,000 IU doses of oral vitamin A. Baseline characteristics of the two groups were virtually identical for age, severity of measles, and for vitamin A and general nutritional status. Ninety-one percent of the children were vitamin A deficient and, of the subjects given vitamin A supplements, 7 percent died, of the controls; 12 percent died. This difference in mortality was most obvious for children under 2 years of age but was not statistically significant. A subsequent trial of similar design from Capetown, South Africa, reported a significant reduction in case fatality among severe measles cases treated with vitamin A[34]. This randomized, double masked, placebo controlled trial of vitamin A involved 189 children with complicated cases of measles. Subjects received either 400,000 IU of retinyl palmitate or placebo. The children who had received vitamin A had fewer days with diarrhea and respiratory disease and significantly less mortality (2 deaths) compared to the untreated group (12 deaths, $p = 0.05$).

Measles vaccination should remain the primary public health effort for the reduction of measles mortality. Nevertheless, as these studies have shown, treatment with vitamin A may have an important role to play in reducing the rate of adverse measles outcomes. Although the effect of vitamin A on less severe cases remains to be demonstrated, it would seem clear at this point that all measles cases should be treated with vitamin A.

MEASLES MORTALITY AND VITAMIN A: ADJUVANT THERAPY FOR SEVERE, HOSPITALIZED CASES

Author, Year and Country	Design and Sample Size	Main Results	Comments
Ellison, 1932, (UK)	600 measles cases, half received vitamin A as cod liver oil.	Mortality: Treated/Control RR = 0.43	Not randomized
Barclay et al, 1987, (Tanzania)	Randomized trial, 90 cases received vitamin A (200,000 IU), 90 controls.	Mortality: Treated/Control RR = 0.54	Randomized, partly masked
Hussey et al, 1990, (South Africa)	Randomized trial, 92 cases received vitamin A (400,000 IU), 97 cases received placebo.	Mortality: Treated/Placebo RR = 0.21 Complications: Pneumonia RR = 0.44, Diarrhea RR = 0.40	Double masked

Vitamin A and Mortality

There are many anecdotal reports of the association between xerophthalmia (vitamin A deficiency) and mortality. Two published reports more carefully document this association. McLaren noted in an account of his work in Jordan among malnourished, hospitalized children that there was a 64% mortality rate among children with corneal xerophthalmia, a 56% mortality rate among those with only conjunctival signs, and only

a 15% mortality rate among those with no signs of xerophthalmia[35]. Sommer, in his early epidemiologic work in West Java, Indonesia, noted a relative risk of mortality of 0.25 for normal children compared to children with vitamin A deficiency[36]. These studies stimulated a number of clinical trials to determine whether vitamin A supplementation could reduce mortality in children.

The results of several high dose vitamin A supplementation trials among children have been reported. The Aceh study in Indonesia was the first published trial to show that vitamin A nutriture may have a profound impact on child survival[37]. In this randomized, double masked trial, high dose (200,000 IU) vitamin A capsules were given every six months to children one to seven years of age. Villages assigned to the vitamin A treatment experienced a 34% reduction in mortality compared with untreated villages. The sample included over 25,000 children. Eleven percent of study children were missing follow-up information, 2% had active xerophthalmia at baseline, and anthropometry on a 10% subsample revealed that 3.0% of the program and 3.7% of the control children were <80% of median weight for height.

A similarly designed study from Hyderabad, India reported no effect of 200,000 IU of vitamin A every six months on mortality[38]. This prospective, double masked, placebo controlled trial among 15,775 preschool children, showed no difference in morbidity or mortality rates between those in the vitamin A group and those who received placebo. There was significant attrition of subjects and poor compliance in this study which could reduce the power to detect an effect. The prevalence of night blindness and Bitôt's spots was 6% at baseline. Nutritional status was not reported.

During a double masked, community trial in Nepal among 24,805 preschool children, high dose vitamin A or, alternatively, a recommended daily allowance (RDA) of vitamin A was given every four months; this trial demonstrated that high dose vitamin A could reduce mortality by 30%[39]. The baseline prevalence of xerophthalmia was 3.0% and estimated infant mortality was 82/1000 live births in this population. Acute malnutrition among all study subjects as indicated by MUAC less than 11.5 cm was 3.6%.

Two additional trials of vitamin A with differing designs have also been reported. A low dose, weekly supplementation trial (a dosage regimen to simulate an improved dietary intake) from Madurai, India revealed a 56% reduction in childhood mortality among the treated children[40]. This trial was randomized, controlled, and double masked; 15,528 children were studied. The weekly treatment was 8333 IU of vitamin A with vitamin E or vitamin E alone. Eleven percent of subjects at baseline had some form of xerophthalmia while 31% were stunted, 23% were wasted and 18% were both stunted and wasted. These measures of vitamin A status and general nutritional status indicate that there were profound nutritional deficiencies in this population.

Lastly, a controlled trial of fortified MSG (monosodium glutamate) in West Java, Indonesia noted a significant reduction in childhood mortality in villages receiving this fortified condiment[41]. Children in the control villages were 1.8 times more likely to die. There were 5775 eligible children from program villages and 5445 from control villages. Baseline prevalence for Bitôt's spots of a subset was 1.24% among program children and 0.77% among controls.

The various studies examining the role that vitamin A plays in childhood mortality are summarized in the following tables.[1]

VITAMIN A AND MORTALITY
FINDINGS FROM POPULATION STUDIES

Author, Year and Country	Design and Sample Size	Main Findings	Comments
Sommer et al, 1983, (West Java, Indonesia)	Observational cohort. 3,481 children.	Mortality: XP/Normal RR = 1.4, BT/Normal RR = 6.6	Evidence of an association between vitamin A deficiency and mortality.
Sommer et al, 1986, (Aceh, Indonesia)	Intervention trial, random allocation by village. 12,991 vitamin A (200,000 IU), 12,209 controls.	Mortality: All ages, Treatment/Control RR = 0.73; preschool, Treatment/Control RR = 0.66	Control mortality increased with age, treated mortality declined with age.
Tarwotjo et al, 1987, (Aceh, Indonesia)	Secondary analysis for intent to treat. 9,776 received treatment, 2,447 did not, 12,173 controls.	Mortality: Non-recipient/Control RR = 3.0	Evidence of self selection among recipients.
Muhilal et al, 1988, (West Java, Indonesia)	Fortification study, not randomized. 5,775 children in study villages, 5,445 controls.	Mortality: Fortified/Control RR = 0.69	Not randomized, fortification by village, visit at 11 months to detect mortality.
Vijayaraghavan et al, 1990, (Hyderabad, India)	Intervention trial, random allocation by village. 7,691 vitamin A (200,000 IU), 8,084 placebo.	Mortality: Vitamin A/Placebo RR = 0.95. Association between XP and mortality RR = 2.3	Loss to follow-up, 8% vitamin A, 13% placebo; no treatment received, 5.6% vitamin A, 9.1% placebo.
Rahmathullah et al, 1990, (Madurai, India)	Intervention trial, random allocation by cluster. 7,764 vitamin A (8,333 IU weekly), 7,764 placebo.	Mortality: Vitamin A/Placebo (0-11 mos) RR = 0.5, (12-35 mos) RR = 0.46, risk reduced for all causes, particularly among stunted children	Mortality declined with age; 88% of subjects were contacted at weekly intervals.
West et al, 1991, (Sarlahi, Nepal)	Intervention trial, random allocation by cluster. 14,487 high dose vitamin A (200,000 IU), 14,143 low dose vitamin A (1,000 IU).	Mortality: High dose/low dose (6-72 mos) RR = 0.70, (6-12 mos) RR = 0.78	Mortality declined with age in both groups, 88% received capsules from staff.

Legend

XP = xerophthalmia
BT = Bitot's spots
IU = International Units

[1] I would like to acknowledge the input of Dr. Ronald Gray in the development of these tables.

VITAMIN A AND MORTALITY
A COMPARISON OF STUDIES FROM INDIA

	Vijayaraghavan et al, 1990 Hyderabad, India (no effect)		Rahmathullah et al, 1990 Madurai, India (reduced mortality)	
Population	n = 15,775		n = 15,419	
Age Range (< 1 year)	0-5 (22.5%)		0-5 (8.9%)	
Vitamin A Deficiency at Baseline	6%		11%	
Vitamin A Dose	200,000 IU every 6 months		8,333 IU every week	
Compliance: No dose received All doses received	Vitamin A 8% 58%	Placebo 11% 57%	All 0% 42%	
Mortality per 1,000	5.5	5.8	Vitamin A 4.8	Placebo 10.4
Mortality in Relation to Compliance No dose 1 dose 2 doses	17.6 9.7 2.3	17.2 10.8 2.2		
Follow-up Visits	Every 3 months		Weekly	

Several issues remain after review of the mortality studies above. Seven randomized trials, with the exception of the one study from Hyderabad, indicate an important effect of vitamin A on childhood mortality. The Hyderabad study suffered from lost to follow up and from the limited extent to which the doses, either vitamin A or placebo, were actually delivered to the study subjects. Both of these problems could result in obscuring a real effect of vitamin A.

Another issue is the generalizability of the results of these studies. All of the populations involved in the clinical trials were, by design, very malnourished and subject to high morbidity and were in south or southeast Asian countries. These trials might then be characterized as trials of the efficacy of vitamin A. The extent to which vitamin A administered through a program can reduce childhood mortality in more representative populations is likely to be less. Nevertheless, reductions in childhood mortality of even 10% are still important. Lastly, the effect of vitamin A supplementation on childhood mortality in regions where there are very different morbidity and malnutrition levels may not be the same. For example, in areas with high prevalences of malaria and AIDS such as sub-Saharan Africa, vitamin A supplementation may not result in the same degree of mortality reduction as that observed in the studies described above. Neither malaria nor AIDS related mortality are known to be affected by vitamin A supplementation.

IV. Interventions to Combat Vitamin A Deficiency

Vitamin A Supplementation[42,43]

Two forms are available for the delivery of vitamin A supplements: capsules and liquid concentrate. Recently, vitamin A has become available as a liquid concentrate that can be dispensed from pre-calibrated, reusable plastic bottles. This form of delivery reduces costs and allows greater flexibility in dosages which may be more compatible with existing primary health care infrastructures. The most widely used form of massive doses of vitamin A, however, are soft gelatin capsules containing 200,000 IU of vitamin A.

Vitamin A capsule distribution programs have several advantages as a means of delivering vitamin A to preschool children. The costs of the capsules are minimal and of those costs, the majority is for the gelatin capsule. The results of administering a large dose capsule of vitamin A are seen very quickly in cases of night blindness (days) and Bitôt's spots (weeks). Since vitamin A is stored in the liver, large doses can be given biannually to meet children's needs. Biannual campaigns of large dose capsule distribution could be an effective way of delivering vitamin A. The weaknesses lie in that such campaigns may not reach the difficult to reach, and distribution may rely on the primary health care system which may or may not be particularly effective. Mega-dose supplements are generally regarded as a short-term interim measure for the control and prevention of vitamin A deficiency. For children over one year of age, the recommended dosage for vitamin A capsule supplementation is 200,000 IU given two times per year. The dose for children younger than one year of age or children who are significantly underweight is 100,000 IU per dose, twice a year.

Vitamin A capsule distribution programs have been instituted at the national or regional level in many countries at various times including India, Bangladesh, Indonesia, Haiti, Philippines, Sri Lanka, El Salvador, Thailand, Tanzania, and Malawi. In addition, a successful community-based (initiated and financed) program has been implemented in Caruaru, Brazil.

Vitamin A Fortification[42,43]

Nutrient fortification of foods is a common means of ensuring adequate dietary intake of specific nutrients in many developed countries. The marginal costs of the additional nutrient(s) are minimal and are spread over all consumers. Moreover, there is no need to effect changes in dietary habits if the proper vehicle is chosen. Problems still confront governments wanting to initiate fortification programs, however. There are some technical problems such as degradation of the nutrient while "on the shelf" and changes in the appearance, taste or smell of the fortified food. Additionally, political problems have occurred when non-traditional food vehicles have been recommended (wheat flour in Bangladesh) or when health care providers raised issue with the nutritiousness of the vehicle (MSG in Indonesia). Lastly, a vehicle may prove to be consumed less universally than had been thought as in the case of the poorest segment of the population consuming unrefined sugar (and thus not fortified sugar) in Guatemala. Nevertheless, vitamin A fortification of a common food vehicle is generally regarded as a medium-term strategy and remains an important means of delivering vitamin A.

The first example of food fortification was the addition of a cod liver oil concentrate to margarine in Denmark during World War I. Vitamin A fortification of food for widespread use by young children throughout the world first occurred in 1965 when all nonfat dry milk distributed by the United States Government food donations program (PL 480) was fortified with vitamin A. The specific objective was to provide the recommended daily allowance of vitamin A in 40 grams of nonfat dry milk--the target amount for child recipients. All nonfat milk distributed through international food donation programs is now fortified.

Several requirements must be met prior to initiating a food fortification strategy. These were outlined by the Food and Nutrition Board of the United States National Academy of Sciences in a 1974 policy statement[44]. Some of the requirements include:

1. The food vehicle selected to supply the nutrient should be a food or food ingredient universally consumed by the target population with relatively little daily or seasonal variation.
2. Fortification should not adversely affect acceptability of the fortified food.
3. Fortification must be centralized in a small number of well-equipped and administered plants serving the targeted geographic areas to ensure uniform processing and production.
4. Fortification must be economically feasible.

Vitamin A Dietary Interventions[42,43]

Strategies to alleviate vitamin A deficiency have been implemented mainly in Asia and have employed vitamin A supplementation of children or fortification of common food vehicles with vitamin A. Relatively little attention has been focussed on nutrition education or behavior change through social marketing efforts which promote increased consumption of vitamin A rich foods. Interventions that attempt to increase dietary intake of locally available vitamin A sources by educating caregivers or by promoting common foods rich in vitamin A have several theoretical advantages. If such an intervention could be implemented it could be more independent of the health care system over the long run and thus, perhaps, more sustainable. A dietary intervention can be tailored to a particular site, season and population. Additionally and frequently forgotten, there are usually marginal benefits from the foods that are promoted, eg. iron from dark green leafy vegetables promoted for their vitamin A content. Moreover, the effects may be felt by the entire community not just the child, similar to fortification but unlike capsules.

The long-term sustainable strategy to prevent and control vitamin A deficiency requires an improved dietary intake of locally available and affordable food sources rich in vitamin A. Dietary modification can occur only through behavior change. The diets consumed by or fed to vulnerable groups must include more bio-available sources of vitamin A. This requires nutrition and health education and social marketing either to change the foods offered to individuals or to change methods of preparation of these foods. Such interventions are not easy to implement. There needs to be a sensitivity to locale and there needs to be a commitment over time. Dietary habits are not changed

easily or quickly. In order for social marketing strategies to be culturally appropriate, and thus maximally effective, they must be based on a thorough understanding of the cultural beliefs about, and attitudes toward, consumption of the food sources being promoted. In some countries, vitamin A education programs initially can be developed within existing, broadly based health and nutrition education efforts. In many countries, however, there are social structures such as women's groups and religious organizations that could be the forum for education and promotion. It goes without saying that promoting the production of low-cost β-carotene rich vegetables and fruits should be an important component of any dietary strategy.

Vitamin A and Pregnancy and Lactation

There is no direct evidence in humans of the relationship between low vitamin A levels during pregnancy and reproductive failure, or congenital defects in ocular or nonocular organ systems. However, children born with congenital xerophthalmia are more likely to have been born to mothers who were reportedly xerophthalmic themselves, or suffering from nightblindness during pregnancy[45]. Clearly, there needs to be research to describe the vitamin A status during pregnancy, to describe the maternal and fetal sources and utilization of vitamin A and provitamin A carotenoids and to relate these factors to maternal pregnancy outcomes and perinatal outcomes. The relationship between vitamin A deficiency and vaginitis (and thus, perhaps, prematurity) is suggested by the role of vitamin A on epithelial linings but has never been reported in the scientific literature.

The WHO and International Vitamin A Consultative Group (IVACG) have recommended that in areas where dietary intake is known to be inadequate, pregnant women consume 10,000 IU (3,000 mg RE) of vitamin A daily in the form of supplements. (More than 10,000 IU increases the risk of teratogenicity.) This measure protects the woman from pregnancy-induced xerophthalmia, raises her own bodily stores of vitamin A, and thus provides an adequate amount to the fetus without risk of toxicity. Vitamin A deficiency is presumed to be a disease that afflicts weanlings based on the assumption that breastfed infants receive adequate levels of vitamin A through breast milk for the first six months of life. When maternal diets are low in vitamin A, breast milk is proportionally low, although the exact mechanism of mammary uptake of serum retinol is not well-understood. The goal for the period of lactation is to maintain a high vitamin A concentration in breast milk. When short-term dietary improvements are not possible, supplementing the woman at parturition with 200-300,000 IU of Vitamin A will safely maintain maternal stores and breast milk levels in the normal range for at least one month. The WHO recommends using 110 mg retinol palmitate or 66 mg retinol acetate at the time of delivery or once during the next four weeks. Following the first postnatal month, 10,000 IU supplements are recommended for mothers whose diets are inadequate in vitamin A[46].

Vitamin A Intervention Impact Evaluations

The impact of vitamin A interventions have been evaluated in several sites. Several supplementation programs have been evaluated[47,48,49,50]. None of these

programs have been able to demonstrate substantial reduction in the prevalence of nutritional blindness in children under six years of age. The effectiveness of most supplementation programs has been disappointing in this regard. This is not attributed to the efficacy of vitamin A supplementation but to the efficiency of the delivery system. Results indicate that the high coverage rates often achieved at the outset of a program drop off progressively to produce final overall coverage rates of approximately 60 to 65 percent. Often, the inefficient delivery system fails to consistently reach the most inaccessible and vulnerable population of children.

Examples of successful vitamin A fortification programs in developing countries are limited. The national level sugar fortification programs in Guatemala, Costa Rica, Honduras, and Panama met with limited success. They managed to only temporarily reduce the prevalence of subclinical vitamin A deficiency. International price increases for vitamin A resulted in early domestic termination of the sugar fortification programs. Renewed efforts are underway in Central America to again, fortify sugar and eliminate vitamin A deficiency. Monosodium glutamate (MSG) fortification in the Philippines and in Indonesia have met with numerous technical and political impediments to national implementation. Consequently, neither country currently maintains a national MSG fortification program. In Bangladesh, a successful technology for wheat fortification has been identified. Unfortunately, as mentioned above, wheat is not a staple in the Bangladeshi diet. The feasibility of reliance on an imported dietary item for the fortification program is problematic. Fortification of sugar in Guatemala and MSG in Indonesia have been evaluated and shown to be an effective means for improving vitamin A status[45,51].

Dietary interventions have frequently been discussed, have sometimes been executed but only occasionally have been evaluated and the results reported. Several of these interventions standing alone have been found to be useful[52,53,54]. When compared to other interventions, however, in an evaluation biased toward interventions with short term effects and limited to vitamin A specific outcomes, a dietary intervention did not perform as well as a supplementation or fortification intervention[55]. More carefully designed dietary programs with thoughtfully executed evaluation components are needed to determine the true value of such an intervention.

Conclusions

There is no reason to believe that clinical vitamin A deficiency and certainly not sub-clinical states of deficiency, have been eradicated from the developing world. In spite of many years of intervention and attention in some regions of the world, many other populations have suffered through worsening economic and social situations and declining states of health and nutrition. Vitamin A deficiency by whatever definition may well have increased. The body of evidence suggests that, beyond those with frank xerophthalmia, children with a 'sub-clinical state' of vitamin A nutriture may benefit from vitamin A interventions. Thus, it seems appropriate to broaden the definition of vitamin A deficiency. While identifying vitamin A deficiency by any definition remains problematic, in many cases common sense, based on previous epidemiologic investigations, is useful in predicting which populations may suffer from a less than sufficient state of vitamin A nutriture.

Several studies agree on a very important role of vitamin A in childhood mortality. The generalizability of these findings to all situations and all populations remains undetermined, though additional studies yet to be reported may be helpful. Nevertheless, it seems prudent at this time to consider this inexpensive and safe intervention as an important component of the arsenal of health and nutrition interventions for developing countries. The role of vitamin A in morbidity incidence or severity has yet to be adequately determined. Two important reasons beg for further definition of this relationship. First, there may be an important role for vitamin A in the treatment of specific morbid conditions over and above xerophthalmia; examples of such might be treatment in cases of pneumonia or specific forms of diarrhea. Secondly, in an environment of limited health care resources there will undoubtedly be competition for those resources; the relative importance of vitamin A interventions for various childhood morbidities must be known in order to make informed decisions.

Vitamin A interventions designed to decrease rates of xerophthalmia or to reduce childhood mortality may be reaching the target population to a greater or lesser degree. Careful systems analyses and operations research would be helpful to improve the coverage of those efforts falling short of their goals. Additional, innovative routes for improving the vitamin A status of an individual or a population should be considered. These may include different target groups, such as infants or lactating women, and should consider longer term strategies, such as dietary and fortification interventions. Additionally, the relationship of multiple micronutrient deficiencies and protein-energy malnutrition with vitamin A deficiency can not be ignored. Further investigation of these interrelationships is warranted.

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The Impact of Breastfeeding on Infant and Child Morbidity and Mortality[1]

Mary Ann Anderson, PhD,RD[2]

Abstract

A review of recent, well controlled studies confirms a dose-response, and age-specific relationship between breastfeeding in infancy and reduced morbidity and mortality from diarrhea and acute respiratory infections as well as overall mortality. These protective effects are most pronounced during the first six months of life. In terms of reduction in risk of diarrhea or acute respiratory infection and resultant mortality, exclusive breastfeeding through 4-6 months of age confers the greatest benefit, partial breastfeeding is intermediate, and no breastfeeding is the most life-threatening. However, data from the Demographic and Health Surveys in 24 countries indicate that exclusive breastfeeding during the first 4 months of life is practiced on average by only 15% of infants. While the health risks of partial or no breastfeeding in infancy are greatest in environments where access to potable water and sanitation are low, the reduction of diarrheal morbidity associated with breastfeeding is still high even in developed country settings, possibly due to immunologic factors uniquely found in human milk. Sources of bias, as well as standard definitions of breastfeeding practices are discussed. If exclusive breastfeeding for the first 4-6 months and continued breastfeeding through the first year of life were to become universal, 2 million infant deaths could currently be averted per year.

It has long been known that breastfeeding has a major positive impact on child survival and reduced fertility in developing countries. The health impacts of breastfeeding are the most pronounced in the most adverse environments and early in infancy. Better designed research studies of the last decade have gone a long way to quantify these benefits, while controlling for sources of bias which were not addressed in earlier work. While recognizing the many nutritional, child spacing, maternal health and economic benefits of breastfeeding, the focus of this paper will be on the impact of breastfeeding on infant and child morbidity (due to diarrhea or acute respiratory infection) and mortality in developing countries. Examples from developed countries will be cited as relevant to illustrate particular points.

One of the biggest discoveries arising from recent research is the clear dose-response relationship between the amount of breastmilk an infant consumes and its decreased relative risk of morbidity and mortality; the more breastmilk received the better the health outcome, especially in early infancy. In the first six months of life

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exclusive breastfeeding is at the most desirable end of the spectrum and no breastfeeding at the most negative end. Thus it has become important to clearly and consistently define the type of breastfeeding practices when studying impact on morbidity and mortality.

Breastfeeding Definitions

A useful schema for breastfeeding definitions is shown in Figure 1 (Labbok and Krasovec, 1990). It makes an important distinction between full and partial breastfeeding. Likewise within "full breastfeeding", there are two distinct categories: namely "exclusive breastfeeding" in which infants receive no other liquids or solids and "almost exclusive breastfeeding" in which breastfed infants also receive water, juice or ritualistic feeds. The "partial breastfeeding" category should be used for all infants who receive breastmilk substitutes (food-based fluids) or other semi-solid or solid foods in addition to breastmilk.

At a recent consultation between the World Health Organization (WHO), A.I.D., and UNICEF in June 1991 it was suggested that the categories shown in Figure 1 be slightly modified and expanded on as follows: (1) a better term for "almost exclusive breastfeeding" is "predominant breastfeeding", (2) receipt of vitamins, minerals or medicines by drops or syrup should be allowed in the "exclusive" category as well as wet nursing or expressed breastmilk if the infant is receiving no other foods or liquids, and (3) infants receiving oral rehydration solution in addition to breastmilk should be placed in the "predominant breastfeeding" category.

Because of the dose-response relationship between type of infant feeding and health outcomes, this paper will focus on reviewing studies which adhere to the above definitions of infant feeding behavior and which disaggregate impact on morbidity and mortality for exclusive, predominant, partial and no breastfeeding categories. The misclassification bias that results from failing to make these distinctions between types of breastfeeding can lead to a serious underestimation of the health benefits, especially when partially breastfed infants are grouped with those exclusively breastfed.

Magnitude of the Problem of Suboptimal Breastfeeding Practices

Given that exclusive breastfeeding is the optimum infant feeding practice for assuring favorable health outcomes for infants from birth through four to six months of age, how common is this behavior? For the first time comparable data from the nationally representative, A.I.D.-funded Demographic and Health Surveys (DHS) in 24 developing countries surveyed between 1986 and 1989 are available to answer this question. Figure 2 shows the high rate of any breastfeeding among infants 0-4 months of age, ranging from a low of 71% in Brazil to a high of 100% in Togo, Ghana, Uganda, and Burundi. The percentage of women who do not breastfeed their infants is low in most cases. It is this type of crude statistic on breastfeeding prevalence that has led to complacency and a misperception in many quarters that there is not much of a problem with breastfeeding practices in developing countries.

However, Figure 3, which shows the percent of infants 0-4 months of age who are exclusively breastfed by country from those same DHS surveys, paints a very different picture. The optimal behavior, exclusive breastfeeding, is often rare and

averages only about 15% across the 24 countries with a range from 1% in Nigeria to 84% in Burundi. The percentages of breastfed infants who also receive water or breastmilk substitutes and other foods, in contrast to those exclusively breastfed, are shown in Figure 4. It is clear from these data that the prevalence of suboptimal breastfeeding practices, such as predominant or partial breastfeeding, is high throughout the developing world.

Other common suboptimal breastfeeding practices with negative health consequences are delayed initiation of breastfeeding postpartum and the discarding of colostrum, and ceasing breastfeeding too soon. Breastfeeding durations of a year or more are desirable.

Sources of Bias in Association Between Breastfeeding and Morbidity and Mortality

There are many potential sources of bias when comparing mortality and infection rates between breastfed and other infants (Kramer, 1987). The most common sources of bias in breastfeeding and health impact studies fall into two major categories: (1) reverse causality, and (2) low comparability in socioeconomic status between study groups. Reverse causality occurs in breastfeeding studies when the outcome being studied, e.g. death or illness, precludes or terminates breastfeeding, rather than the reverse, that is failure to breastfeed causing the illness or death. Thus while there is a causal relationship between breastfeeding and illness or mortality, the temporal sequence is the reverse of that hypothesized. Another example is low birth weight infants who are at increased risk of morbidity and mortality but who also are less likely to be breastfed (Barros et al., 1986). Reverse causality bias leads to an overestimation of the benefits of breastfeeding.

Socioeconomic and demographic differences between mothers who breastfeed and those that bottle-feed are potential confounders because these factors are associated both with infant feeding practices and with morbidity and mortality. Thus in many developing countries where breastfeeding is more common among the lower income, less educated population and bottle-feeding is practiced by the upper income, well-educated group, comparison of infant health outcomes by type of feeding, without controlling for these major socioeconomic differences, leads to an underestimation of the benefits of breastfeeding. In contrast, in the U.S., breastfeeding is practiced by well-educated middle and upper income groups and bottle-feeding is more common among lower income groups, thus comparison of health outcomes by these modes of infant feeding without controlling for socioeconomic status could overestimate breastfeeding's benefits.

