Ethical Issues in Tuberculosis Vaccine Trials

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Bacille Calmette-Guérin (BCG) vaccines are widely used, even though estimates of efficacy have ranged from zero to 80%. BCG is a relatively safe vaccine, but it can cause disseminated infection, especially in immunocompromised hosts. Thus, the development of a more reliably efficacious and safer vaccine is important to the control of tuberculosis. The testing of any new vaccine in human populations presents a number of ethical challenges that must be addressed. These include (1) the appropriateness of conducting such trials in developing countries; (2) the use of a BCG-vaccinated population as the control group; (3) the provision of tuberculin skin-test screening and preventive therapy to study participants; (4) the involvement of various “communities” in the trial(s); (5) the structure and process of ethical review; (6) establishing an effective method of obtaining informed consent; and (7) the roles and responsibilities of researchers and others in ensuring that trial results are available to the study population after the trial ends.

This article discusses some of the ethical issues raised by the prospect of conducting clinical trials of new vaccines against tuberculosis in human research subjects. The ethical issues surrounding the conduct of clinical trials, especially perinatal zidovudine trials, tuberculosis preventive therapy trials, and HIV vaccine trials conducted in developing countries, have recently become the subject of controversy and intense debate [1–16]. The inability to resolve these generic ethical issues quickly has hampered the ability of developed countries to assist developing countries in addressing their most important health problems, including HIV disease. If these issues remain unresolved, they will also adversely impact the ability of developed countries to assist developing countries in planning and conducting tuberculosis vaccine trials.

However, in addition to these generic ethical issues, there are other ethical issues specific to tuberculosis that must be resolved before vaccine trials can go forward. Although we appear to be several years away from tuberculosis vaccine trials in humans, it is not too early to begin considering the ethical issues that will have to be addressed, considering the length of time it may take to arrive at a satisfactory solution. It would indeed be a tragedy if one or more new vaccines became available and trials could not be conducted because the relevant ethical issues had not been resolved. We must deal with the ethical aspects of trials as carefully and thoroughly as we deal with the scientific aspects.

Before proceeding further, I want to clarify the scope of the discussion in this article. The ethical aspects of trials encompass a broad range of considerations and refer to a whole range of expectations that society has regarding the virtues and moral behavior of anyone involved with trials, including scientists, support staff, and participants. This broad definition encompasses general principles regarding the conduct of research developed by appropriately constituted multidisciplinary bodies of experts [17, 18]; standards of conduct and practice guidelines proposed by professional societies [19, 20]; regulations issued by governmental bodies [21]; and unwritten societal expectations and norms regarding individuals’ behaviors. A full discussion of all these is beyond the scope of this article.

Investigators in the United States should be familiar with publications such as the Belmont Report [22] and the US government regulations concerning human-subjects research [21]. Those conducting research internationally should also be familiar with 2 publications of the Council for International Organizations of Medical Sciences [17, 18]. The following comments will be restricted primarily to controversial issues raised in recently published articles or discussed at recent meetings and to issues that are somewhat, if not exclusively, specific to tuberculosis vaccines.

Although a variety of ethical frameworks can be used to analyze ethical problems and issues, the following discussion is based on the 3 basic ethical principles articulated in the Belmont Report: respect for persons, beneficence, and justice [22]. These principles have proven to be very useful in analyzing ethical issues related to biomedical research. Respect for persons incorporates 2 convictions: first, that most individuals should be treated as autonomous agents capable of making their own informed decisions, and second, that persons with diminished autonomy should be protected. The principle of beneficence requires that we maximize possible benefits and eliminate or minimize possible harms. Justice in the research context refers to the equitable distribution of the benefits and burdens of research. I will assume that the process for ensuring
that these principles are followed involves an ethical review committee (e.g., an institutional review board).

