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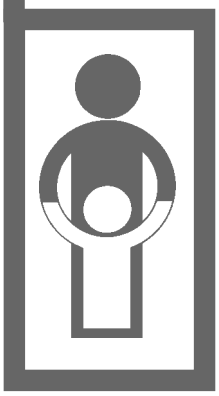
Report of the meeting of the working group on clinical trials of new TB vaccines

WHO, Geneva, 19 April 1999



DEPARTMENT OF VACCINES AND BIOLOGICALS

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Preface

Tuberculosis (TB) presents tremendous problems to both the public health and the medical research communities. The disease is a major cause of adult mortality (it is arguably the most important of all specific infectious diseases in this regard) and is thus high on the priority lists of national and global public health concerns. Modern methods of control emphasizing case-finding and chemotherapy following the DOTS (directly observed therapy – short-course) strategy are effective, but their implementation is in practice difficult, especially in poorer populations where the disease is most severe. In addition, most countries rely upon BCG vaccination for prevention of tuberculosis. However, we now recognize that the usefulness of current BCG vaccines and vaccination programmes is restricted largely to prevention of severe childhood forms of the disease and that they have limited impact against adult pulmonary disease, which is responsible for the huge public health burden of tuberculosis.

Against this background there is an important initiative to develop, evaluate and implement one or more improved vaccines against tuberculosis. This too has proved a major challenge, as the immune response against tuberculosis is complicated and we have, as yet, no clear correlate of protective immunity. Despite these difficulties, several vaccine products are now nearing initial phase-I and phase-II testing in humans. It is thus none too early to consider phase-III clinical evaluation of these new vaccines and their possible ultimate implementation into tuberculosis control.

The Immunology of Mycobacteria (IMMYC) Steering Committee of the World Health Organization (WHO) plays a leading role in coordinating the global research effort on new tuberculosis vaccines. As part of this activity, IMMYC has formed a Working Group on Clinical Trials of New TB Vaccines, which provides a forum for exploring various options for testing of new vaccines. This document records the proceedings of a meeting of this working group held on 19 April 1999.

The original papers that were reviewed in this report remain the sole property of the authors and should be requested from them (for address details, please refer to Annex 2: List of participants).

Glossary

AIDS	acquired immunodeficiency syndrome
ARI	annual risk of infection
BCG	bacille Calmette-Guérin (vaccine)
CDC	Centers for Disease Control (USA)
CMI	cell-mediated immunity
DOTS	directly observed therapy – short-course
EPI	Expanded Programme on Immunization
FDA	Food and Drug Administration (USA)
HIV	human immunodeficiency virus
IMMYC	immunology of mycobacteria
INH	isoniazid
IPT	isoniazid preventive therapy
MTB	Mycobacterium tuberculosis
PPD	purified protein derivative (diagnostic tool)
TB	tuberculosis

Introduction

A meeting of the WHO/IMMYC Working Group on Clinical Trials of New TB Vaccines was convened at the WHO Headquarters on 19 April 1999. It provided a 'think-tank' for generating ideas about how to design and conduct vaccine trials for hypothetical new anti-tuberculosis vaccines. During the course of the meeting, experts in the field presented 10 different research approaches covering a variety of designs and study populations. Subsequent discussions around the proposals revealed common themes and pointed the way forward for future discussion and planning.

Scope of the problem

The control of tuberculosis now and in the foreseeable future will be challenged by the impact of HIV on TB and the emergence of multi-drug resistant disease, in addition to the continuing difficulties of case-finding, poor treatment compliance and programme logistics in poor populations. Although BCG vaccination has been effective in reducing TB morbidity in children, its impact on disease in adults and on the transmission of *M. tuberculosis,* has been small if not negligible. The disappointing performance of BCG has led to research on new vaccines for tuberculosis. There are several candidate vaccines under development that will be available for clinical testing in the near future. To test the clinical efficacy of a new vaccine beyond phase II will require coordinated efforts. Many issues need to be addressed in this exercise, including: study design, types of measurement, how to handle HIV, previous BCG vaccination, exposure to environmental mycobacteria, the long and variable latent period of TB, and the heterogeneity of clinical tuberculosis.

