



Tuberculosis Vaccines

EDCTP Stakeholders' meeting

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1 Introduction

The EDCTP stakeholders' meeting on tuberculosis vaccines is the second of a series of EDCTP stakeholders' meetings. It was organised by EDCTP together with the Netherlands-African Partnership for Capacity Development and Clinical Interventions against Poverty Related Diseases (NACCAP) and hosted by the Netherlands Organisation for Scientific Research, Science for Global Development (NWO/WOTRO).

The aim of the meeting was to make recommendations to EDCTP in terms of suitable products in the pipeline for phase II/III clinical trials; identify potential sites in Africa to conduct the trials; identify the capacity strengthening needs for conducting the clinical trials in Africa and formulate recommendations on the funding procedure to meet these aims. In addition, EDCTP wanted to have a first impression of the financial commitment and participation of the Member States for clinical trials on TB vaccines.

The meeting was chaired by Dr Marie Paule Kieny, Director of the Initiative for Vaccine Research (IVR) at the World Health Organisation (WHO). IVR conducts and coordinates activities related to product research and development and implementation research for vaccines and delivery devices. Dr Kieny has considerable experience on HIV/AIDS and hepatitis C vaccines design and worked at INSERM. She is also vastly experienced in research and training in tropical diseases.

2 Overview participating organisations

2.1 AERAS Global TB Vaccine Foundation (AERAS)

AERAS focuses on developing new vaccines against TB and ensuring their availability to all who need them. AERAS actively pursues and helps fund joint development activities with leading TB vaccine developers around the world as well as develops candidate vaccines in its own laboratory. AERAS is funded mainly by the Bill & Melinda Gates Foundation, the U.S. Centres for Disease Control and Prevention, the Dutch Ministry of Foreign Affairs and the Danish International Development Agency.

More information on AERAS can be found at <http://www.AERAS.org>

2.2 Bill and Melinda Gates Foundation (BMGF)

The mission of BMGF's Global Health Program is to encourage the development of lifesaving medical advances and to help ensure they reach the people who are disproportionately affected. The BMGF Global Health Program focuses on funding in access to existing vaccines, drugs, and other tools to fight diseases common in developing countries and in research to develop health solutions that are effective, affordable and practical.

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More information on BMGFs' Global Health program can be found at <http://www.gatesfoundation.org/GlobalHealth>

2.3 European Commission (EC)

The European Commission (EC) is the main funder of EDCTP through Article 169 of the European Treaty. The EC was present by a representative of DG Research.

More information can be found at goals and activities of the European Commission can be found at: http://ec.europa.eu/index_en.htm

2.4 European Developing Countries Clinical Trial Partnership (EDCTP)

EDCTP was represented through the Member State representatives, the Partnership Board (PB), the Developing Countries Coordinating Committee (DCCC), the Executive Director, the chair of the General Assembly and the Secretariat.

More information on EDCTP can be found at: <http://www.edctp.org>

2.5 GlaxoSmithKline Biologicals (GSK)

GSK Biologicals is the centre of all GlaxoSmithKline's activities in the field of vaccine research, development and production. GSK is committed to the developing world not only as the largest supplier of vaccines to these countries but also as the only vaccine company world-wide with new vaccines in clinical development against TB, malaria and HIV.

More information on GSK Biologicals can be found at <http://www.gsk-bio.com>

2.6 KNCV Tuberculosis Foundation (KNCV)

The mission of KNCV Tuberculosis Foundation is to eliminate tuberculosis worldwide through development and implementation of effective control strategies. KNCV advises national tuberculosis programmes (NTP) on a wide spectrum of tuberculosis control aspects, such as planning and budgeting, implementation, monitoring and evaluation, operational research, human resource development, laboratory networks and drug management. In addition, KNCV directly assist countries financially, and helps countries getting access to other financial resources. KNCV is financed by public governments and private organisations.