One caveat that should be kept in mind when thinking about the ethical issues to be addressed is that they are intertwined with the scientific issues. For example, some of the ethical issues will differ depending on the purpose of vaccination; that is, whether the vaccine is intended to prevent infection and/or disease in persons not yet infected with Mycobacterium tuberculosis or whether it is intended to prevent disease in persons already infected. This important interplay between science and ethics in any given trial and the evolving nature of both science and ethics make it hazardous to draw definitive conclusions now about how any particular future trial should be conducted. The following discussion should be viewed as the beginning of an ongoing dialogue on the topic and not a compendium of definitive answers to future ethical concerns.

Some of the major ethical issues that must be addressed before conducting clinical trials of tuberculosis vaccines are (1) the need to conduct trials in one or more developing countries; (2) the need to use a standard BCG vaccine in the control group; (3) the need to provide tuberculin skin-test screening and/or preventive therapy to study participants; (4) the involvement of various “communities” in the trial(s) and how and when they should be involved; (5) the structure and process of ethical review; (6) establishing an effective method of obtaining informed consent from study participants; and (7) the roles and responsibilities of researchers, vaccine manufacturers, international and national health organizations, and economic development agencies in ensuring that trial results are appropriately available to the study population after the trial ends.

The issue of conducting trials in developing countries relates primarily to the principle of justice. Populations in poor countries clearly have been exploited for testing interventions that were ultimately used in rich countries and unavailable to poor countries. From a scientific and economic standpoint, one would like to conduct the tuberculosis vaccine trial in a population in which the outcomes of interest—namely, the incidence of infection and/or disease—are high enough to provide a reasonably accurate estimate of the safety and efficacy of the new vaccine, with a small enough sample size to make the study feasible. For tuberculosis, many populations in developing countries will meet these criteria, and few populations in developed countries will do so. From an ethical perspective, this may not be a major problem because those populations with low incidence of tuberculosis will not benefit much from the development of a new tuberculosis vaccine, whereas populations with a high incidence could potentially benefit a great deal.

This is not to say that populations in developed countries cannot or should not participate in phase I, II, and III trials. In fact, for pragmatic, business, and political reasons, vaccine manufacturers and trial sponsors may prefer to conduct phase I trials in developed countries. However, conducting phase II and III trials of new tuberculosis vaccines solely in developed countries may not be feasible, and conducting them in developing countries is not only scientifically desirable but ethically appropriate. A critical issue, to which I will return later, is how much needs to be done “up front” to ensure that the vaccine will be available to persons in the participating developing country if it proves to be safe and effective.

A second issue is whether a standard BCG vaccine must be used in the control group. We know that currently available BCG vaccines are not reliably efficacious for prevention of tuberculosis, although they are widely used, especially in developing countries. The efficacy of protection against all forms of tuberculosis estimated from controlled clinical trials varies from zero to 80% [23]. However, clinical trials and case-control studies involving young children, especially when disseminated and severe disease are used as endpoints, more consistently show that BCG vaccination can reliably offer a moderate to high level of protection to children without prior Mycobacterium tuberculosis infection [24, 25].

In virtually all BCG studies (trials and observational studies), the end point measured has been protection against clinical and/or laboratory-proven disease, since an adequate method for measuring protection against new M. tuberculosis infection following BCG vaccination is not available. This is because tuberculin skin-testing is the only accepted method of measuring new M. tuberculosis infection, and BCG vaccination (i.e., BCG infection) usually causes the vaccinated individual to become reactive to the tuberculin skin test.

Although all clinical trials of BCG vaccination conducted in the past have included a placebo control arm, the above findings suggest that the ethical acceptability of using a placebo control arm rather than a BCG-vaccinated control arm is not straightforward. In general, the decision should depend on the certainty or strength of the evidence that BCG is protective in the population being studied, as well as the evidence that it is or is not harmful. This would, in turn, depend on the characteristics of the study population, such as age, prior vaccination status, and tuberculosis infection status. It would also depend on the immune status of the population to be studied as well.