Summary of proposals

Ten protocols were presented and discussed. Each is described briefly below along with major points which arose in its discussion. Characteristics of the trials are summarized in Table 1 (see Annex 1). Actual working documents will be available from WHO on request.

1. New TB vaccine trial using school randomization in a population with high neonatal BCG coverage

Drs Mauricio Barreto and Laura Rodrigues

These investigators are currently studying the effect of BCG when given as a second dose in school children (ages 7–16 years) in two geographically distinct regions in Brazil. In this study, 764 schools (356 000 children) have been randomized to receive the intervention or not. All (attending) children in schools randomized to receive a second dose of BCG were vaccinated. Children attending control schools were examined for signs of tuberculosis and BCG scar, but received no vaccine or placebo. Approximately 85% of children had a BCG scar, and approximately 30% were considered tuberculin "positive", indicating prior infection. Incident tuberculosis is captured through the passive surveillance activities of the local tuberculosis control programmes. All cases are validated and subject to an independent review using standard criteria for TB. The regions for study were chosen because they had a comparable level of neonatal BCG vaccination but differed in the prevalence of leprosy and environmental mycobacteria. The study was powered to detect a second-dose efficacy of 50% in uninfected children within three years. The total costs (direct and indirect) for the trial are on the order of US$ 1.2 million.

The proposed clinical trial of a new vaccine would have a design similar to that of the ongoing second dose BCG trial. In this case the new (second) vaccine would be administered in childhood, which is advantageous in that it precedes the increase in incidence associated with early adulthood, and it coincides with the age of minimum HIV prevalence. The control schools could receive either BCG, a placebo, or no vaccine at all (as in the present trial). The investigators are currently examining various related methodological issues, such as the problems of linking ascertained cases to the vaccination database, and potential selection biases associated with non-attendance at school and refusal to be vaccinated. The acceptability of such a design for a new vaccine in Brazil and the ethics of including a placebo control will depend upon the results of the ongoing trial – as a demonstration of high efficacy with the second BCG would probably lead to implementation of repeat BCG as a national policy. This school-based approach may well be applicable to other societies. It would be appreciably more expensive than the current trial, due to the necessity for detailed informed consent and adverse reaction procedures (more than were necessary with BCG), but it would still be relatively inexpensive for a trial of this magnitude.

Discussion points

- The current trial is elegant in its design to look at the potential effects of exposure to environmental mycobacteria by including the two study regions. It also includes leprosy as an outcome, which will add important value.
- The current study uses Brazilian (Moreau strain) BCG. In three case-control studies, this BCG was found to give about 80% protection against TB meningitis. No information is currently available on protection against pulmonary tuberculosis associated with this vaccine.
- The power calculation for the study is based on the cumulative long-term protection of the vaccine. The passive follow-up of the population is relatively cheap and can be extended for many years, as is proposed for the ongoing trial.

2. Feasibility consideration for a controlled trial of a new TB vaccine in Karonga District, northern Malawi

Dr Paul Fine

This proposal described a possible randomized controlled trial of a new TB vaccine in the general population in Karonga District in northern Malawi (population 200 000), a site where BCG vaccination has failed to protect against pulmonary TB. The document discussed various trial hypotheses. The simplest hypothesis was that the new vaccine would protect against pulmonary TB in adults, regardless of their prior history of exposure to mycobacterial antigens or HIV status (90% power to detect efficacy of 18% in five years). The most rigorous was that it would only protect HIV-negative individuals who had never met *M tuberculosis* before receiving the new vaccine (90% power to detect efficacy of 39% in five years). These power calculations assume recruitment of the total population, but consider only cases in adults over 15 years of age. Subjects would be recruited through house-to-house surveys and randomly allocated vaccine (or placebo) if eligible. TB would be ascertained through an 'enhanced' passive case-finding mechanism based upon screening of all attendees at health centres. The advantages of this trial site and population include the fact that it is an area where BCG has failed, a good infrastructure for TB research is in place, and there is extensive background information about the population and about TB and leprosy. There are also disadvantages: the HIV epidemic in Malawi will complicate the analysis and conduct of the proposed trial; the high background level of exposure to environmental mycobacteria and previous vaccines may make results non-transferable, and the incidence of tuberculosis is relatively low (approximately one per thousand). Such a trial might be carried out for approximately US$ 5 million.

