Both equity and human rights principles dictate the necessity to strive for equal opportunity for health for groups of people who have suffered marginalization or discrimination

Home Sweet Home – Anne Rook
Pencil drawing on inkjet print
(32 x 48 cm)

'History counts its skeletons in round numbers.
A thousand and one remains a thousand,
as though the one had never existed.'

Hunger Camp at Jaslo **(Poem) – Wislawa Szymborska**

Anne Rook

Paris, France

Anne Rook has exhibited extensively in Britain, France, and Japan. She has also produced several artists' books, a number of which are in the Victoria and Albert Museum, London. Among her publications are: *Prints Now*, Gill Saunders and Rosie Miles, V & A Publications, 2006; and 'Sunek/ Thrust', 26th Biennial of Graphic Arts, Ljubljana, 2005.

In 2000 she was commissioned to produce an outdoor sculpture for 'Riverside' East International Norwich.

Her main solo exhibitions were 'Last week's shopping' @ Isidore Krapo, Bordeaux (2003); 'Verger Virtuel', Faculte de Pharmacie, Paris (2002); 'The Morning Room', Strangers' Hall Museum, Norwich (2002); and 'Sages comme des Images', Cable Street Gallery, London (1998).

Her main group exhibitions were 'Forest', Artislong Gallery, Kyoto (2006); Itami Museum of Arts & Crafts, Itami, Japan (2006); International Biennale of Graphic Arts, Ljubljana (2005); 'Rien à déclarer', Bordeaux, curated by Steve Williams (2004); 'Garden of Earthly Delights', curated by Indra Khanna, Brockwell Park, London (2004); and 'Riverside' East International, Norwich (2000).

Anne Rook works and lives in London.

CHAPTER 25

Ethical Aspects of New Tuberculosis Vaccine Research

Mary E Edginton

Abstract

An analysis of the main ethical issues associated with the research of new vaccines against TB.

Introduction

The need for a better vaccine to prevent TB has been highlighted in previous chapters of this book. (See Chapters 8, 10, 13–16, 18, 19, 23.) The vaccine (BCG) currently used in high TB burden countries is old, well known to have varying effectiveness (1), and is inappropriate considering the enormity of the TB epidemic. It is, therefore, entirely appropriate that new vaccines are being developed and tested. The way the research is conducted and the way a vaccine proved to be effective and without side effects—then made available to communities, especially those in high TB burden countries—must be in line with current accepted wisdom and thinking on ethics.

Not all modern research is conducted ethically. Two well-known examples of unethical research in recent times were the Tuskegee study on hundreds of mostly poor men (400 with diagnosed syphilis) who were followed without treatment, although effective treatment was available for most of the study period. This disgraceful study led by public health authorities was stopped only in 1972 (2). The second was the study on thousands of Ugandans in the

late 1990s. The cases, infected with HIV, were observed over many months in terms of risks for spread without being offered any treatment (3). Closer to the topic of ethics in vaccine studies is another ethically challenging saga in the study of hepatitis E vaccine in Nepal a few years ago. When 'volunteers' objected to the lack of informed consent, soldiers, a vulnerable group, were given the vaccine being tested (4).

Vaccine successes against a number of diseases are well documented (5). Vaccination greatly reduces disease, disability, death, and inequity worldwide. Vaccine preventable diseases include smallpox (now eradicated), diphtheria, pertussis, tetanus, polio, measles, *Haemophilus influenza*-related diseases, hepatocellular carcinoma (through the use of hepatitis B vaccine) and influenza. More recent successes have been shown with vaccines for human papilloma virus (against cervical cancer) and rotavirus (against diarrhoea). The development of the two latter vaccines was done in developed countries although the burden of the target diseases is carried by poor countries (6).

Ethical issues in TB vaccine research will be addressed in this chapter by highlighting the ethical principles relevant to vaccine research as stated in the widely accepted World Medical Association (WMA) Declaration of Helsinki, updated in 2008 (7) and using these as a 'gold standard'. This they may not be and the declaration is without legal standing, but it is the result of extensive consultation and debate, with six updates since 1964. Following the statement of each relevant principle will be a discussion on its application to research on TB vaccines.

Risk Definition and Management

- A prominent statement in the WMA declaration is: 'The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures….' Interventions require continuous evaluation and updating to ensure maximum 'effectiveness, efficiency, accessibility and quality'. Most of the procedures involve 'risks and burdens'. Risks should be anticipated as far as possible and managed. If risks and burdens outweigh potential benefits, research must not continue.

