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# Reproductive Epidemiologic Research in Developing Countries

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*This paper discusses the scientific rationale for carrying out reproductive epidemiologic research in developing countries, and the generalizability of results of research done in developed countries to developing countries. Practical problems encountered in doing research in developing countries include limited resources, overcommitted researchers, cost, and study monitoring. Cultural differences that affect the design and conduct of research activities in developing countries are also discussed. Ann Epidemiol 1990;1:187-194.*

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## INTRODUCTION

Family Health International (FHI) is an organization committed to contraceptive research in and for developing countries. We have been doing this since 1971 under a mandate from our funding agency—the United States Agency for International Development (USAID). USAID annually provides millions of contraceptives to developing countries and therefore funds research to provide the safest and most effective methods at the least cost. As part of its research, FHI develops new contraceptives, secures approval from the Food and Drug Administration (FDA) for new methods (USAID can not provide contraceptive methods that are not approved by the FDA), evaluates new methods developed by others, and provides data for FDA approval. FHI also evaluates the use of existing contraceptive methods in new settings, the noncontraceptive risks and benefits of the various contraceptive methods, the acceptability of new or modified contraceptives, and the optimal methods of providing family planning services in various settings. We also provide technical assistance to developing countries to help prevent the spread of acquired immunodeficiency syndrome (AIDS). Training investigators in developing countries in the clinical trials and epidemiologic methodologies needed to undertake reproductive and contraceptive research on their own is also an FHI priority.

As a US research agency funded by USAID, FHI's reasons for carrying out reproductive epidemiologic research in developing countries are clear. The more general scientific reasons for performing research in developing countries include answering research questions of specific relevance to a particular developing country and answering research questions of interest to the developed world in populations with a higher prevalence of the disease or exposure in question. This paper discusses in greater detail the scientific rationale for carrying out reproductive epidemiologic research in developing countries, practical problems that will be encountered in implementing such research, and cultural differences that can affect the design and conduct of research activities in developing countries.

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## SCIENTIFIC REASONS FOR CONDUCTING REPRODUCTIVE EPIDEMIOLOGIC RESEARCH IN DEVELOPING COUNTRIES

### Research Questions of Interest to Developing Countries

Data are needed for planning policy, planning health programs, and choosing appropriate therapies in developing countries. In the absence of data from the developing world, data derived from developed countries are often generalized to developing countries. The generalizations are not always justified. Here are some examples of research questions that are especially pertinent to developing countries, for which data from the developed world may not be adequate<sup>1</sup>: What dose of contraceptive hormones is appropriate for an 80-lb malnourished Bangladeshi woman? Can women in Sri Lanka, where anemia is widespread, tolerate the additional menstrual blood loss associated with intrauterine contraceptive devices (IUDs)? Perceptions of menstruation vary by culture (1). Does this variation affect the acceptability of contraceptive methods that affect bleeding patterns? Can paramedics safely perform tubal ligations and vasectomies in countries where there is a shortage of doctors (2)? How do high levels of maternal mortality affect the risk/benefit ratio of oral contraception? What is the effect of oral contraception on liver cancer in countries, such as Taiwan, where liver cancer is relatively common because of the high prevalence of hepatitis B? What is the effect of oral contraception on breast cancer in countries, such as Indonesia, where breast cancer is relatively rare? How do women in developing countries perceive the risks and benefits associated with different methods of contraception (3)? Do men in developing countries prefer plain, lubricated, or spermicidal condoms?

Family-planning programs in developing countries need accurate answers to these questions in order to provide the best possible services. Women in these countries need the answers in order to make the best choice of contraceptive method. In some cases, developed and developing countries clearly have different answers to the same questions. In other cases—for example, perception of risks—the answers are surprisingly similar. In practice, the findings of studies conducted in the West serve as the basis for most health policy decisions in developing countries simply because alternative data are so limited.

It is also important to bear in mind that the underlying health conditions in developing countries are usually very different from those in the West. Western researchers may be unaware of the ramifications of those differences: For example, oral contraceptives are less effective when taken along with rifampicin, a treatment for tuberculosis, which is widespread in the developing world.

### Research Questions of Interest to Developed Countries

Sometimes contraceptive research questions pertinent to developed countries cannot be answered in those countries because of low prevalence of exposure or low incidence of disease. For example, there is considerable interest in whether prophylactic antibiotics at IUD insertion will reduce the incidence of pelvic inflammatory disease (PID) after insertion, and hence there is a need for a clinical trial to evaluate this. Because current clinical practice in the United States recommends against IUD insertion in any woman at risk of sexually transmitted diseases (STDs), specifically to minimize the risk of PID, the outcome of interest is so rare that the sample size required to conduct

<sup>1</sup> For background reading on health issues in developing countries, please consult the bibliography provided.

the study is prohibitive. Such a study can be more efficiently conducted in a clinical setting where postinsertion PID is more common (4).