More information on KNCV can be found at <http://www.kncvtbc.nl>

2.7 South African Tuberculosis Vaccine Initiative (SATVI)

The mission of SATVI is the development of new and effective tuberculosis vaccines. SATVI strives to achieve this goal through high quality basic science, clinical and public health research, within an academic centre of excellence. The SATVI programme is being led by the University of Cape Town, with the support of the Department of Health, particularly at provincial, regional and district levels. International collaborating institutions include universities around the world (USA, UK, Denmark, and Germany). SATVI has the support of a number of international organisations, including the WHO. Major funding for SATVI is provided by the

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AERAS Global TB Vaccine Foundation (AERAS). Other funders include the National Institutes of Health (US), the European Union, and various other foundations.

More information on SATVI can be found at <http://www.satvi.uct.ac.za>

2.8 TBVAC

TBVAC is a cluster for tuberculosis vaccine developments composed of academic teams and industrial partners possessing complementary expertise. The major objective of the TBVAC project is to identify, develop and evaluate in pre-clinical and clinical Phase I trials new and improved vaccines. The Fifth Framework Programme (FP5) of the EC initially funded TBVAC.

More information on TBVAC can be found at <http://www.tb-vac.org>

2.9 Vakzine Projekt Management GmbH (VPM)

VPM is a private company for development of biopharmaceuticals, including vaccines for infectious diseases. VPM develops products together with other private companies and public academia. VPM does not provide grants or scientific expertise, but only focuses on the management of projects. VPM is involved in the management of projects based on products developed by TBVAC.

More information on VPM can be found at <http://www.vakzine-manager.de>.

2.10 World Health Organisation (WHO)

The World Health Organisation (WHO) was represented by the Initiative for Vaccine Research (IVR), which plays a major co-ordinating role in the tuberculosis vaccine field. IVR conducts and co-ordinates activities related to product research and development and implementation research for vaccines and delivery devices. Based at WHO headquarters in Geneva, the disease portfolio of the initiative includes tropical diseases, HIV/AIDS, tuberculosis, malaria, meningitis, respiratory diseases, diarrhoeal diseases, Japanese encephalitis, cervical cancer and measles.

More information can be found at: http://www.who.int/vaccine_research/about/en/

2.11 Others

Each European Member State was invited to send two representatives; the legal European Network Officer for EDCTP together with one researcher representing the TB vaccine research of that specific Member State.

Researchers that received an EDCTP grant on TB vaccines were invited, as were the most important African TB vaccine research groups.

Governmental representatives (government or research councils) from the Netherlands, Germany, Norway and United Kingdom attended the meeting. Furthermore, researchers from the UK, France, Germany, the Netherlands, Denmark, Norway, Spain, Switzerland and Belgium were also present.

3 Science and Products

WHO presented an overview on the scientific state of the art (see annex 6). In summary it is recognised that the effectiveness of the currently used BCG vaccine is variable and there is a great need for a pre-exposure TB vaccine for infants and young children as well as a post-exposure vaccine that is suitable for mass vaccination campaigns, including a therapeutic vaccine. To realise this several approaches may be required including improvement of the current BCG vaccine; development of attenuated *M. tuberculosis* vaccines; adjuvanted proteins, peptide or DNA sub-unit vaccines; and virus-vectored vaccines.

The Global Partnership to Stop TB, housed at WHO observed that although there are many promising vaccines along the pipeline and that since animal models can yield only limited information, only clinical efficacy trials will bring us closer to a licensed vaccine. Furthermore, Stop TB advised that TB vaccines should not be developed in isolation, but along with ensuring a well-stocked pipeline of candidate TB vaccines there must be a parallel development and supply of diagnostics, capacity to perform clinical trials and an enabling infrastructure.