Discussion points

- The implications of previous research studies were discussed, including their advantages in providing background context and reference. But there are disadvantages in that the population has already been heavily "intervened". The design assumed that past BCG vaccination provided no protection against tuberculosis and was immunologically irrelevant for the new vaccine.
- The high prevalence of HIV infection in this population, which is typical of much of sub-Saharan Africa, may, for safety reasons, preclude the use of live active vaccines or BCG as a comparison arm. Available evidence indicates that BCG does not protect against adult tuberculosis in this population, and hence might not be advocated as a control, but infant BCG will probably still be continued on account of its utility against leprosy and against childhood forms of TB.

- Power calculations are based on the cumulative number of TB cases over time, and include no breakdowns by age. Given the relatively low incidence expected, It may not be possible to discriminate between protection against early or late developing disease. Ideally a trial should be sufficiently powered to allow stratification, at least by age.

3. Evaluating a vaccine for the prevention of TB in infected adults, regardless of HIV status, in a high prevalence region, South Africa

Dr Bernard Fourie

The hypothesis of this study is that the relapse rate of treated TB cases can serve as a marker for the competence of cell-mediated immunity (CMI). Enhancing the host immune response in active TB patients through vaccination might reduce the risk of relapse. Thus, a therapeutic effect of a new biological agent (vaccine or other), in terms of reduction in relapse risk, might be a surrogate for potential post-infection vaccine efficacy. If the vaccine were proven effective in therapy, a more conventional population-based preventive vaccine trial could be done. The proposed trial is based upon the experience of the investigators with an *M vaccae* immunotherapy trial in Durban. It is a standard randomized, placebo-controlled clinical trial of the new TB vaccine, given in one or two doses, among patients with active TB undergoing proper chemotherapy. The intervention would take place under controlled conditions in hospital. The authors estimate a relapse rate of 10% among HIV-positive patients, within 24 months of completing treatment. Assuming the new vaccine could "work" in HIV-positives, then the authors estimate 1950 HIV-positive patients allocated to receive either: (a) one dose of the new vaccine, (b) two doses, or (c) a placebo, would have 90% power of showing an efficacy of 50%, in terms of extension of disease-free life. A multi-centre approach would probably be required to recruit this number of cases within a reasonable period of time. The working paper discussed several analysis issues such as the stratification by HIV status.

Discussion points

- The proposed study design recommended inclusion of HIV-negative as well as HIV-positive subjects, but was powered only to observe an effect in the HIV-positives. Though several of the proposed designs presented at this meeting have included vaccine effects in HIV-positives in power calculations, we must be cautious about expecting too much from any new vaccine.
- This study bears interesting parallels with the "Cornell model" of latent murine tuberculosis and may provide a useful link to animal models.
- The study could use DNA fingerprinting techniques to determine that the relapse in TB was from the same organism and not the result of reinfection.

4. Planning of a tuberculosis vaccine trial and possible protocols

Dr Mohan Digambar Gupte

This paper described general features of vaccine trials based on experience with recent tuberculosis and leprosy vaccine trials in South India. The suggested design is a total-population randomized placebo-controlled trial. Although BCG is currently given in infancy in this population, the author proposes the use of a placebo (the failure of BCG to protect against pulmonary tuberculosis in the Chingleput trial may make this acceptable). Ascertaining outcome would be through active case-finding. Various implementation details are provided, drawn, in particular, from procedures employed in the 5-arm leprosy vaccine trial recently reported from Avadi, South India.

