PN-AEC-556

TECHNOLOGY DEVELOPMENT AND ADAPTATION: CHALLENGES FOR FIELD RESEARCH IN THE 1990's[1]

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1. INTRODUCTION

During the 1970's and 1980s there has been a resurgence of research on the major tropical diseases. This was stimulated by increased investment in this area at a time when striking advances were being made in immunology and molecular biology. During this time many young laboratory scientists in developed countries have become interested in the major disease problems in developing countries and have worked to increase our understanding of tropical diseases at a cellular and molecular level with the goal of developing new or improved tools for disease control.

Out of this research new tools are beginning to emerge, some of which hold great potential for the control of the major tropical diseases. Problems have arisen, however, in obtaining rigorous evaluations of these new tools in realistic field situations. Following promising results in laboratory investigations or in small clinical trials, it has been difficult to develop the necessary field research studies to evaluate tools in situations where they may be useful for disease control. The major reason for this is the dearth of persons able to design and conduct

[1]To be presented at a "Colloquium on International Health and Development in the 1990's" convened by The Johns Hopkins University School of Hygiene and Public Health. April 6-8 1988. Cross Keys Inn, Baltimore, Maryland.

good field research studies in most of the tropical disease endemic areas. Not only is there a shortage of persons with the necessary epidemiological training to conduct field studies, but also those that are so trained often find that the local obstacles to such research are overwhelming and often those most able to conduct field research are assigned to other tasks.

Field research to evaluate and monitor the adequacy of new disease control tools is essential if such tools are to be deployed rationally in disease control programmes. In this paper two components of field research are discussed. Firstly, some ideas are presented as to how field research potential might be strengthened in the tropical disease endemic areas and, secondly, some suggestions are made for field research study designs that are needed to evaluate the impact of new interventions and to monitor their continuing effectiveness in disease control programmes.

The difficulties associated with field research activities have been appreciated by many organisations involved in the development of improved disease control measures and has been of special concern to the WHO Tropical Diseases Research Programme (TDR). Through this programme many new tools have been developed to the stage at which they need field evaluation, but it has been very difficult to solicit high quality research proposals for this latter activity. This weakness has been recognised since the initiation of the Programme in 1975 and a number of initiatives have been taken to try to improve the situation. These have met with only limited success in the first 10 years of the Programme and, recently, some new initiatives have been formulated that is it is hoped will have a major impact in the 1990's. Some of the steps that have been taken by TDR to develop field research capacity in the tropical disease

endemic areas will be described briefly and the plans for future developments will be outlined. These problems faced by TDR are shared by many groups and the proposals may have relevance for such groups.

Research is needed not only to evaluate the efficacy of new disease control tools when they are taken from the bench to the field but also it is needed to determine the best way to deploy the tools for disease control. Interventions which have good efficacy in carefully controlled field trials may perform less well when taken up into routine health service use. Even if they retain their efficacy (ie. protect or cure those to whom the intervention is administered) in the latter situation, the overall impact of an intervention will depend upon the ability of the health services to maintain good coverage in the at-risk population. This requires operational research. It is critically important to develop the capacity to conduct research on both efficacy and effectiveness within national and district disease control programmes.

2. THE TROPICAL DISEASES RESEARCH PROGRAMME

The Special Programme for Research and Training in Tropical Diseases (TDR) was set up in 1975 to bring the resources of modern science to bear on the control of the major tropical diseases. Six diseases were selected for inclusion in the programme - malaria, schistosomiasis, leishmaniasis, filariasis, trypanosomiasis (both African trypanosomiasis and Chagas' disease) and leprosy. These diseases were chosen because of their major impact on public health in much of the tropics, the inadequacy of methods of controlling them and the likelihood that research would lead to better disease control methods. TDR provides a mechanism for international scientific collaboration and attempts to coordinate and facilitate

national and international disease research programmes. The activities of TDR are directed through a number of Scientific Working Groups, with associated Steering Committees, made up of eminent scientists who define the priorities for research on the different diseases and who review submitted applications for research support. Attempting to strengthening the capacity for scientists in the tropical disease endemic areas to conduct high quality research has been an important component of TDR since its inception and approximately 20% of the budget has been devoted to this activity. At present the annual budget of TDR is about $26 million (WHO, 1987).