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3.1 Products in the pipeline

TBVAC and AERAS presented an overview of the products they have in their pipelines:

Name	Type		Phase	Testing	Estimated Costs (€M)
TBVAC					
Ag85B-ESAT6 fusion protein (with IC31 adjuvant)	Post-BCG boosting or initial priming	SSI	Phase I completed in 2007	2x Ph-2a & 2x Ph-2b in 2008-10	5.0 RQ (0.2+0.3+2.5+2.0)
MVA-85A vaccinia vector also AERAS	Post BCG boosting	UOXF	Phase I/IIa completed in 2007	Phase 2b in 2008-12	10.0 (5.0 RQ)
Mtb72 fusion protein also AERAS	Post BCG boosting	GSK	Phase I completed in 2007	2x Ph-2a & 2x Ph-2b in 2008-11	17 (8.5 RQ : 0.3+0.15+4.0+4.0)
rBCG-Hly	Live vaccine replacing BCG	VPM/MPU, Germany	Phase I planned in 2007	Ph1 in Africa 2008-9	0,4 RQ
HBHA	Post BCG boosting	IP-L (FR)	not yet planned	Ph1 in Africa 2010	0,4 RQ
Mtb-PhoP	Live vaccine replacing BCG	U-ZA (ES)	not yet planned	Ph1 in Africa 2010	0,4 RQ
AERAS					
rBCG-403	Live vaccine replacing BCG	USA	Phase I planned for 2007	2008-10 All Phase I	1.4
Ad35-402	Post BCG boosting	Crucell (NL)	Phase II completed 2008	2008-10 3x Phase I	.8
AERAS-405	Oral Shigella	AERAS	Phase I Q3 2007	Q4-2007 All Phase I	1.9
Ag85B-TB10.4 fusion protein	Post BCG boosting	SSI	Phase I Q3 2007	Q4-2007 All Phase I	1.3
AERAS-402 AERAS-405	Phase II Safety	Crucell AERAS		2007-2008 Phase II Safety Studies	5.6
rBCG-403 AERAS-405	Prime Boost Studies	AERAS AERAS		Q2-2008	.2
AERAS-402	Prime Boost Studies	AERAS		Q2-2008	.2

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AERAS-403		AERAS			
All Products	Expanded Phase II	AERAS		Q4-2008	13.9
Selected Products	Adolescent Phase III	AERAS and Partners		Q3-2010	40.1
Other					
RUTI	Therapeutic vaccine	A F SL/IGTP (ES) ¹	Phase I starts in 2007	2009-2010	0,25 M€ (phase IIa)

1. Archivel Farma,S.L. in collaboration with the "Institute Germans Trias i Pujol" (IGTP).

TBVAC stressed that three of their products are ready for phase II testing in the very near future, another will be ready for Phase I in 2008 and two will be ready for Phase I clinical trials in 2010.

In conclusion: TBVAC has 4 products, AERAS 1 product ready to go into clinical trials in Africa, while another 3 will be ready within one to two years. Both TBVAC and AERAS agree that the MVA-85A vaccine is the most advanced in development.

3.2 Summary discussion on products and science

- EDCTP will have to spend all the money before 2010
- TBVAC has 4 products ready to go into clinical trials in Africa, AERAS has one product and 3 others within a year. To test the 5 products, € 19M + money from AERAS will be needed. From EDCTP there is € 11.5M available, if Member States come up with another € 11.5M this will make up € 23 which would be enough to tests all the vaccines ready for testing at the moment
- Selection of the scientifically most promising vaccines is difficult, because correlates of protection are still unclear. Proofs of concept studies for all concepts are necessary and EDCTP should make sure to test and compare different concepts, preferably within one (multi-site) trial. Therefore, it is suggested that EDCTP should not test only the products that are available for testing now
- Since the protective mechanism against TB have not yet been fully elucidated it is difficult to favour specific approaches on a scientific base. Other criteria like costs should therefore be included as well and EDCTP should also take a pragmatic approach taking into account matters such as what products will be co-funded by Member States; which products are applicable under African circumstances (easy to store and to administer); production costs and what products are ready in time to be tested before 2010
- Another criterion mentioned included the question whether a pharmaceutical industry was interested in producing the product because one cannot test a vaccine in phase II without a finished product
- Trials should be done in Africa because immune status of Africans is different from that of Europeans
- It was remarked that clinical trial phases should not be divided. Although EDCTP is focussing on phase II/III but when a Phase I study is linked to a phase II study, the phase I would not be excluded from funding by EDCTP and would be considered a capacity strengthening activity when conducted in Africa

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- Especially for adolescents and adults, multi-site studies are preferred because one needs a large number of participants, which is difficult to achieve
 - For development purposes, therapeutic vaccines are to be considered under vaccines rather than drugs
 - The question was brought up if AERAS products should be funded by EDCTP while they are already well-funded
-

4 Sites in Africa

4.1 Represented sites

The table below lists African sites which were represented at the meeting. In addition to these sites others were mentioned during the presentation from SATVI and MRC, the Gambia.