Discussion points

- This paper raised the issue of whether the vaccine (trial) should target a particular sub-population or be targeted broadly. The efficiency of the total population approach was questioned.
- Given the epidemiology of tuberculosis in India, with most cases occurring in adults, prolonged observation of the study population will be desirable. This raised concerns about the stability of the study population and the effect this would have on the estimate of vaccine effect.
- The details of how the proposed vaccine would be given (preferably in the evening, to avoid sunlight) initiated an interesting discussion about whether ambient sunlight would affect the take of the vaccine – perhaps through suppression of dermal Langerhans cells, and whether a daytime control would be required. Animal models could potentially provide an answer to this. The fact that routine vaccinations are generally performed in the daytime would need to be considered, in order that effects observed in a trial can be translated appropriately into programme recommendations.

5. A large simple trial of a tuberculosis vaccine

Dr Robert Horsburgh

This paper proposed evaluating a new vaccine in both developed and developing country high-risk settings (described as incidence greater than .001 per annum in the "developed"-country setting and greater than .004 in the developing-country setting). The suggested design, for each population, was a randomized placebo-controlled trial among adults with all those enrolled evaluated at entry for BCG status, and tested with tuberculin and "non-tuberculous antigens". PPD positives would be questioned about prior INH treatment. It is recognized that recruitment would have to be multi-centre in an industrialized country. Power calculations were presented assuming confirmation of a 50% efficacy over a 10 year follow-up – under these conditions, approximately 100 000 HIV-negative and PPD-negative individuals would have to be followed up in the developed-country setting, and 30 000 in the developing country setting.

Discussion points

- It was commented that the title of this paper was misleading – the proposed trial was by no means "simple"! This term is better reserved for designs such as the school-based approach proposed by Drs Barretto and Rodrigues.
- The incidence rates assumed in this paper were high. It was commented that it is a common experience for trials to find that incidence rates are in fact lower than originally supposed in the power calculations.

6. A randomized, controlled trial of a "post-infection" TB vaccine, to be conducted in the United States

Dr Richard O'Brien

In the United States, recently infected individuals represent a potentially identifiable group at potentially high risk for the development of active TB. Although preventive therapy among individuals with latent tuberculous infection is recommended, the effectiveness of preventive therapy is lessened by poor compliance with the recommended regimen. A "post-infection" vaccine might thus be of benefit in countries like the USA, with low TB incidence rates. This paper explored the feasibility of a randomized, placebo-controlled multi-centre trial to be carried out among newly infected persons. Preventive therapy would be given to all individuals, as is recommended by the CDC. At study entry, all eligible participants would be allocated randomly to receive either the new TB vaccine or placebo, in a blinded manner. The subjects would be monitored for TB for 15 months. The sample size estimates for this trial range from 28 000 to 35 000 subjects, depending on TB incidence rates expected. Given the size, logistic complexity and cost of this approach, which implied recruitment of virtually all recently infected individuals notified in a year in the entire USA, it was concluded that a trial of this sort was unlikely to be feasible.

Discussion points

- This proposal raised the issue that TB vaccine trials in the United States cannot be done without using preventive therapy for TB in latently infected persons. This issue may arise in other countries.
- Other study populations are potentially accessible in the United States such as Native Americans and recent immigrants, but the study of these populations would raise difficult ethical issues about the study (exploitation?) of vulnerable populations.
- The proposed study implied a multi-centre approach involving very many TB treatment centres over the entire country. This would be impracticable for a very large trial unless the intervention procedures were extremely simple.

7. Testing efficacy of new post-exposure vaccine against adult pulmonary TB in high-risk settings with standard TB control activities

Dr Gunnar Bjune

The concept underlying this approach is to simultaneously evaluate the effect of a new TB vaccine on the prevention of post-primary disease (in particular reactivation, but also reinfection) and on production of a correlate of this protection in an "ultra-high" risk community. Since there is no good clinical distinction between primary and post-primary TB, the study group would comprise individuals at particularly high risk for the development of post-primary disease – in particular adults with "positive" tuberculin tests, in certain high-risk settings. The proposed study would be a randomized (at individual level), double-blind, placebo-controlled trial. The trial would have to account for HIV infection. The outcome of the main trial would be clinical disease, but an important sub-aim would be to evaluate the time course of potential surrogate markers (e.g. IFNg, whole blood assay), by intensive follow-up of a subset of approximately 200 strongly tuberculin-positive 60–70 year old subjects randomized to receive vaccine or placebo. Among possible study populations discussed were high-risk "captive populations" such as certain refugee camps and southern European prisons. Case detection would be done through the special health systems of these populations.