For example, although they are relatively safe, as live attenuated strains of the M. tuberculosis complex, BCG vaccines can cause symptomatic and disseminated infection in immunocompromised hosts. Thus, since BCG can cause disseminated disease in HIV-infected persons, it would be more ethically justifiable to compare a new vaccine with placebo rather than with BCG in HIV-infected persons, provided that the new vaccine was more attenuated than BCG or was nonliving. A trial of this sort would not address a trivial scientific issue: in the future, it is anticipated that an increasing proportion of tuberculosis cases will occur among HIV-infected individuals [26].

In general, however, it may be difficult to ethically justify assigning uninfected persons to a placebo control group. This would certainly be the case for young, previously unvaccinated
and uninfected children, given the rather compelling data on the safety and efficacy of BCG vaccine against severe disease in this group [19]. For other groups of uninfected persons, the issue becomes a bit more murky, especially given the inconsistent efficacy of the vaccine against all forms of tuberculosis and the paucity of data on efficacy in some populations. In some such groups, a placebo control might be justifiable, especially if potential study participants were made aware of the existence and availability (or nonavailability) of BCG vaccination as an option. For some trials, one might consider allowing individuals in the control group to choose whether they want to be vaccinated with BCG or placebo. However, this could introduce unmeasurable biases into the trial, since there is a possibility that those who chose BCG might differ in some significant way (e.g., in their risk of infection or disease) from those who chose placebo.

If the data from the literature indicate no protection from BCG and there is reason to believe BCG would not be protective, a BCG control arm should not be used and a placebo control arm would be fully justified. For example, if the population to be studied is already tuberculin skin-test-positive, a placebo control is ethically justifiable since there is no evidence that BCG is protective in this population.

A third major ethical issue for tuberculosis vaccine trials is whether tuberculin skin-test screening and preventive therapy should be offered to study participants. Depending on the study design, this could be one of the most difficult or one of the easiest issues to resolve. If, for example, the study involves the comparison of a new vaccine and a BCG vaccine, both of which result in marked tuberculin reactivity after vaccination, then skin-test screening of the study population might be meaningless and preventive therapy for newly infected persons who are at high risk of developing tuberculosis (i.e., skin-test converters) would be impossible, since newly infected persons could not be identified.

In other situations, where there is a placebo control arm and/or the new vaccine does not lead to tuberculin skin test conversion, the problem would be more complex. Clearly, if one of the main end points of the trial was to determine vaccine protection against infection with M. tuberculosis, then skin-test screening of the population would be required, and even if preventive therapy were not a standard of care in the trial community, one would be hard-pressed to find an ethical justification for withholding it from a known recent skin-test convert, especially since isoniazid is so inexpensive. Obviously, giving preventive therapy to such persons would compromise the study if an important objective of the trial was to determine efficacy against clinical disease. However, if clinical disease is the main outcome of interest, there may be no compelling argument for skin-test screening and preventive therapy for newly infected persons.

The arguments against routine skin-test screening and preventive therapy in a vaccine trial are that (1) skin-testing and preventive therapy are recommended for very few groups, even in developed countries [27]; (2) tuberculin skin-testing and test interpretation are fraught with difficulties [28]; (3) preventive therapy is associated with serious adverse reactions, especially if not carefully supervised [27]; (4) preventive therapy is not the standard of care in most developed countries; and (5) skin-test screening and preventive therapy are not likely to become the standard of care in developing countries, at least in the near future. There may be some populations, e.g., HIV-infected persons, for whom the arguments in favor of routine skin-testing and preventive therapy, even in developing countries, are stronger than the arguments against. Therefore, the institutional review boards and ethical review committees will have to make judgments on a case-by-case basis.

The next 3 issues are related to one another: the involvement of various communities in the trials, as well as how and when they should be involved; the structure and process of ethical review; and the establishment of effective methods of obtaining informed consent. During my participation in a variety of meetings during the past 2 or 3 years, I have heard from a variety of representatives from developing countries and “at risk” communities that they want to more fully participate in all phases of clinical trials, from the planning of the trial and its execution to the interpretation and dissemination of the data. They want to understand and participate in deciding what interventions will be tested and how, as well as have the opportunity to review and comment on the study report and participate in the decision on what actions will be taken as a result.