Because many older studies present spurious results due to the biases described above, this paper's review of the literature on infant and child morbidity and mortality reduction associated with breastfeeding will draw for the most part on well-designed, carefully controlled, more recent studies. A good illustration of analytical methods used to reduce bias and the impact of such statistical controls on the magnitude of infant mortality reduction associated with breastfeeding is a Malaysia study (Habicht et al., 1986). Even after adequately controlling for potential reverse causality and confounding factors, this study and others still find the protective effect of breastfeeding to be highly significant (Millman and Cooksey, 1987; Kramer, 1987).

Morbidity Reduction by Type of Infant Feeding

Diarrheal disease and acute respiratory infections are singled out for review here because it is against these two infections that breastfeeding is known to have its greatest protective effects. Furthermore, these two diseases make a major contribution to infant and child mortality in the developing world (causing more than 50% of all under-five deaths according to WHO 1990 estimates) and thus are being emphasized in child survival programs. There are several different ways in which breastfeeding may protect infants against infection (Institute of Medicine, 1991):

- hygiene/reduced exposure to pathogens
- enhanced nutritional status
- antimicrobial, anti-inflammatory, and immunologic-stimulating agents
- promotion of desirable gut flora and intestinal mucosal renewal and recovery
- contraceptive effects which may lengthen birth interval and reduce family size

Diarrhea

In developing countries, where access to potable water and sanitation are low, breastfeeding is a particularly critical intervention for preventing diarrhea (Feachem and Koblinsky, 1984). In a longitudinal study of more than 3,000 infants in Cebu, the Philippines (Popkin et al. 1990), the incremental and statistically significant increases in diarrheal disease risk with each addition to the breastmilk diet of water, teas, non-nutritive and nutritive liquids are clearly illustrated with multivariate statistical controls used to minimize bias. For infants 2 months of age residing in urban areas, compared to exclusive breastfeeding the relative risk of diarrheal morbidity was 3.2 for breastfed infants who also received non-nutritive liquids, 13.3 for breastfed infants who also received nutritive foods/solids, and 17.3 for infants who received no breast milk. The relative risks for infants in these three feeding groups remained high compared to exclusive breastfeeding through 6 months of age, namely 3.2, 10.6, and 13.4, then became insignificant in the second half of the first year of life. The relative risks in the rural area at 2 months of age were lower than in the urban area though still high, that is 2.2 for breastmilk plus non-nutritive liquids, 5.7 for breastmilk plus nutritive foods/solids and 5.7 for no breastfeeding. Similar risks were found through 6 months of age.

Another well-controlled study of diarrheal morbidity by type of infant feeding practices in Lima, Peru (N=153) also shows elevated relative risks with consumption of liquids, infant formula and solids in addition to or in lieu of breastmilk (Brown et al., 1989). In infants 0-2 months of age, compared to exclusive breastfeeding the significantly elevated relative risks of diarrhea prevalence were 1.9 for breastmilk plus other liquids, 1.6 for breastmilk plus artificial milk, 2.6 for breastmilk plus solids and 3.4 for no breastmilk (Figure 5). At 3-5 months of age the relative risks for these same

feeding groups were 2.0, 2.3, 3.3 and 5.5 respectively. At 6-8 months and 9-11 months, the relative risks of diarrhea prevalence in infants who received no breastmilk compared to those who received breastmilk plus solids were 1.7 and 1.6 respectively. An important finding of this study was that the impact of breastfeeding on reduced diarrheal morbidity was greater for diarrheal prevalence than incidence (Figure 6) which suggests that in addition to protecting against new infections, breastfeeding also reduced the duration (and perhaps severity) of diarrheal episodes that did occur.

A study in Imo State, Nigeria of 882 infants and children (Huttly et al. 1987), corroborates in Africa the findings of the two previously cited studies in Asia and South America, while controlling for confounding. At 0-2 months of age the relative risks of diarrhea compared to exclusively breastfed infants were 3.3 for partial breastfeeding and 10.2 for no breastfeeding. At 3-5 months of age the relative risk for partial breastfeeding was 4.8 and there were no cases in the not breastfed category. In the 6-23 month age group there was no significant difference between the partially breastfed and not breastfed groups.

The variations in relative risks of diarrheal morbidity with different modes of infant feeding across studies and between urban and rural areas in the Philippines may be due to greater exposure to enteric pathogens in certain settings due to less access to potable water and sanitary excreta disposal, drinking of unboiled water, crowding or other factors not studied. In conclusion, while the addition of non-nutritive liquids to the breastmilk diet during the first six months of life elevates diarrheal morbidity risk 2 to 3-fold, the addition of nutritive liquids and solids may be even more hazardous and increase risk of diarrheal morbidity 2 to 13 times. Most in jeopardy are infants who receive no breastmilk and experience relative risks of diarrheal morbidity which are 3 to 17 times higher than those of exclusively breastfed infants. In general, these risks diminish to insignificant levels after 6 months of age. However, a careful, prospective study of 4,612 children 12-36 months of age in Bangladesh suggests that in very adverse environments, where the prevalence of malnutrition is high, continued breastfeeding affords significant protection from bloody and chronic diarrhea and lowers case fatality rates for these two diseases among severely malnourished children through three years of age (Briend et al., 1988).

The greatest impact of breastfeeding on reducing gastrointestinal infections and resultant infant mortality is observed in populations with poor sanitation and lack of potable water in the developing world (Habicht et al. 1988). Nevertheless, even in cleaner environments in developed countries, such as Scotland where 618 children were longitudinally studied for two years (Howie et al., 1990) and in the U.S. where 60 case-control pairs of infants were compared (Koopman et al., 1985), the prevalence of diarrhea is also markedly lower in breastfed versus formula-fed infants (See Figures 7 and 8). Thus the protective effects of breastfeeding are important in industrialized as well as in developing countries. This protection is attributable to the many ways in which breastfeeding may prevent infection in addition to the avoidance of pathogens as described earlier. Of particular importance are the immunologic factors unique to human milk through which breastfed infants may remain asymptomatic even after direct exposure to enteric pathogens which have contaminated the nipples and areola of the nursing mother (Institute of Medicine, 1991). Because diarrhea is rarely fatal in developed countries due to prompt treatment at readily accessible health services, these

differences in morbidity between breastfed and bottle-fed infants have not received as much attention as they deserve, given the health care and economic burdens that these preventable diarrheal episodes place on the infant, its family and the health system.

Acute Respiratory Infections

Protective effects of breastfeeding against acute respiratory infections(ARI) are less dramatic than for diarrheal disease but nevertheless significant. In the Peru Study cited earlier (Brown et al., 1989), the relative risk of the prevalence of acute lower respiratory infection (ALRI - the most fatal) compared to exclusively breastfed infants 0-5 months of age was 2.1 for breastfeeding plus artificial milk, 6.9 for breastfeeding plus solids, and 5.5 for infants who received artificial milk plus solids but no breastmilk (Figure 9). In older infants 6-11 months of age the relative risk of ALRI was doubled (1.9) for infants who received artificial milk plus solids versus infants who received breastmilk plus solids. Again we see that relative risk is lower in the second half of the first year of life, versus earlier, but still significant. In another small longitudinal study in Indonesia (N=33) time spent breastfeeding was inversely correlated with number of days infants were ill with respiratory infections (Launer et al., 1990).

Mortality

A historical review from 1870-1950 of the large differences in postneonatal mortality rates between breastfed and bottle-fed infants in developed countries is displayed in Figure 10 (Wray, 1990). Postneonatal death rates of breastfed infants were at least half those of bottle-fed infants across the entire time-span and in all countries. Even in face of precipitously declining mortality rates and thus smaller absolute differences between the two groups over the eighty years studied the clear survival advantage of the breastfed infants continued throughout. Given the current low infant mortality rates in developed countries, and access to potable water and sanitation and sophisticated health delivery systems, there is now little difference in infant survival between those breastfed versus bottle-fed. However, there are clear morbidity disadvantages of bottle-feeding as described earlier.

Some of the studies reviewed in Figure 10 and among the 21 developed country and 27 developing country studies recently included in the comprehensive review by the Institute of Medicine (1991) are older ones that probably suffer from some bias in differences between groups. However, the consistency of the findings makes it safe to assume on average that infant mortality from all causes will be at least twice as high in bottle-fed infants versus breastfed infants in the developing world.

The persistent relationship between breastfeeding and infant survival across the range of mortality rates in Figure 10 is a useful analogy to apply while interpreting the similarly wide range of infant mortality rates that prevail in different regions of the developing world and the seemingly positive relationship between breastfeeding practices and infant mortality across countries. That is, it seems counterintuitive that infant mortality rates should continue to be so high in parts of Asia and Africa where breastfeeding practices are also the most favorable in contrast to the lower infant mortality rates and negative breastfeeding practices in Latin America. However, the

observed mortality rates could be twice as high without breastfeeding. Obviously differences in mortality rates between regions are due to a complex set of causes of which breastfeeding is only one.

Mortality due to Diarrhea and ARI

A recent, well-designed, population-based study of infant deaths by type of feeding in Brazil (357 cases and 714 controls) provides strong evidence of the protective effect of breastfeeding on mortality due to diarrhea and ARI (Victora et al., 1987). Figure 11 illustrates the dose-response relationship found between type of feeding mode (amount of breastmilk received) for infants 0-12 months and the reduced relative risk of mortality due to diarrhea. Compared to exclusively breastfed infants, the relative risk of mortality due to diarrhea for partially breastfed infants who received combined diets of breastmilk plus other milk and non-milk supplements ranged from 2.6 to 5.7, whereas the relative risk of diarrhea mortality among those who received no breastmilk ranged from 15.6 to 18.3. The younger the infant, the greater the relative risks (RR) of mortality from diarrhea associated with suboptimal breastfeeding practices (RR of 3.1) or not breastfeeding (RR of 24.7) as illustrated by the data for infants below two months of age (Figure 12).

Although less dramatic than for diarrhea, data from the same Brazil study on the reduced risk of mortality from respiratory infections (Figures 12 and 13) are also impressive. Compared to exclusive breastfeeding, partial or no breastfeeding are associated with double or triple the risk of mortality due to respiratory infections.

Based on the infant feeding practices described in the DHS surveys, current regional infant mortality levels and the relative risks of diarrhea and ARI mortality found in Brazil, estimates of the total number of infant deaths due to these causes associated with suboptimal breastfeeding practices in developing countries have been calculated by Huffman et al. (1991). The estimates derived are conservative because they restrict themselves only to deaths due to diarrhea or ARI and do not include the additional benefits of breastfeeding on other illnesses, child spacing, or nutritional status. The assumptions used by the authors were that:

- diarrheal disease (DD) and ARI each account for 25% of all infant deaths each year;
- 60% of all DD or ARI deaths are of infants 0-5 months of age;
- 50% of infant population is 0-5 months of age;
- rural mortality is twice as high as urban;
- relative risk of cause-specific mortality by age and breastfeeding (BF) practices is as follows:

	Exclusive BF	Partial BF	No BF
DD			
0-5 mos.	1	3	18
6-11 mos.	1	1	3
ARI			
0-5 mos.	1	2	2.5
6-11 mos.	1	1	1.5

The results of these calculations are shown in Figures 14 and 15. In terms of currently prevailing breastfeeding practices, it is estimated that breastfeeding is averting six million infant deaths per year, the vast majority of which (71%) are due to diarrhea in infants 0-5 months of age. Thus any erosion of current desirable breastfeeding practices could significantly increase mortality rates. This argues for protecting existing, favorable breastfeeding practices. Furthermore, it is estimated that if optimal breastfeeding practices were made to prevail everywhere (exclusive breastfeeding for 4-6 months and continued partial breastfeeding thereafter), 2 million infant deaths could be averted out of the 9 million that occur in the developing world each year. Large portions of the deaths potentially preventable by breastfeeding are due to diarrhea (52%) and acute respiratory infections (32%) in infants 0-5 months of age. These projections suggest that more than half of all current diarrhea deaths and one third of all ARI deaths in infancy could be prevented if optimal breastfeeding practices were made universal.

Conclusion

This review of the best epidemiologic data available suggests that breastfeeding has a major impact on child survival, with the risk of death from all causes for non-breastfed infants approximately double that of those breastfed. Breastfeeding confers significant protection against the incidence and severity of diarrheal diseases and acute respiratory infections and reduces case-fatality from these infections. These protective effects are greatest in the first six months of life when exclusive breastfeeding is practiced, but continue to be significant throughout the first year of life in some settings, and possibly longer in the most adverse environments. Breastfeeding is an invaluable resource to be protected because it is currently responsible for averting approximately six million infant deaths in the developing world each year in addition to its many other benefits.

It is appropriate to quote from the 1990 "Innocenti Declaration on the Protection, Promotion and Support of Breastfeeding" signed by 30 countries and co-sponsored by WHO, UNICEF, A.I.D. and the Swedish International Development Authority (SIDA):

> "As a global goal for optimal maternal and child health and nutrition, all women should be enabled to practise exclusive breastfeeding and all infants should be fed exclusively on breastmilk from birth to 4-6 months of age. Thereafter, children should continue to be breastfed, while receiving appropriate and adequate complementary foods, for up to two years of age or beyond."

Universal achievement of this goal is of high priority and could avert an additional two million infant deaths annually.

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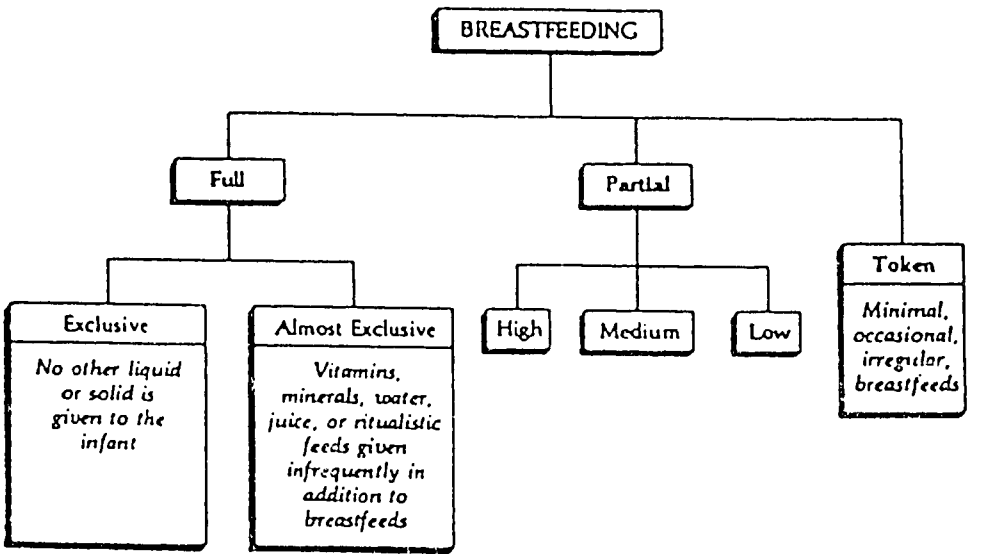
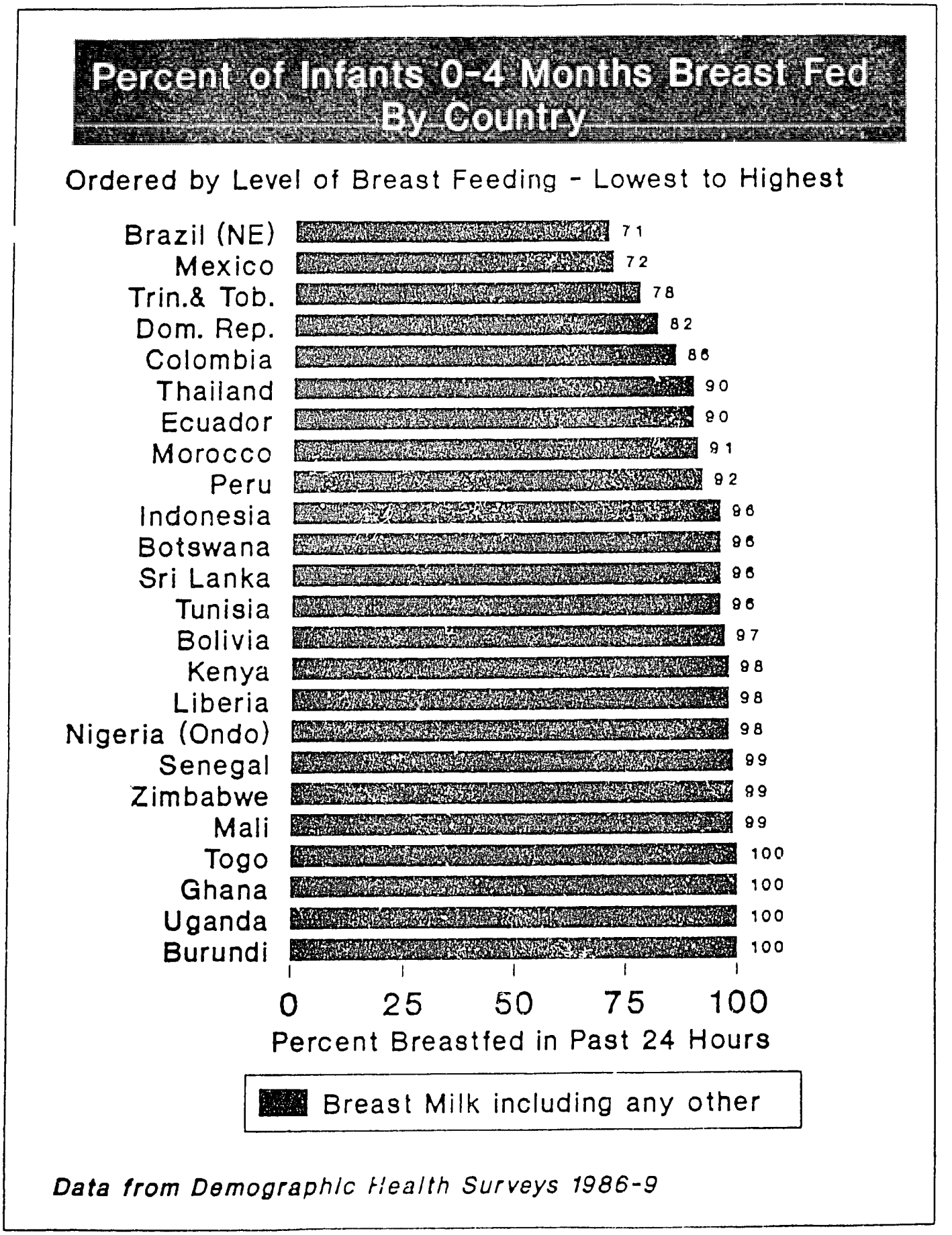
Figure 1

Schema for breastfeeding definition



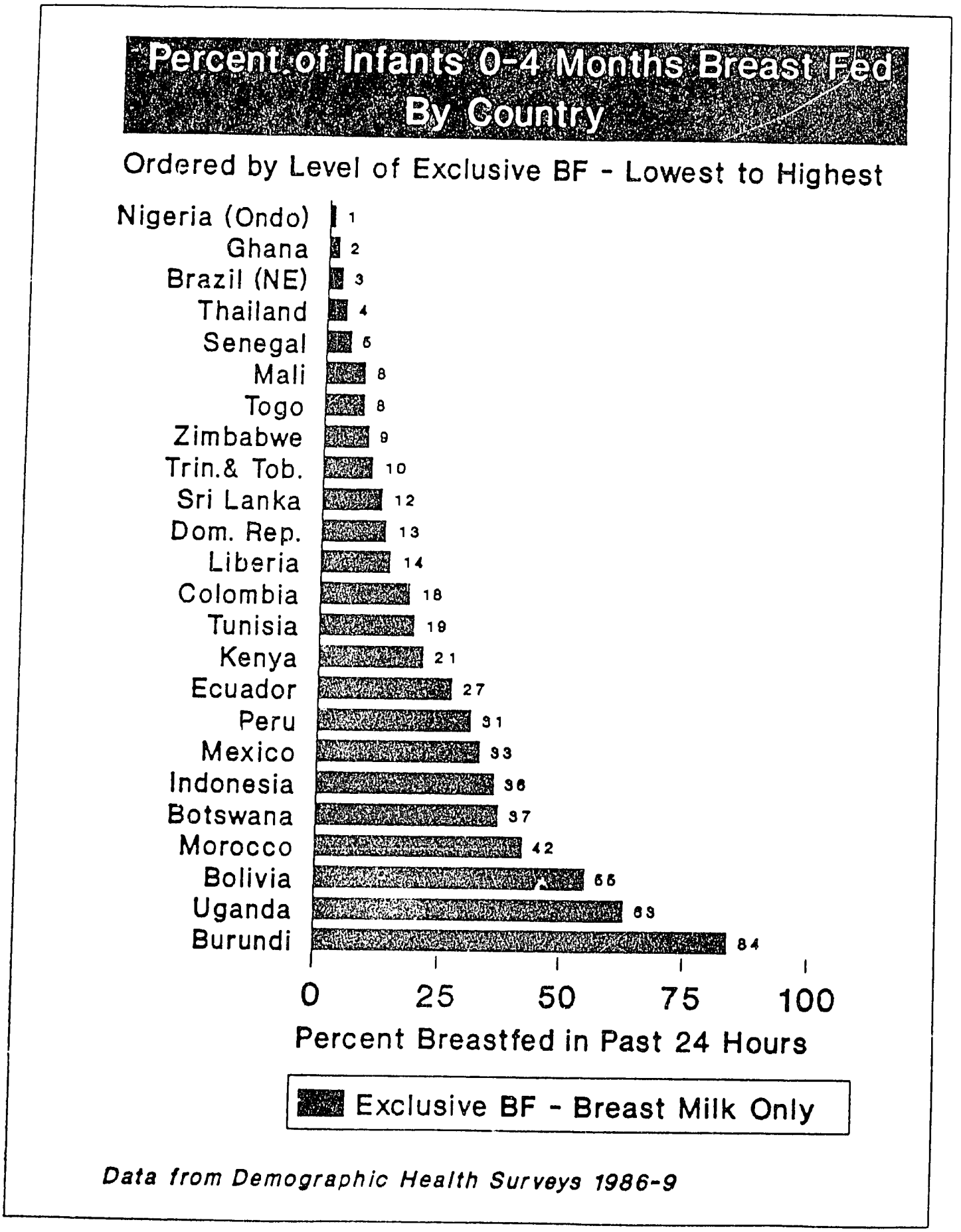
Labbok, Miriam; Krasovec, K., "Toward Consistency in Breastfeeding Definitions," Studies in Family Planning, Vol 21, No. 4, July/Aug 90.

Figure 2



Data from Demographic Health Surveys 1986-9

Figure 3



Data from Demographic Health Surveys 1986-9

Figure 4

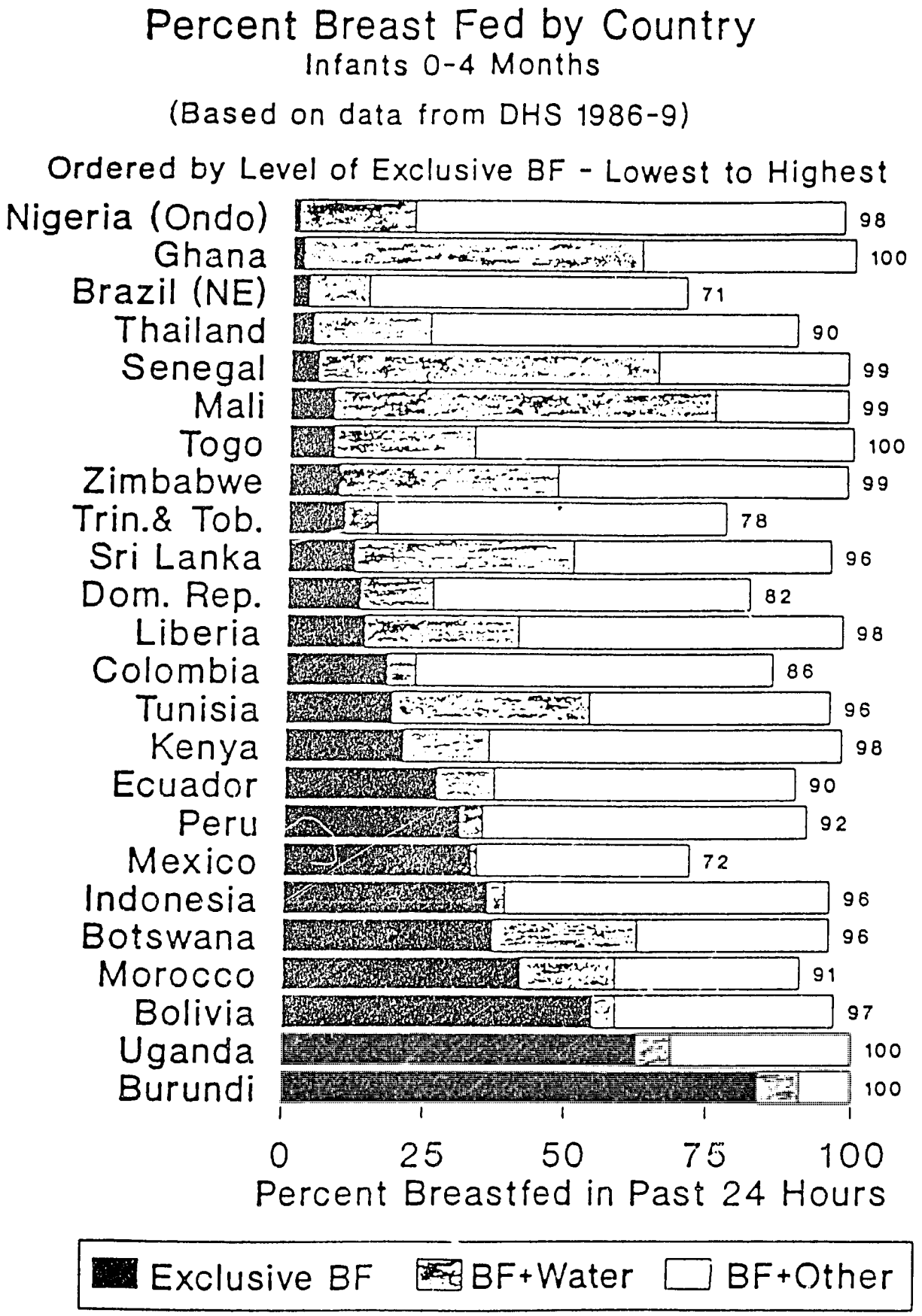
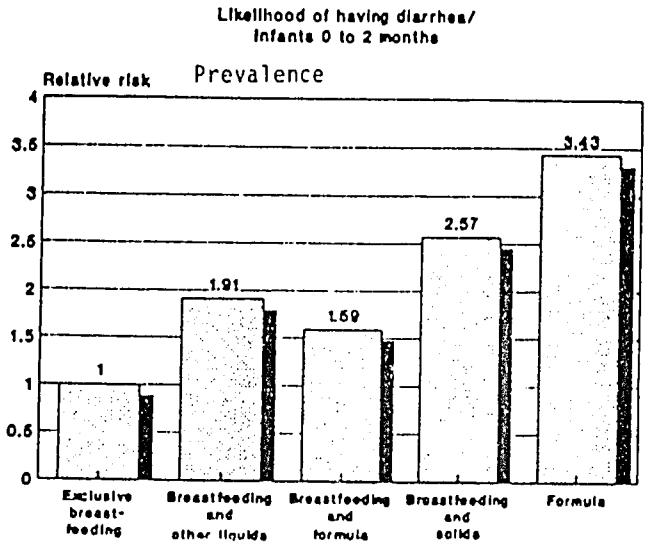

Percent Breast Fed by Country
Infants 0-4 Months
(Based on data from DHS 1986-9)
Ordered by Level of Exclusive BF - Lowest to Highest
Nigeria (Ondo) 98
Ghana 100
Brazil (NE) 71
Thailand 90
Senegal 99
Mali 99
Togo 100
Zimbabwe 99
Trin.& Tob. 78
Sri Lanka 96
Dom. Rep. 82
Liberia 98
Colombia 86
Tunisia 96
Kenya 98
Ecuador 90
Peru 92
Mexico 72
Indonesia 96
Botswana 96
Morocco 91
Bolivia 97
Uganda 100
Burundi 100
0 25 50 75 100
Percent Breastfed in Past 24 Hours
Exclusive BF
BF+Water
BF+Other

Figure 5

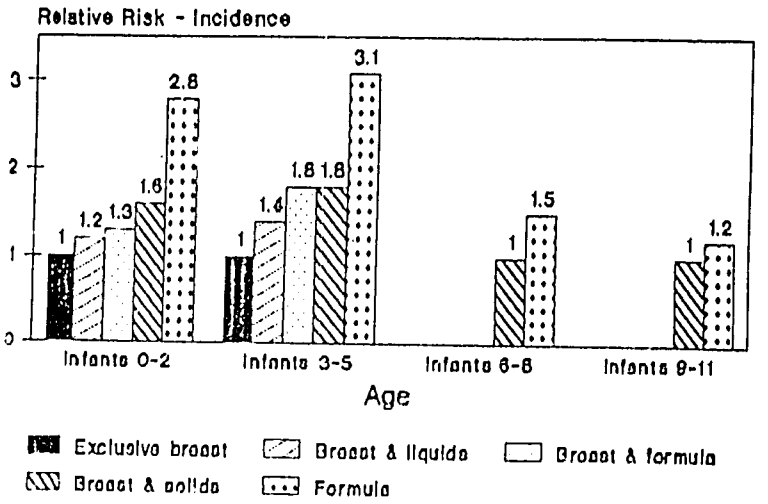
EXCLUSIVELY BREASTFED INFANTS ARE LESS VULNERABLE TO OTHER ILLNESSES.
Data from a low-income urban area in Lima, Peru.