Discussion points

- The idea of a small but powerful trial in very high-risk population is attractive, and could involve some industrialized countries.
- It is recognized that working with refugees poses particular ethical problems. Research studies are generally rejected by nongovernmental organizations that attend to refugee populations.
- The evaluation of a new vaccine in prisons may be justified because TB is such a serious problem in prisons.
- It there were a reliable correlate of immunity, one could design vaccine trials with the correlate as the endpoint/outcome – but there is a dilemma because a clinical trial of an effective vaccine is needed to validate the correlate of immunity. This dilemma provides the rationale for this trial which would attempt to examine both outcomes in a statistically powerful setting.

8. A randomized, placebo-controlled trial of a TB vaccine among nurses, Botswana

Dr Thomas Kenyon

This proposal was for a randomized placebo-controlled clinical trial among nurses employed by the Government in Botswana. The rationale for targeting nurses for the study is that they provide a stable population with high incidence and prevalence of tuberculous infection. This target population has a high prevalence of HIV infection, and a consequent high incidence of tuberculosis (c. 400 per 100 000). The proposed study would have to account (probably in the analysis) for concurrent or previous use of preventive therapy for tuberculosis infection, HIV infection (> 20% in Botswana), and the use of antiretroviral therapy and other interventions to prolong survival and reduce risk of tuberculosis. Recruitment would be through the Botswana Nurses Association and would make use of established District Health Management Teams. Nurses would be tuberculin tested at recruitment, and blood samples would be collected for storage and later immunological analysis. The outcomes of most interest for the trial are tuberculosis, death and adverse events. Passive case-finding through self-reporting, employment records and the TB Control Programme is proposed. A small sample size would be possible if the vaccine were to provide high protection in HIV-positives.

Discussion points

- The sample size was estimated using a high vaccine efficacy (70–80%) and assuming protection in HIV-positives. These expectations are extremely optimistic. This raised the issue of whether a new vaccine trial should target HIV-negatives (vaccine most likely to "work") or HIV-positives (high incidence of outcome).
- The issue of adverse reactions in HIV-positives would require particularly careful consideration in this and other trials.
- The widespread use of preventive therapy would increase the sample size. Might this be included in the randomization process?
- Discussion of this study raised the issue that separate designs might be necessary to determine the efficacy of a vaccine against early versus reactivation disease.
- The protocol raised some of the complexities to expect when studying TB in a country with a high level of HIV and which is mounting an intensive programme to control the HIV epidemic (e.g. introduction of preventive therapy and anti-retrovirals).

9. Trial design for assessing the efficacy/effectiveness of a new tuberculosis vaccine

Dr Manjula Datta

This paper proposed a controlled clinical trial of a new vaccine in adolescents between the ages of 15 and 20 years in a defined geographic area in South India. This target population is chosen because the incidence of TB is high ($190/10^5$), though approximately half of the population remains PPD "negative". BCG vaccination rates are still low in some of these populations because of the late start and low coverage of the Expanded Programme on Immunization (EPI) in India. HIV seroprevalence is also very low. Except for the restricted age group, the proposed field methods are similar to those of the Chingleput trial. Recruitment would be at the community level through house-to-house evaluations. All individuals would be skin tested with tuberculin and preferably also with MOTT antigens. The vaccine would be allocated randomly at the individual level. There would be both active and passive ascertaining of tuberculosis with periodic symptom surveys and selective follow-up of cases in the community. An alternative mechanism for follow-up would include the use of government surveillance records. Sample size is estimated to be 35 000 per arm to achieve a 50% reduction in TB incidence over 10 years, with minimum drop out.