New vaccine trials are not without risk. Risks must be anticipated, kept to a minimum, and managed appropriately. This would include follow-up of groups that receive new vaccine and those who do not (controls). Follow-up end points must be carefully defined and include incident TB disease and side effects of the vaccine. Results unfavourable enough to stop the study must be defined from the start.

Informed Consent and Special Consideration of Vulnerable Populations

- The declaration highlights the fact that some research populations are vulnerable and may be 'economically and medically disadvantaged'. Informed consent should be written or if not written, formally documented and witnessed. In situations where informed consent cannot be given by subjects, including those with mental or physical disabilities or those who may suffer social disadvantages, research should not be carried out on such subjects unless the purpose of the study relates directly to such disabilities. In the case of research requiring legally incompetent minors (below a defined age as required in the relevant country), consent must be obtained from the appropriate legally competent persons.

Populations with high TB burdens are usually vulnerable. They are likely research subjects for new vaccines. Special protection of individuals is necessary, including sensitivity concerning the planning and process of informed consent. This needs to include, in a language that subjects are familiar with, details of how the vaccine study will be conducted, its purpose as well as any possible adverse reactions. If children are subjects for vaccine trials, planning must ensure that consent is obtained from an appropriate parent or carer.

Approval of Ethics Review Bodies

- The WMA document states that research protocols should be submitted for consideration, comment, and guidance, and where appropriate, approval of an ethics review committee.

Many people would want formal approval of such a group, 'appropriate' being too subjective. Such approval is commonly a requirement of a research or academic institution, but in addition local ethics groups on which communities are represented, should be consulted for advice and approval. This is particularly important in settings where traditions and culture differ from those of researchers.

To equip members of such committees for what is often a difficult task requiring a sound knowledge of ethics, experience, and wisdom, there should be appropriate training.

Researchers as Health Providers

- The declaration expresses concerns that where researchers are responsible for providing medical care to patients in addition to a research role where they obtain informed consent and collect data, special considerations should apply. These include ensuring that consent is obtained by objective persons who are independent of the research process. Refusal to participate should never compromise care, or the relationship with carers.

If the person responsible for patient care is the same as the researcher, this could result in coercion of the patient to participate or reluctance on the part of the patient to refuse lest care be compromised. This situation could be less common in vaccine trials where the research is likely to be a specific process.

Comparison with Best Current Prophylactic Intervention: 'The Placebo Debate'

- The WMA declaration states that any new intervention should be tested against the 'best, current' interventions. Placebos or no intervention can be used where 'no proven prophylactic, diagnostic or therapeutic method exists'.

When this was published, it elicited considerable debate, summarized in several reviews (8, 9). Many agreed that placebos should not be used if an effective intervention for a condition exists, and this should be provided for the control group. Some believed that the use of placebos is important to ensure valid measurement of intervention efficacy, as long as withholding effective treatment was not life threatening or potentially causing serious morbidity. A plea for a 'middle ground' stance has been made, that placebo-controlled trials are permitted but only when there are compelling methodological justifications, that those receiving them will not suffer serious harm and that risks will be minimized. The WMA declaration (section 29) was in fact revised in 2002 to cover the 'middle ground'.

In the case of TB vaccine trials, the vaccine in existing use (BCG) has effectiveness rates ranging between 0 per cent and 80 per cent in different populations (1). The lack of effectiveness in many populations would suggest that there is no compelling reason to use it in place of placebo. A more important issue regarding BCG-experienced versus placebo controls relates to the science of the new vaccines and whether they are designed to supplement or interact with BCG effects.

Responsibilities of Researchers in Ensuring Availability of Vaccines Proven to be Useful

- The WMA declaration states that at the end of the study, all study subjects must have access to the best proven interventional method as proven by the study.
- It goes further: 'Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results.…' In 2004, section 30 of the declaration was amended to emphasize that post-trial arrangements must be described in research protocols submitted to review committees.

The UNESCO Declaration on Bioethics and Human Rights (10) affirms these concepts in its aims: 'to promote equitable access to medical, scientific and technological developments', and 'benefits resulting from any scientific research and its applications should be shared with society as a whole … in particular with developing countries'.

Modern ethical thinking urges debate and action on issues of justice in the distribution and availability of interventions shown to be effective and safe. The focus is on provision of a new vaccine (or drugs) from a trial that demonstrated effectiveness to all study participants, and on ensuring its access by the whole community in which the research took place or the population of the participating country.