Adapted from data in: Brown, K. et al., 1989, Pediatrics 83 (1):31-40.

Figure 6

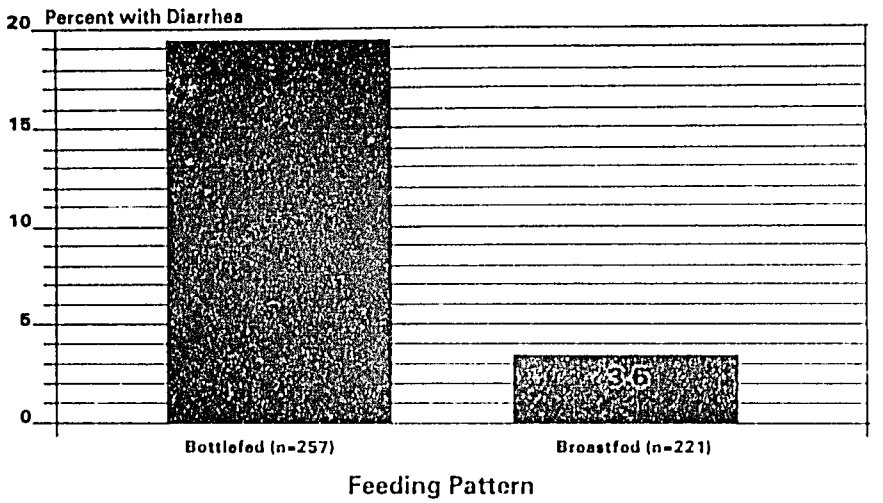
Relative Risk of Diarrhea by Feeding Practices and Age Group, Peru



Adapted from data in: Brown, Black et al., 1989.

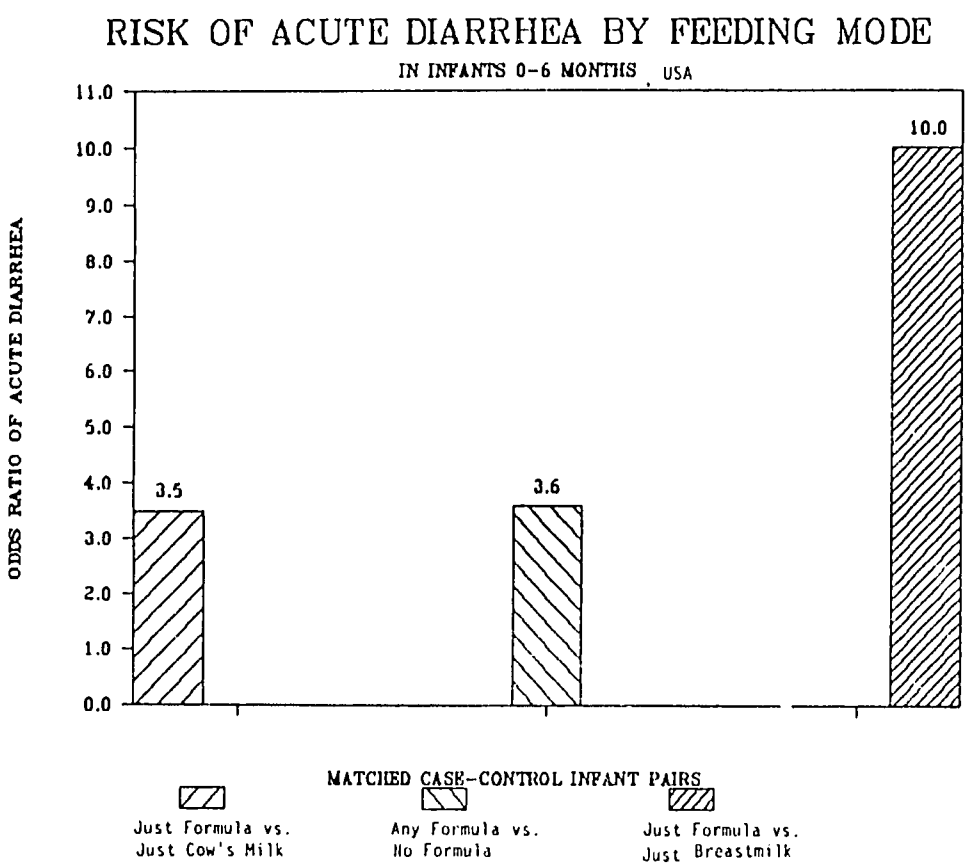
Figure 7

Prevalence of Diarrhea, Infants 0-13 weeks by Feeding Pattern, Scotland



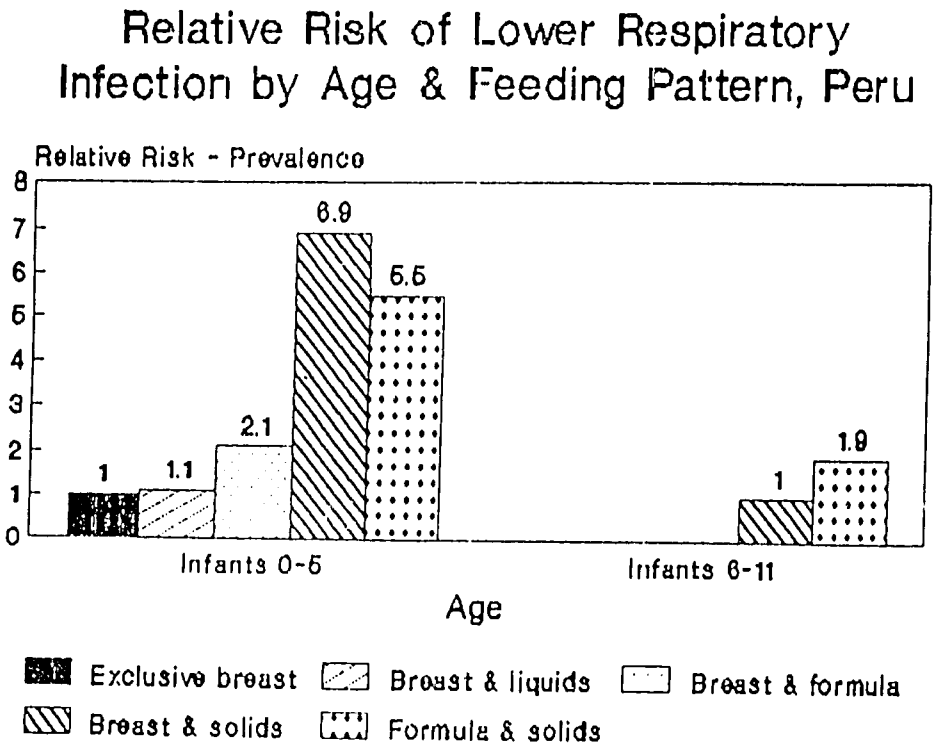
Adapted from data in: Howie, Forsyth, et al., 1990. British Medical Journal 300:11-16.

Figure 8



Adapted from data in: Koopman, J.S. et al., Am. J. Public Health, 75 (6): 477-80, 1985.

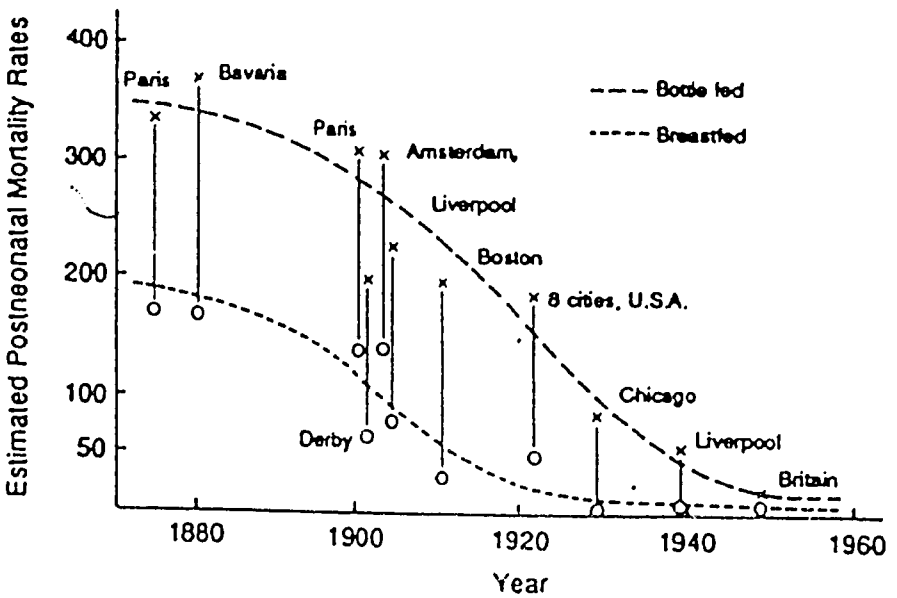
Figure 9



Adapted from data in: Brown, Black et al., 1989.

Figure 10

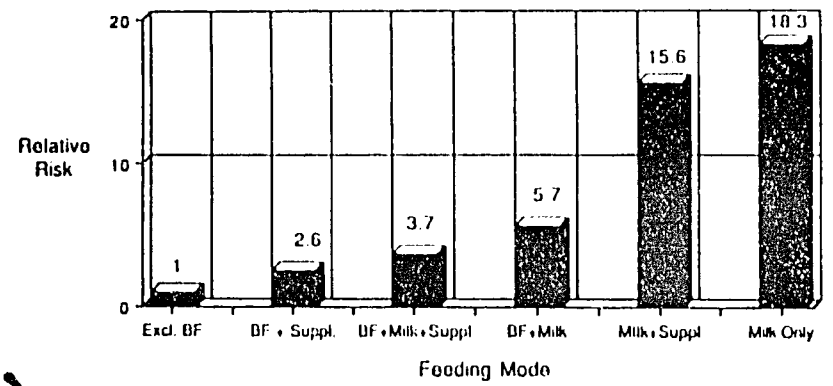
Estimated Postneonatal Mortality for Breastfed vs. Bottlefed Infants, 1870-1950



Source: From Wray in Nutrition During Lactation. Institute of Medicine, National Academy Press, 1991.

Figure 11

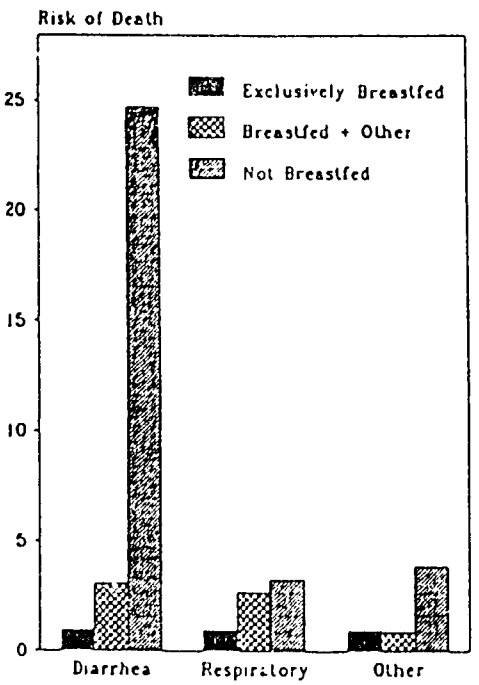
Relative Risk for Mortality Due to Diarrhea by Feeding Mode
in Porto Alegre and Pelotas, Brazil
(Infants Ages 0-12 Months)



Adapted from data in: Victora, C. et al., Lancet, i:319, 1987.

Figure 12

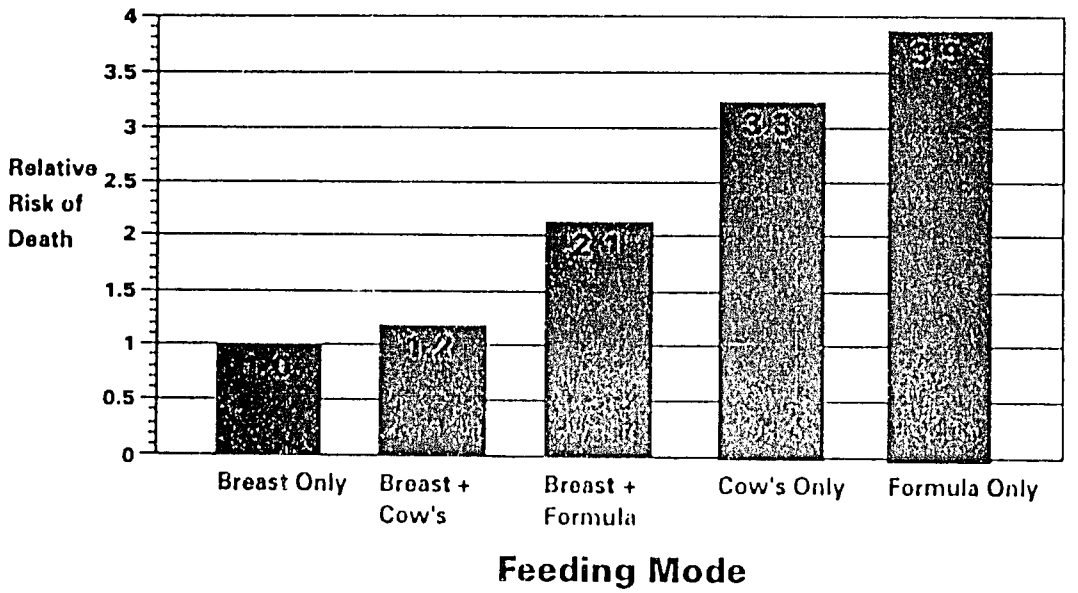
Relative Risk of Mortality from
Infectious Diseases, by Feeding
Pattern, Infants <2 Months, Brazil



Adapted from data in: Victora, C. et al., Lancet, ii: 319-22, 1987.

Figure 13

Relative Risk of Death Due to Respiratory Infections by Feeding Mode (Infants 0-12 months, Brazil)

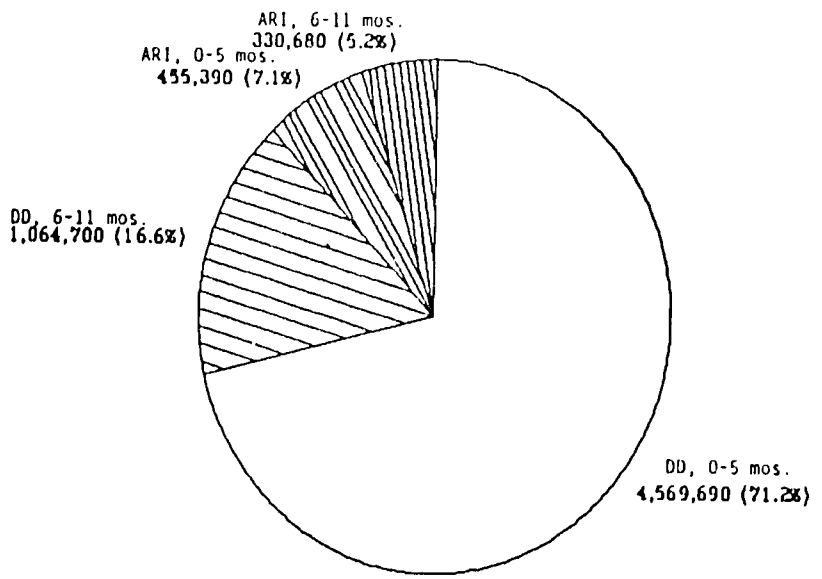


Adapted from data in: Victora, C. et al., Lancet: 319, 1987.

Figure 14

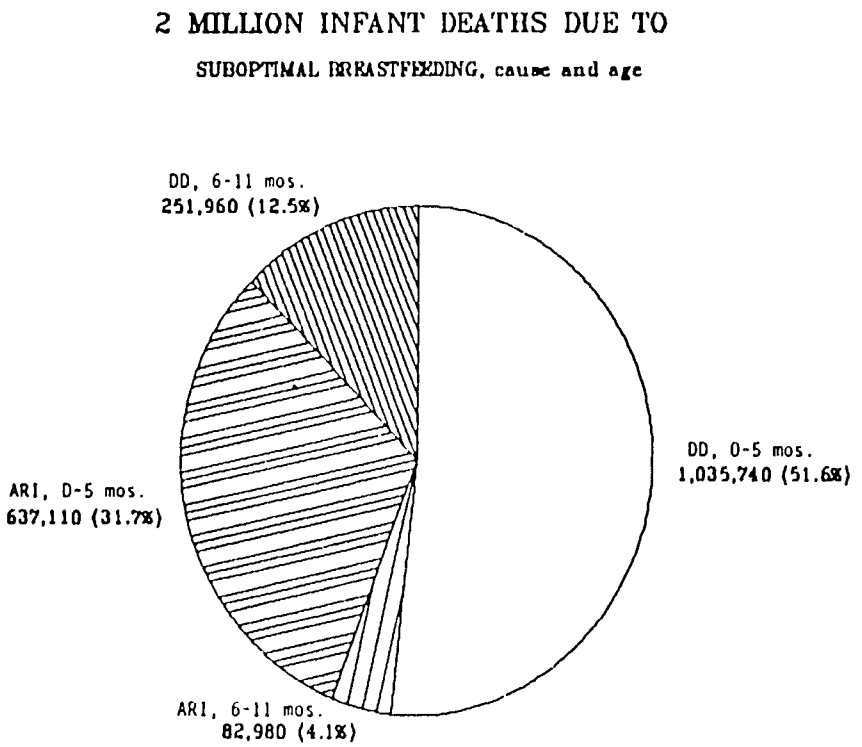
6 MILLION INFANT DEATHS AVERTED

BY BREASTFEEDING BY CAUSE OF DEATH,AGE



Adapted from data in: Huffman, S. et al., Center to Prevent Childhood Malnutrition, 1991.

Figure 15



Adapted from data in: Huffman, S. et al., Center to Prevent Childhood Malnutrition, 1991.

Malaria: The Impact of Treated Bed-Nets on Childhood Mortality in The Gambia

Pedro L. Alonso[a], Allan G. Hill[b], Patricia H. David[c], Greg Fegan[d], Joanna R.M. Armstrong[c], Andreas Francisco[a], K. Cham[e], and Brian M. Greenwood[a,*]

In rural Gambia, as in many other parts of sub-Saharan Africa, malaria remains one of the most important causes of death in children under five.[1] When vaccination coverage rates are high and deaths due to the common infectious diseases of childhood are reduced, malaria may be the principal cause of death.[2] Malaria is particularly important to control not only because of its direct effect on mortality and morbidity but also because it acts in conjunction with other diseases to increase both morbidity and mortality rates from other causes.[3]

THE STUDY

In recent years, there has been growing concern about the development of drug-resistant strains of malaria, provoking renewed interest in vector control and the reduction of man-vector transmission rates.[4] The efficacy of insecticide-treated materials has been unclear since previous studies have based their results on the effects on the vectors rather than on the malaria morbidity and mortality rates in the human population.

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[1] BM Greenwood, AK Bradley AM Greenwood et al. Mortality and morbidity from malaria in a rural area of The Gambia, **Trans R Soc Trop Med Hyg** 1987 81:478-86. U and A Brinkmann, Malaria and health in Africa: present situation and epidemiological trends, **Trop Med & Parasitol** 1991, 42:204-13.

[2] BM Greenwood, AM Greenwood, AK Bradley et al. Deaths in infancy and early childhood in a well-vaccinated, rural West African population. **Ann Trop Paediat** 1987 7:91-9.

[3] DCW Mabey, A Brown, BM Greenwood. Plasmodium falciparum malaria and Salmonella infections in Gambian children. **J Infect Dis** 1987 46:181-202.

[4] JA Rozendaal. Impregnated mosquito nets and curtains for self-protection and vector control. **Trop Dis Bull** 1989 86:R1-R41; CF Curtis, JD Lines, P Carnevale et al. Impregnated bed nets and curtains against malaria mosquitoes. In: **Appropriate methods of vector control**, ed. CF Curtis, CRC Press, Florida, 1990:5-46; WHO. The use of impregnated bednets and other materials for vector-borne disease control. (WHO/VBC 89.981). WHO, Geneva, 1987. For a recent general review, see SC Oaks et al, 1991, **Malaria: obstacles and opportunities**, Institute of Medicine, US National Academy Press.

In 1988, therefore, the UK Medical Research Council began a systematic trial of a combined intervention for the control of malaria in central Gambia around the small town of Farafenni. On the North Bank of the Gambia river, some earlier work had suggested that chemoprophylaxis with Maloprim (dapsone + pyrimethamine) and Permethrin-treated bed-nets had reduced malaria morbidity but the intervention was too small scale for much to be said about mortality.[5] For the new double-intervention trial with permethrin-treated bed-nets and Maloprim used in combination, a new site was chosen south of the Gambia river and east of Farafenni town. The area included 73 villages in all, of which 17 of the larger villages, generally those with 400 or more people, had joined the government's Primary Health Care scheme. The 56 smaller villages are here referred to collectively as 'non-PHC' villages. Both the interventions, the treated bed-nets plus the chemoprophylaxis, were conducted in the PHC villages with the non-PHC villages serving as controls (see Table 1).

Table 1: Summary of activities in the PHC and non-PHC villages

Period	PHC treatment villages (17 villages: children= 2616)		Non-PHC controls (56 villages: children= 1795)
PRE-INTERVENTION PERIOD			
June 1988 to July 1989	Census followed by routine collection of data on births, deaths and migration with verbal autopsy questionnaires for all children dying under age 6		
INTERVENTION PERIOD			
July 1989 to June 1990	Treated bed-nets plus 1/4 strength Maloprim for half of all children 6 months to 5 years	Treated bed-nets and placebo for the other half of all children 6 months to 5 years	Mortality and morbidity surveillance only
POST-INTERVENTION PERIOD			
May-June 1990	New census with up-dating of all records of births and deaths plus a single round retrospective demographic survey with a full birth history for all women of reproductive age. Verbal autopsy analysis.		

The total population of all the villages averaged 21,157 individuals, comprising mostly Mandinka-speakers with some Fula as well as other smaller ethnic groups. In this area of flat Sudan savanna, with mangrove swamps at the river's edge, the rainfall is close to 1000 mm. per year: in 1988, it was 1051 mm and in 1989 it was 887 mm. The rainy season from June to October is the most important season for the transmission of malaria by the Anopheles gambiae complex and most malaria deaths are concentrated in September, October and November of each year. In this paper, only the effects of

[5] RW Snow, SW Lindsay, RJ Hayes, BM Greenwood. Permethrin-treated bed-nets (mosquito nets) prevent malaria in Gambian children. **Trans R Soc Trop Med Hyg** 1988: 82:838-42.

interventions on the mortality of young children are discussed. Full details of the conduct of the intervention, the dipping of the bed-nets and the chemoprophylaxis are available elsewhere.[6] The effects of the bed-nets on the incidence of clinical malaria and the prevalence of malaria infection will be reported separately. [7]

The interventions in the PHC villages

In July 1989, all bed-nets in the PHC villages were first washed and then dipped in a Permethrin solution designed to produce a dose of about 500mg per m^2 of net. Altogether, 5380 bed-nets were treated in this way, 88% of all nets in use in the villages. In all, 92% of all children in the PHC villages slept in treated bed-nets during the intervention trial. Before the intervention began, it should be noted, 96% of children in the PHC villages had been sleeping in untreated bed-nets. Even in the non-PHC villages, 77% of children had been sleeping in untreated bed-nets. Then, all children in the PHC villages in the target age group, 6 months to five years, were randomized into two groups for receipt of either 1/4 strength Maloprim (25mg dapsone + 3.13 mg pyrimethamine) or a placebo of similar colour and taste. Chemoprophylaxis was continued for 20 weeks, July to November 1989, the main period of malaria transmission. Detailed compliance records were kept and random urine tests were conducted for the presence of dapsone. Compliance in the treatment and placebo groups was the same (95%) and more than 75% of the children in the treatment and control groups took their tablets on 90% of the required occasions.

Mortality surveillance

Once the study area had been identified, a full census of the 73 villages was carried out, listing all usual residents of each compound and family by name, age and sex. From 1 July 1988, village reporters recorded all births, deaths and permanent migration movements occurring in their villages. This information was collected weekly and checked by MRC field assistants, men and women with secondary school education from the area or nearby. At the MRC field station near Farafenni, these data were regularly entered into a computer so that up-dated census files could be maintained and checked on a continuous basis.

In addition, a single-round retrospective survey of the lifetime fertility and childhood mortality experience of all women of reproductive age in the study area was carried out early in 1990 for two reasons. First, information on the longer-term trends in childhood mortality was needed to be sure that childhood mortality had not been on diverging paths in the pre-intervention period in the PHC and non-PHC villages. There were some concerns that mortality might have been changing at a different rate in the larger PHC villages compared with the non-PHC villages. In addition, despite the care

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[6] P Alonso, SW Lindsay, JRM Armstrong, M Conteh, AG Hill, PH David, G Fegan, A de Francisco, AJ Hall FC Shenton, K Cham, BM Greenwood. Reduction of mortality in Gambian children by insecticide-treated bed-nets. **Lancet** 337: 1499-1502, 22 June 1991.