3. PREVIOUS TDR ACTIVITIES TO STRENGTHEN FIELD RESEARCH

In order to develop capacity for field research in the tropical disease endemic areas TDR has made several initiatives since 1975. At that time it was recognised that there were few places in developing countries with institutions with recognised strengths in field research. Many of the major field studies in the tropics had been undertaken by largely expatriate groups and when these studies had come to an end there were insufficient trained nationals left behind to continue field research programmes or to initiate new studies. Thus institutional strengthening became a key component of TDR's research strengthening plans. A number of institutions were selected for specific strengthening. Attempts have been made to develop not only institutions with field research potential but also those with the potential for basic research on the tropical diseases in fields such as immunology and molecular biology. This has been done in the belief that as far as possible endemic countries should develop their own capacity to produce new disease control tools and also, very importantly, to be able to adapt tools elaborated elsewhere for use as

locally appropriate.

An essential feature of institutional strengthening has been staff training and many individuals from the selected institutions have been sponsored for postgraduate training at masters and doctoral levels, usually in universities in developed countries. It has been recognised as being important to develop high level academic training capacity in the endemic countries and support has been given for the development of postgraduate courses. In particular, with respect to field research, support has been given for the initiation of five postgraduate training course in epidemiology (in Singapore, Cali in Colombia, Rio de Janeiro, Nairobi and Dar es Salaam). It has been considered especially important to develop epidemiological training programmes in the tropical disease endemic areas as the opportunities for fieldwork training on courses in developed countries are very limited.

Unfortunately there have been few good proposals for field research submitted to TDR Steering Committees from researchers in the endemic countries. TDR is not alone in this respect, and other groups supporting research on tropical diseases have faced similar problems (e.g. the WHO Diarrhoeal Diseases Control Programme). Several mechanism have been tried to improve this situation. Firstly, workshops have been organised at which draft protocols submitted by participants have been improved through group discussion between participants and consultants. Secondly, protocols submitted for funding to TDR have been reviewed by the relevant Steering Committees and recommendations for improvement have been returned to the proposers - this review process has sometimes also involved site visits by secretariat or Steering Committee members or consultants. These various strategies have met with only limited success and it is recognised

that there is a need to develop additional ways of improving the quality and quantity of field research in the endemic areas. Some of the methods proposed are outlined in the next section.

4. NEW INITIATIVES TO STRENGTHEN FIELD RESEARCH ACTIVITIES

4.1 Fellowships for advanced epidemiological field research training

Many of the skills needed for successful field research on tropical diseases are not those taught on epidemiology courses, especially courses in developed countries where the opportunities for relevant fieldwork experience may be, at best, limited. In developed countries, practical epidemiological skills are usually learned by junior researchers working under the supervision of experienced workers, as is also the case in the laboratory sciences. The opportunities for such "apprenticeship" training in the developing countries are very limited as, in many, there are no established traditions of field research and experienced field epidemiologists are few.

There are some ongoing epidemiological field studies in the tropical disease endemic areas that might be used for more extensive "hands on" training in field work methods. In an attempt to further exploit such opportunities TDR is providing fellowships for individuals wishing to undertake advanced training in field epidemiological research. The fellows will be attached to ongoing successful field projects, often in countries other than their own, for a period of two or three years to develop their epidemiological skills in the design, conduct and analysis of intervention trials and other field epidemiological investigations. The fellowships are intended for those who have a basic grounding in

epidemiology but who lack supervised field experience.