Another example of a question that could be more effectively studied in developing countries would be the efficacy of condoms in preventing heterosexual transmission of human immunodeficiency virus (HIV). Two kinds of populations are of particular interest: discordant couples, that is couples in which one partner is HIV positive and the other HIV negative; or a population at high risk of sexually acquired HIV (prostitutes, with STD clinic patients). But in the United States discordant couples have now been well counseled in safe sex practices and some of the HIV-positive partners are taking zidovudine (AZT), so seroconversion of the HIV-negative partner is becoming much less common. These changes increase the required sample size of any study in this group. Among high-risk groups in the industrial nations, it is also necessary (and difficult) to rule out the possibility of drug-related infections. In some developing countries, on the other hand, heterosexual transmission is the most prevalent form of transmission, and intravenous drug use remains uncommon. Thus, research among these populations would permit more rapid and valid answers to questions on heterosexual transmission.

The association between oral contraceptives, liver cancer, and hepatitis B virus (HBV) provides another example of a research question that can be answered more effectively in a developing country. Two studies in Britain found an increased risk of liver cancer (a rare disease in developed countries) in women using oral contraception (5, 6). However, these studies both excluded women with markers for HBV because they were too few for separate analysis and because HBV is a known risk factor for liver cancer. To study the question of whether women who have had hepatitis B can safely take oral contraceptives, we must find populations in whom both hepatitis B is more common and oral contraceptive prevalence is sufficiently high. Prevalence of HBV surface antigens (HbSAg) is less than 0.3% in the United States, although rates as high as 6.7% have been reported in some immigrant populations (7). Although in some developing countries, prevalence of HbSAg is higher, use of "the pill" is not common. Few countries meet both requirements, but in Hong Kong, HbSAg is present in 10 to 12% of the population, and about 70% of women of reproductive age use birth control pills.

A final example comes from our own experience. When we at FHI wished to conduct a randomized clinical trial to determine whether oral contraception would affect the number of crises among women with sickle cell disease, we collaborated with investigators in a sickle cell clinic in Jamaica. Not only does this clinic have excellent resources for research, but also they have a relatively large number of women of reproductive age among their clinic patients. In contrast, most sickle cell clinics in the developed world have far fewer patients; thus performing our research in Jamaica allowed us to investigate this question more efficiently than we could in the United States.

### **Restrictions on the Generalizability of Research between Developing and Developed Countries**

Under some circumstances, studies undertaken in developing countries for scientific reasons, such as disease prevalence, may not always be generalizable to the West because of other factors unique to the cultural setting. Some of the limitations are empirical. For example, the findings of research to determine the effectiveness of condoms in prevention of HIV transmission in a tropical country may be affected by

high rates of condom breakage due to adverse storage conditions. Other limitations have to do with significant differences in the populations. Because of interactions between oral contraceptives and rifampicin, clinical trials to determine the efficacy of oral contraceptives may not apply to Western countries unless women being treated for tuberculosis are excluded from the trial. There are also genetic and racial differences in some risk factors or endpoints of interest that would limit generalizability.

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## PRACTICAL ISSUES IN CONDUCTING RESEARCH IN DEVELOPING COUNTRIES

### Resources and Working Conditions

Shortages of equipment are common, and researchers should be prepared to provide and maintain most of the necessary equipment. Researchers should also bear in mind that maintenance technicians are in short supply, electric power is often erratic, dust-free environments are rare, and customs regulations are not designed for scientific convenience. Many a shipment of perishable supplies has become unusable in a customs warehouse. It is essential to determine, for example, whether it is feasible to deliver perishable supplies on a regular basis.

Shortages often extend to supplies as basic as paper, let alone file cabinets, typewriters, ball-point pens, White-out, and so on. If one can afford it, a FAX machine is an excellent investment to aid communications with a research site. Local communications may be more difficult; telephone lines can take months or years to install—often the personnel budget must include a messenger. Electricity and water may be regularly (or irregularly) unavailable. Nevertheless, much excellent work comes out of unlikely looking laboratories; thus, it is important to remain open-minded.