[7] Alonso et al, forthcoming.

and attention which goes into the routine recording of vital events in the surveillance area, there are always a few events which slip through the net. Some of these can be picked up during the annual dry season re-enumeration of the population. Accordingly, a household form including the basic Brass questions on children ever-borne alive and surviving to interview was designed, as well as a simple birth history for all women of reproductive age, regardless of marital status. The childhood deaths from the birth histories were then matched with the MRC records to ensure completeness of coverage. Only a small number of discrepancies were found, largely due to errors in the retrospective dating of vital events in the single-round survey.

Cause of death ascertainment

All the parents or guardians of children who died in the study period (1 July 1988 until 30 June 1990) in both PHC and non-PHC villages were interviewed by a senior field assistant using a special questionnaire developed initially on the North Bank and at Bassé for the ascertainment of the likely cause of death. This form was then examined independently by three physicians familiar with the area and with the symptoms of the main causes of death in the area. Each then decided on the principal cause of death using whatever information was on the form or on attachments to it. These attachments often included the child health card, sometimes a record of treatment for a prior illness, and occasionally a report from a clinic or a hospital if the child had been taken there before death. In 43.4% of the 318 valid cases, all three physicians agreed on the main cause of death for the children of all ages who had died during the period of the intervention. In 93.4% of all valid cases, two of the physicians were in agreement. On four main causes, acute respiratory infections, diarrhea/malnutrition, acute gastro-enteritis and tetanus, the agreement between the three physicians was over 50 per cent. For malaria, they agreed in 44% of cases. It turned out that the most difficult cases were neonates or children under six months; in almost a third of the cases of deaths under six months, a final cause of death could not be determined. Recognizing these difficulties and indeed the problems of post-mortem cause of death ascertainment without a hospital autopsy, the three physicians then conferred with all the evidence before them. Overall, a final diagnosis was agreed upon for 73% of the cases, 66% for children who died at 6 months of age or older. It is this final diagnosis agreed between the three physicians which is used here.

RESULTS

Childhood mortality

The routinely collected surveillance data can be used quite readily to estimate childhood mortality for the two years before and after the interventions. The only difficult feature is the estimation of the denominators, the children at risk, since there is considerable movement in the area and it is impossible to keep track of all short-term migration. In view of the seasonal nature of many of these movements, it was decided to estimate the mid-period population by taking the average number of children present in the area. The end of period populations had been updated to take account of losses or omissions picked up in the annual re-enumeration of the population. These results from period life table calculations are summarized in Table 2.

Table 2: Childhood mortality for PHC and non-PHC villages south of Farafenni before and after the introduction of bed-nets

	Primary Health Care villages			Non-Primary Health care villages		
	IMR	$_4q_1$	$_5q_0$	IMR	$_4q_1$	$_5q_0$
1988-89	0.110	0.157	0.249	0.093	0.100	0.184
Deaths	59	75	134	35	32	67
1989-90	0.072	0.045	0.114	0.116	0.103	0.207
Deaths	41	25	66	43	35	78

Note: The separation factors for the calculation of the probabilities of surviving or dying were taken from the data, since in almost all cases, dates of birth and death were known in the form of day, month and year. IMR = infant mortality rate.

The data in Table 2 have several interesting features. One is the level of childhood mortality indicated. Although we have come to expect values of around 100 per thousand for infant mortality, it is a surprise to see that this value is still the figure in The Gambia where there has been a good Primary Health Care system since 1983 and where immunization coverage is remarkably high. Each year from 1985 onwards, The Gambian government has carried out an EPI survey around December-January with the results shown in Table 3. The figures for the whole country in 1989 and 1990 are very impressive, especially so since the coverage in the Central and Eastern regions was as high as in the Western region around Banjul. The mortality figures have to be interpreted in the context of this high immunization coverage, since some common causes of childhood mortality in West Africa, such as measles and tetanus, are almost absent from the cause of death data from Farafenni.

A second interesting feature of the mortality data by age is the high rates for the age group 1-4 relative to the infant mortality rates. It was once thought that one explanation for the high later childhood mortality in West Africa might be measles but this is clearly not the case since measles mortality has been drastically reduced by the immunization program. Another factor must be responsible for the high ratio of mortality of 1-4 year-olds to the mortality of infants. These dramatic reductions in mortality of the 1-4 age group were not matched in the non-PHC villages for the same period. Some fall in infant mortality was recorded in the PHC villages. This seems surprising but there is good evidence that more infant deaths than previously thought are related to malaria in this area. In addition, there appear to have been some complex interactions between malaria and other illness which complicate the identification of the effect of the bed-net intervention.

Table 3: National immunization coverage rates estimated from the annual EPI coverage surveys (percentages)

Antigen	1985	1986	1987	1989	1990
BCG	92	97	90	98	98
DPT (3)	68	72	77	83	87
Polio (3)	62	69	83	89	92
Measles	75	80	82	81	85
Yellow fever	70	73	81	87	85
Fully immunized	52	61	61	70	78

To look further back in time at trends in childhood mortality in the two different sets of villages before the intervention began, mortality rates were calculated from the birth histories obtained from women of reproductive age in January-February 1990. In addition, it was possible to go back to the data tapes from the 1983 national population census and to produce tables of the proportions dead of children ever-borne alive by age of mother for exactly the same villages included in the intervention trial. The data from the birth histories are more reliable since it was possible to re-check some results with reference to the MRC surveillance data. The level and trends in under 5 mortality are shown in Figure 1. Much the same results are obtained from the indirect estimates from the 1983 census but omission of children ever-born as well as dead children by comparison with the surveillance data make these results difficult to interpret. The data in Figure 1 strongly suggest that whilst there had been a slow improvement in child mortality before the intervention, the mortality in the two sets of villages chosen for the intervention was not very different despite the different sizes and different participation in the national primary health care system by the two types of villages. A clear demonstration of the role of malaria in the mortality decline can be seen in the graph of deaths by month for PHC and non-PHC villages (see footnote 6).

THE IMPACT OF THE BED-NETS

General mortality

The data in Table 4 show that the probability of dying for 1-4 years olds fell sharply in 1989-90 to 29% of the 1988-89 level in the PHC villages. Mortality in this age range was unchanged in the non-PHC villages. These results can be expressed in a more detailed way using the rate ratios of the age-specific death rates from the life tables (Table 4).

Table 4: Age-specific death rates and rate ratios before and after the intervention.

PRE-INTERVENTION			
Age	PHC villages	Non-PHC villages	Ratios
0	115.9 (58/509)	99.1 (35/353)	1.169
1-4	44.5 (75/1685)	27.7 (32/1156.5)	1.609
POST-INTERVENTION			
0	75.2 (41/545.5)	135.2 (43/318)	0.556
1-4	11.8 (21/1775)	28.4 (35/1232)	0.416

The effect of the bed-nets on the mortality of the 1-4 year olds is particularly clear although the decline in infant mortality is also significant. There is no obvious explanation for the higher initial levels of 1-4 year old mortality in the PHC compared to the non-PHC villages in the pre-intervention period. There is a suggestion in the cause of death data from the two sets of villages that malaria and severe diarrhea/malnutrition with gastro-enteritis may be more important causes in the larger PHC villages. Whatever the reasons for the initial differences, the bed-net intervention has reversed this relationship between the mortality in the two sets of villages. Although some of the numbers are very small, examination of the rate ratios for single years of age reveals that the decline in mortality in the PHC villages was especially marked for one year old children. In the PHC villages, deaths in this age category fell from 35 to 8 over the two years; for the non-PHC villages, the number of deaths of one year olds rose from 14 to 18.

The results from the morbidity surveillance, including measurement of body temperatures and blood slides for those with fever, and the studies of the mosquito populations, will show that these mortality results are directly associated with a proportionate reduction in cases of mild and severe clinical malaria and in overall transmission rates (Alonso et al, forthcoming).

Cause-specific mortality

Although the intervention was directed at children aged 6 months to 6 years, this section will examine the mortality of all children under 6. We have retained the data on the younger children both to keep the numbers as large as possible and because we have good evidence that the intervention had a substantial and surprising impact on childhood mortality in general (Table 4). In addition, by working with all the under fives we can more easily make comparisons with life table measures of childhood mortality from other populations.

The main causes of death for all children dying before and after the intervention are shown in Figure 2. The 'don't know' category includes both those deaths for which the three physicians could not agree and those deaths where no single cause could be identified by any of the physicians reading the post-mortem questionnaires. Before the intervention, in both the PHC and the non-PHC villages, malaria was thought to be the main cause of death in 28% of all deaths. If we exclude the deaths of those under 6 months, malaria deaths constituted 39% of all deaths in the pre-intervention year taking both PHC and non-PHC villages together.

Turning to changes in cause-specific mortality by treatment group, we see from Figure 3 the relatively small changes recorded in the non-PHC villages. There were some changes in the numbers dying of acute respiratory infections, meningitis, acute gastro-enteritis and septicaemia but the most notable feature of Figure 3 is the relatively small change in the number of malaria deaths. Figure 4 presents the mortality data on cause of death for the PHC villages. The sudden fall in deaths due to malaria is obvious. The reduction in the numbers of malaria deaths in the PHC villages was not made up by increases in other categories. On the contrary, it seems that the bed-nets intervention had an effect on some other significant causes of death, deaths attributed to acute respiratory infections in particular. There are problems in looking at these changes in specific causes both because of the uncertainty which surrounds the post-mortem cause of death assignment and because of small numbers. In an attempt to examine some of these changes in a relatively simple way, the ratio of the numbers of deaths in the pre- and the post-intervention periods have been calculated for PHC and non-PHC villages separately. Overall, the ratio of all deaths of children under age 5 in PHC and non-PHC villages was 1.77 (158/89) largely because of differences in the size of the two study populations. Figure 5 shows these ratios as well as the average for all the causes combined. Taking into account the small numbers in some categories (see Appendix 1 for the basic data), there are some remarkable reductions in the ratios for the acute respiratory infections and the diarrhea/malnutrition categories between the pre- and post-intervention periods. The change in deaths due to the acute respiratory infections is especially significant because of the number of deaths due to this cause (in the pre-intervention period, 38 under fives died of this cause in the PHC and non-PHC villages combined).

The effects of the Maloprim administered to half the children in the PHC villages were swamped by the more powerful effects of the treated bed-nets. There were only 12 deaths, 2 in the Maloprim group (attributable to malaria) and 10 in the placebo group (6 attributable to malaria).

Although not detectable in the mortality data, the data on morbidity shows that even for those children not sleeping in treated bed-nets, there were reductions in the frequency of fevers and of positive blood slides. This observation points to the possibility of a more general community effect which may be very important when compliance rates for the intervention are lower than in this study. The effects on the mosquitoes are thought to operate both through the insecticide and through the emulsion in which the insecticide is dissolved. Different emulsions may have different effects in deterring mosquitoes from even entering the sleeping areas. Work continues on this problem and on the development of waterproof emulsions which can resist washing.

It should be noted that in both the PHC and the non-PHC villages, weekly blood slides were made for all children with a temperature of over 37.5°C. Those with parasitaemia were referred to the Village Health Worker for treatment. Field workers were asked to follow up on these children and to arrange further treatment outside the village if necessary.

Theoretical explanation

The results indicate a strong direct effect of the treated bed-nets in an area where the use of bed-nets was well established before the intervention began. If such high levels of compliance can be achieved nationally, major reductions in both malaria-specific and overall childhood mortality can be anticipated. The effects described here are clearly much larger than can be anticipated in the national program but the trial has brought to light some new aspects of the disease. One is the proportional reduction in the numbers of infected bites, in mild and severe cases of malaria as well as in malaria-related deaths. [8] Some mild cases still became severe cases but the additional effect of the Maloprim was to reduce the numbers of severe cases as well as deaths. The bed-nets and chemo-prophylaxis therefore have different effects on the demography of malaria since Maloprim is effective on just one part of the continuum from infected bite to malaria death whereas the effects of bed-nets were seen at every level in this transition. It seems that the reduction in malaria mortality is due to reduction in biting rates by mosquitoes and is not due to the reduction in other insect-borne diseases such as sleeping sickness and kala azar, which are now quite rare in The Gambia. There is a possibility that elimination of some flies might have reduced enteric infections but the reduction in acute respiratory infections is greater than the reductions in the diarrheas and the severe gastro-enteritic infections.

The 'frailty protection' effect resulting from the avoidance of malarial infections is more difficult to explain. As with measles infections, there may be considerable and lasting gains to be had from the avoidance of infection by the malarial parasite and the avoidance of the consequences, such as anaemia, of this infection.

The demographic impact of the bed-nets

There are a variety of ways of estimating what might be referred to as the 'gross' and 'net' effects of the bed-net intervention on childhood mortality. Here we compare the mortality outcomes we might anticipate by re-analyzing the life tables constructed from the surveillance data using the new information on cause of death. Three different comparisons are made. One is to compare the mortality before the intervention with the mortality which would ensue if all the deaths whose main cause was judged to be malaria were eliminated. A second comparison is between this mortality in the absence of malaria with the observed mortality rates in the post-intervention period in the PHC

[8] See BM Greenwood, K Marsh and RW Snow, Why do some African children die of severe malaria? **Parasitol Today** 17(10): 277-81.

villages. Finally, we can check our calculations by comparing these results with the data from the non-PHC villages.

Table 5 contains the basic data for these comparisons. Using the data from the PHC villages first, we can see that the elimination of all malaria deaths would reduce infant mortality to 83% of its pre-intervention levels but the reduction in the mortality of 1-4 year-olds would be much greater: 56% of pre-intervention levels. Moving to the last line of the table to consider the same comparison for the non-PHC villages, similar figures are obtained. Overall, the elimination of all deaths believed to be directly due to malaria would reduce the probability of dying before age 5 to about 70% of pre-intervention levels.

Table 5: Comparison of changes in childhood mortality following the elimination of malaria deaths and the use of bed-nets

PHC VILLAGES			
	IMR	$_4q_1$	$_5q_0$
With malaria	109.6	156.7	249.1
No malaria	91.0	88.4	171.3
Bed-nets	72.4	44.6	113.8
Ratios			
No malaria/malaria	0.83	0.56	0.69
Bed-nets/malaria	0.66	0.28	0.46
NON-PHC VILLAGES			
1988-9 with malaria	93.0	100.3	184.0
1989-90 with malaria	116.1	102.9	207.0
Mean 1988-90	104.5	101.6	195.5
No malaria (2 yr average)	102.2	66.0	161.4
Ratios			
No malaria/malaria 1988-90	0.98	0.65	0.74

Much more exciting is the comparison between the pre-intervention levels and the actual mortality outcomes as measured in the post-intervention year. As we see from the middle section of Table 5, the mortality of the 1-4 year olds was cut to 28% of pre-intervention levels and the probability of dying before age 5 fell to 46% of its pre-intervention level. Quite clearly, the prevention of malaria has had a powerful synergistic effect on some other causes of death such as acute respiratory infections. In The Gambia, the case for this effect is stronger than it might be elsewhere in Africa

because some possibly confounding causes of deaths (measles in particular) have already been controlled by the time of the intervention. We refer to the effective immunization program which makes it unlikely that the reductions in childhood mortality can be simply explained by the temporary absence of some other epidemic causes of death such as whooping cough or measles. Certainly, no exceptional outbreaks of other causes of death such as meningitis were recorded during the intervention trial.

Conclusion

This study has shown that general and malaria-specific mortality in children under 5 have both been sharply reduced by the introduction of Permethrin-treated bed-nets. The extra reduction in mortality provided by the use of Maloprim taken as a prophylactic was probably slight and difficult to detect in this study because of the very strong effect of sleeping in a treated bed-net (see footnote 6). Work not discussed in detail here shows that both the mosquito population and malaria morbidity were both reduced by the intervention. The effects of the treatment of the bed-nets with Permethrin reported here are clearly due to the treatment and not just to the use of bed-nets since a large proportion of children had been sleeping in bed-nets before the intervention began.

There are two additional findings of importance to those interested in malaria-eradication programs. One is the clear additional effect on other causes of death of the treated bed net intervention. This 'frailty protection' effect is substantial but largely unexplained. More basic research is this area is called for.

A second finding is that not all children have to be sleeping in bed-nets for the benefits of the treatment to be felt. If the community as a whole participates in the intervention, some small rates of non-compliance need not invalidate the effectiveness of the intervention.

It must be remembered that the dipping of the nets was carried out entirely by village women under the supervision of the Village Health Worker and the Traditional Birth Attendant with the support of the women's association. No major difficulties were encountered during this process although several women did wash their nets in the middle of the intervention, thereby diluting the effects of the insecticide. The experience in the Farafenni area leads us to believe that the washing and dipping process, including making up the solution with the correct concentration, can be undertaken successfully with the minimum of supervision in other contexts. The costs of the solution are a few US cents per net dipped.

There are no signs that the intervention has produced any toxicity or other adverse reactions; the chemicals are difficult to detect two weeks after the dipping has taken place. [9] There are some unanswered questions about the implications of the loss of immunity whilst protected from mild infection when using a bed-net, and the effects of the bed-nets on adult mortality and morbidity have not so far been studied in detail. Mosquitos will soon develop some resistance to Permethrin but by altering the type of insecticide used every few years, it should be possible to keep ahead of these changes.

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[9] RW Snow, M Jawara, CF Curtis **Bull Ent Res** 1987 77:279-86; RW Snow, SW Lindsay, RJ Hayes, BM Greenwood **Trans R Soc Trop Med** 1988.

Other behavioral adaptations of mosquitos denied easy access to human blood are difficult to predict. There are some indications that adults in the intervention villages received additional bites. If the mosquitos were to move to animal hosts, the cycle of malaria transmission would be broken.

For estimating the mortality effect of the use of treated bed-nets elsewhere, it may be worth remembering a number of distinctive characteristics of malaria in The Gambia. One is the highly seasonal nature of transmission; we have no evidence whether the results will be the same in populations in which malaria is present all year round. Secondly, the Anopheles gambiensis does not bite during the day whereas other species have different biting habits. Thirdly, the high level of immunization achieved in The Gambia may make the effects of malaria control on mortality clearer than elsewhere since the number of competing risks from other infectious diseases has been limited. Finally, the form of living arrangements of the Mandinka, large families living in crowded compounds with wives, co-wives and children sharing a common sleeping room, may be responsible for some of the especially strong effects of the bed-nets on malaria and overall mortality. In rural Gambia, a 1991 survey revealed that 62% of beds in PHC villages and 51% of beds in non-PHC villages had bednets around them. [10]

[10] M Aikins and S Bennett, National bednet survey, MRC, The Gambia.

TABLE A: Main cause of death by age of death for the pre-intervention period: Primary Health Care (PHC) and non-Primary Health Care (non-PHC) villages combined.

Cause of death	Age at death (months)								All
	0	1-5	6-11	12-23	24-35	36-47	48-59	60+	
ARI	5	8	8	10	1	3	1	1	37
Malaria	0	2	10	14	18	10	5	11	70
Mening.	1	2	2	2	3	1	0	1	12
Diar/mal	0	1	2	3	4	0	0	0	10
Gastero'	0	4	10	9	0	1	0	1	25
Septaec.	0	2	2	3	0	1	0	0	8
Tetanus	1	0	0	0	0	0	0	0	1
Miscell.	2	1	0	1	2	0	1	1	8
No agree	7	8	8	11	2	3	0	2	46
Unknown	19	5	1	0	1	0	1	1	30
Total	36	37	38	54	37	19	9	17	247

TABLE B: Main cause of death by age of death in the post-intervention period: Primary Health Care (PHC) and non-Primary Health Care (non-PHC) villages combined.

Cause of death	Age at death (months)								All
	0	1-5	6-11	12-23	24-35	36-47	48-59	60+	
ARI	4	11	0	2	2	2	0	0	21
Malaria	0	2	2	5	4	5	2	7	27
Mening.	1	2	3	0	0	0	0	0	6
Diar/mal	0	0	0	1	1	0	0	1	3
Gastero'	0	1	1	1	1	0	0	0	4
Septaec.	0	2	1	0	0	0	0	0	3
Tetanus	0	0	0	0	0	0	0	0	0
Miscell.	3	0	0	0	0	0	0	0	3
No agree	7	8	8	11	2	3	0	2	41
Unknown	19	5	1	0	1	0	1	1	28
Total	34	31	16	20	11	10	3	11	136

TABLE C: Main cause of death by age of death for the pre-intervention period: Primary Health Care (PHC) villages only.

Cause of death	Age at death (months)								All
	0	1-5	6-11	12-23	24-35	36-47	48-59	60+	
ARI	3	4	7	7	1	2	1	1	26
Malaria	0	2	9	11	12	6	5	7	52
Mening.	0	1	1	0	3	0	0	1	6
Diar/mal	0	0	2	3	3	0	0	0	8
Gastero'	0	3	6	7	0	0	0	0	16
Septaec.	0	0	2	2	0	0	0	0	4
Tetanus	1	0	0	0	0	0	0	0	1
Miscell.	2	0	0	1	2	0	0	0	5
No agree	4	3	2	6	5	2	0	1	23
Unknown	9	4	0	1	1	0	1	1	17
Total	19	17	29	38	27	10	7	11	158

TABLE D: Main cause of death by age of death for the pre-intervention period: Non-Primary Health Care (NPHC) villages only.

Cause of death	Age at death (months)								All
	0	1-5	6-11	12-23	24-35	36-47	48-59	60+	
ARI	2	4	1	3	0	1	0	0	11
Malaria	0	0	1	3	6	4	0	4	18
Mening.	1	1	1	2	0	1	0	0	6
Diar/mal	0	1	0	0	1	0	0	0	2
Gastero'	0	1	4	2	0	1	0	1	9
Septaec.	0	2	0	1	0	1	0	0	4
Tetanus	0	0	0	0	0	0	0	0	0
Miscell.	0	1	0	0	0	0	1	1	3
No agree	2	4	2	8	2	2	0	1	21
Unknown	11	0	1	0	0	0	1	1	14
Total	18	15	5	16	6	5	3	7	75

TABLE E: Main cause of death by age of death for the post-intervention period: Primary Health Care (PHC) villages only.

Cause of death	Age at death (months)								All
	0	1-5	6-11	12-23	24-35	36-47	48-59	60+	
ARI	2	5	0	1	1	0	0	0	9
Malaria	0	1	2	0	1	4	0	2	10
Mening.	1	1	1	0	0	0	0	0	3
Diar/mal	0	0	0	0	1	0	0	1	2
Gastero'	0	0	1	0	1	0	0	0	2
Septaec.	0	0	1	0	0	0	0	0	1
Tetanus	0	0	0	0	0	0	0	0	0
Miscell.	0	0	0	0	0	0	0	0	0
No agree	5	4	6	3	0	1	0	1	20
Unknown	8	5	0	0	1	0	0	0	14
Total	17	20	9	16	10	9	2	6	61

TABLE F: Main cause of death by age of death for the post-intervention period: Non-Primary Health Care (NPHC) villages only.

Cause of death	Age at death (months)								All
	0	1-5	6-11	12-23	24-35	36-47	48-59	60+	
ARI	2	4	1	3	0	1	0	0	11
Malaria	0	0	1	3	6	4	0	4	18
Mening.	1	1	1	2	0	1	0	0	6
Diar/mal	0	1	0	0	1	0	0	0	2
Gastero'	0	1	4	2	0	1	0	1	9
Septaec.	0	2	0	1	0	1	0	0	4
Tetanus	0	0	0	0	0	0	0	0	0
Miscell.	0	1	0	0	0	0	1	1	3
No agree	5	7	1	5	3	1	1	0	23
Unknown	9	3	1	0	0	0	0	0	13
Total	18	15	5	16	6	5	3	7	89

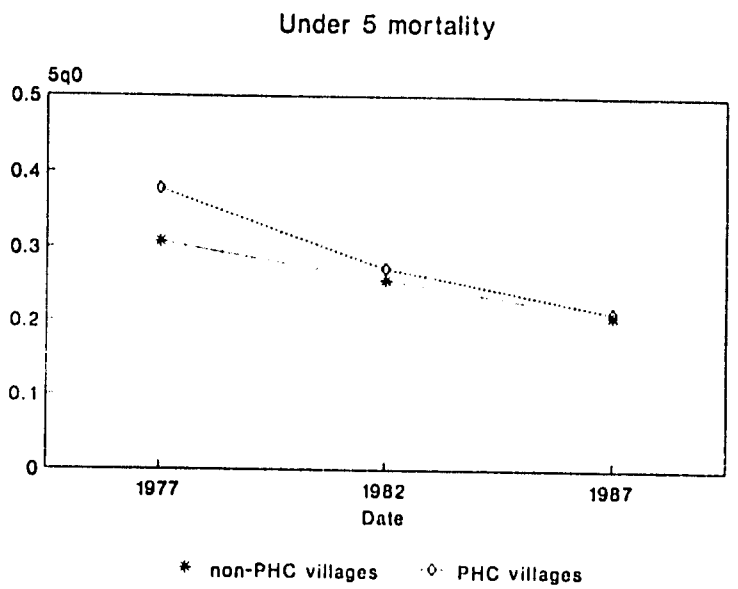
Under 5 mortality
5q0
0.5
0.4
0.3
0.2
0.1
0
1977
1982
1987
Date
non-PHC villages
PHC villages

Figure 1

Main causes of death for all under 5's before and after the use of bed-nets

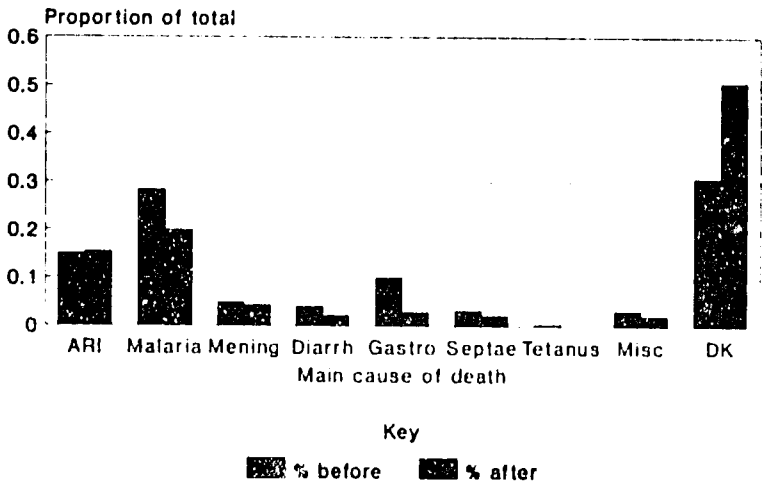

Figure 2

Numbers of deaths by main cause in non-PHC villages before and after the use of bed-nets

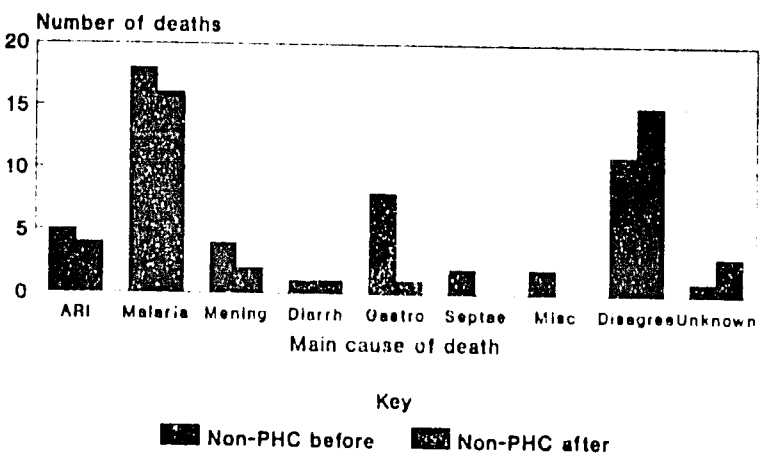

Figure 3

Numbers of deaths by main cause in PHC villages before and after using bed-nets

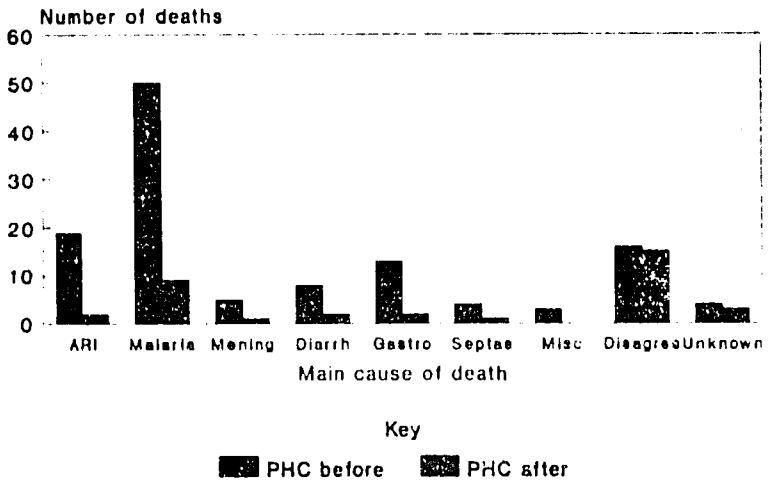

Figure 4

Ratios of numbers of deaths by cause in PHC and non-PHC villages before and after the use of bed-nets

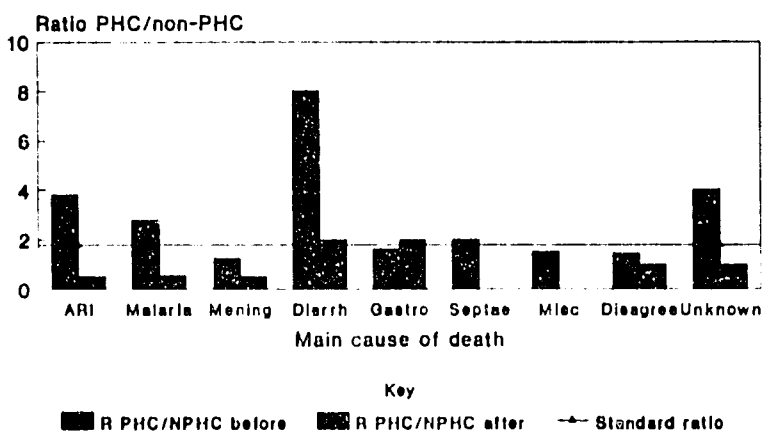

Figure 5

Behavioral Interventions: Toward Improved Health Behaviors[1]

Bonita Stanton, M.D.[2]

INTRODUCTION

It is noteworthy that a session of this seminar has been devoted to the generic topic of health behavior change. Devotion of a unique session to this health strategy serves to recognize--to legitimize--behavioral change as a unique, free standing, constituent of the health intervention armamentarium.