<i>African institutions represented at the meeting</i>		
<i>Name of Institution</i>	<i>City</i>	<i>Country</i>
<i>Medical Research Council Laboratories</i>	<i>Fajara</i>	<i>The Gambia</i>
<i>Armauer Hansen Research Institute</i>	<i>Addis Ababa</i>	<i>Ethiopia</i>
<i>Kenya Medical Research Institute (KEMRI)</i>	<i>Kisumu</i>	<i>Kenya</i>
<i>South African TB Vaccine Initiative, University of Cape Town</i>	<i>Cape Town</i>	<i>South Africa</i>
<i>Cheikh Anta DIOP University</i>	<i>Dakar</i>	<i>Senegal</i>

4.2 Presentations on sites in Africa

Tumani Corrah (the Gambia) presented an overview of the burden of TB disease in Africa, which illustrates the need for many sites. Prof. Corrah stressed the need for sister sites, linked to nodes of excellence.

4.2.1 SATVI

Greg Hussey presented SATVI, explaining the focus on translational research, including phase I to phase IV vaccine trials. SATVI has extensive experience including epidemiological studies and immunological studies. SATVI has experience in data management, ethics, regulatory affairs and advocacy.

SATVI works closely together with the University of Cape Town, University of Stellenbosch and with the SA Department of Health. SATVI also has many international collaborators. In the Western Cape SATVI undertakes correlate of protection studies in young children using percutaneous BCG. This research project is also focussing on capacity strengthening. In addition SATVI performs studies with the UOX MVA vaccine.

SATVI is assisting in strengthening capacity in two sister sites in Uganda and Kenya.

SATVI acknowledges that the absence of a blueprint, difficulties in diagnosing paediatric TB, lack of consensus on clinical endpoints, determining causes of death, identifying mycobacterium naive persons, ethical issues and lack of human resources capacity are major challenges.

SATVI works closely together with health services (that gain from trials because they receive education and training) and the communities, based on mutual trust. Because it takes at least 5 years to build up a trial site suitable to perform industry standard phase III studies, SATVI stresses the need to first consolidate existing sites in Africa before building up new ones. African leadership and South-South capacity strengthening should be a priority.

4.2.2 MRC, the Gambia

Richard Adegbola presented work from the MRC in the Gambia. The MRC has conducted over 40 clinical trials to date. MRC mainly works within 4 field sites located in different ecological settings in the Gambia. The institution also has a sophisticated laboratory. MRC the Gambia participates in a multi-site trial in which Benin, Guinea, Kenya, Senegal and South Africa are also involved. Except for South Africa and Senegal, the other sites definitely need to be strengthened in one way or another. Among these include sites in Zambia (Ndola, Macha), Tanzania (NIMR, KCMC) Uganda (Mulago) and Kenya (KEMRI), Ghana (Noguchi) that are either promising or very experienced and well-established.

MRC the Gambia stresses the need to build on what is already there. Furthermore, needs include laboratory and administrative capacity, trained personnel and long-term surveillance and monitoring.

4.3 Summary discussion on Sites in Africa

- Sites in high and low HIV prevalence are needed to compare the effectiveness of TB vaccines in both populations
- It is important to network existing, strong, sites with each other and with less experienced sites
- A prerequisite is co-operation with health services and a functioning surveillance and monitoring system. Therefore, TB vaccine trials should only be executed in countries with a running national TB control programme
- Should EDCTP fund sites and products as a package or should EDCTP grant products and then look for sites ready to do the job? What about a site that has no product? EDCTP calls should be formulated broader in order to be able to maintain sites without a product
- AERAS stresses that it is also strengthening sites in developing countries (South Africa and India) and that those sites have not been reserved for specific products. In Africa (Kenya, Uganda), cohort studies will be performed as a way to strengthen the capacity using grants from EDCTP, NACCAP (the Netherlands) and Sida (Sweden)
- Furthermore, EDCTP is planning to fund capacity building for sites in Madagascar and Tanzania

5 EDCTP procedures

5.1 Overview EDCTP procedures

EDCTP can fund proposals through an open call or a brokering procedure. Both were explained to the audience. More information can be found in the Guidelines for Stakeholders' meetings (see Annex 2).