One should also be aware of the potential effects of national strikes, the local work ethic (Sri Lanka keeps Buddhist, Hindu, Moslem, and Christian holidays, for example), and political instability. FHI had several studies unexpectedly terminated when Khomeini took over Iran, and when we published results of those studies, our Iranian colleagues could not be listed as coauthors. On the other hand, FHI studies in Haiti continued with minimal difficulty during periods of unrest surrounding the overthrow of Duvalier.

### Monitoring

A scientist working with a colleague in a developing country should expect to invest considerable time and effort in monitoring the study. Site visits are important. Monitoring should include evaluation of the quality of recruitment, data collection, and follow-up. Furthermore, practical issues such as the adequate maintenance of equipment and the safe storage of records and supplies may need to be more closely monitored than would be the case in a developed country. Many of the decisions required to solve the various problems that occur in any research project need on-site involvement. This means regular communication. In one FHI study, the on-site study manager made a weekly phone call to the FHI monitor. However, if telecommunications are poor, more site visits will be needed.

### Overcommitted Researchers

Good researchers in developed countries are sometimes overcommitted. In developing countries the situation is magnified. There are many reasons for this, including a

shortage of physicians and scientists because of emigration. This is often exacerbated by the poor salaries of university and government physicians, who must also have a private practice in order to make ends meet. It is impressive that there are so many good scientists able to emerge under these working conditions. It is not unusual to find such scientists undertaking clinical trials for several international agencies at the same time. Sometimes this creates competition for patients, but it always creates competition for time and attention. The potential collaborator is advised to determine in advance the developing country colleague's work load. On the other hand, there are often junior staff, interviewers, and social scientists available because of underemployment in these areas.

### Cost

Rarely is cost a significant factor in deciding to work in a developing country. Whereas salaries and other costs associated with the study are often lower, the travel costs of monitoring may offset this. There are situations, however, in which a high incidence of the disease of interest reduces sample size requirements, thus making the study more cost-effective, as was true of our Jamaican study of oral contraceptive use and sickle cell anemia.

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## CULTURAL DIFFERENCES THAT CAN AFFECT THE CONDUCT OF SCIENTIFIC RESEARCH

### Cultural Differences in Health Policy

*Defining health and research priorities.* Health priorities are often different in developed and developing countries. Researchers investigating a question of low priority in the host country may encounter a strong lack of interest. An investigation of oral contraceptive use and breast cancer in a country like India is overshadowed by far more immediate problems, such as infectious disease and malnutrition. Western perceptions of what the developing countries' health priorities *ought* to be (for instance, primary health care) are sometimes different from what the developing country perceives as most important. Some governments have been so resistant to recognizing an AIDS problem that prevention activities in their countries have been seriously hampered.

It is generally accepted in public health circles that screening should not be done if treatment is not available. Because treatment availability varies from one country and, within each, to another, from urban to rural areas, the diseases appropriate for study can vary as well. We should not assume that a treatable condition in the developed world is treatable everywhere. Breast cancer provides a good example in the developed world.

*Establishing standards of care.* It is sometimes said by United States-based pressure groups or consumer groups that the same standards of medical care should hold for research or services in the developed and the developing world. This expectation is unrealistic. A more pertinent ethical question in developing countries is how to provide medical care at all, given the limited number of physicians. In countries where physicians are scarce, other medical personnel need to be trained to provide family-planning services, including surgical services, and to evaluate the quality of the services. It is unethical to withhold services because there are insufficient numbers of physicians to provide them if these services can be provided effectively by others.

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It is also important to remember that risk/benefit ratios differ. Where curative services are limited, prevention takes on additional importance. While it continues to be important to know the side effects of, say, oral contraception, one must remember that pregnancy may carry a risk of mortality that is 100 times greater in developing than in developed countries.

### Cultural Differences in Attitudes toward Information

**Need to inform and the desire to know.** There is much gray area in the field of research ethics. Nowhere is this more true than in AIDS/HIV research. As in the United States, in developing countries ethical issues surround testing, notifying, counseling (or lack of it), prevention, and treatment. Competition for scarce resources in treatment is even greater than in the United States. In some countries women (and men) will refuse testing if they are to be told the results. The National Institutes of Health (NIH) requires notification in studies they fund, although waivers can be obtained. The consequences of knowing HIV-positive status are potentially even more serious in some developing countries than in the United States. A woman who tests positive may be abandoned by her husband; and if her status is determined before his (as during pregnancy), it is often assumed that she is the source of the infection in the couple. Abandoned wives have few career options in many developing countries, and some turn to prostitution to support themselves. Furthermore, the advantages of knowledge are considerably less in the developing world because early treatment is less available.