The implications of this legitimization are substantial for both developed and developing countries. With the recognition that purposeful behavioral change is an intervention in its own right (whether or not it accompanies other more biomedical or technical interventions) comes the obligation to establish comprehensive approaches based on the substantial advances made in the multiple disciplines concerned with behavioral change.

If we are serious in our belief in the importance of behavioral change, we are obligated to draw upon the accumulated experience of all of the social sciences concerned with behavior--the fields of diffusion, communications, anthropology, sociology, health education and psychology. That there can be a process for developing a behavioral intervention that simultaneously does not have to be re-invented for each intervention, can be situationally appropriate and can add to the overall knowledge base of behavioral change, is fundamental to progress in this field. While mechanisms (albeit of varying effectiveness) exist for identifying and incorporating biomedical innovations into public health policy, similar strategies for identifying and incorporating successful behavioral innovations have rarely been established. The predominance of a disease-oriented approach to public health policy formulation has arguably hampered the delineation of and incorporation of broad strategies and approaches to behavioral change. If the perspectives of disciplines traditionally focussed on behavioral change (psychology, sociology and health education) were utilized in formulating the research tasks,

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[1] Prepared for the Johns Hopkins Institute for International Programs/World Bank Joint Seminar on Child Health Priorities for the 1990s, Baltimore, Maryland, June 20-22. The ideas expressed in this paper draw heavily on work in progress with a multi-disciplinary team examining issues in the design of behavioral interventions and diarrheal diseases: Robert Black, M.D., M.P.H. (Epidemiologist), Patrice Engle, Ph.D. (Developmental Psychologist), and Gretel Pelto, Ph.D. (Anthropologist).

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generalizable approaches may be identified which could be incorporated into a broad range of educational-preventive strategies. To be of greater than theoretic or restricted relevance, the research tasks must facilitate the identification of constructs about behavioral change which are demonstrated to be both generalizable and pragmatic.

In this brief paper I wish to make 3 points:

1. There is substantial evidence that behavioral interventions can both change behaviors relevant to child survival and improve health outcomes.
2. Not all behavioral interventions are the same.
3. There is a need to establish a more deliberate process for the development and implementation of behavioral interventions.

These issues are germane to all countries, independent of economic development. However, while I shall briefly mention behavioral interventions in both developed and developing countries, this paper will focus principally on hygiene and sanitation behavior in relation to diarrhea in developing countries.

1. BEHAVIORAL INTERVENTIONS CAN CHANGE BEHAVIOR

To place in perspective the role of behavioral change in the health intervention armamentarium, it is useful to review the numerous examples of behavioral intervention that have had dramatic and sustained impact. Examples of successful outcomes of behavioral interventions have included both reduction of risk behaviors (i.e., decrease in high risk sexual practices among gay men, decrease in smoking prevalence, change in eating patterns), increases in promotive behaviors (i.e., increase in prevalence and duration of breastfeeding, increased use of bicycle helmets and seat belts, increase in exercise) and improved health outcomes (i.e., decreased blood pressure.) (Joesef 1989; Muller 1980; Pierce 1989; Walker 1989; Catania 1989; Evans 1986; Fortmann 1990)

These interventions have used multiple channels, messages and approaches to effect change and have identified multiple target audiences (i.e., demonstrated and presumptive high risk groups, opinion leaders, health care providers, legislators). (Kelly 1991; Peachmenot 1984; Paunio 1991; Dryfoos 1991)

If the question is posited in relationship to childhood diseases in developing countries, there is again considerable evidence both that behaviors can be changed and that morbidity can be decreased by these changes (i.e., decreased environmental littering, increased handwashing, increased contraceptive prevalence rates, prolonged breastfeeding and increased use of health facilities and decreased diarrheal disease rates.) (Stanton 1987; Joesef 1989; Kahn 1982; EDP 1988)

In summary, there is strong empirical evidence in both developed and developing countries that purposeful behavioral change can be effected through intervention programs utilizing a variety of target behaviors, target audiences, channels and messages.

2. NOT ALL BEHAVIORAL INTERVENTIONS ARE THE SAME

While indeed it is clear that behavioral interventions can influence health behavior

and health outcome for children in developing countries, it is equally true that the ranges of impact are enormous. For example, in an analysis of 49 studies examining the impact of improved water supply and personal hygiene, Esrey and colleagues (1990) observed decreased rates of diarrheal disease morbidity ranging from 0 to 100% and decreased rates of diarrheal disease mortality ranging from 43 to 79% .

Generally we have attributed these substantial variations in impact on morbidity and mortality to differences and/or biases in participant selection and/or outcome measurement (including differences in definitions of the dependent variables and duration). Thus, for example in three excellent reviews of the impact of water-sanitation behavioral interventions on diarrheal diseases, as indicated in Table 1, the methodological issues examined were essentially confined to issues in participant recruitment, definitions, confounding variables, and statistical analysis. (Blum 1983; Esrey 1986; 1990)

TABLE 1: SUMMARY OF METHODOLOGICAL ISSUES CONSIDERED IN REVIEWS OF THE IMPACT OF WATER-SANITATION BEHAVIORAL INTERVENTIONS

BLUM and FEACHEM (1983):

1. Lack of adequate control
2. One-tone comparison
3. Confounding variables
4. Health indicator recall
5. Health indicator definition
6. Failure to analyze by age
7. Failure to record facility usage

ESREY and HABICHT (1990); ESREY ET AL (1990):

Studies with Positive Findings:

1. Was there self selection of participants ?
2. Were there confounding variables ?
3. Were the measurements blinded ?
4. Was congruity confirmed ?
5. Were differences in water and sanitation conditions confirmed ?

Studies with Negative Findings:

6. Could the population benefit ?
7. Was the difference in the intervention (comparison) groups sufficient to produce an effect ?
8. Was the sample size adequate ?
9. Were confounding variables controlled for ?
10. Was congruity confirmed ?

Although superficial recognition of the importance of differences in the development and delivery of the behavioral component of the actual intervention are alluded to, attempts to dissect these differences are few.

3. NEED TO ESTABLISH A MORE DELIBERATE PROCESS FOR THE DEVELOPMENT AND IMPLEMENTATION OF A BEHAVIORAL INTERVENTION

Many of us who have worked in this field are aware of and troubled by our struggles with a substantive analysis of the design of behavioral interventions per se. Obviously a comparative analysis of the advantages or disadvantages of different approaches to effecting behavioral change will not be possible if these approaches have not been articulated. For example, a behavioral intervention to decrease use of river water for drinking purposes might consist of weekly home visits by a village health care worker discussing self-reliance and empowerment of mothers. Alternatively, it might rely on daily radio announcements for one week stating the health hazards of the use of river water for drinking. Finally, it might take the form of a local ordinance imposing a fine on any persons caught removing water from the river in a drinking pot. To formulate these three brief, seemingly simple, intervention strategies, multiple choices between intervention options had to be made regarding presumed mechanism of behavioral change, channel, target audience, and dose that will influence the likelihood of effecting behavioral change, the rapidity of onset of such change, and the duration of change. A comparison of these three intervention strategies for these and other effects would clearly be most useful for evaluation of impact and for directing the development of subsequent behavioral intervention programs.

But, how do we begin a meaningful comparison of strategies in which so many of the variables are different?

Arguably to conduct such a comparison there is a need for a framework which simultaneously includes: 1) delineation of the stages essential to the design and implementation of an intervention; 2) integration of relevant perspectives, organizing frameworks,and experience from multiple disciplines; and 3) neutrality as to the promotion of any single theoretical perspective. Utilizing a framework developed by an interdisciplinary team (Stanton, in press), we may consider examination of the process of developing a behavioral intervention as consisting of five tasks.

TABLE 2: STAGES IN THE DESIGN OF BEHAVIORAL INTERVENTIONS*

1. Descriptive/correlational studies
2. Selection of the intervention of the highest priority
   a. Identification of health promoting or demoting behaviors and/or beliefs
   b. Identification of behaviors that are alterable
   c. Determination of the frequency and distribution of risk (protective) behaviors
   d. Assessment of severity of outcome of risk (protective) behaviors
   e. Identify target groups
3. Selection of the theory, model or paradigm underlying presumed mechanism of behavioral change
4. Operationalization of the theory in the intervention design
5. Communication of the message
   a. Determine the presentation of the message
   b. Selection of the channel and source
   c. Formulate the message

* Adapted from Table 3 in Stanton B, Black R, Engle P and Pelto G. Theory-driven Behavioral Research for the Control of Diarrheal Diseases. In Press, Soc Sci Med.

Descriptive/correlational studies: The diarrheal disease literature is replete with such studies. Examples include studies describing diarrhea morbidity, studies describing actual handwashing and feeding practices, and associations between these practices and diarrhea rates, etc.

These studies set the scene for the next tasks, those related to:

Selection of the intervention of the highest priority: The broad issue of how to identify the highest priority intervention for a specific setting must be considered before other aspects of intervention and its evaluation are examined. Currently, there are no clear guidelines for delineating the risk behavior of highest priority for the purposes of initiating an intervention. In an attempt to begin to develop such a framework, we have suggested that several "substeps" or processes are necessary.

Identification of health promoting/demoting behaviors: In this sub-task we seek to identify those local practices which place persons at increased risk and those local practices which may be protective. Examples of the types of behaviors (and beliefs) to be assessed in this sub-task might include: do they wash their hands before eating? do they boil their water before drinking?

Identification of behaviors that are alterable: Clearly it is pointless to base an intervention on a behavior which realistically cannot be changed. Thus, for example, to conduct this task we might assess whether the villagers could afford to boil water, whether would women would be permitted to go to the village tubewell to obtain safe water.

Determination of the frequency and distribution of risk (protective) behaviors; and, **Assessment of severity of outcome of risk (protective) behaviors**: These tasks are self-explanatory and essentially serve to validate that the intervention will be of public health importance.

Identification of target groups: This task underscores the importance of specifying differences in the target audience. For example, should the intervention be directed at opinion leaders within the community? Is the intent to change the behaviors of the majority of community dwellers, or rather does the situation require targeting of the resistent, highest risk individuals? Should the intervention be targeted at the primary users within a family or should it be targeted at those with financial power?

Selection of the theory or model or paradigm: In this task we seek to identify the presumed mechanism for bringing about the behavioral change. Will the intervention rely on fear? enhanced belief in self? role modelling? peer pressure? an integrated model combining several of these constructs? Choice of such constructs will not only dramatically influence the actual intervention, but would shape the questions posited and relationships hypothesized in the earlier stages already discussed.

Operationalization of theory in the intervention: In this task the abstract concepts of the underlying theory or model are translated into culturally relevant perceptions of the problem or targeted behaviors. The "components" of the model must each be defined and interpreted generally and specifically. Further discussion and illustration of this process are available elsewhere (Stanton, In Press; Black, Submitted).

Communication of the message: This task consists of three major activities: the presentation of the message (should the intervention be presented as new an exciting or as traditional?), selection of the channel and source (person-to-person, mass media, written material) and formulation of the message.

Certainly we are not suggesting that this framework is the final or definitive framework--any more than Blum or Esrey suggested that theirs were final epidemiologic frameworks. Rather, this framework is put forth to begin the process of utilizing the tremendous experience and knowledge existing in multiple social science disciplines as well as in epidemiology to design behavioral interventions. Further, this framework can initiate a dialogue regarding the way in which we are currently addressing the development of behavioral interventions in the context of developing countries. Clearly we are conducting many of these tasks--but are they being done regularly and are we performing them as well as we could or should?

Having stated the need for a framework to enable utilization in an iterative fashion of relevant behavioral intervention experience, two questions immediately emerge. First, does a research experience with purposeful behavioral change upon which researchers and interventionists in child survival in developing countries could base their efforts in fact exist? Second, is this research experience already being utilized in the design of behavioral interventions to improve child survival in developing countries?

In response to the first question, obviously in the social sciences there is a rich research tradition concerned with purposeful behavioral change. Several of these disciplines are primarily devoted to descriptions of the origins or motivations for behavior (i.e., Social Learning Theory, Behavioral Theory, Cognitive Theory, Interactional Theory). Others are concerned with modifiers of behavioral principle (i.e., Developmental Theory, Personality Theory) and still more are devoted to particular aspects of behavior especially as they relate to behavioral change (i.e., Diffusion Theory, Communications Theories). While it is beyond the scope of this paper to summarize the research findings from all of these areas, clearly the answer to the first of my posited questions is yes, a rich, relevant experience with behavioral change does exist.

Of even greater importance, the focus on behavioral change differs between these fields and disciplines. Thus, for each of the stages noted in the framework, not only will the perspectives differ, but the experience and potential contribution may be greater from some of the behavioral sciences than from others. It is therefore essential that we must advance beyond the concept of viewing the contribution of the social sciences as relatively homogenous and rather must attempt to access and integrate their unique and complimentary perspectives in the complicated process of purposefully changing behavior.

To address the second question (Is this experience being utilized?) we undertook a review of the hygiene and diarrheal disease literature utilizing the framework presented

as the organizational structure.

Methods:

The analysis had two components. First, the articles were assessed as to whether they articulated the process involved in the development and delivery of behavioral interventions. That is, did they address the need to perform the individual steps or tasks specified in the framework? For example, was the need to select the target audience articulated and was the process for such a selection described? Second, the articles were examined as to whether they cited or otherwise referred to the existing literature concerned with purposeful behavioral change, both the methodologic literature and/or specific research findings.

The relevant literature was categorized as Epidemiologic (Statistical), Anthropologic, Psychologic, Health Education, Communications (including Social Marketing), Sociology or Diffusion.

To avoid a random and possibly biased selection of diarrheal disease and hygiene articles, a decision was made to obtain all papers published in the peer-reviewed literature that were cited in the most recent review of the impact of hygiene/sanitation on diarrheal diseases. Accordingly, I utilized the 17 articles which were cited in Table 1, "Catalogue of studies (since 1986) on Diarrhea, Nutrition and Mortality in Children" in: Esrey, S, Potash J., Roberts L., and Shiff C. Health Benefits from Improvements in Water Supply and Sanitation: Survey and Analysis of the Literature on Selected Diseases. WASH Technical Report No. 66, July 1990.

It is important to note that this review is not a criticism of individual studies. Not all studies would necessarily have to address each of the stages and surely every study would not be expected to cite relevant literature from all of the social sciences concerned with behavioral change. I would argue, however, that as a body of literature, all of the stages should have been addressed, the process should have been well described and there should have been a comprehensive and directed utilization of the relevant literature.

CHART 1

Assessment of Published Child Survival Behavioral Intervention Literature (Diarrheal Disease Prevention): Description of the Process and Reference to Existing Literature

Stage	Descriptive Studies	Selection of Intervention of Highest Priority					Operative Theory to Effect Behavior		Communication of the Message		
Article	Descriptive Process/Lit	Health/Promotive Process/Lit	Health Demotive Process/Lit	Alterable Process/Lit	Severity Process/Lit	Target Process/Lit	Select Behavioral Theory Process/Lit	Operationalize Process/Lit	Present Message Process/Lit	Select Channel Process/Lit	Formulate Message Process/Lit
Pickering 1985	Epid./Epid. Stat/Stat	Epid./Epid. —/[Anthro.]	Epid./Epid. Anthro/[Anthro]	— —	Epid./Epid.	Epid./Epid. Anthro/[Anthro]	— —	Not applicable	Not applicable	Not applicable	Not applicable
Esrey 1988 (AJPH)	Epid./Epid. Anthro/— Stat/Stat	Epid./Epid. Anthro/—	— —	— —	Epid./Epid.	— —	— —	Not applicable	Not applicable	Not applicable	Not applicable
Esrey 1988 (JE)	Epid/Epid. Stat/Stat	Epid./Epid.	— —	— —	Stat/Stat Epid./Epid.	Epid./Epid.	(X statistical) (Epid./Epid.)	— —	Not applicable	Not applicable	Not applicable
Baltazar 1988	Epid./Epid. Stat/Stat	Epid./— Anthro/—	Epid./— Anthro/—	— —	Epid./Epid. Anthro/—	— —	(_ Epid.)	Not applicable	Not applicable	Not applicable	Not applicable
Alam 1989	Epid./Epid Anthro/—	— —	— —	— —	— —	Epid./—	— —	— —	Health Ed _	— —	— —
Victoria 1988	Epid./Epid. Stat/Stat	— —	— —	— —	— —	— —	— —	Not applicable	Not applicable	Not applicable	Not applicable
Han 1989	[Epid./Epid.]	Epid./Epid.	Epid./Epid.	— —	— —	X —	— —	— —	— —	— —	— —
Habicht 1988	Epid./Epid.	Epid./Epid. Stat/Stat	Epid./—	— —	—	Epid./Epid.	(Epid./Epid.)	Not applicable	Not applicable	Not applicable	Not applicable
Stanton 1987a	Epid./Epid. Anthro [Anthro] Stat/Stat	Epid./Epid. Anthro [Anthro]	Epid./Epid.	— —	Epid./Epid.	— —	— —	Not applicable	Not applicable	Not applicable	Not applicable
Stanton 1987b	Epid./Epid. Anthro/— Stat/Stat	Epid./Epid. Anthro/— Health Ed./ Health Ed.	Epid./Epid. Anthro/—	Epid./Epid. Anthro/—	Epid./Epid. Anthro/—	— Epid. Health Ed.	— Health Ed.	— —	Health Ed./Health Ed.	Health Ed./Health Ed.	— —
Stanton 1988	Epid./Epid. Anthro/— Stat/Stat	Epid./Epid. Anthro/— Health Ed./ Health.Ed.	Epid./Epid. Anthro/— Health Ed./ Health Ed.	Epid./Epid. Anthro/—	Epid./Epid. Anthro/—	— Epid. Health Ed.	— Health Ed.	— —	Health Ed./Health Ed.	Health Ed./Health Ed.	— —
Huttley 1987	Epid./Epid.	— —	— —	— —	— —	— —	— —	Not applicable	Not applicable	Not applicable	Not applicable
Young 1987	Epid./Epid. Anthro/— Stat/Stat	Epid./Epid. Anthro/—	— —	— —	Epid./Epid. Stat/Stat	— —	— —	Not applicable	Not applicable	Not applicable	Not applicable
Lindskog 1988	[Epid./Epid.]	Epid./Epid.	— —	Epid. _	Epid./Epid. Stat/Stat	— —	— —	Behavioral Component of Intervention (if any) not described			
Esrey 1989	Epid./Epid. Anthro/— Stat/Stat	Epid./Epid. Anthro/		Epid. _	Epid./Epid.	— —	— —	Behavioral component of Intervention (if any) not described			
Esrey 1987	[Epid./Epid.	— —	Epid./Epid.	— —	Epid./Epid.	— —	— —	No behavioral component to the intervention			
Lindskog 1987	Epid./Epid. Anthro/Anthro Stat/Stat	— /Epid.	—/Epid.	— —	Epid./Epid.	— —	— —	No behavioral component to the intervention			

Results:

Descriptive/correlational studies: All of the articles describe the process utilized for conduct of the descriptive study. Reference to an existing literature to guide this process is complete, with universal reference to the epidemiologic literature. However, apart from oblique reference to anthropologic observation (without citation of an actual anthropologic reference) and one direct citation from the health education literature, there is no reference to the social science literature.

Selection of the intervention of highest priority:
Identification of health demoting/promoting behaviors: In general, recognition and articulation of this process for health demoting behaviors is quite complete and the epidemiologic literature-- both methodologic and descriptive--is extensively cited. Again, however, apart from a few indirect allusions to the need to document behaviors, no methodologic papers from the social sciences are cited and only one descriptive paper from anthropology is cited.

Identification of behaviors that are alterable: Review of the 17 papers indicates that in fact little attention has been paid to deliberately seeking to establish which behaviors may in fact be alterable. In the few instances in which the process for this exercise (or even the need for it) was noted, again only the epidemiologic literature and the anthropologic literature was referenced.

The process of postulating impediments to altering specific behaviors is an essential component of much psychologic theory - as well as communications theory. Likewise, diffusion theory enables us to understand what kind of behaviors are most likely to be amenable to change depending on characteristics of the targeted community (Rogers 1979).

Identification of the target population: Little specification of the process of identifying target groups exists in this body of literature. In a broad demographic sense, many of the studies identify "mothers" as the target group, but further specification of, for example, opinion leaders or determination of whether the intervention is intended to introduce a new idea to a community, to reach the "masses" or to address the so-called laggards is essentially missing from all studies. Although communications theory and the diffusion literature offer substantial, practical research experience in this regard, reference to prior research findings or methodology is virtually absent.

Select Behavioral Theory to Guide the Intervention: A full discussion of the need for the utilization of theory in designing behavioral interventions is beyond the scope of this short paper. Nevertheless, it is perhaps worthwhile to summarize the main rational for this contention which is widely supported in the social science literature. First, specification of theory aids identification of the range of motivations for the relevant activities among the potential recipients. Second, articulation of theory enables examination of the concordance of the presumed process of behavioral change with the belief system of the target population. Third, theory directs researchers to select among alternative actions at each stage of the intervention process. Finally, explicit postulation

of a set of theoretical assumptions enables the research to become a test of a theoretical model and thus contributes to our general understanding of behavior and its change. (Stanton In Press)

In spite of the importance of behavioral theory, none of the studies referred to a specific behavioral model or theory. (Contrarily, biostatistical and epidemiologic models were cited.) In two studies reference was made to principles of behavioral change from the health education literature.

Communication of the message: Finally, we turn to the last set of tasks, those related to communication of the message. For many of the studies, communication of the message was not applicable because the study did not carry the intervention process to this stage. For those studies which did actually intervene, there was limited description of the process of presenting the message, selecting the channel and/or formulating the message. Only the health education literature was referred to.

That there was so little articulation of the need to select the presentation of the message is perhaps surprising because for all interventions a decision must be made. A wide variety of approaches for selection of presentation have been developed which are both simple and directive. For example, utilizing existing theories on dynamic aspects of persuasion, theorists have proposed a more elaborate method for selection of approaches to present the message. A series of factors appear to be involved when individuals are galvanized into action. These "initiators of action" include characteristics such as the need to maintain the status quo, the need for change, tendencies to respond actively rather than reactively. This preference for either change or maintenance can be expressed either cognitively or affectively. Accordingly, some subsets of persons wish to maintain the status quo (rather than grow) with regard to cognitive (rather than affective) function. Thus persuasion campaigns aimed at such individuals should describe the innovation as consistent with current ideation and beliefs. Conversely, to appeal to individuals or sub-cultures who desire something new and exciting (affective growth), a communications campaign would promote those aspects of the innovation that differed from current practices. (McGuire 1978)

Communications research has been directly concerned with issues in implementation that focus on pragmatic questions concerning channel (face-to-face, radio) and source (important person in the community, peer, etc.) Interventions may be able to build upon this experience as well as that from other fields to delineate circumstances in which one approach is more likely to be effective than another. For example, studies from the diffusion literature indicate that characteristics of the targeted individuals ("receivers") should influence choice of channel; early adopters may be more likely to listen to mass media channels than late adopters. The point again is not that any one discipline or approach should be accessed, but rather that there is a substantial body of literature and experience that can--should--inform future intervention efforts.

Finally, it is noteworthy that in each of these papers at least one of the review papers discussed earlier--that by Blum (1983) and those by Esrey (1986;1990)--were cited and obviously employed to guide the research design. Clearly analytic frameworks are useful to interventionists.

In summary then, articulation of the need for conduct of the relevant tasks was variable. Citation of relevant epidemiologic methodologic literature and research findings

were in general comprehensive and well chosen. By contrast, there was minimal citation of research findings from the anthropologic and health education literature and no reference to research findings from the psychologic, communications and diffusion literature. Of greatest significance, there was essentially no citation of the methodologic literature from any of the social sciences.

CONCLUSIONS

Several broad conclusions can thus be made. First, behavioral interventions clearly can impact on both health behaviors and health outcomes. Second, not all behavioral interventions are alike. However, their development should be - and can be - purposeful, directed and iterative. Third, such purposeful and iterative development of behavioral interventions requires a more deliberate process, one that utilizes and integrates (but is not encumbered by) the substantial multidisciplinary experience potentially available.

We should advance beyond the point of vague reference to the need for interdisciplinary approaches or of treating the social sciences as though they are interchangeable. Specific, directed accessing of their varied and unique contributions will enable major steps forward. The utilization of a framework identifying the necessary steps and tasks to be undertaken in designing a behavioral intervention will clearly facilitate this process. Accordingly, purposeful behavioral change may, as suggested by the title of this paper, be successfully added as a categorical and free-standing constituent, rather than merely an adjuvant, to the child survival intervention armamentarium. There can be little doubt that the articulation of epidemiologic and statistical principles to be addressed by hygiene-diarrhea studies and other studies in the field of child survival has greatly benefitted the design of such studies. In a similar fashion, it is likely that as we develop a more rigorous methodology for design and implementation of the behavioral component of interventions, behavioral change rates will be both greater and more predictable in magnitude, duration and direction.