5.2 Summary discussion EDCTP funding procedure and timelines for initiating funding procedure

It was generally agreed that an open call would be the appropriate funding procedure for TB vaccines. EDCTP should aim to support as many products as possible because it is not possible at this stage to indicate which candidate is likely to be the most successful. It was suggested that it would not be wise to make a selection at this point. It was stressed that apart from EDCTP there are not many other possibilities for funding.

The possibility of doing head-to-head trials of different vaccine candidates was discussed. It was suggested that this was not useful in Phase I and early Phase II trials but could be interesting in efficacy trials. However, the difficulties of trying to achieve this were also acknowledged.

In terms of the call text the following suggestions were made:

- The impact of the HIV epidemic in Africa will need to be taken into consideration. Trials should be carried out in regions with different HIV incidence
- Correlates of protection in TB are not known and it was recommended there is a need to look into this. This could for instance be a focus for a PhD or postdoctoral project associated with the trial
- Clinical trials sites should be in countries with an efficient TB control programme
- It is only ethical to test a new BCG vaccine (replacing BCG) in a site where there is a good follow-up with TB treatment
- Therapeutic vaccine candidates should be included in the call
- There was a long discussion on the call text focussing on Phase IIb or Phase II in general. The final consensus was that the text should call for Phase II trials in general because there are a number of interesting candidates and focussing on Phase IIb only would limit the number of products that are available now tremendously. Ideally EDCTP will fund a few Phase IIa and a few Phase IIb trials.

Regarding whether EDCTP should put all its money on one call or hold some back for a second call next year, it was recommended that EDCTP should launch a large call this year and a smaller one focussing on new upcoming TB vaccines such as recombinant BCG vaccines next year.

Consensus recommended procedure

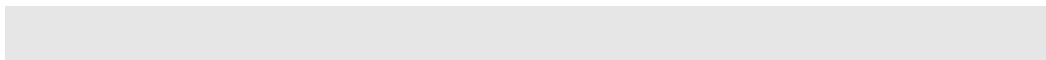
The result of the discussion was consensus that EDCTP should issue two open calls for final proposals which will be reviewed by a broad-based committee that will consider capacity building as well as product evaluation aspects. One call should be launched as soon as possible and call for support of Phase II clinical trials, with capacity building and networking elements. This call should be followed by a smaller call next year which should focus on supporting smaller proof of principle studies of around 400,000 euros each. The emphasis of this second call should be the new upcoming TB vaccines candidates which are not yet ready for testing this year.

Possible funding partners:

The table below lists the European countries that were represented at the meeting:

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Country	Type of support
Denmark	Did not specify but mentioned specific funding to the value of 30m Danish Krone per year of the Danish Ministry of Health to SSI for vaccine development for TB, HIV and malaria.
France	Did not make a pledge.
Germany	Germany will continue to support the German vaccine candidate in the TBVAC consortium and will be able to support German applicants who work on other products.
Netherlands	NACCAP indicated willingness to discuss with programme board to participate to this call. The Ministry of Development Aid indicated they only fund public private partnerships when it comes to product development.
Norway	Did not make a pledge.
Spain	Willing to support RUTI TB vaccine candidate. In addition willing to co-funding if Spanish researchers are involved with the call.
Sweden	Happy to support call using core funding previously donated to EDCTP.
United Kingdom	Willing to provide general support.