It can be ethical not to tell patients they have a particular disease if that is the cultural and legal norm, if patients do not want to know, and if there is no treatment for the disease. This was the source of great difficulty I once experienced setting up a case-control study of hormonal contraception and cervical cancer. An excellent cancer registry in a developing country had never been used for anything but reporting incidence to the World Health Organization. No case-control studies, or any other studies requiring patient contact, had ever been conducted using this database. The reason given by the director of the registry was that most doctors did not tell their patients they had cancer (and, he stressed, he himself would not want to be told). Participation in a study might make participants aware that their doctors had not informed them.

The rarity of malpractice suits in developing countries may sometimes mean that physicians are not constantly reminded that they need to worry about such matters as informed consent. Indeed, it is a common complaint of physicians in developing countries that "If I read them that consent form, they will never agree to the procedure." Western patients are sometimes intimidated by consent forms; the problem is greater with less medically sophisticated patients in a developing country. It is therefore incumbent on researchers to write consent forms that are both sensible and understandable. FHI now submits all consent forms to a process whereby they are evaluated for reading difficulty; they must be readable at the sixth-grade level or less. This evaluation includes length of sentence and number of multisyllabic words; "the pill" is better than "oral contraceptives" for instance. Simplification is not always feasible. (In English, "spermicides" presents us with an as yet unsolved problem.)

Researchers and clinicians should keep in mind the difference between *informed consent* and *informed choice*; i.e., consent does not imply choice. A good example is provided by treatment of breast cancer: A patient may consent to radical mastectomy after having it explained to her; this is informed consent. But if she did not have alternative treatments explained and offered, she did not make an informed choice.

Sometimes patients, especially those who are poor and uneducated, are threatened by choice and prefer the physician to make decisions. But it is important to be reasonably sure that the patients are not being taken advantage of because of this. It should, for instance, be made clear that if a patient does not agree to "volunteer" for a study, medical care is still available. One should be skeptical of a clinician who claims his or her patients will do whatever he or she asks. This may be true, but is not necessarily desirable.

**Other cultural differences.** Cultural differences can range from the important to the apparently trivial. Our studies have been delayed for equal lengths of time as our collaborators have debated whether or not patients should be informed of their diagnoses, or whether the driver in a study, who is male, should be paid more than the interviewers, who are usually female.

Open disagreement is alien to many cultures. The American way of open, and perhaps heated, discussion, leading to consensus can cause offense in other cultures, especially those of Southeast Asia. Sometimes a collaborator will verbally agree, but then do something else; this is not due to deviousness, but because disagreement is culturally difficult. This can make the negotiation of protocols and contracts, and resolution of implementation problems difficult even for an experienced researcher.

One is often unaware of what gives offense in a different culture, and the potential pitfalls are many. Americans tend to be impatient and want to skip the "courtship" part of establishing a research relationship. Yet it is essential to listen to one's collaborators' concerns and to understand their priorities. It is often important to meet all the players in the team and their supervisors (the courtesy calls), and to listen as carefully to them as to the principal investigator. This can require a great deal of time, but probably saves time in the long run since it can avert later problems or facilitate their resolution. Although this observation may seem a cross-cultural truism, it is very hard to put in practice.

The "right" thing to do varies with the culture, and it can be difficult for a Western scientist to distinguish between the ethical and the nonethical in an alien setting. Many developing country medical institutions have ethical committees, and these days many countries have national AIDS committees that oversee the ethics of all AIDS research. Clearly, one should be sensitive to the requirements of such committees and value their guidance. The Western researcher who insists on his or her own standards will not be well received.

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## CONCLUSIONS

It is possible to undertake epidemiologic research in developing countries that will be of scientific value to both the developed and the developing world. The logistics of research in the developing world are difficult but not insuperable. Many of the obstacles can be overcome with a little creativity. Cultural differences raise both practical and ethical problems that have implications for the conduct of scientific research. Research is likely to be easier and more profitable if it is undertaken in a spirit of genuine collaboration. Colleagues in developing countries have much to offer in terms of insight and skills, and should not be regarded merely as a source of pliable patients.

Furthermore, successful collaboration requires patience. Perceived time pressure is not shared by much of the rest of the world. Government approvals and other bureaucratic hurdles can take longer than might appear reasonable to Westerners. Successful

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collaboration requires sensitivity. It is important to listen to what colleagues are saying and to be sensitive to the tacit implications. It is also necessary to remain aware that patients as well as scientific colleagues may have a different perspective.

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