4.2 Outline protocols for priority field studies

The traditional passive method of allocating funds for research, in which grant committees review submitted proposals according to scientific merit and relevance to programme priorities, does not work well for field research on tropical diseases. Not only has the quality of submitted proposals been generally poor but the objectives of the research proposed have often not been those of highest priority. To improve this situation it is planned that TDR steering committees will play a more active role in defining field research priorities, not only by listing the most important questions for research but also by developing outline protocols for studies that would answer these questions. Each steering committee will have an associated "field studies sub-committee", consisting of some members of the steering committee and additional ad hoc members as necessary. Each of these sub-committees will be charged with the responsibility, in close liaison with their steering committee, to list the priorities for field research and to outline protocols for this research. Where possible, scientists from the tropical disease endemic areas, who might be in a good position to conduct research of the kind likely to be proposed, will be included in the sub-committees so that they can take an active part in the drafting process.

In some circumstances special meetings of appropriate scientists will be organised to define priorities and draft outline protocols in particular study areas. An example of this is a meeting that was held in Nairobi at the end of 1987 to review what was known about the interrelations of the tropical diseases and the AIDS virus and to draft

outline protocols for high priority research on this topic (WHO, 1988).

To convert outline protocols into specific proposals for funding, adapted to local circumstances, will in itself be a substantial undertaking. There are several ways in which this process may be facilitated. Firstly, the assistance of a consultant might be sought, ideally from the endemic area but, if such an individual is not available, otherwise from a developed country. Such consultants would be charged not only to give assistance with the design of the study but also to advise, on an ongoing basis, on its conduct and analysis. Secondly, potential investigators might be brought together for a special protocol development workshop at which the participants, together with such consultants as may be necessary, would work together to expand outline protocols into detailed, and costed, study designs adapted to their own geographical areas and circumstances. Such consultations and workshops could be organised as part of the activities of field research networks.

4.3 Field research networks

Those trained in epidemiology or other field research related disciplines often face formidable obstacles to conducting field studies when they return to their home countries or institutions. In developed countries recently trained epidemiologists have easy access to others working on similar problems to whom they can turn for advice and support. Such a mechanism is usually not available in developing countries, where the scarcity of trained manpower is such that an epidemiologist or social scientist may be in a position of considerable isolation. The Schools of Public Health and other institutions that are responsible for training

such individuals are usually unable to provide much supervision or guidance to students once courses have finished and the students have to sink or swim on their own initiatives.

TDR is planning to launch a major new initiative aimed at strengthening capacity for field research in the endemic areas through the creation and promotion of networks of field researchers and centres. It is proposed to build up links between field researchers in the endemic areas by the organisation of regular regional or sub-regional workshops to bring together those conducting TDR-related field studies. At these workshops investigators will be able to exchange ideas and information on methods developed in the context of their own field studies; to design protocols for new studies; to be briefed by "experts" on new developments (e.g. on priority issues for research, on new field tools); and to present preliminary results from field studies for critical review. Short instructional courses might be run in conjunction with such workshops to increase capabilities to use particular methods or techniques. Workers in developed countries might participate in the networks with emphasis on the transfer of skills in field research methods and organisation.

The functions of the proposed networks may be summarised as follows:

1. To facilitate communication between field researchers in the endemic areas in order to strengthen their capacity to conduct multidisciplinary field studies.
2. To facilitate continuing training in field research, through regular workshops and short training courses organised at regional centres.
3. To serve as a focus for collaborative research studies and to provide a mechanism by which protocols would be developed for high priority field studies.
4. To foster the links between field researchers and national disease control programmes.

5. To disseminate information through the network on new advances in field research methods and tools.

6. To provide a focus for the strengthening of regional resource centres in order that they could provide assistance or advice for individual researchers on special aspects of field studies.

7. To promote further field research studies by appropriate expansion of the network to include additional researchers and institutions.

8. To link field researchers in the endemic areas with those in developed countries, with the objective of transfer of skills.