This presents tremendous challenges to researchers because most have not come to expect this involvement, have not been trained in how to effectively involve potential participants, and do not have the substantial additional resources that such an arrangement may require. Biomedical researchers may need to collaborate with experienced social scientists to help them understand the culture of the country/community, identify its decision-making process and leaders, and identify ways of having input in and legitimizing the proposed study. This whole area of involving participants in a trial is one in need of additional research and research-practice refinement.

The general structure and process of ethical review have been outlined in other documents [17, 21], and the process should be familiar to all investigators. If the sponsor of the trial is in the United States or another developed country and the vaccine is being studied in a developing country under an Investigational New Drug application, then the involvement of ethical review committees in both the developed and the developing country would be expected. If US federal funds or resources are involved, the sponsor in the developing country will need to work with the US Office for the Protection from Research Risks. Careful attention should be paid to having persons on the developed country’s ethical review committee who are familiar with research in developing countries and to having per-
ons on the developing country’s ethical review committee who are not scientists or government employees.

A great deal has been written on the topic of informed consent [29]. Nevertheless, establishing effective methods for obtaining and documenting informed consent is a major challenge. Development of an adequate consent form in the developed country is difficult but seems easy when compared with the tasks of (1) ensuring an accurate translation of the nuances of meaning into another language and (2) ensuring that the process allows effective conveyance of that meaning in a noncoercive manner in another cultural setting. This is another area where collaboration with an experienced social scientist familiar with research in the developing country may be useful. It is also an area in which one would expect the local ethical review committee to provide considerable assistance.

The most difficult and controversial ethical issues recently raised regarding the conduct of clinical trials in developing countries have concerned the roles and responsibilities of researchers to work with vaccine manufacturers, international and national health organizations, and economic development agencies to ensure that interventions shown to be safe and effective are appropriately available to the study population and other relevant populations after the trial ends [30]. These issues have not traditionally been of great concern to researchers, and, until recently, even the most enlightened researcher would have responded that as long as there was a reasonable likelihood that the intervention might be implemented sometime in the future in the country where the study was being done, there was no ethical concern. However, although I would argue strongly that researchers are not responsible for obtaining resources to implement any intervention they show to be safe and effective in a developing country, I do believe our ethical duty goes beyond what we may have conceived it to be in the past.

First, I believe scientists have a responsibility to think about how their work might fit into the health care system of the country where the study is taking place and about the long-term implications of their studies. In other words, we do have an obligation to consider who has a realistic probability of reaping the benefits of the research and when. If the participants in the trial or persons like them are not likely to benefit or if the benefits are clearly unlikely to be experienced within this generation or sooner, then the ethical justification for including those people in the trial should be seriously questioned.

Furthermore, although science and advocacy should be mixed with care [31], I believe we should enter into trials, especially those in developing countries, with the intention of advocating and supporting interventions we show to be safe and effective. In some cases, before beginning a trial, it may be possible to seriously discuss these issues with vaccine manufacturers, international and national health organizations, and economic development agencies. Although these discussions may not yield “up front” solid commitments of financial support, they could help the researcher better understand what data and information these organizations would need to make such commitments in the future, and the researcher could possibly obtain such information during the course of the trial.

In summary, the development of a more reliably effective vaccine against tuberculosis is critical to the global control of the disease. As new vaccine candidates become available for testing in human populations, the ethical issues associated with such testing are important to discuss and resolve. The specific ethical issues to be addressed are intimately related to the scientific questions being asked, the populations being studied, and other epidemiological issues. Although the ethical issues are complex and controversial, beginning the discussion of these issues now should enable us to successfully address them and move forward with the study of new tuberculosis vaccines. International organizations such as the Council for International Organizations of Medical Science and the World Health Organization should take the lead in ensuring that the dialogue continues until the issues are resolved.

References