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Synergy and Interaction Among Childhood Infectious Diseases: An Example from Bangladesh

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Abstract

This research had two objectives: first, to examine the possibility of an interaction of the proportion of days with diarrhea and proportion of days with fever on the growth of Bangladeshi children; second, to consider the effects of various levels of energy intake, diarrhea and fever on weight gain in the same population. Data from a one year longitudinal study were used. Both objectives were explored with linear regression analyses. We found that the proportion of days with both diarrhea and fever was significant while the coefficients for the proportions of days with each separately were not. Children with both diarrhea and fever merit special attention.

For a subset of children with data on food intake, the quantitative effects of energy intake, diarrhea and fever on weight gain over a one year period were studied. Only children with above median levels of energy intake and in the lowest terciles of diarrhea and fever prevalence would be expected to gain the amount that children of the NCHS standard gain.

INTRODUCTION

Interaction, synergy and frailty can each have multiple meanings. To fix ideas we employ the statistical usage of the term interaction--the difference between the effect when factors A and B are present together from the added effects of A and B separately (e.g. Scheffe, 1959). What is called interaction depends on the statistical model as is made clear in the definition of Rothman, Greenland and Walker (1980): interaction is "the interdependence between the effects of two or more factors within the confines of a given model." Synergy and its opposite, antagonism then are taken to refer specifically to whether a given interaction term is positive or negative respectively. Interaction and synergy in public health program interventions due, for example, to effects of a given intervention on multiple causes of death, are considered elsewhere (Mosley and Becker, 1991). Similarly, frailty, defined as specific increased biological susceptibility to disease or death for some individuals in a population, or more generally as unobserved heterogeneity of disease or death risks in a population, is also treated elsewhere (Weiss, 1990, Vaupel and Yashin, 1985).

This paper explores two examples of interaction and synergy of biological processes in the development of an adverse child health outcome--malnutrition. In both cases the statistical model is linear regression so the effects documented (if any) will be departures from additivity. It has been quite persuasively argued that departures from additive risks are important to public health (Rothman, 1986; Saracci, 1980). Though nutritional status could be made a dichotomous variable--adequately nourished and malnourished--by the choice of some cutpoint and thereby allow testing of multiplicative

interactions via logistic analyses, we prefer to utilize the continuous nature of nutritional status data.

In the first example, we consider two morbid conditions--diarrhea and fever and the effect of these singly and in combination on weight gain. The usual statistical procedure for detecting interaction is contrasted with the alternative of actually constructing a third variable denoting the presence of both diarrhea and fever on a given day. In the second example, actually in a model without significant statistical interaction, we consider the effects on growth during a one year period, of energy intake, diarrhea and fever for various observed levels of these in the population. The purpose is to document the magnitude of the effects of each factor and their combined effects.

Previous relevant studies in this population

The growth of children in the study population in Matlab Bangladesh deviates substantially from that of international reference populations with nearly all children weighing below the National Center for Health Statistics (NCHS) fifth percentile by 15 months of age (NCHS, 1979; Brown et al. 1982a). The field study was designed to evaluate the determinants of this growth faltering. Children were found to have limited intakes of energy despite extensive and prolonged breastfeeding; children 5-30 months old received an average of 63-71 kcal/kg body weight/day (Brown et al 1982b). These children also had high rates of morbidity, such as respiratory, enteric, and skin infections, particularly during the first two years of life (Black et al 1982a; Black et al. 1982b). Children with diarrhea for a higher proportion of days had poorer growth (Black, Brown and Becker, 1983; Black, Brown and Becker, 1984).

The data on weight, fever, diarrhea, and energy intake for one month periods were used to determine the effects of the last three on weight change using a random effects model (Becker et al., 1991). The regression equation is:

$$CW = 76 + 1.5E - 132D - 309F \qquad (1)$$

where CW represents change in weight (in grams), E represents energy intake in kilocalories per kg per day, D represents the proportion of days with diarrhea, and F represents the proportion of days with fever. Predictions using median levels of E, D, and F as contrasted with recommended levels of E and the elimination of diarrhea and/or fever showed the greater importance of energy intake in determining a child's growth.

METHODS

Field work and data processing

The field methods of the study have been described previously (Black et al., 1982b). Briefly 177 children 2 to 48 months of age in two villages in Matlab were enrolled for a one year prospective study and 20 births were added during the year. A field worker visited each mother-child pair every other day to inquire about any illness on that day or on the preceding day. Information was recorded on number and consistency of stools, vomiting, nasal discharge, cough, anorexia and fever. An episode

of diarrhea was defined when there were four or more liquid stools on one day and it was considered resolved on any day with less than three stools. Fever was reported by the mother and confirmed by rectal temperature on visit days. Each child's weight was measured monthly; the nude or lightly clothed children were weighed to the nearest 0.1 kg on a Salter scale, which was calibrated against known weights.

For 70 children 5 to 18 months of age at the start of the study, measurements of dietary intake were scheduled monthly in the home; 66 children had complete data that could be used for this study. In addition to the monthly measurements, at least one special study was scheduled during diarrheal or febrile illness for each child and also during the two-week period of recovery from those illnesses (Brown et al, 1982b). For each child, all foods served during the entire day were weighed by a trained observer. Raw food ingredients were weighed on a beam balance scale accurate to 0.1 g and cooked menu items were weighed again after preparation. The child's portion was weighed before serving and the weight of leftover food was subtracted to estimate the amount of the item eaten. The latter was expressed as a fraction of the total weight of the cooked menu item, in order to calculate the amount of each food item eaten. Energy intakes were then calculated by multiplying the amount of food consumed by the energy content as reported in Indian food composition tables (Gopolan, Rama Sastri and Balasubramanian, 1977). The consumption of breastmilk was quantified during a 12-hour period using a test-weighing technique and 24-hour consumption was estimated using a correction factor determined from 24-hour studies (Brown et al, 1982c).

Analysis of synergy/interaction effects of diarrhea and febrile illnesses

The dependent variable for this linear regression analysis is the change in weight between the beginning and ending of the study for 170 children who were observed more than 180 days. To provide more stable estimates, the beginning and ending weights were calculated as the average of the two first and two last weights respectively. The difference of these two was taken as weight change for the year after adjustment to provide an estimate for 365 days. Independent variables were age of the child, initial weight and the proportions of days with diarrhea, fever, or both. In Model 1, diarrhea and fever were counted separately (i.e. counted doubly), and an interaction term was formed as the product of the two. Alternatively, in Model 2, days with both diarrhea and fever were classified in a third variable. In addition to simple regression, stepwise procedures were also used. Residual plots were produced to check the assumption of linearity.

Analysis of relative effects of diarrhea, fever and energy intake on growth

To extend previous analyses of determinants of growth (Becker et al., 1991), summarized by equation 1, we consider the distribution of energy intake, fever and diarrhea in the same population and predict the change in weight for various combinations of these during a one month period. Specifically, for each of the three variables a cutpoint was made at the median of the observed values (of means over one month intervals) for the 66 individuals. Then the distribution of individuals among all the possible combinations of the three variables (E, D and F) was determined. Thus, writing

H to represent the group of children with values of a given variable above the median and L to represent the group with values below the median, the 8 possible combinations for E, D and F in that order are: HHH, HHL, HLH, HLL, LHH, LHL, LLH, LLL. The children in the best group are those in HLL representing high energy intake, low diarrhea and low fever; similarly the worst combination is LHH. The groups HLH and HHL were combined since the effects of diarrhea and fever were considerably less than that of energy intake and since using 8 groups yielded less than 10 children per group. For the same reasons, the groups LLH and LHL were combined. The illness burden in these cases is denoted as "medium." Thus the 8 groups were collapsed to 6.

The change in weight was linear in the age range 5 to 18 months (Becker, Black and Brown, 1991); therefore we simply chose the median age of children at the beginning of the study for the comparisons. The predicted weight gain after one year is compared with what children gain at the median of the NCHS/CDC standard population (Dibley et al. 1987, NCHS, 1979). Though we anticipated assessing increased mortality risks due to malnutrition for the various groups using the empirical relationship found from another study in Matlab (Chen et al. 1980), in actuality, the groups were too small and the time frame of the study too short to produce accurate estimates.

RESULTS

Synergy/interaction effects of diarrhea and febrile illnesses

The dependent variable for these analyses--weight change over a one year period for the 170 children--had a mean value of 1.6 kg with a minimum of 1.2 kg and maximum of 3.5 kg. With respect to the independent variables, the mean age of the children at the beginning of the study was 22 months (range 2 to 49 months) and the mean initial weight was 8.3 kg (range 4.1 to 14.5 kg). For diarrhea and fever, the children had an average of 10 percent of days with diarrhea, 6 percent of days with fever, and 2 percent of days with both (Table 1, Model 2). When the interaction variable is created as a product of the percent of days with diarrhea times the percent of days with fever (Model 1) instead of having a separate category for days with both (Model 2), the percentages of days in the three groups (D,F, and D+F) are only slightly different. The right skewness of both diarrhea plus fever (D+F) variables is considerably greater than that for either diarrhea or fever separately. For the product variable one would expect this from a simple mathematical argument (e.g. if X1 and X2 are symetrically distributed then X1 + X2 is symetrically distributed but X1*X2 has right skewness). Also as expected, the correlations between the variables are higher using the interaction variable constructed as the product of the individual variables (Table 2).

In the regression analyses the product interaction and separate variable for D+F gave different results (Table 3). For ease of reading, the coefficients in the table are multiplied by 1000, effectively converting from kilograms to grams of weight change per year. Thus the intercept in Model 1 is 2.2 kg. In Model 1 without the interaction term, the effects of diarrhea and fever are negative but nonsignificant. When the multiplicative interaction term is added, the signs of the coefficients for the main effects are reversed and the coefficient for the multiplicative term is large and negative but not significant

(p=.24). The switching of signs of the main effects when an interaction term is introduced is a common result in regression (i.e. when X_1 and X_2 have a positive correlation, then the covariance between β_1 and β_2 is negative). In the stepwise results, only age and the interaction variable remained in the equation ($p < .01$ and $p=.06$ respectively).

The results for Model 2 are statistically different. In this model the coefficient for D+F is significant at the .02 level; the coefficients for diarrhea and fever separately are both positive but not statistically different from zero. In the stepwise regression, as in Model 1, only age and the variable for both D+F remain.

Next we compare the magnitude of the effects estimated from the different models. For a child with one percent of days with both diarrhea and fever (i.e. 4 days in a year), the weight gain which is forgone is estimated as (.01)*(4710) = 47 grams. This is a relatively large effect. In Model 1, each one percent of days with fever would result in a deficit of 12 grams and the corresponding effect for diarrhea is 2.5 grams. The effect of having both illnesses is therefore more than additive ($12+2.5=14.5 < 47$) and more than multiplicative as well ($12*2.5 = 30 < 47$).

Thus, the percentage of days with both diarrhea and fever is an important variable on its own. Over 40% of the children had more than one percent of days with both. Table 4 shows mean values of other variables according to the terciles of this variable. Children in the tercile with the highest levels are slightly younger than those in the other groups and as anticipated they have higher percentages of days with diarrhea and fever separately.

Relative effects of diarrhea, fever and energy intake on growth

These analyses are restricted to the 66 younger children of the same population with food intake studies. The initial column of Table 5 shows the distribution of these children across the 6 combinations of energy intake and illness variables. One might expect that due to heterogeneity from other factors (e.g. socio-economic status) the distribution of children in the 6 groups would not be uniform. However, using a chi-squared test, the hypothesis of equal proportions of children in each of the 6 (or 8) cells is not rejected.

Using regression equation 1, those in the best group with moderate energy intake and low diarrhea and fever are predicted to grow 179 grams per month (last column of Table 5)[1]. At the other extreme, those with low energy intake and high levels of diarrhea and fever are predicted to grow only 86 g in the same period or only half as much. The predicted values for all 6 groups are graphed in Figure 1.

How would these groups fare in growth over a one year period? To assess this we use the same prediction equation and contrast predicted growth with the mean growth

[1] In the analyses which yielded equation 1, days with both fever and diarrhea were double counted and the product interaction term between the separate variables diarrhea and fever was tested and found non-significant. From the results presented above, it may be worthwhile to redo those analyses constructing the third variable for the proportion of days with both diarrhea and fever.

levels in the NCHS standard (Table 6). Only those with both moderate energy intake and below average levels of both diarrhea and fever would grow at levels comparable to children at the mean level in the NCHS standard population. Those in the worst group would only achieve half of the NCHS mean yearly growth and other groups fall in between.

Discussion

Previous analyses of these data found negative effects of diarrhea and fever on growth (Black, Brown and Becker 1984; Becker, Black and Brown 1991). However in those analyses, days with both fever and diarrhea were double counted (i.e. in each separate variable). When days with diarrhea plus fever are counted in a separate category and used in regression analysis, we find that this is a highly significant variable in determining weight gain. The combined effects of increased catabolism due to fever and malabsorption due to diarrhea coupled with limitations on energy intake due to the socioeconomic context make weight loss a probable outcome for children with above average days of both fever and diarrhea.

Previous analyses of these data showed that fever was most prevalent during rotavirus diarrhea (33% of days) while much less prevalent (7%) during E coli diarrheas (Black, et al. 1982b). Yet analyses of weight gain in 60-day intervals showed that only the proportion of days with E coli had a significant negative effect on weight gain (Black, Brown and Becker, 1984). These results and those of the present study need to be reconciled--perhaps by including etiology of diarrhea in the current model as well.

The presence of the significant interaction between diarrhea and fever in affecting nutritional status could send several messages to public health personnel. First, children with both diarrhea and fever could merit special attention. Second, to the extent these results represent a biological synergism, the removal (via treatment) of one of the two factors would eliminate both the main effect of the factor and the entire interaction effect.

The results of predicting weight change over a one year period for various subgroups of the population demonstrate that if diarrhea and fever could be reduced, and energy intake increased to levels already present for the best-off decile of the population (8 of 66 children), then growth could be expected to match that of the NCHS/CDC median. The levels of diarrhea, fever and energy intake that were found in this group were 2% of days with diarrhea, 4% of days with fever and 78 kcal per kg per day for energy. Diarrheal intervention programs are already an integral part of health services in Matlab; from this study one can conclude that specific interventions with respect to fever and food intake merit further consideration.

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FIGURE 1

Predicted monthly weight gain (g.) by levels of energy intake and illness

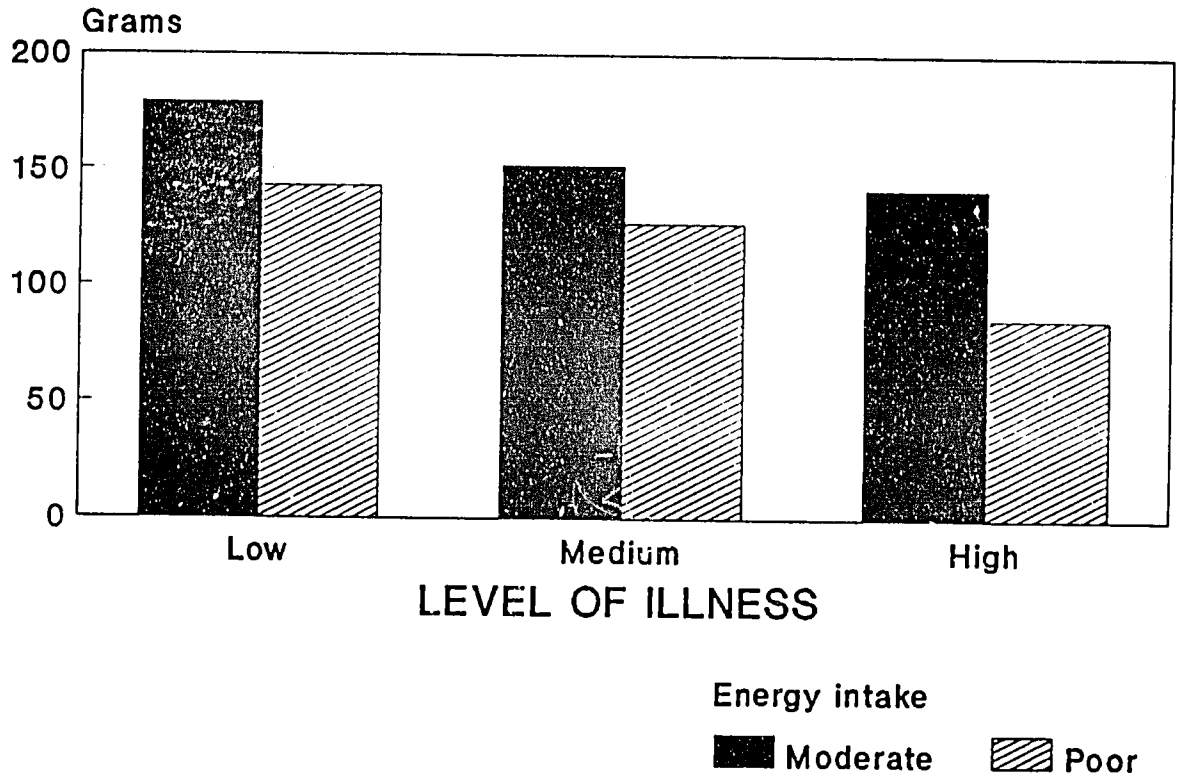

Table 1: Mean and median values of percent of days with diarrhea, fever and diarrhea + fever according to model of interaction

Model	Illness Category		
	Diarrhea	Fever	Diarrhea+Fever[a]
Model 1			
mean	11.7	7.8	1.2
median	7.1	6.3	.5
range	(0,55.7)	(.8,31.6)	(0,12.7)
Model 2			
mean	10.1	6.2	1.6
median	6.0	5.2	.5
range	(0,46.2)	(.3,19.5)	(0,13.5)

[a] Diarrhea+Fever is the product of the percentage of days with diarrhea and the percentage of days with fever in Model 1 and the actual percent of days with both diarrhea and fever in Model 2.

Table 2: Correlations between the percentage of days with diarrhea, fever, and diarrhea+fever according to definitions of diarrhea+fever[a]

Pair of variables	Model	
	Model 1	Model 2
(Diarrhea, Fever)	.43*	.09
(Diarrhea + Fever, Diarrhea)	.77*	.60*
(Diarrhea + Fever, Fever)	.78*	.40*

[a] See footnote of Table 1 for definitions of Model 1 and Model 2.

* $p < .01$ for test of null hypothesis that the true correlation coefficient is zero.

Table 3: Estimated regression coefficients (x1000) for equations predicting yearly weight change with different models.

Model	Intercept	Independent Variable					r^2
		Age	Initial weight	Diarrhea	Fever	Diarrhea+Fever	
Model 1							
All variables w.o. interaction	2217	-16**	-16	-250	-1196	---	.13
with interaction	2106	-16**	-13	374	221	-7213	.14
Stepwise selection	2066	-18**				-4880*	.14
Model 2							
All variables with 3rd variable	2132	-15**	-19	471	394	-6334**	.15
Stepwise selection	2080	-18**				-4710**	.14

* significantly different from 0 with $p < .1$.

** significantly different from 0 with $p < .05$.

Table 4: Mean values of selected variables by prevalence of diarrhea + fever during the year[a]

Variable	Prevalence of diarrhea + fever (terciles)		
	None	.3% to 1.4%	1.6% to 13.5%
Initial age (months)	23.1	21.3	20.9
Initial weight (kg)	8.6	8.3	7.9
Percent of days with:			
Diarrhea	3.2	7.9	18.8
Fever	5.0	5.5	8.2
Number of children	56	56	58

[a] All children were observed at least 180 days.

Table 5: Mean values of age, energy intake (per kg) and percentages of days with fever and with diarrhea and expected monthly weight change by level of energy intake and illness.

Level of: Energy intake	Illness	Number of children	Age (mo.)	Energy (per kg)	Diarrhea (%)	Fever (%)	Expected monthly weight change (g)
ALL GROUPS		66	17	70	11	9	144
moderate	low	8	14	78	2	4	179
"	medium	11	18	83	12	10	152
"	high	14	16	88	20	13	142
poor	low	13	14	55	2	4	143
"	medium	13	16	58	12	7	127
"	high	7	15	56	18	17	86

Children with mean energy intakes (per kg) above the median level are grouped as 'moderate' intake, those below the median as 'poor' intake. With respect to illness, those with below median levels of diarrhea and of fever are considered labeled as 'low', those with diarrhea or fever above the median level and the other below it as 'medium', and those with both above the median levels, as 'high'.

Table 6: Predicted weight gain after one year and percent of NCHS standard weight, by level of energy intake and illness.

Level of: Energy Intake	Illness	Initial Age (1)	Initial Weight (2)	Predicted: Weight gain in one year (3)	Predicted: Weight after one year (4)=(2)+(3)	NCHS expected weight[a] (5)	Percent: of NCHS weight for age (6)=(4)/(5)	Percent: of NCHS expected weight gain (7)=(3)/2100[b]
moderate	low	14	7.2	2148	9.3	12.5	74	102
"	medium	18	7.4	1824	9.2	13.3	69	87
"	high	16	7.0	1704	8.7	12.9	67	81
low	low	14	7.7	1716	9.4	12.5	75	82
"	medium	16	8.0	1524	9.5	12.9	74	73
"	high	15	6.9	1032	7.9	12.7	62	49

[a] Average of boys and girls

[b] The NCHS mean weight gain is 2100 grams for all intervals of 12 months in the range of initial age of these children.

Cost-Effectiveness in Child Health: A Minimum Information Approach to Planning and Forecasting

Larry Forgy[1]

I. INTRODUCTION

Cost effectiveness in child survival activities is a difficult but crucial issue both in setting health priorities and in implementing interventions. There are many competing interventions that are intended to reduce child mortality, and the choice among them will have significant impact on the level and type of mortality. Planners would like to achieve the maximum impact for the least cost, by adopting the most cost effective set of interventions available. To do this, however, requires a systematic method of evaluating the myriad of possible interventions, and combinations of interventions, for both effectiveness and cost.

Many of the possible interventions have been the subject of cost-effectiveness studies. However, most of these studies consider only a single intervention in a static context. Programs usually are evaluated only at their current levels of operation and only within the existing demographic and economic conditions of the study area. Quite often, this approach is quite justified, since there is usually very little information available beyond that single point in time, place and operations. This method avoids the difficulty of trying to infer what costs or effects would be under conditions not encountered. Perhaps less justified is the practice of examining a single intervention, without much effort to determine how its efficacy is affected by the existence or nonexistence of other activities.

However, the issue of how to achieve the maximum reduction in mortality at minimum cost requires consideration of how to choose an entire set of interventions at varying levels of operation and under diverse circumstances. This paper is an attempt to set out an analytical model of cost effectiveness for sets of child survival interventions. It incorporates changes in costs of interventions, as will as varying degrees of efficacy. Particular child survival programs will be affected by the presence and level of operation of other programs.

The paper begins with a section discussing what is needed to model cost effectiveness in these programs. Following that, three models are briefly presented, each slightly more complicated than the previous one. Available data is then used to perform calculations with the third model, and results are presented in the next section. Finally, conclusions and recommendations from the exercise are discussed.

II. MODELING COST-EFFECTIVENESS

Cost-effectiveness is a method of comparing alternative ways of achieving a stated goal. If there is only one way of achieving the goal, there is no necessity for cost-

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effectiveness analysis. In child survival activities, however, there are usually numerous methods to be compared. The fact that it is used to make comparisons indicates that cost-effectiveness analysis can be used to optimize the use of resources. The models presented in this paper are optimization models. There have been other such optimization models. Barnum, et al, developed a very sophisticated model for Cali, Colombia that has over 200 parameters.

An important point that affects the type of model used is the quality and quantity of data available. Existing data is somewhat sparse, and the cost of data collection is high. A model should be as parsimonious as possible, but rich enough to capture the important points of reality. A legitimate concern in any modeling exercise is the question of how much detail existing data will support.

Any exercise in cost-effectiveness will require the following minimum information:

- A goal or objective.
- A set of potential activities.
- The cost of each potential activity.
- The effects of each activity on the goal.

Each item on this list has a number of difficulties. These include philosophical and methodological issues in definitions, as well as a large supply of measurement issues. In terms of child health, there are a number of obstacles to be overcome.

A GOAL OR OBJECTIVE

One absolute requirement is definition of a measurable objective to be accomplished. Quantifying the outcome of child health interventions, however, presents a number of difficult choices. In general, researchers have looked at both processes (such as number of immunizations) and outcomes (such as number of child deaths). Health outcomes may be a preferable measure, but they are notoriously difficult to measure. The simplicity of mortality measures is the major reason that most outcome goals are stated in terms of child deaths. Several recent works have considered discounted years of healthy life (DYHL) as an outcome measure that is able to incorporate morbidities as well. This has some real advantages over the use of mortality, but measurement issues, remain significant. This study will also use mortality reduction as the goal activities are intended to achieve.

POTENTIAL ACTIVITIES

There are a multitude of possible child survival interventions, some very similar to others and some very unique. In order to be able to make comparisons across alternative interventions, the problem is to reduce the list to a manageable size. Each simplification makes the information requirements of the model easier, at some cost to the depiction of reality. Careful compromises need to be made in choice of number and

type of interventions. The list should include a wide range of activities, including individual curative care, public health activities, IEC activities, and others. The models discussed here use classes of interventions that are general and intended to represent the range of possible activities.

COST OF ACTIVITIES

Often, only anecdotal information is available on cost of interventions. The costs of a particular program operating at a certain level is useful, but suffers from two major shortcomings. First, these studies often report only the average cost of operations without doing further analysis of what the marginal cost might be. Second, they usually consider cost only at the current level of operations without estimates of how changes in scale of operation will affect costs. One conclusion of this type of study is to point toward the need for more detailed and economically useful data on costs of interventions. This study attempts to infer simple cost curves for the interventions considered.

EFFECTS OF ACTIVITIES

Describing the effects of activities on the stated goals is the key to be able to do cost-effectiveness analysis. It is very difficult to do, with information needs rising rapidly as more potential interventions are considered. As with cost information, what little is known about effects is reported for the current level of operations. It is quite likely that the effectiveness of each intervention changes with the level of intensity of operation. Furthermore, very little is known about how interventions interact, a crucial point for this type of analysis. This study attempts to capture the most important effects of interventions without developing more detailed information.

How the interventions affect the goals of the exercise is the chief variation in the models described in this paper. The first model is a simple linear programming approach. Following a discussion of some deficiencies of such an approach, a model with nonlinear, rising cost curves is examined. Finally, the third model allows for both rising cost and falling effectiveness in the interventions under consideratic

III. A LINEAR PROGRAMMING APPROACH

One of the simplest optimization methods is linear programming. It is used here to develop estimates of the cost-effectiveness of several child mortality goals. These goals were set during a conference in 1988 in Talloires, France. That conference produced the well known Declaration of Talloires, which set out seven mortality goals to be achieved by the year 2000. These goals were:

- The global eradication of poliomyelitis.
- Elimination of neonatal tetanus deaths by 1995.
- A 90 percent reduction in measles cases and a 95 percent reduction in measles deaths compared with the pre-immunization levels by 1995.

- A 50 percent reduction from 1990 levels of deaths due to diarrhea in children under the age of 5 years, and a 25 percent reduction in the diarrhea incidence rate.

- A one third reduction in the 1990 case/fatality rates associated with acute respiratory infection in children under 5 years.

- A 50 percent reduction from 1990 levels of current maternal mortality rates.

- Reduction of infant and under-5 child mortality rates by one third, or to 50 and 70 per 1,000 live births respectively, whichever achieves the greater reduction.