Discussion points

- The possibility of recruiting in schools was discussed, but relatively few 15–20 year olds attend school in South India. The target age could be reduced, so as to capture a higher proportion of the population in schools, but this means reducing trial power as the incidence of disease would be reduced.
- Data were shown suggesting that BCG failed to provide any protection over 15 years of age. There is some evidence from the Chingleput trial that BCG given to adults may actually increase the risk for TB. Further analysis of these data are needed.

10. A tuberculosis vaccine trial in the "best of all possible worlds"

Dr Christopher Whalen

The goal of this proposed trial is to determine the vaccine *effectiveness* of a new tuberculosis vaccine, including the total, direct and indirect vaccine effects. It is based on a hybrid design that contains a multi-centred randomized clinical trial nested within an international community-based study. The community trial would randomly assign 15 pairs of communities to receive or not receive the vaccine intervention. All sites would provide standard tuberculosis control activities in accordance with WHO guidelines, including passive case-finding and directly observed therapy. The intervention in the selected communities would, in this instance, be a standard placebo-controlled, randomized clinical trial of the new vaccine. Individuals 15 years of age and older in the selected community would be assigned randomly to receive the new vaccine or a placebo. The primary outcome for the study would be the development of tuberculosis. Secondary outcomes include tuberculous infection. Both communities within a country will have similar surveillance for incident tuberculosis and standard collection of baseline information such as tuberculin skin test status, HIV status, and previous BCG vaccination.

The direct effect of the vaccine would in theory be estimated from an analysis of the trials in the intervention communities (by comparing incidence rates of tuberculosis between the vaccinated and unvaccinated individuals). The indirect effects of the vaccine would, in theory, be estimated by comparing the incidence rates of tuberculosis among unvaccinated persons between the intervention and the control communities. In addition, serial tuberculin skin test surveys could be done to compare the annual risk of infection and the average age of infection at the start and completion of the trail. The overall effects of the vaccine, both indirect and direct, would be estimated by comparing the rates in the vaccinated individuals to the rates in the control communities. Finally, the overall effect of the vaccine would be estimated by comparing the rates of the two communities.

Discussion points

- Much discussion focused upon the practical feasibility of measuring indirect effects of a tuberculosis vaccine using such a study design. Herd protection effects have proved difficult to demonstrate even with simple infections with solid permanent immunity.
- The cost of such a trial would be very large and there would be immense logistic difficulties introduced by the intent to compare pairs of communities in different settings. It is unlikely that so large a trial could be carried out for more than one vaccine. This raises a kind of paradox – the question of how to (pre-)select the (one or small number of) vaccine(s) to be evaluated in large trials!
- The proposed study assumed that the protective effect of the new vaccine was uniform across populations, which may not be correct, given the well-known variability of BCG's efficacy.

Commentary

Dr John Clemens

Dr Clemens was invited to provide commentary on the proposed studies, introducing a discussion on methodological aspects of the various designs. He began by raising several questions which are fundamental to the TB vaccine initiative:

Goals and feasibility

What are the objectives in designing and implementing a trial for a new tuberculosis vaccine? Is the goal to produce a product for registration with the Food and Drug Administration and other regulatory agencies? Or is it to demonstrate vaccine efficacy or effectiveness? Will the goal of the first TB vaccine trials be to elucidate the immunology of the host immune response to TB so that a correlate for protective immunity can be used in the future?

In the end, one wants a licensed product for distribution. To accomplish this goal, the role of industry and the relationship between industry and the TB community needs to be clearly articulated so that a uniform message is sent to industry that the TB community is prepared to move forward.

What are the interests of industry versus the WHO? The argument both to industry and to WHO will need to be phrased in economic terms, at least in part, but with an understanding of their different underlying agendas. For industry, the economic argument will emphasize profit; for the WHO, it will emphasize affordability and cost-benefit.