Initially these networks will be based around those doing field research on diseases included in the TDR programme. Once the networks are well established, however, it is likely that those with other disease interests will be incorporated.

The development of field research in close liaison with national disease control programmes is viewed as especially important as it is through such links that newly developed disease control tools may be introduced into widespread use and subjected to ongoing evaluation. Thus, there will be a preference to include in the networks those research groups that are either in national control programmes or have established close links with such programmes.

The importance of integrating those with social science skills and experience into the research networks should be stressed. This component is likely to be critically important in evaluating the performance of new interventions and tools in disease control programmes - as also will be the contribution of health economists.

5. FIELD RESEARCH REQUIRED FOR EVALUATING NEW DISEASE CONTROL TOOLS

As discussed above, a critical impediment to the proper evaluation of

new tools and interventions against the tropical diseases is the acute shortage of those trained and experienced in the appropriate disciplines for such research in developing countries. Not only is there a shortage of those with epidemiological training but there are similar shortages of health economists and social scientists, whose skills are likely to be equally relevant in the implementation and evaluation of disease control tools and strategies. There is a need to develop strengths in these areas in parallel, possibly, at least in part, through the sorts of networking arrangements outlined above.

As well as enlarging the cadre of individuals and groups with the necessary skills for field research there is a need to give careful consideration to the types of field research and study designs that are needed to evaluate the role of new interventions, especially as they are put into routine use by disease control programmes. The classical method of evaluating the efficacy of a new vaccine in preventing disease, or a new drug in treating disease, is the randomised controlled trial. Subjects in such trials are allocated, at random, to receive either the new drug or vaccine or to receive the "conventional" vaccine or treatment (which may be a placebo if effective preventative or curative interventions are not available). Those in each "arm" of the trial are followed prospectively and disease incidence rates (in the case of vaccine trials) or "cure" or improvement rates (in the case of therapeutic trials) are measured and compared. The methodologies for such trials have been well worked out and they are, without doubt, the least ambiguous way of assessing the efficacy of an intervention under controlled conditions. This method has been used, for example, to assess the effects of ivermectin in the treatment of onchocerciasis and is the approach being used to assess the efficacy of the armadillo-derived *M. leprae* vaccine

against leprosy in large trials in Venezuela and Malawi.

Some interventions are employed at the community level rather than at the individual level (eg. installation of improved water and sanitation; vector control programmes; introduction of a village health worker) while others, although applied to individuals, may depend for their effectiveness, at least in part, upon use by many individuals in a community (eg. use of household esidual insecticide or insecticide impregnated mosquito nets to reduce malaria transmission; treatment with ivermectin of those in communities infected with onchocerciasis to reduce transmission of the infection). The design of trials to assess the impact of these kinds of intervention has been less well developed than those in which individuals are randomised and, too often, evaluations have been based on comparing a small number of "treated" communities (sometimes only one!) with a similar number of "untreated" (or control) communities. The wide variations in disease rates between communities which occur for many infectious and parasitic diseases, even over quite small areas, has frequently been neglected with the consequence that trials have either been uninterpretable or erroneously interpreted, because of failure to take account of the community-to-community variations in the design or analysis. In general, the consequence of such variation is that the statistical power of controlled trials in which communities rather than individuals are randomised will often depend more on the number of communities included than on the total number of individuals in the trial.

There are many circumstances, however, in which randomised controlled trials of the kind discussed above, whether based on individuals or communities, are ruled out for reasons of cost or ethics or for other

reasons (Smith, 1987), and alternative methods of evaluation must be employed. This applies particularly when interventions are being introduced, or have already been introduced, into routine disease control programmes. Often the impact of an intervention when it comes into routine use is less than would have been predicted based on the results of controlled trials. For example, changes may have been made in the formulation of the intervention; supervision of its correct application may be less rigorous than in a controlled trial; changes may have occurred in the infectious agent or vector. It is important, therefore, to devise means of measuring and monitoring the impact of an intervention in routine use to determine if it is failing to achieve its expected effect and if it is not why it is not.