6 Annexes

Annex 1 :Member state and third party contribution to the stakeholder meeting

<i>Estimate of all costs covered by hosting country</i>	
Item	Amount
Travel	
Hotel	
Catering	€ 992.21
Administration support	In kind
Venue	In kind
Other	Not applicable
Sum	€ 992.21

Signed by organising Member State: The Netherlands

Name: Judith de Kroon

Date: 21 April, 2007

Annex 2:EDCTP Guidelines for Stakeholder meetings

Introduction

This document aims to describe all aspects related to the aim, organisation and outcome of the EDCTP stakeholder meetings.

EDCTP aims to organise to 2 types of stakeholder meetings: 7 meetings will focus on disease specific topics and one meeting will concentrate on Nodes of Excellence. The disease-specific topics will have a focus on products in the pipeline. These topics are listed below:

- Malaria treatment and malaria in pregnancy (combined meeting)
- Malaria vaccines
- TB treatment
- TB vaccines
- HIV treatment
- HIV vaccines
- HIV microbicides

The Nodes of excellence meeting will focus on the integrated approach of EDCTP towards the establishment of regional nodes of excellence in sub-Saharan Africa with particular focus on reference laboratories and centres specialised in data management encompassing clinical trials design, conduct, and analysis skills, building on sites with existing capacities and competences in these areas.

These guidelines aim to describe the generic approach towards organising both types of meetings. All stakeholder meetings on disease related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP. The expected outcome, communication aspects, timelines and financial issues concerning stakeholder meetings will be clarified. In addition the role of the hosting member state, the organising committee including the independent chair as well as the expected list of participants are described.

To ensure transparency these guidelines are made public and the EDCTP Secretariat will ensure that the implementation will be carried out and documented correctly.

Aim and objectives of a stakeholder meeting

A stakeholder meeting is a one day meeting. It is the start of a process that leads towards EDCTP funding one or more projects through a call or brokering procedure.

The expected outcome of these meetings is:

1. To make recommendations to EDCTP for:
 - The development of cooperative projects and coordination of efforts
 - Priorities for EDCTP:
 - for disease specific topics EDCTP requires priorities in terms of product and sites whereas
 - for nodes of excellence EDCTP needs priorities in terms of sites, location as well as required skills and capacity
2. Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms. These will be followed up by the EDCTP secretariat.
3. Establishment of trust in the EDCTP approach with our stakeholders.

The meetings with a disease-specific topic will have the following objectives:

- Identify products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend priority in terms of product and sites
- Recommend if the funding procedure is a call or brokering or no-go
- Recommend EDCTP timelines concerning the initiation of funding for each topic area

The stakeholder meeting on Nodes of Excellence has similar priorities:

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- Identify potential sites
- Identify needs in terms of skills and capacity
- Recommend priorities in terms of needs and sites
- Recommend if the funding procedure is a call or brokering or no- go
- Recommend EDCTP timelines concerning the initiation of funding

Organisational aspects

All stakeholder meetings on disease-related topics will be hosted by one of the participating European Member States whereas the stakeholder meeting about Nodes of Excellence will be hosted by one of the African partners participating in EDCTP.

All meetings will be organised by an Organising Committee that consists of:

- An independent expert to chair
- A representative of the hosting country. For the European Member States this is the European Networking Officer (ENO) representing the country while for the Nodes of Excellence meeting this role should be fulfilled by the relevant member of the Developing Country Coordinating Committee (DCCC),
- The Partnership Board (PB) and DCCC disease experts
- The Executive Director and Operations Manager from the EDCTP Secretariat

The independent chair will be identified by EDCTP Secretariat, PB and DCCC representatives of the organising committee before the date of the stakeholder meeting is set. The candidate will be approved by the GA in a written procedure. If the hosting country is identified before a chair is selected the representative of the hosting country will also be involved in selecting the chair. The Terms of reference for the Independent chair are the following:

To work with the EDCTP stakeholders' meeting planning group to ensure that the meeting is planned and implemented transparently avoiding or declaring any conflict of interest to give an optimal, independent and objective advice to the EDCTP. This, via the EDCTP Secretariat should take into account the following:

1. The presence of appropriate representation of all significant bodies including industry, private-public partnerships and other stakeholders that are relevant to the topic; ensuring that the representation at the meeting is sufficiently senior to contribute with authority
2. There are appropriate and effective arrangements for conducting the meeting including drafting and approving of the agenda; noting of the attendance; ensuring of adequate participation and deliberation of all the relevant issues
3. Provision in an agreed timescale of a good quality report of the meeting.