The calculations presented here illustrate how such a general linear model could be formulated. A formal statement of this approach is contained in the Appendix. With this method, a certain objective is stated. In this case, it is to minimize the cost of several possible activities. That objective is constrained by several other factors (constraints) which must be met. In this case these constraints include the reduction in deaths from several causes. Once the objective is stated and the constraints are identified, various levels of interventions can be selected to determine which set of interventions satisfies the constraints at the minimum cost. In practice, this is done with the aid of a computer, which can try a large number of combinations quickly. The results presented here were computed using the linear optimization feature of the Quattro Pro program.

For these calculations, data was used from the World Bank database for the less developed countries. To achieve the Talloires goals required a reduction in annual mortality of 5.26 million deaths. These reductions are listed by goal in Table 4.1. The first five categories in the table are determined by specific mortality patterns. The final infant and child mortality goal of 400,000 is the residual reduction required to achieve the target goal of 70 per thousand.

Table 4.1
Required Increment in Annual Deaths Averted to Achieve the Talloires Goals

Diarrheal Disease	1,750,000
ARI	850,000
Measles	1,300,000
Neonatal Tetanus	790,000
Maternal Mortality	170,000
Infant and Child Mortality	400,000
Total Annual Mortality Reduction	5,260,000

To reach these goals, a set of seven possible interventions were considered. These interventions, and the costs assumed for each are:

INTERVENTION	COST
- EPI: providing full immunization to mother and child.	$18.00
- ORT: treatment of an episode of diarrheal disease.	1.20
- FP: providing family planning services to a couple for one year.	20.00
- NTR: nutrition supplements to an individual for one year.	15.00
- W&S: water and sanitation services per household annually.	10.00
- MH: a maternal health program for women at risk.	30.00
- MED: medical treatment, prescriptions, or preventive care.	5.00

With the mortality reduction goals defined and the interventions chosen, it is then necessary to specify how those interventions will affect the probability of death from each cause. Table 4.2 shows the assumptions used on the effectiveness of these interventions. The approach to deriving these numbers was to determine the changes in probability of death from an intervention. To do this we determine the probability of death from a particular cause, and then estimate the degree of change in that probability that would result from use of any particular intervention. These calculations are based on the fact that there are about 125 million children born in the developing world each year, of which about 14 million die, giving a probability of death of about 0.112 (a mortality rate of about 112 per 1,000). Each time an intervention is used, it will affect this probability of death.

One example of this process is the EPI coefficient for measles. The UNICEF State of the World's Children Report indicates that about 2.87 million children, or about 2.3 percent, would have died of measles in the absence of immunizations. Therefore, we conclude that immunization reduces the probability of death from measles by 0.022 (since the vaccine is only 95% effective). Similarly, with four million diarrheal disease deaths each year, there is a 3.2 percent probability of death (or a proportion of 0.032). If the application of ORT can reduce this by one third, then the impact of ORT on the probability of diarrheal disease death is 0.01. Other entries in the table were derived in the same manner.

Table 4.2
How Interventions Affect the Probability of Death

	EPI	ORT	FP	NTR	W&S	MH	MED
Diarrheal Disease	0.001	0.01	0	0.025	0.01	0	0.001
ARI	0.001	0	0	0.005	0	0	0.005
Measles	0.022	0	0	0.01	0	0	0.0005
Neonatal Tetanus	0.018	0	0	0	0	0.0001	0.0001
Maternal Mortality	0	0	0.01	0.0001	0.001	0.020	0.0001
Inf. and Cld. Mort	0.006	0	0.05	0.001	0.001	0.001	0.0005

Although the entries in this table represent the change in probability of death that comes from each intervention, a convenient way to interpret it would be to move the decimal point over three places and think of it as the number of deaths prevented per 1,000 interventions. For example, this table assumes that every 1,000 fully immunized mothers and children prevents one diarrheal disease death, one ARI death, 22 measles deaths, 18 neonatal tetanus deaths, and six other deaths (primarily pertussis). Other columns can be interpreted similarly.

Given the relative effectiveness of these interventions and the numbers of deaths to be prevented, the computer then tries combinations of interventions that achieve the required reductions in mortality to reach the Talloires goals and selects the combination which has the minimum cost. These results, shown in Table 4.3, indicate that the annual recurrent cost of achieving these goals would be about $2.2 billion.

Table 4.3
Annual Cost for Additional Interventions to Achieve the Talloires Goals

Intervention	Optimal Quantity	Cost
EPI	43,110,190	$ 775,983,424
ORT	86,116,616	103,339,939
FAMILY PLANNING	781,809	15,636,188
NUTRITION	28,514,404	427,716,055
WATER & SANITATION	0	0
MATERNAL HEALTH	7,302,205	219,066,165
GENERAL MEDICAL	132,863,558	664,317,792
TOTAL		$ 2,206,059,562

Testing of the sensitivity of this model to changes in the assumptions revealed a relatively stable total cost estimate. Very large changes in the table of probabilities or in unit costs were required to force the model to predict costs outside the range of $2 to $2.4 billion. The composition of the optimum set of interventions, however, varies dramatically with changes in the table of probabilities, but less so with changes in the unit costs. It is more appropriate, therefore, to think of this calculation as providing a general estimate of the cost of achieving these goals than as a prescription for which interventions to consider at what level. It is generally the case with linear programming solutions that the level of each intervention can changed greatly with small changes in the statement of the problem. Thus the fact that the solution presented here contemplates no water and sanitation activities does not imply that these activities are not cost effective under different assumptions, nor that they do not have significant consumption benefits.

The linear programming approach provides estimates of the marginal cost of deaths prevented from each cause specified in the goals. This is the measure of how much the total cost would rise if any of the deaths-prevented goals were increased by one. The marginal cost of each of the goals is shown in Table 4.4. Marginal cost

calculations developed by such models are for the prevention of a death from one of the possible causes, rather than the marginal cost of any particular intervention. In general, a single change made anywhere in the model will affect all of the marginal cost calculations to some extent.[2]

Table 4.4
Marginal Cost of Each Goal

Diarrheal Disease	$120
ARI	862
Measles	744
Neonatal Tetanus	3
Maternal Mortality	1495
Inf. and Child Mort.	101

These marginal cost estimates are, of course, conditional on the choice of the proper model and the correct coefficients. They were found to vary significantly with changes in the model coefficients, and should be viewed with greater skepticism than the total cost estimates discussed above. It is important to note, however, that there are major differences in the marginal cost of reducing various types of mortality. This indicates that this solution is actually sub-optimal. That is, the same mortality reduction could occur at lower cost if some of the high cost goals were reduced and some of the low cost goals increased. Ultimately, the lowest cost solution would produce the same marginal cost for each type of mortality reduction.

However, the linear nature of this model produces suspicious results when the goals are adjusted. This same expenditure of $2.2 billion can be shown to predict a reduction of 15 million deaths. Since this is more deaths than occur, this is clearly unrealistic. The problem is in the method of linear programming itself, which tends to have large changes in the solution from small changes in the conditions of the problem.

In addition, there are significant non-linear interactions that cannot be captured in this model. The relationships among mortality causes is not merely additive, for example. If 50 percent of diarrheal disease deaths are eliminated, it is possible that the number of deaths from malaria and other causes will rise. Conversely, improving nutrition may make interventions to combat diarrheal disease and ARI more effective. The issue of how each intervention changes the environment within which other interventions work and how morbidity patterns interact will require a more sophisticated

[2] This can be illustrated by an example involving the low marginal cost of neonatal tetanus death prevention. Raising the tetanus target from 790,000 to 790,001 deaths averted results in the model adjusting the least cost combination of interventions to achieve the entire set of goals to include increases in EPI, ORT, maternal health and general medical interventions. Family planning and nutrition interventions can then be decreased. The net total cost of all these changes to achieve the additional neonatal tetanus death averted is only $3.

model than the one presented here. Such a model would probably involve a significant number of non-linear relationships and conditional probabilities.

IV. A RISING COST MODEL

The previous section noted that the multiple mortality goals of the Declaration of Talloires produced a sub-optimal solution. If we abandon the linear programming approach, it is possible to develop a model which sets the goal at the maximum reduction in mortality from any cause. In addition, dropping the linear model allows another improvement to be added. It is assumed that as the quantity of each intervention rises, the marginal cost of that intervention also rises. This assumption allows us to produce the typical upward sloping supply curves for each intervention.

Because we have one objective (minimize deaths) and one constraint (the budget), we can write out a very simple form for the problem. While the calculations may be cumbersome, this simplification allows us to state the problem as the solution to a single equation. This allows relatively simple methods of solving nonlinear equations. This section discusses the formulation and solution of this model.

Allowing cost to vary requires a more complicated description of the cost of interventions. Typically, it is assumed that there are some fixed costs and some rising marginal costs, which produce the standard U shape cost curves of falling and then rising average costs.

The simplest description of these costs would be:

Total costs = fixed cost + variable costs
= F + (V*x)*x

Average costs = F/x + V*x
Marginal cost = 2*v*x

This would produce a cost curve such as shown in figure A.

With costs curves defined, it is possible to write the single equation that can be solved to provide the minimum cost solution. In this case, optimization is found by minimizing this function, subject to a maximum allowed budget. This can be done through a mathematical technique known as Legrange multipliers. The general form for the objective function subject to the budget constraint is:

$$Deaths = D - \sum_i \sum_j \alpha_{ij} x_j + \lambda(B - \sum_j (F_j + V_j x_j^2))$$

where D = the current level of deaths, B = the budget, i is an index of types of mortality and j is an index for types of interventions.

As with all of this class of models, the solution can be shown to be the set of interventions where each activity has the same relationship between marginal productivity and marginal cost. With this model it is possible to derive a solution that can be calculated on simple spreadsheet. Using the assumptions on effectiveness from the linear programming model, and cost assumptions shown below, we get the following results.

Deaths averted:	5,262,779
Recurrent cost:	1,662,709,384
Fixed cost:	1,204,954,031
Total cost:	2,867,663,416

At this target level of deaths, deaths by particular causes break down in the following way:

Deaths by cause prevented:

Diarrheal Disease	2,031,952
ARI	643,723
Measles	409,139
Neonatal tetanus	196,687
Maternal mortality	869,242
Infant and Child mort.	1,112,037

The quantity of each intervention, and its cost, at the optimal solution can also be calculated. For the 5.2 million mortality reduction, this is:

Interventions:

	Amount	Numbers of Deaths Averted	Unit costs Fixed	Unit costs Variable	Costs at Solution Average	Costs at Solution Marginal	Costs at Solution Total
EPI	10,110,000	485,280	5	.0000015	20.165	30.33	203,868,150
ORT	157,968,750	1,579,688	0.5	.00000002	3.66	6.32	578,066,895
Fam.PL	18,956,250	1,137,375	6	.000001	24.96	37.91	473,076,914
Nutr.	12,985,031	533,685	5	.000001	17.99	25.97	233,536,193
W&S	379,125	4,550	7	.00001	10.79	7.58	4,091,233
Mat.Hl.	33,331,406	703,293	20	.0000002	26.67	13.33	888,824,654
Gen.Med	113,737,500	818,910	2	.00000002	4.27	4.55	486,199,378

Unfortunately, one consequence of this simple model is that the results are a set of interventions of the same proportions for any level of mortality reduction. For example, for the set of parameters used in this solution of the model, we will always use 15.6 ORT treatments for every EPI intervention. There is a single set of interventions that is scaled up or down, depending on the desired magnitude of mortality reduction. This result comes from the fact that although marginal costs are rising, they are rising at a constant rate. Thus, the ratios of marginal costs across interventions will always be constant. It would be possible to specify different shapes of these cost curves, but we are already beyond the bounds of what is known about costs.

A second problem is the linear properties of the interventions means that their effects are not bounded in any way. Given enough of each intervention, the model would show that you are able to eliminate all child deaths. Clearly this is not the case.

Just as interventions have rising cost, they also have declining productivity. This leads to the formulation of the third model.

V. A RISING COST, DECLINING PRODUCTIVITY MODEL

In addition to rising costs, interventions may have varying levels of effectiveness. Jamison and Mosley comment on this issue in their disease control priorities chapter:

> "One might, in general, expect rising marginal costs and decreasing marginal effectiveness as interventions are extended through populations; these combine to dilute cost-effectiveness. Thus favorable case cost-effectiveness estimates can be real, but their margin of applicability may be limited. In principal it is desirable to acquire some sense of the responsiveness of intervention cost-effectiveness to a range of parameters, particularly the extent of application of the intervention."

Thus, it is probably prudent to assume that the known, single measures of effectiveness are merely points on an effectiveness curve. Even though treatment of each child is an independent event, we can assume that the first children treated are those who would benefit the most. Each succeeding child will show less effectiveness of the intervention. In total, there will be a limit to the number of children that can be saved by a particular intervention, after which point, the intervention will have no effectiveness. All this indicates that we have some sort of decay rate on effectiveness, and that the boundary will be the number of children dying of particular causes for which the intervention can have an effect. Thus, interventions are assumed to have a variable effect on deaths that diminishes as the quantity of the intervention rises. This sort of decay rate is typically modeled in the following way:

$$D = \sum_i d_i \, e^{-\sum_j \alpha_{ij} x_i}$$

where d_i is the current number of deaths of type i.

This is a standard and very flexible method of showing decay in some quantity. In this context, the alpha parameter is the effectiveness of the intervention at the current level of mortality. That is, if alpha were 0.1, the first ten interventions would prevent one death. This type of specification requires only a limited amount of information: the current level of deaths, current level of intervention, and current effectiveness. In effect, it assumes that current conditions identify one point on a curve of a general type.

This assumption of the type of curve is not very restrictive. It can be shown that these effectiveness curves for different interventions can cross, such as in Figure B. They can also be interactive without blowing up. A simple specification of additive

alphas allows each intervention's effectiveness to be affected by other interventions, such as in Figure C. Here, the effect of the sum of the two interventions is less than the sum of the effects of the separate interventions.

It is also possible to include a number of social and environmental factors as well. For example, if the level of caloric intake affected the efficiency of ORT, this could be reflected in an exogenous shift in the value of alpha.

This model of effectiveness can be combined with the assumptions about rising cost from the earlier model to form a very general specification:

$$L = \sum_i d_i \, e^{-\sum_j \alpha_{ij} x_i} + \lambda \left(\sum_j F_j + \sum_j V_j x_j * x_j - B \right)$$

Unfortunately, this specification does not have a simple analytical solution. As in the second model, the solution is found to be the set of interventions where the ratios of marginal productivity to marginal cost are equal, but with two types of nonlinearity, there is not a general solution. However, finding the solution is simplified by the fact that these functions are all monotonic and well behaved. It can be shown that there is only one root because the second derivative cannot change signs.

The solution follows natural intuition. Interventions have declining productivity and rising cost, and scarce resources are allocated among them until the benefit per dollar is equal across all interventions. This model can be estimated as shown in the next section.

VI. FILLING OUT THE MODEL

All of these models require the same basic sorts of information. While the nonlinear, rising cost, falling productivity model appears more complicated, its data needs are essentially the same as the simple linear model. In this section, we consider what the goals and interventions of a general cost-effectiveness model for child health might be. This information is then used in the rising cost, declining productivity model to indicate what an optimal allocation of resources might be.

Unfortunately, very little is actually known about the type of effectiveness and cost information needed here. There is some information in the Barnum, et al. study, which was generated by using a survey of experts. Other data has been generated by the World Bank project, and information from that effort was used here to set up the parameters of the model.

We need four types of information for the basic model:

- Mortality data.
- Potential interventions.

- Costs of interventions.
- Effects of interventions on mortality causes.

This information would be fundamental to any type of cost-effectiveness study. If available, a richer model can be developed with demographic, social, economic or other types of data. Using data from the World Bank project and elsewhere, the following parameters were used in the simulation presented here:

DEATHS:

Child deaths were divided into 10 categories set out by Lopez, 1990. Two categories were combined for measles, pertussis and diphtheria; and one category was divided into neonatal tetanus and other perinatal causes.

Table 6.1.

Causes of Under-5 Deaths in Developing Countries

Diarrheal Disease	4,000,000
Tuberculosis	300,000
Acute Respiratory Infections	2,800,000
Measles, Pertussis, Diphtheria	2,200,000
Malaria	750,000
Other infections and Parasitic Diseases	450,000
Neonatal Tetanus	775,000
Other Perinatal Causes	2,425,000
External Causes	200,000
Other and Unknown Causes	700,000
TOTAL	14,600,000

Source: Lopez, 1990.

Choice of interventions is a difficult task. There are an enormous number of potential interventions of differing approaches and levels of operation. Jamison and Mosley provide a general discussion of the most common health interventions in their summary of the World Bank project. From this work, 16 basic interventions were distilled that cover the general categories of education, service provision, and public health activities. There are, of course, a number of interventions not included that will be highly cost-effective, but will not operate on a large scale. As such, the general mortality and cost estimates should not be affected to a large extent.

The 16 interventions are listed in Table 6.2. The table also provides information about the costs of each intervention. These costs are divided into a fixed and a variable component. In the long run, all costs are variable, but for reasonable ranges of operating levels, we can assume that a portion of cost is represented by a fixed component. Another part of cost will rise with the level of operations. Table 6.2 shows the proportion of cost of each intervention that can be considered as fixed and the portion that can be considered variable. To better interpret the variable costs, the final column shows the amount of each intervention required to raise the average cost by $1.

Table 6.2.

Assumptions About Costs of Interventions

Intervention	Fixed Cost	Variable Cost	# of Interventions to raise ave. cost $1:
EPI	10	0.000001	1,000,000
Antenatal and Delivery Care	10	0.000001	1,000,000
Breastfeeding Promotion	8	0.000001	1,000,000
Malaria Prophylaxis	4	0.000001	1,000,000
Improving Domestic Hygiene	8	0.000001	1,000,000
Pneumococcal Immunization	4	0.00001	100,000
Oral Rehydration Therapy	1	0.000001	1,000,000
Rotavirus Vaccine	4	0.00001	100,000
Family Planning	15	0.0000002	5,000,000
Antihelminthic Treatment	3	0.000001	1,000,000
Micronutrient Treatment	1	0.0000001	10,000,000
Nutrition Supplement, antenatal	5	0.000001	1,000,000
Nutrition Supplement, infant	5	0.000001	1,000,000
Antibiotics for ARI	10	0.00001	100,000
Water and Sanitation	10	0.000001	1,000,000
General Medical Consultations	3	0.00000005	20,000,000

Finally, we must have some measures of the effectiveness of each intervention on mortality. In this case, we need a total of 160 measures of effectiveness to cover the effects of 16 interventions on 10 causes of death. Our assumptions are listed in Table 6.3. These have been put together from a brief review of literature, some simple calculations discussed in the linear programming model, and guesswork. The need for more information for this matrix is substantial.

The way to interpret this table is to consider each entry as indicating how many deaths would be reduced in each cause of death by application of one intervention. For example, the first entry in the table indicates that for each fully immunized child, we will prevent 0.001 of a diarrheal disease death. That is, for every 1,000 immunizations, diarrheal deaths will fall by one. However, recall that this is only at the current levels of mortality. As interventions are applied and mortality falls, the real effectiveness of each intervention decreases.

Table 6.3.

Estimates of the Effectiveness of Interventions
By Cause of Death at Current Developing World Mortality Rates

Intervention:	EPI	Antenatal	Breastfeeding	Malaria Prop.	Domestic Hygiene	Pneumon. Imm.	ORT	Rotavirus	Fam. Planning	Antihelminthic	Microntrient	Nutrition, antenatal	Nutrition, infant	Antibiotic, ARI	Water and San.	Gen. Med. Cons.
Cause of Death:																
Diarrheal Disease	.001	.001	.005	0	.001	.0001	.01	.02	0	.0001	0	.001	.001	0	.005	.001
Tuberculosis	.002	0	0	0	.001	0	0	0	0	0	0	0	0	0	0	.0001
Acute Respiratory Infections	.001	0	.005	0	.001	.01	0	0	0	.001	0	.001	.001	.01	0	.001
Measles, Pertussis, Diphtheria	.022	0	.001	0	0	0	0	0	0	0	0	0	0	0	0	.0005
Malaria	0	0	0	.004	0	0	0	0	0	0	0	0	0	0	.0001	.001
Other Infect. and Parasitic Dis.	0	.001	0	0	.001	0	0	0	0	.001	0	0	.001	0	.001	.0001
Neonatal Tetanus	.018	.001	0	0	0	0	0	0	.001	0	0	0	0	0	0	0
Other Perinatal Causes	0	.01	.001	0	.001	0	0	0	.004	0	.001	.03	0	0	0	.001
External Causes	0	0	0	0	.001	0	0	0	0	0	0	0	.001	0	0	.001
Other and Unknown Causes	.001	.001	0	0	.001	0	0	0	0	0	.001	0	.001	0	.0001	.0001

VII. RESULTS

Using the parameters from the previous section, the model was calculated for a reasonable range of spending levels. The results are shown in Figure D. As can be seen, decreases in mortality become more and more difficult as spending and the number of interventions increase. The marginal cost of saving another life rises quite substantially.

Unlike the two previous models, the most cost-effective strategy for child survival will include different quantities of each intervention at different targets for mortality reduction. To illustrate likely strategies, it is possible to examine the solution for any particular level of mortality. To compare this solution with that of the earlier models, it is possible to explore the strategy to eliminate about 5.2 million child deaths. If the classification of deaths into specific categories is disregarded, we can ask what it would take to reduce total child deaths from 14.6 million to 9.4 million. From this simulation, this would cost about $1.7 billion per year, somewhat higher than the results of the model with constant effectiveness.

To achieve these results, there will be a need to employ some of each of our 16 interventions. Figure E shows how expenditure would be allocated for the goal of 9.4 million deaths. More than 83% of all spending would be in five categories: EPI, general medical consultations, antenatal nutrition supplements, family planning, and general antenatal and delivery care. Interventions not included in the simulation could change the results, but are likely not to have a major impact.

The costs of interventions is included in Figure F. As can be seen, the marginal cost of each intervention is higher than the average cost. Many of these costs are high, particularly for EPI. Nevertheless, it is quite likely that costs for these programs will rise substantially as service delivery increases. An average cost of about $28 for a fully immunized child may not be an unreasonable estimate for higher levels of coverage. One issue that this figure does point out, however, is that marginal cost may differ substantially from average costs. Though marginal cost is the relevant measure for decision making, average cost is usually the only reported number.

VIII. CONCLUSIONS

The major reason for modeling such a complex question as the cost-effectiveness of child survival interventions is that the use of models can illuminate results that were not immediately obvious. While most researchers would generally agree that some mix of interventions is an optimal strategy, models such as these can help to point toward reasonable strategies.

Modeling of these questions, however, is still in a primitive state. Much of the data that would be required for this type of exercise is nonexistent, forcing an uncomfortable reliance on a number of assumptions. Beyond the data, the very general specification used here is among the most common in economics, and can serve as a general framework for this type of analysis. Nevertheless, it is important to think carefully about what we think the true specifications are for these functional forms.

Among the most pressing needs is information about true cost functions of child survival interventions. For the most part, current cost data is restricted to point estimates

and anecdotal information. What is necessary is to know how costs behave as the level of activity rises. Additional work on this might include nonmonetary costs to consumers such as waiting time, rising costs of inputs, and other factors affecting cost, such as population density and level of development. It is likely that unit costs are not linear, but that they rise as the goals are approached. Because countries are at different stages of development in the target areas, marginal cost will vary across country, so total costs must be revised to reflect this. The rising marginal cost question is a difficult issue, however, with surprisingly little evidence upon which to compute cost curves. Most information available consists of collections of historical observations of program costs. No one consulted[3] was aware of studies specifically addressing the issue of how costs rise with the level of coverage of any intervention.

A second major need is to understand how efficacy of interventions is affected by the presence or absence of other child survival interventions and by general conditions. Very little work has been done on how various services complement or substitute for each other. Somewhat more has been done on how conditions in the country affect efficacy, but more is needed. Ideally, the model should be able to incorporate such disparate factors as the general level of caloric intake, status of girl children, or any number of other variables.

This type of analytical approach should be evaluated for its ability to serve as an important health sector tool. It would seem to have applications for planning of new projects and for monitoring and evaluation. In planning, it can not only suggest reasonable organizations of services, but also point out what factors may be important opportunities for lowering costs. In monitoring and evaluation, the method can provide indications of where costs or results differ from expectations.

This is a research agenda filled with major activities and difficult questions. The potential benefits, however, are also major. Modeling exercises such as these have the possibility to contribute significantly to our understanding of child survival in developing countries.

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[3] Andrew Creese at WHO, Howard Barnum at the World Bank, and David Parker at UNICEF all expressed the desire to see studies which estimated true cost curves, but were unaware of such studies even for programs as heavily analyzed as EPI.