Methodological issues

The proposals covered a broad spectrum of research designs relevant to vaccine evaluation. Randomization was proposed in all designs, but the studies differed as to whether the individual or community (e.g. school) would be the unit of randomization. The approach chosen would have implications for conduct of the trial and analysis. All designs were controlled, but the decision to use a placebo varied and would raise important ethical issues. In settings where there was prior evidence that BCG had "failed" to protect against pulmonary TB, or when a post-infection vaccine is used, a control arm with BCG may not be justified. The proposals included a number of different study populations, ranging from restricted groups (occupational cohorts, patients with active disease) to less restrictive groups (e.g. community populations).

The initial characterization of the study subjects as regards co-morbid conditions (e.g. HIV infection), skin test reactivity, etc., would add to the complexity and cost of the studies but may be necessary for analysis and interpretation. The large, simple trial of an unrestricted population was contrasted with the small, intensive study of a highly selected risk group. All groups included tuberculosis as the main endpoint, though one design used relapse rates and another included annual risk of infection as a potential measure of indirect effects. The specificity in the definition of tuberculosis could affect the assessment of relative versus absolute effects of the vaccine. Among the issues which drew lengthy discussion was the duration of any trial and whether a new vaccine should be evaluated for long-term or short-term efficacy. Sample size calculations were generally based on cumulative incidence of TB during the entire period of follow-up. Studies may be under-powered to detect short-term efficacy or effectiveness after a certain period.

Correlates of protective immunity

The evaluation of tuberculosis vaccines would be facilitated if a reliable and valid correlate of protective immunity were available. At present, several measures are being evaluated as potential correlates of protection against tuberculosis. These correlates should first be validated in a trial of an effective vaccine. Thus, an essential component of the field trials is the storage of appropriate samples from study subjects which can be used at a later time in nested case control studies. It was cautioned that a correlate for one vaccine may not be a correlate for another vaccine. Evaluation of immunological responsiveness to the vaccine is an important element in the conduct of these trials.

Other issues

Many of the proposed studies would recruit individuals from vulnerable populations. Mechanisms for informed consent from these populations must be worked out in advance.

Is it ethical to include a placebo? If the aim is to replace BCG it will eventually be necessary to show that the new vaccine is better than BCG, but a control group with BCG is not always necessary or justified.

HIV will impact on trial design in most areas where such vaccines might be tested. The diagnosis of HIV will have important implications for counselling, treatment for HIV, and for the use of preventive therapy. This will have a bearing on the overall cost of the study.

Most of the proposed trials are large and may require international cooperation. There may be a role for WHO in providing central coordination for logistics, data management, case review, etc.

Synthesis

Group discussion

Currently, there are many potential vaccine products that could be developed for field testing in the future. The testing of any one of these products in a phase-III clinical trial would be expensive. Moreover, to be convincing, efficacy would best be established in two or more independent trials, including at least one trial where BCG 'fails'. Is there an optimal strategy for vaccine efficacy testing?

Given the cost of large, phase-III studies based in communities or populations at moderate risk of TB, there was general agreement in the working group that some sort of triage system should be developed for assessing the efficacy of new vaccines first in small, restricted study populations at high risk for the development of tuberculosis, then later in larger, community-based trial(s). The outcome of these 'screening' trials could include an 'efficacy surrogate' such as relapse of TB following standard therapy accompanied by immunotherapy, or perhaps even an in vitro surrogate. Preliminary estimates of actual efficacy might be obtained in special settings of high *Mycobacterium tuberculosis* (MTB) transmission and risk for disease (coal miners, jails, health-care workers, etc.).

Several criteria for moving to phase-III trials were discussed. First, there must be safety information in humans from phase-I and phase-II clinical trials. It is recognized that long-term untoward effects may not be known given the limited duration of observation in early phase-I and II studies. Second, there should be evidence for sustained activity in animal models. This criterion seems advisable, though not necessarily essential – e.g. if there is some other evidence that the new product will provide protection. Third, the vaccine should produce some immunological response that is considered protective against tuberculosis.