One time when there may be a good opportunity to assess the impact of a new intervention is when it is first introduced into widespread use. This may be done by introducing the intervention in a phased way in different districts of a country with concomitant monitoring of the rates of disease, against which the intervention is directed, in the different districts before and after the intervention is introduced.

Such a design might be considered for example when malaria vaccines are first introduced. For the evaluation of potential malaria vaccines a careful sequence of studies has been formulated. Initial studies will assess the safety and acceptability of the vaccines in non-immune volunteers. Then small controlled trials will be conducted in areas not endemic for malaria involving artificial challenge with malaria parasites. Such trials will be extended, subsequently, to non-immune migrants in endemic areas and then to the indigenous population in endemic areas. The primary outcome measure in all these efficacy studies is

likely to be the development of parasitaemia and possible mild symptoms of malaria. It is unlikely that many will develop severe malaria as the trial populations will be carefully monitored and as soon as evidence of malaria is detected it will be treated, as it would be unethical to do otherwise. Thus it is possible to envisage a situation, at the end of this sequence of studies, in which there is evidence of efficacy, but not against the endpoints which are of greatest public health interest. The most important consequence of malaria is death, but it is doubtful whether this is an allowable endpoint for study in controlled trials. It seems likely that there may be pressure for widespread use of such vaccines in the absence of measures of their value in preventing mortality from malaria. While it may seem reasonable to assume that a vaccine which reduces parasitaemia levels will also prevent malaria deaths, it would also be prudent to introduce the vaccine into regions in such a way that the impact on mortality may be assessed. Thus the vaccine might be introduced into different districts of a country at different times and comparisons made of mortality rates in districts which have received or not yet received the vaccine. A "stepped wedge" design of this kind is being used for the introduction of hepatitis B vaccine in The Gambia to assess the protective effect of this vaccine against liver cancer (The Gambia Hepatitis Study Group, 1987). It is likely that this kind of study design could have many applications as new interventions are introduced in the future.

The "stepped wedge" design, or variants of it, may be useful to measure the impact of a new intervention during the time it is being introduced into a country or region. Methods are also required to continue to assess the impact of an intervention once it is in general use. In general, randomised trials are ruled out in this situation and

other methods must be sought. In some circumstances adequate assessment of impact may be estimated by simply monitoring the coverage achieved by the control programme and checking the potency of the intervention being applied. For example, the impact of measles vaccine may be assessed in this way and, if their are doubts about the potency of the vaccine, seroconversion rates may give an adequate surrogate measure of vaccine efficacy. For some vaccines, however, there is not a good correlation between serological or similar measures and protective efficacy. This is the case for BCG against tuberculosis and, because of the variable estimates of vaccine efficacy obtained from randomised controlled trials there has been great uncertainty about the value of this vaccine as a tuberculosis control tool.

Among some workers there has been a reluctance to consider methods other than randomised controlled trials to assess the protective effect of BCG. Because the incidence of tuberculosis is relatively low, such trials must generally involve many thousands of individuals followed for many years. They are expensive to conduct and need careful and sustained supervision. As a consequence, despite the millions of doses of BCG that have been administered in Africa over the past several decades to young children, there was not, until recently, any evaluation of the protection that had been provided against tuberculosis. In my view case-control studies offer an alternative approach to this problem and might be used in this situation, and in similar situation, much more frequently than has been the case in the past.

