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Ethical issues considered in Tamil Nadu Leprosy Vaccine Trial

MD Gupte, DK Sampath

For more than eight years, we have been involved in a massive field-based comparative leprosy vaccine trial in Tamil Nadu, covering some 300,000 people. The study is supported by the Indian Council of Medical Research. The trial was launched in January 1991, and the study protocol was approved shortly before the publication of International Guidelines for Epidemiological Studies. This paper will discuss various ethical issues raised by these international guidelines in the context of the trial.

A number of candidate anti-leprosy vaccines became available during the 1980s. After an in-depth technical review of these candidate vaccines, it was considered essential to compare them in a single study (1). The three vaccine preparations being tested are *M leprae* + BCG, ICRC and Mw. The two control preparations are BCG and a placebo.

Before the vaccination exercise, the entire population of the selected geographical area was enumerated and screened for its eligibility for inclusion in the trial. Vaccination was completed in two and a half years, after which the population was kept under surveillance and examined periodically for the occurrence of leprosy. All documents regarding consent, feedback, post-vaccination complications and surveillance have been stored for future reference.

An ethical review of such research must address a number of questions. These questions are discussed below.

Was the study protocol submitted for independent ethical review?

An independent ethical review was conducted by a committee conversant with local cultural norms and chaired by a retired judge of the Madras High Court. The committee included experts in leprosy, internal medicine and clinical pharmacology, an advocate and a representative of the community. The committee's report was sent to a national advisory committee consisting of epidemiologists, leprosy experts and policy makers. The ethical committee was involved in collecting feedback from volunteers post-vaccination and by periodic review and field visits. It continues to be involved in monitoring the trial.

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Was the Phase III trial of efficacy preceded by a Phase II trial for safety?

Before the large-scale vaccine trial was launched, Phase II trials of all the candidate vaccines, with a maximum of 300 volunteers, were conducted after obtaining permission from the Drugs Controller of India. The Phase II trials provided essential information on the vaccines' short-term toxicity and possibly efficacy through proxy measures.

Does the study protocol respect the principles of autonomy, beneficence and justice?

The three basic principles of clinical and epidemiological research — autonomy, beneficence and justice — have been described in various international statements and guidelines. The first principle also provides protection to people with impaired or diminished autonomy. In the leprosy vaccine trial, information about the nature of the study was made available by oral presentations in the local language to groups of people in the villages taken up for study, and efforts were made to motivate individuals to participate, without compromising the voluntary nature of the programme.

Regarding the principle of beneficence, patients detected with leprosy were given prompt treatment. And as for the question of justice, random allocation of individuals to the five arms of the trial ensured equal distribution of risks and benefits among

trial participants. However, it is common in trials of this nature for children and women to get better coverage than men.

Some questions regarding the just nature of the trial remain. It is being conducted essentially in rural areas (with some coverage in towns), where the population's mobility is expected to be low, people are available for vaccine and surveillance is expected to be easier. This population is also generally more deprived than its urban counterpart. Yet any vaccine found to be effective in preventing leprosy would benefit urban people. Some critics may also argue that researchers prefer rural populations for initial vaccine research because the rural poor are seen to be more pliable and less assertive, and can be conveniently handled in large numbers through surrogate consent.

Is the study randomised and double-blinded so that it is both more scientifically acceptable and ethical?

The leprosy vaccine trial was randomised: participants were assigned randomly to one of the candidate vaccines, to BCG or a placebo, to clarify a genuine uncertainty about the various regimens. The trial is a double-blinded study: both participants and investigating physicians are unaware of which preparation has been administered to a particular participant.

If a placebo is proposed, is it appropriate?

Comparing a new regimen to a placebo — a dummy preparation without any therapeutic effect with respect to the research question being studied — is justifiable only if there is no established intervention to treat or prevent the disease being investigated. International guidelines require the use of the most appropriate currently established therapy when studying a condition that can cause death, disability or serious distress. Any new procedure found superior must be offered promptly to the members of the control group. If a placebo is to be used, it should be safe and not lead to any irreversible harm. Vaccine preparations against leprosy lead to the formation of a scar at the vaccination site. A placebo preparation should not lead to any such consequence.

In the leprosy vaccine trial, the use of a normal saline as placebo meets both technical and ethical requirements. The ethical committee accepted the inclusion of BCG as a control preparation because it is not expected to have any significant public health impact on the prevention of leprosy while its exact role remains unclear. Care was taken not to deny BCG inoculation to infants according to the Universal Programme of Immunisation in force.

Using a placebo in the present study has helped unravel several important issues – both for basic science and for public health practice. It will be difficult, hereafter, to consider BCG as an anti-leprosy vaccine blindly anywhere in the world.

> Written consent was obtained . . . however the form did not mention . . . presence of a placebo

(However, as time passes, use of a placebo in any clinical trial will be frowned upon. Interestingly, authorities concerned with clearances for newer drugs still consider a placebo-controlled trial the gold standard. The use of a placebo can be defended in the interest of the community but balanced with individual interest.)

Was the participants' informed consent taken?

Various international codes and guidelines spell out the need for free and informed consent. This is essential because of the risk of harm to some of the participants. Human rights require that the autonomy of the individual is respected. For a study to meet these requirements, the individual must decide freely to participate in the study after receiving and understanding the following information — the study's aims, methods, duration of participation, expected benefits to the individual and community, foreseeable risks and benefits to the participant, available alternatives, medical services for research-related injuries, and compensation for disability or death on account of such injury.