In the development of new vaccines, a dialogue between the basic scientists, the vaccine developers and the clinical/field trial experts would be beneficial. Based on the discussions from this meeting, there are several messages that can be conveyed from the clinical trialists:

- There is a major need for determining the correlates of protective immunity against TB. This is often said – but little progress is being made, and the issue deserves more resources.
- TB is "several diseases". There is a strong incentive or rationale to develop animal models for evaluating vaccines against reinfection and reactivation disease, and against a background of environmental mycobacterial exposure, and not just against primary disease.

- If a live attenuated vaccine were developed, the vaccine would need very careful testing in HIV seropositive individuals before proceeding.
- In the triage system proposed, it would be ideal to link the results of trials to animal models for TB. Comparison of results from humans and animals would help to establish the validity of animal models.
- There is a need for improved diagnostics for active disease and for infection.
- There are questions concerning whether mycobacterial vaccines or their action might be sensitive to sunlight/UV exposure, which could readily be addressed with current animal models.

Several other potential and very high-risk study populations were mentioned though not included explicitly in the proposals presented at the meeting. These included South African coal miners, Russian prisoners and household contacts of infectious cases.

In planning TB vaccine trials, an efficient approach would be to perform trials in areas where substantial infrastructure for vaccine trials already exists or where relevant data have already been collected. The HIV PAVE sites set up through the "HIVNET" by the United States National Institutes of Health are an example. Other well-developed sites, in addition to those mentioned in the several proposals, are available in the Gambia and Viet Nam. It was noted that an ongoing five-arm trial of new leprosy vaccines in South India affords a unique opportunity to evaluate the effect of these vaccines on preventing TB, for a modest cost of introducing tuberculosis surveillance into an ongoing trial. This is an example of an opportunity to capitalize upon available resources and infrastructure, which could provide important information to the TB vaccine effort. Given the complexity of the tuberculosis problem, and the time and financial resources which will be required to implement convincing trials of new vaccine products, the TB vaccine research community needs to take advantage of such opportunities.

Annex 1:
Summary of proposed designs for trials of a new TB vaccine

Table 1. Summary of proposed designs for trials of a new TB vaccine

Author	Study population	"High-risk" groups	HIV+ in trial?	Unit of randomization	Placebo	Outcome	Ascertainment	Approx. sample size	Comments
Barreto/ Rodrigues	School children, Brazil	No	No	School	(Y)	TB, adolescents & young adults	Passive	> 10^5	Large simple trial, relatively cheap
Bjune	Refugees, prisoners	Yes	Probably	Individual	Y	post 1° TB immune response	Active	> 10^3	Target very high-risk population, and combine with surrogate evaluation
Datta	Age 15-20 South India	No	No	Individual	Y	TB, young adults	Passive	> 10^4	Population where BCG failed versus TB, infrastructure in place
Fine	All ages Karonga, Malawi	No	Yes	Individual	Y	TB, adults	Enhanced Passive	> 10^5	Population where BCG failed versus TB, infrastructure in place
Fourie	TB cases, multicentre	Yes	Yes	Individual	Y	Relapse	Active	> 10^3	Immunotherapeutic effect as screen Based on *M vaccae* trial experience
Gupte	All ages, South India	No	No	Individual	Y	TB	Passive	> 10^5	Based on leprosy trial experience, infrastructure in place
Horsburgh	Developed and developing	No	Yes	Individual	Y	TB, adults	Passive	> 10^4	Optimistic sample sizes
Kenyon	Nurses, Botswana	Yes	Yes	Individual	Y/IPT	TB, adults	Passive	> 10^3	Low sample size based on assumed high efficacy in HIV-positives
O'Brien	Recently infected, USA, multicentre	Yes	No	Individual	Y / IPT	TB	Active	> 10^4	Concluded not feasible
Whalen	2 areas in each of 15 countries	No	Yes	Community	Y	TB, adults ARI	Passive	> 10^4	Very expensive and complicated

IPT = Isoniazid preventive therapy, ARI = annual risk of infection

Annex 2:
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