Benefits to Study Participants

A growing body of experts is of the opinion that interventions proved to be successful must be made available to all study participants (11-14).

Some statements call for 'discussions' before the research starts and there has been reticence to commit researchers by using vague statements such as 'If any arrangements have been made'. The UNAIDS guidelines (on HIV vaccine research) state that any HIV preventive vaccine demonstrated to be safe and effective, as well as other knowledge and benefits resulting from HIV vaccine research, should be made available as soon as possible to all participants in the trials in which it was tested, as well as to other populations at high risk of HIV infection. The application to TB vaccines is clear.

Benefit for participants is referred to as 'justice as reciprocity' which means a repayment for participants' time and possible risks. In the case of a study which has identified an effective vaccine, cases will already have received it. However the controls, who have not, should then be given the vaccine. In the event of a

negative result, cases (who received the ineffective vaccine) and placebo controls should receive the vaccine in routine use (existing best possible). When the intervention under consideration is a drug which has been shown to be effective and without risk to study participants, the implication of this clause in the declaration is ongoing supply of the drugs for all study participants.

Benefit to the Population

It is not the prime purpose of clinical trials to seek to redress inequities of wealth and resources. However, many international and local organizations, commissions, and influential individuals now support the 'distributive justice' concept that demands a fair and equal distribution of research benefits. Research initiated and sponsored by developed countries and conducted in developing countries must 'offer the potential of actual benefit to the inhabitants of that country by providing affordable access to the intervention to those communities where the intervention has been tested'. Further, 'if research only has the potential to benefit the limited number of individuals who participate in the study, it cannot offer the benefit to the underdeveloped country that legitimizes the use of its citizens as research subjects'. (15) Rich countries are in a position to purchase for their own citizens the vaccines or drugs tested on people in poor communities, who themselves and their governments lack the resources to procure the interventions proven to be effective. Again many statements in support of this argument are vague. The WMA declaration talks of 'reasonable likelihood' of benefits to researched populations (7). The Council for International Organizations of Medical Sciences (CIOMS) guidelines suggest reasonable availability (of interventions developed through research), although they do state that if there is good reason to believe that a developed product is unlikely to be reasonably available to the population or country where the research took place, it is unethical to conduct the research in that country (16). The WHO's Operational Guidelines for Ethics Committees state that the review process should consider availability and affordability of these interventions to 'concerned communities' (17). Although recommendations may be ill-defined, they do progress within the spirit of promoting benefits for communities that have been researched. More defined statements have been made by the (US) National Bioethics Advisory Commission (NBAC) (18) who have a statement similar to that in the CIOMS that if availability of the new effective product cannot be guaranteed, investigators should justify (to ethics review committees) why the research is required. This delegates a huge responsibility to these committees, and implies that their approval or rejection could be determined by this principle.

The practical issues are how beneficial interventions can be made available, who should be responsible, and for how long. Suggestions include negotiated agreements with product manufacturers, governments, communities, non-profit and private organizations, which should be finalized before research starts. Involving communities through recognized leaders is essential, as they should be empowered to campaign for health care rights. Researchers cannot be expected to organize systems of availability and distribution, but should have roles in their advocacy. Issues of sustainability and long-term provision of vaccines (or drugs) must be defined early on in the discussions in case potential funders or manufacturers are frightened off. When new effective interventions become available, they should, as soon as possible, become standard care in all countries. The negotiated agreement to provide these to the communities where the research took place would only be until they are 'standard' for the country.

Several examples of negotiated agreements are described in the NBAC report (18). These include the WHO, the International AIDS Vaccine Initiative (IAVI), and the Joint United Nations Programme on HIV and AIDS (UNAIDS) (the latter two are concerned with vaccines), all bodies who have negotiated with manufacturers to commit them to low-cost interventions for developing countries. VaxGen, a private company, has a prior agreement with a country government which ensures benefits in return for testing sites.

An ethicist has reminded us that medical interventions are controlled by profit-driven enterprises and that most medical research is driven by the pursuit of wealth rather than medical need (19). The standard of care of countries is, in practice, determined by the prices set by Western pharmaceutical multinationals (20). One large pharmaceutical company has declared their new attitude to development and distribution of drugs in poor countries (21). Perhaps they will lead the rest. All researchers have a responsibility to comply with the highest ethical standards no matter where the research is conducted, and to influence and monitor the practices of sponsoring agencies and industries. Journals must refuse to publish unethical studies, however excellent the science.

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