In the Leprosy Vaccine Trial, written consent was obtained from the participants (for children, from their guardians) in the presence of a witness. However, the consent form did not mention the double-blind nature of the study, the multiple arms of the trial, or the presence of a placebo.

It has been argued that codes developed for clinical research are not fully applicable in epidemiological research dealing with groups of individuals. There may be conflicts between an individual's rights and the public's health. International guidelines state that obtaining informed consent may sometimes be impracticable or inadvisable. The investigator who believes that participants' free, informed consent need not be obtained is expected to convince the ethical committee of the ethical nature of the study. When working with communities accustomed to collective decision-making, surrogate consent may be obtained from a representative of the community.

The participants' lack of knowledge of the possibility of being administered a placebo may have affected the informed character of their consent. However, this was inevitable in view of the nature of the exercise. These factors were explained to the ethical committee and various technical committees at local and national levels. The entire trial process was communicated to the Tamil Nadu government and its approval obtained. At the village level, group leaders were informed of the general nature of the study and house-to-house motivation efforts were made, seeking voluntary participation from the population, as a preliminary effort.

From the feedback cards, it was evident that nearly 80 per cent of the population was aware of the health-related nature of the vaccine programme. A substantial proportion of participants joined the study blindly, or in the belief that the investigators must be doing something good. Thus, despite our efforts, not all participants understood the nature of the study.

International guidelines accept the need for selective disclosure or even non-disclosure for certain epidemiological studies, provided that it does not induce participants to

consent to something they would not otherwise accept. Partial disclosure is permissible to avoid scaring away the participants regarding remote possibilities of side effects. In this context, partial disclosure about placebo and multiple arms in the current enlightened environment of human rights could become questionable. This issue needs an in-depth consideration with respect to various technical, legal, ethical and human rights issues.

It is possible to justify the method adopted for the "informed written consent", which was also cleared by the Ethical Committee. However, one can always question how informed the informed consent was.

Withholding information on placebo did not do harm to any individual in the Leprosy Vaccine Trial. However, this is a weak justification, and to this extent the individual loses one's autonomy. One may ask if it is preferable to administer and obtain a hypothetical consent such as "In the event of myself being one who receives a placebo ..."

Is compensation offered for injuries? Will such compensation serve as an inducement to participate?

Investigators try their best to achieve maximum participation, and ethical guidelines permit reimbursement of travel expense and the provision of some basic health services to participants. Based on the principle of beneficence, investigators are expected to maximise gains and minimise risks. According to ethical guidelines, participants have a right to compensation for damages. Guidelines advise study sponsors to obtain insurance to pay for such compensation. It thus becomes very difficult to draw a line between motivation, inducement and coercion.

In the Leprosy Vaccine Trial, compensation was given on three occasions (out of 170,000 participants), for comparatively mild complications, which incapacitated the participants temporarily from earning their daily wages. The participants were given foodgrains to enable them to meet family commitments during the period of incapacity. Since these complications — and the compensation — occurred some weeks after vaccination was completed in the area, compensation did not serve to induce other people in the village to participate.

Does the trial include pregnant or nursing women?

Pregnant or nursing women were not included in the leprosy vaccine trial for fear of a possible risk to the foetus or nursing infant, and since the trial did not seek knowledge relating to pregnancy or lactation. One unwed pregnant woman offered herself for vaccination in one of the villages but other women waiting for their turn cautioned her that she might not be a suitable candidate for vaccination. Thus the initial efforts at educating have been fruitful. It was explained to her that she was being denied vaccination with a view to avoid any risk to the foetus.

Is the ethical committee accountable?

In the foregoing paragraphs an attempt has been made to identify some of the field-level problems surfacing during the implementation of the programme. Of course, problems arise at other levels also. For example, before the trial, the ethical committee must critically examine and pass the study protocol, the procedures and sometimes even the optimum dosages. In such contexts, it may not be far-fetched to include the ethical committee's liability in claims for damages made by any participant on the basis of tortious liability. This may require establishing a causal connection between negligence on the part of the ethical committee and the damage suffered by the participant.

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News

While patients get the kick, doctors get kickbacks

According to a rough estimate, around Rs 5 crore is paid to doctors in kickbacks by the 40 private scan centres and the four MRI scan centres that function in the private sector in Kerala. The commission for a single scan is Rs 400 and at least 280 scans are taken per day at the various scan centres. The commission for MRI scans is Rs 1,500 and the minimum MRI scans taken a day are five. These are the minimum averages. Commissions are also paid for ultrasound scans and even for blood examinations. ...Even the poor are forced to rely on the private sector where scans are an inevitable part of medical diagnosis, contributing to higher costs. That doctors...compete in prescribing scans is common knowledge....

When the Indian Medical Association sent a letter to scan centres directing them to abide by the terms laid down by the association's ethics committee, the centres went to court and got a stay. The letter contained rates fixed by the IMA for scanning and sought a ban on the giving of commission to doctors who referred their patients to them. Those who cooperated and obeyed these directives would be recognised by the IMA and also allowed to advertise and use the phrase 'IMA recognised' along with the names of their institutions, the letter said. On August 13, 1999, the Kerala high court vacated the stay.

Based on: While patients get the kick, doctors get kickbacks. Leela Menon, *Indian Express***, February 15, 1999, reprinted in the** *Qualified Private Medical Practitioners' Association of Kerala Journal of Medical Sciences***, January-March 1999, p. 29. and HC vacated stay in IMA case, Express News Service,** *Indian Express***, August 14, 1999. in** *QPMPA Journal of Medical Sciences***, July-September 1999, p. 126.**