Figure A

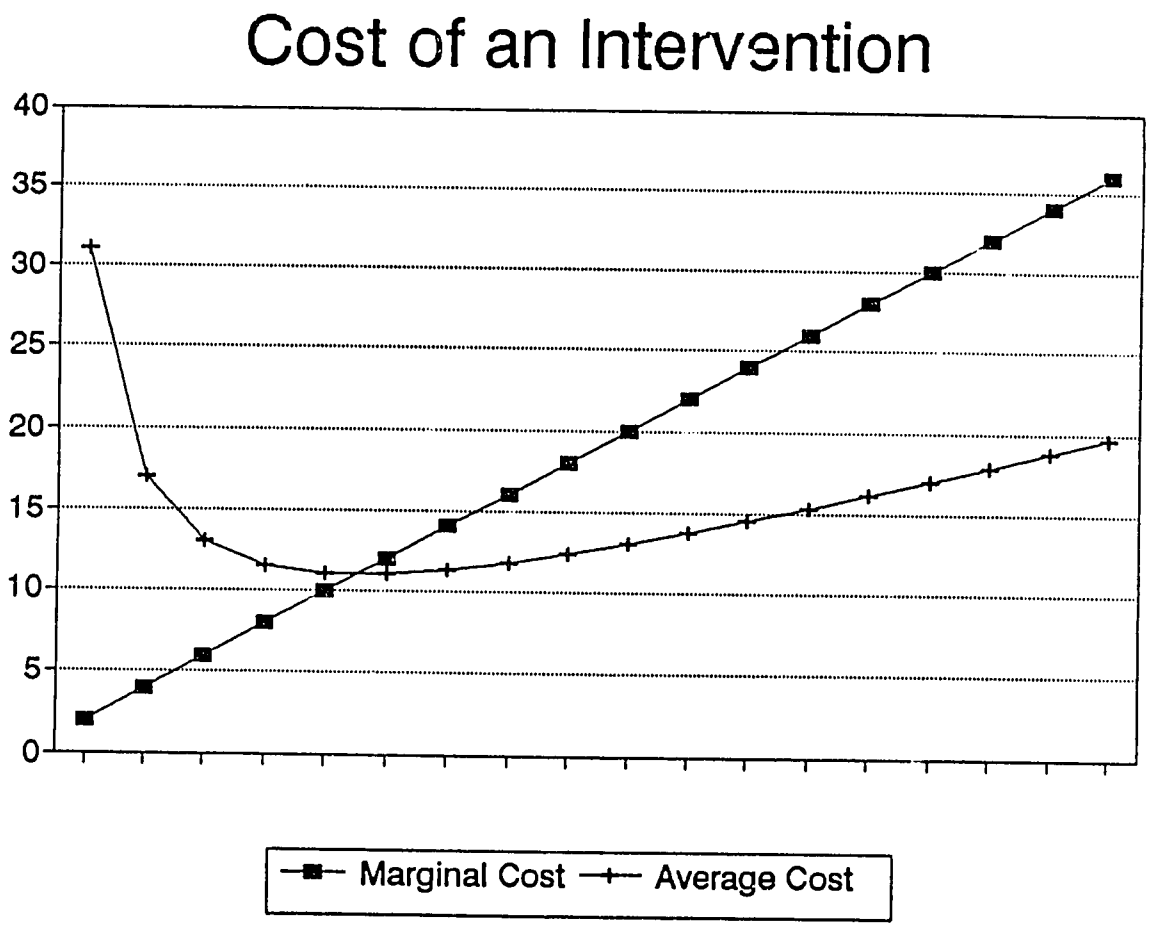

Cost of an Intervention
40
35
30
25
20
15
10
5
0
Marginal Cost
Average Cost

Figure B

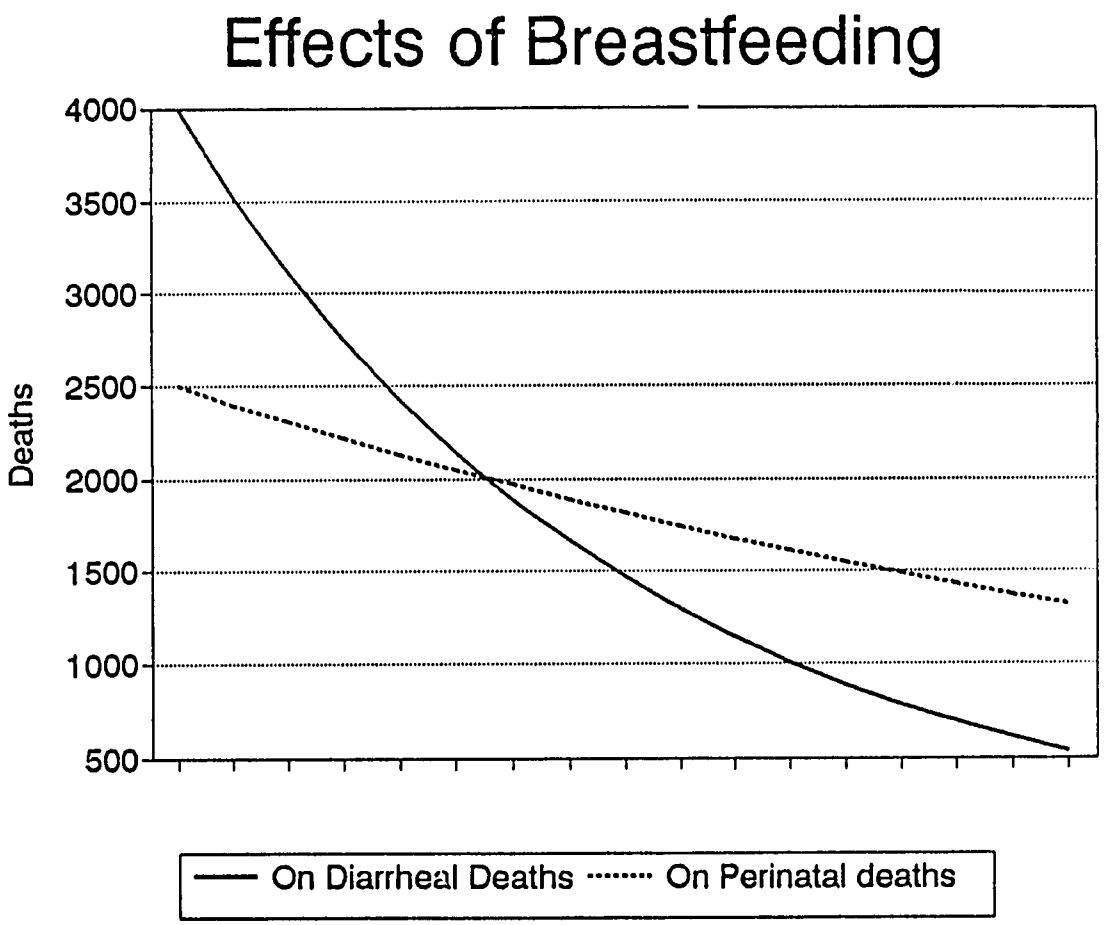

Effects of Breastfeeding
Deaths
4000
3500
3000
2500
2000
1500
1000
500
On Diarrheal Deaths
On Perinatal deaths

Figure C

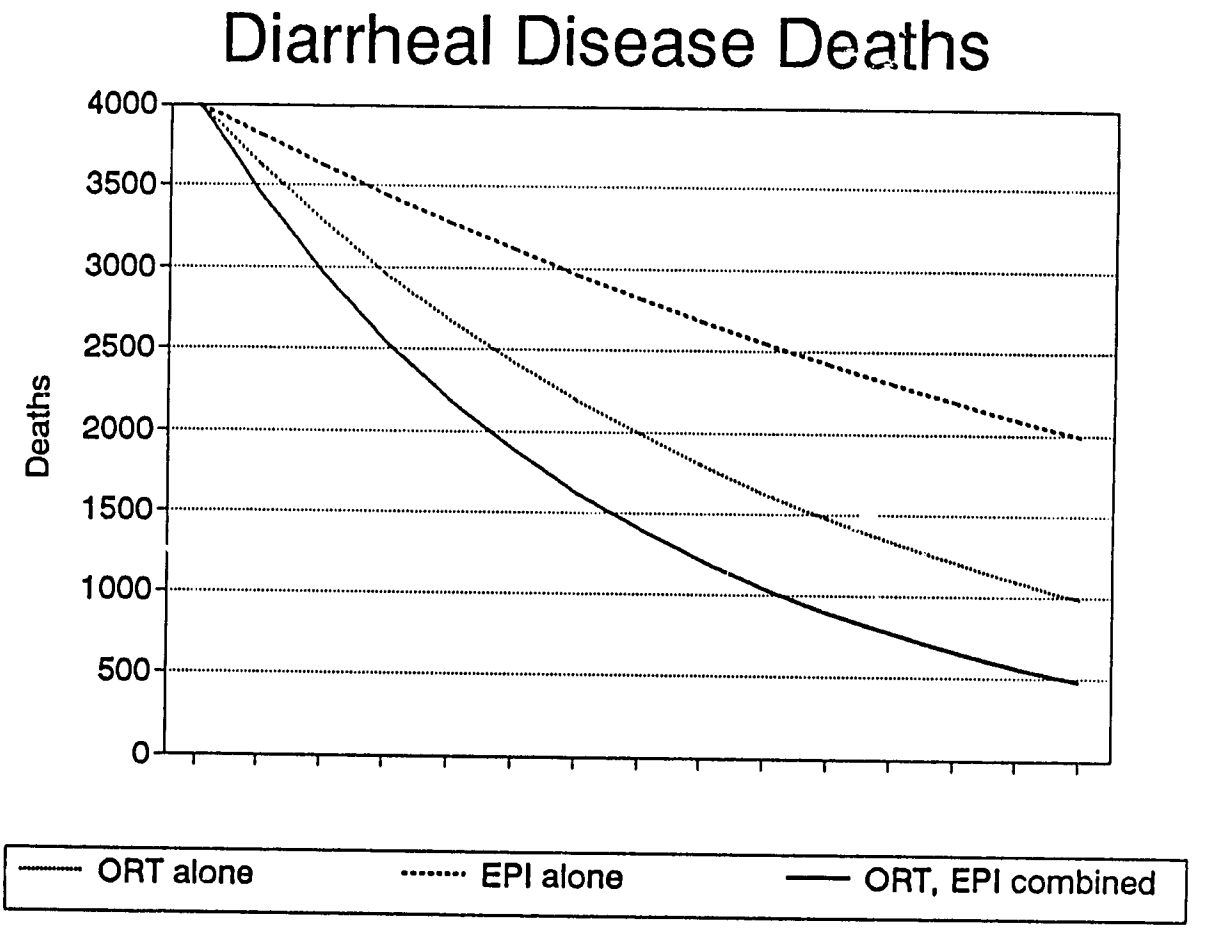

Diarrheal Disease Deaths
Deaths
4000
3500
3000
2500
2000
1500
1000
500
0
ORT alone
EPI alone
ORT, EPI combined

Figure D

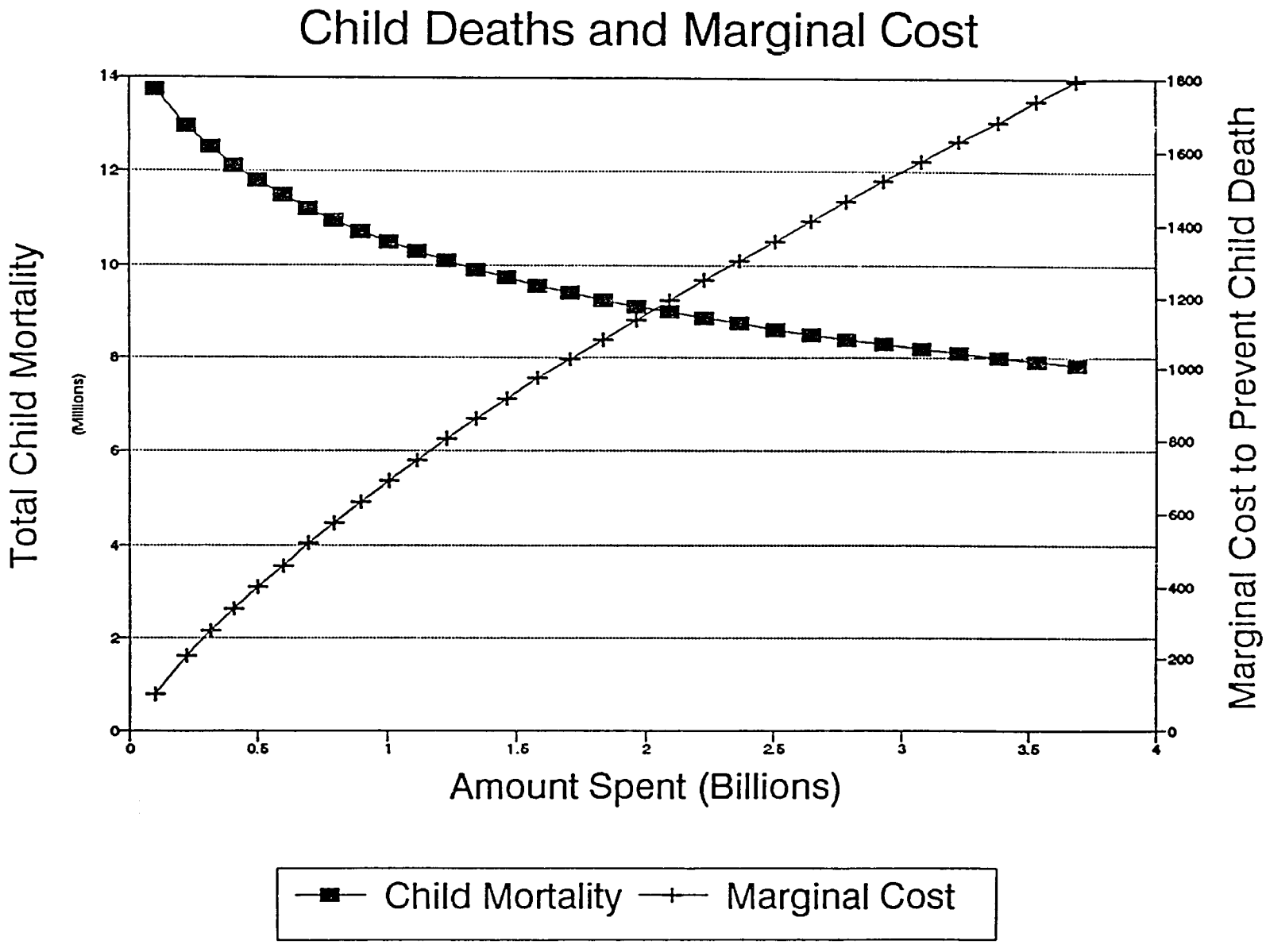

Child Deaths and Marginal Cost
Total Child Mortality
(Millions)
Marginal Cost to Prevent Child Death
Amount Spent (Billions)
0
2
4
6
8
10
12
14
0
200
400
600
800
1000
1200
1400
1600
1800
0
0.5
1
1.5
2
2.5
3
3.5
4
Child Mortality
Marginal Cost

Figure E

Percent of Spending, by Intervention
at target of 9.4 million deaths

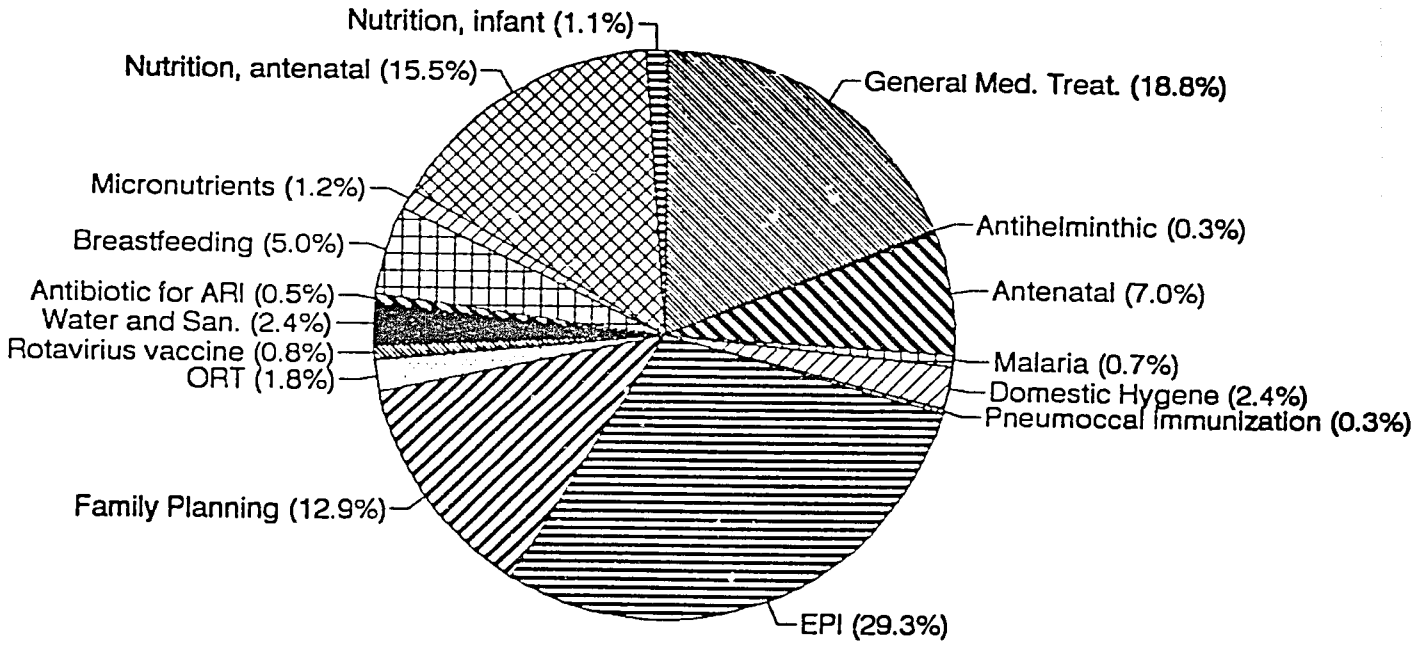
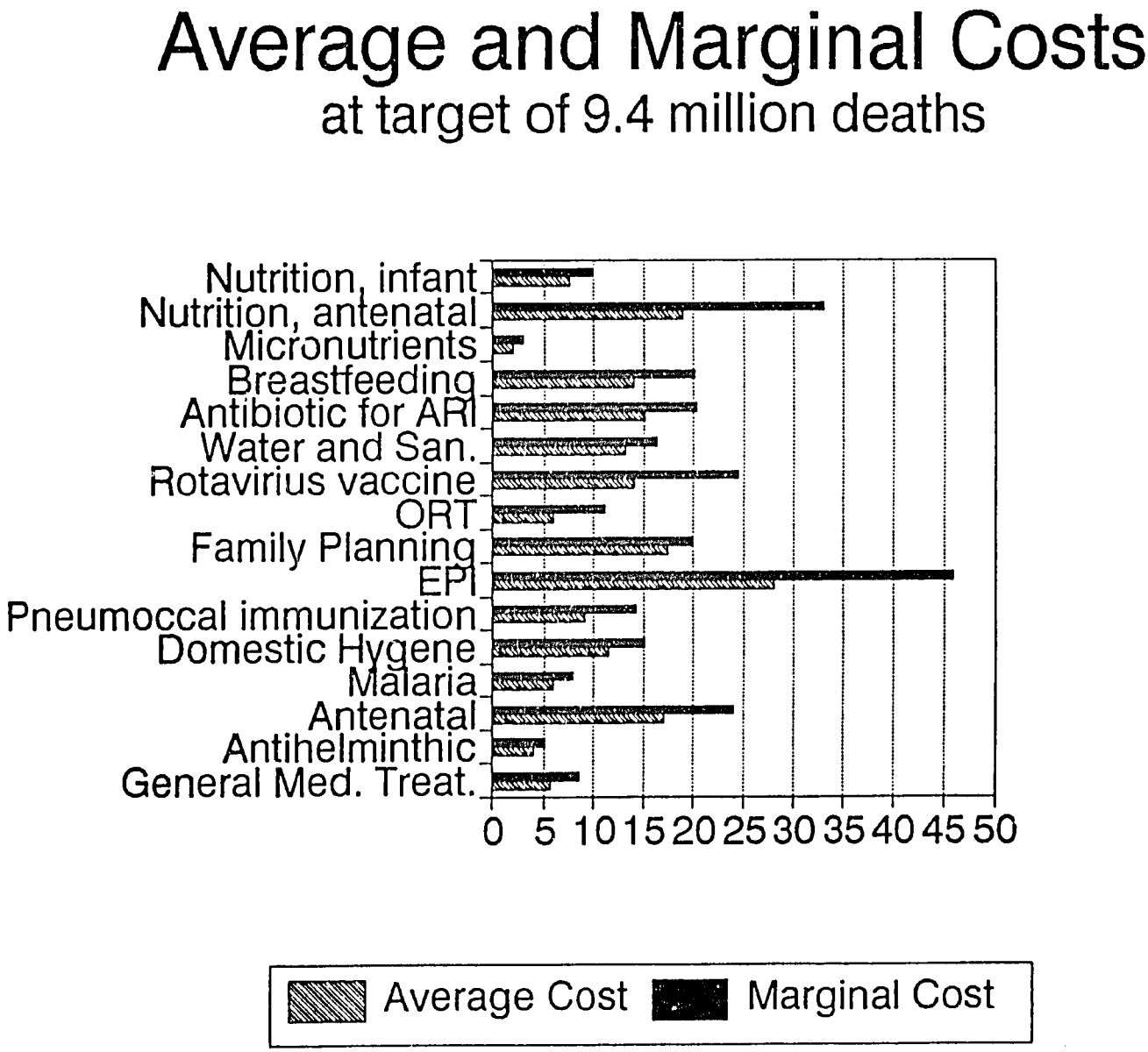


Figure F


Average and Marginal Costs
at target of 9.4 million deaths
Nutrition, infant
Nutrition, antenatal
Micronutrients
Breastfeeding
Antibiotic for ARI
Water and San.
Rotavirius vaccine
ORT
Family Planning
EPI
Pneumoccal immunization
Domestic Hygene
Malaria
Antenatal
Antihelminthic
General Med. Treat.
0 5 10 15 20 25 30 35 40 45 50
Average Cost
Marginal Cost

Appendix A: Linear Programming Model

This appendix formally states the linear optimization problem presented in Section 3.

Let:

E = EPI: providing full immunization to mother and child.
O = ORT: treatment of an episode of diarrheal disease.
F = FP: providing family planning services to a couple for one year.
N = NTR: providing nutrition supplements to an individual for one year.
W = W&S: providing water and sanitation services annually.
S = SFM: a maternal program for a woman at risk.
M = MED: general medical treatment, prescription, or preventive care.

Then the solution to the cost minimization problem is:

$$\text{Minimize Cost} = 18*E + 1.2*O + 20*F + 15*N + 10*W + 30*S + 5*M$$

subject to:

$$0.001\,E + 0.01\,O + 0\,F + 0.025\,N + 0.01\,W + 0\,S + 0.001\,M >= 1{,}750{,}000$$
$$0.001\,E + 0\,O + 0\,F + 0.005\,N + 0\,W + 0\,S + 0.005\,M >= 850{,}000$$
$$0.022\,E + 0\,O + 0\,F + 0.01\,N + 0\,W + 0\,S + 0.0005M >= 1{,}300{,}000$$
$$0.018\,E + 0\,O + 0\,F + 0\,N + 0\,W + 0.0001S + 0.0001M >= 790{,}000$$
$$0\,E + 0\,O + 0.01\,F + 0.0001N + 0.001\,W + 0.02\,S + 0.0001M >= 170{,}000$$
$$0.006\,E + 0\,O + 0.05\,F + 0.001\,N + 0.001\,W + 0.001\,S + 0.0005M >= 400{,}000$$

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Johns Hopkins University Institute for International Programs/
Agency for International Development/World Bank

Joint Seminar
on
Child Health Priorities for the 1990s

June 20-22, 1991

Executive Conference Room 2030
Johns Hopkins School of Hygiene and Public Health
615 North Wolfe Street
Baltimore, MD 21205

Thursday, June 20

9:00-9:30	**Introduction and Welcome**	*Henry Mosley*, Johns Hopkins University *Dean Jamison*, UCLA *Ann van Dusen*, U.S.A.I.D.

Part One: The Impact of Child Survival Interventions: Review of Evidence

Session 1

9:30-10:30	**Overview:**	**Child Mortality Trends in the Developing World**
	Chair:	*Henry Mosley*, Johns Hopkins University
	Paper:	**"Levels, Trends and Differentials in Infant and Child Mortality in the Less Developed Countries"** *Shea Rutstein*, Demographic and Health Surveys
	Discussant:	*Kenneth Hill*, Johns Hopkins University
10:30-11:00	Coffee	

Session 2

11:00-12:30	**The Impact of Child Survival Programs: Vaccine-Preventable Diseases**	
	Chair:	*Ken Hill*, JHU
	Paper 1:	**"Mortality Reductions from Measles and Tetanus Immunization: A Review of the Evidence"** *Michael Koenig*, ICDDR, B
	Discussant:	*Felicity Cutts*, Centers for Disease Control
	Paper 2:	**"Impact of Immunizations to Prevent Acute Respiratory Infections"** *Mark Steinhoff*, Johns Hopkins University
	Discussant:	*James Gibson*, U.S.A.I.D.
12:30-1:30	Lunch	

Previous Page Blank

Session 3

1:30-3:00 **Vaccine-Preventable Diseases (continued)**

Chair: *Joan Aron*, Johns Hopkins University

Paper 1: **"Poliomyelitis and Hepatitis B: Impact of Immunization and Prospects for Eradication"**
Joseph Melnick, Baylor College of Medicine

Discussant: *Ciro de Quadros*, Pan American Health Organization

Paper 2: **"Interventions to Reduce Childhood Morbidity and Mortality from Tuberculosis"**
Hans Rieder, Federal Office of Public Health, Switzerland

Discussant: *Christopher Murray*, Harvard University

3:00-3:30 Coffee

Session 4

3:30-5:00 **Case-Management Interventions**

Chair: *Ron Gray*, Johns Hopkins University

Paper 1: **"The Mortality Impact of Oral Rehydration Therapy in Egypt: Re-Appraisal of Evidence"**
Hoda Rashad, Population Council

Discussant: *Norbert Hirschhorn*, REACH Project, John Snow, Inc.

Paper 2: **"Impact of Community-based Case Management of Pneumonia on Infant and Child Mortality: A Meta-analysis of Six Intervention Trials"**
Robert Black and Sunil Sazawal, JHU

Discussant: *James Heiby*, U.S.A.I.D.

Friday, June 21

Session 5

9:00-11:15 **Nutritional Interventions**

Chair: *Pamela Johnson*, U.S.A.I.D.

Paper 1: **"The Impact of Protein-Energy Supplementation Interventions on Child Morbidity and Mortality"**
Don Rose and Reynaldo Martorell, UC/Berkeley

Discussant: **"Mortality, Malnutrition and Synergies: Determinants and Interventions: A Discussion"**
Jean-Pierre Habicht, Cornell University

Paper 2: **"Vitamin A Nutriture and Child Health"**
Chris Kjolhede, Johns Hopkins University

Discussant: *Ronald Gray*, Johns Hopkins University

Paper 3: **"The Impact of Breastfeeding on Infant and Child Morbidity and Mortality"**
Mary Ann Anderson, U.S.A.I.D.

Discussant: *Julie da Vanzo*, Rand Corporation

11:15-11:30 Coffee

Session 6

11:30-1:00 **Behavioral Interventions**
Chair: *Jim Heiby*, U.S.A.I.D.

Paper 1: **"Malaria: The Impact of Treated Bednets on Childhood Mortality in The Gambia"**
Pedro L. Alonso, Allan G. Hill, Patricia H. David, Greg Fegan, Joanna RM Armstrong, Andreas Francisco, K. Cham, and Brian M. Greenwood
Discussant: *Clive Shiff*, Johns Hopkins University

Paper 2: **"Behavioral Interventions: Toward Improved Health Behaviors"**
Bonita Stanton, University of Maryland Medical School
Discussant: *Peggy Bentley*, Johns Hopkins University

1:00-2:00 Lunch

Session 7

2:00-3:30 **Service Utilization and Intervention Synergy**
Chair: *Allan Hill*, Harvard School of Public Health

Presentation: **Data on Health Service Utilization from the Demographic and Health Surveys**
Ties Boerma, Demographic and Health Surveys

Paper 2: **"Synergy and Interaction Among Childhood Infectious Diseases: An Example from Bangladesh"**
Stan Becker, Robert Black, and Kenneth Brown, JHU
Discussant: *Michel Garenne*, Harvard University

3:30-4:00 Coffee

Part Two: Setting Intervention Priorities: Issues of Cost and Effectiveness

Session 1

4:00-5:30 **Prevention Strategies**
Chair: *Dean Jamison*, UCLA

Discussion 1: **Prevention via Vaccines**
Presenter: *Robert Steinglass*, REACH Project, John Snow, Inc.
Response: *Stan Foster*, Centers for Disease Control

Discussion 2: **Prevention via Environmental and Behavioral Intervention**
Presenter: *Sandy Cairncross*, London School of Hygiene and Tropical Medicine
Response: *John Briscoe*, World Bank

Saturday, June 22

Session 2

9:30-10:30 **Case-Management and Nutritional Strategies**
Chair: *Robert Black*, Johns Hopkins University

Discussion 1: **Case-Management of Respiratory Infections and Diarrhea**
Presenter: *Don Shepard*, Harvard University
Response: *Robert Northrop*, Brown University

Discussion 2: **Nutrition**
Presenter: *Judith McGuire*, World Bank
Response: *Kenneth Brown*, UC/Davis

10:30-11:00 Coffee

Session 3

11:00-12:30 **Conclusions**
Chair: *Ken Hill*, JHU

Discussion 1: **Costing the Year 2000: How Much and Where From**

Paper: **"Cost-Effectiveness in Child Health: A Minimum Information Approach to Planning and Forecasting"**
Larry Forgy, Abt Associates
Discussant: *Peter Berman*, Harvard University

Discussion 2: **Child Health Strategies for the 1990s**
Discussion Leaders:
D.A. Henderson, White House
Dean Jamison, UCLA
Pamela Johnson, U.S.A.I.D.
Henry Mosley, Johns Hopkins University

Johns Hopkins University Institute for International Programs/ Agency for International Development/World Bank

Joint Seminar on Child Health Priorities for the 1990s

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[1] Addresses and phone numbers for some participants have changed since this meeting was held. We have, whenever possible, provided updated information.

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