Case-control studies have been used extensively to study risk factors for chronic diseases such as cancer, but the approach has been relatively little used to evaluate the impact of specific interventions against

disease, especially infectious diseases in developing countries. The basic design of such studies is straightforward. Patients with the disease of interest, say childhood tuberculosis, are recruited into the study usually at, or shortly after, diagnosis and they are questioned and/or examined to determine their past exposure to the intervention of interest (eg. BCG vaccination). A group of controls, without the disease under study, are also selected, chosen to be similar to the cases with respect to age and sex and other potentially confounding factors. The controls are similarly questioned and/or examined to determine their past exposure to the intervention under study. By comparing the histories of exposure of cases and controls it is possible to derive an estimate of vaccine efficacy. This estimate may be biased as those who have been vaccinated may differ from those not vaccinated with respect to other risk factors for disease (eg. socioeconomic status). The bias may be reduced by suitable adjustment for such confounding factors in the design or analysis of a study - though it it never possible to be sure that their effects have been eliminated completely.

About 10 such studies have been conducted in the last five years to evaluate the protective efficacy of BCG against tuberculosis. Most of these have been in developing countries. It is of interest that the range of efficacies estimated have been from zero to 80% in different regions (Smith, 1987) - a range very similar to that observed in the controlled trials, conducted over a 30 year period, mostly in developed countries. These results are still under evaluation and it is too early to draw strong conclusions, but the finding from the case-control studies do suggest that vaccine efficacy varies in different geographical regions

Case-control studies are conceptually simple and can be carried out

quickly and at relatively low cost. Their design and analysis does require a reasonable degree of epidemiological expertise (Schlesselman, 1982) but little more than is covered in basic epidemiology training courses. This study design could be used far more extensively than it has been in the past, and if such studies are designed and analysed with care they may make important contributions to the evaluation of the impact of interventions against diseases in developing countries.

6. STRATEGIES FOR U.S. INTERNATIONAL ASSISTANCE PROGRAMMES

The discussion above has been focussed on plans within TDR to improve the capacity of those in the tropical disease endemic areas to initiate and conduct high quality field research on new disease control tools and on some of the study designs that might be appropriate for such research. The proposals have been outlined in some detail because it is believed that these strategies have relevance for other agencies supporting the development and implementation of new tools and interventions for the improvement of health in developing countries.

Some further ideas for strategies for U.S. assistance programmes are given below:

1. There remains a need for better vaccines, drugs and diagnostic tools to help control the major tropical diseases. New technological advances are likely to be made by scientists in the developed countries and it is vital that there is continued support for this kind of basic research in the 1990's and beyond.

2. There are laboratories in some developing countries with the capacity.

or in which the capacity could be developed, for work on the development of new biotechnological tools. Such laboratories may need external support, especially to establish links with scientists in developed countries with similar research interests. Such links should be made with the objective, wherever possible of transferring technological expertise into developing country institutions.

3. The adaption of new interventions for use in disease control programmes is most appropriately carried out in institutions in the developing countries, possibly in collaboration with developed country scientists. Building local capacity in this area is especially important.

4. When a tool has been developed such that it is ready for field use facilities for production or modification should be transferred, where possible, to the disease endemic areas. In many situations this will result is large cost reductions (eg. production of plasma-derived hepatitis B vaccines).

5. Those developing new tools are often not those best able to evaluate them in the field. There should be closer liaison between the basic scientists and epidemiologists both in developed and developing countries, so that the basic research is directed towards the production of the most appropriate tools for disease control and that the tools are properly field tested at an early stage.

6. Field research in developing countries is hampered by a shortage of trained and experienced field research scientists. It is essential to develop field research capacity in the developing countries. There will be a continuing need for sponsorship of those from developing countries

for training in the U.S. and other developed countries but there should be increasing emphasis towards "on the job" training. U.S. schools of public health could have an especially important role to play by seconding faculty with developing country experience and field research training to field research projects overseas, with a major objective of developing the field research skills of those in the tropical disease endemic areas.

7. A major commitment is required to supporting research on the evaluation of the effectiveness of disease control measures. Operational research studies in ongoing disease control programmes have been given relatively little support in the past but this kind of research is required if high coverage rates are to be obtained and maintained with drug or vaccine interventions.

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(hopkins 21.03.88)