Travel and hotels are arranged in close collaboration between the hosting country and the EDCTP Secretariat and the hosting country is expected to play an active role in this. The hosting country should organise location, catering and administrative support as well as assist delegates with their visa requirements. In addition the hosting country is responsible for sending out the invitations to participants. The final list of participants to be invited will be provided by the EDCTP Secretariat in collaboration with the Organising Committee.

Participants

It is a requirement that the following parties are represented at the stakeholder meeting:

- Funders both from the European Member States and if applicable third parties. Each European Member State will be asked to send one representative. It is up to the individual country to accept this invitation or not
- Product developers, Public Private Partnerships and/or industry (disease specific topics only)
- Representatives of African sites that have the capacity to carry out phase II or III trials
- Experts in the field. Each European Member State may bring one expert of their own choosing

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- Independent experts if applicable.

Most participants will be identified by the Organising Committee with the exception of the representatives of the European Member States. Each European Member State is free to send one expert in the field and one representative of their funding body of their own choosing.

It is normally expected that a stakeholder meeting will have no more than around 40 participants.

Invitations to the participants need to go out at least 6 weeks in advance.

Agenda

The agenda for the stakeholder meeting is set by the Organising Committee using the format developed by the EDCTP Secretariat. The generic format for the meetings on disease specific topics is shown below.

EDCTP Stakeholder Meeting

Topic
location, date 2007
Address
Contact

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	
1.0 Welcome by host	host	
2.0 Approval of the Agenda	All	
3.0 Science and products 3.1 Scientific overview of the field 3.2 Products in the pipeline: relevant stakeholder (more added if required) More added if required		
Coffee break	All	
4.0 Discussion on products and science	All	
5.0 Sites in Africa 5.1 Relevant stakeholder (more added if required) 5.3 DCCC		
Lunch	All	
6.0 Discussion on sites	all	
7.0 EDCTP procedures	SEC	
8.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	
9.0 Summary of recommendation	Chair	

Communication

Because EDCTP stakeholder meetings should demonstrate transparency and independence it is important that the meetings are widely advertised and that the hosting country does not have a perceived conflict of interest with the topic. EDCTP will however, not publish a call for participants. The advertisements for the stakeholder meetings will focus on announcement of topics, locations, aims and dates. They should list a contact address and encourage those that would like more information to make contact. If someone contacts EDCTP with a wish to participate, this request will be passed on to the Organising Committee who will make a decision.

Advertising of the stakeholder meetings will be through the following means:

- Internet:
 - EDCTP website
 - Requesting constituency members to publish at their websites
 - Other relevant websites
- Paper advertisement:
 - Publishing of adverts in Lancet as soon as all the dates are set
- Ask EDCTP constituencies to communicate to appropriate parties
- If the opportunity arises mention of EDCTP stakeholder meetings in presentations or meetings

Timelines

EDCTP

The dates for the various stakeholder meetings will be set as soon as the independent chair and hosting country have been identified and once the chair agrees to the Terms of Reference. It is expected that the stakeholder meetings for TB vaccines, malaria vaccines, HIV vaccines and HIV treatment will take place during the first quarter of 2007. The stakeholder meetings for Nodes of Excellence, malaria treatment/pregnancy, TB treatment and HIV microbicides are scheduled for the second quarter of 2007.

Financial issues

If the stakeholder meeting is hosted by a European country, it is expected that this country will at least as a minimum cover the costs for use of the location, catering during the meeting, administrative support and any other local expenses. If the hosting country is African these costs need to be discussed with the EDCTP Finance Manager. EDCTP will normally pay for travel and hotel for external participants as well as for PB and DCCC members. EDCTP expects that the European Member states will at least pay for travel and hotel of the participants they delegate. EDCTP will pay for travel and hotel of European MS participants and experts only if the European Member State is unable to do so.

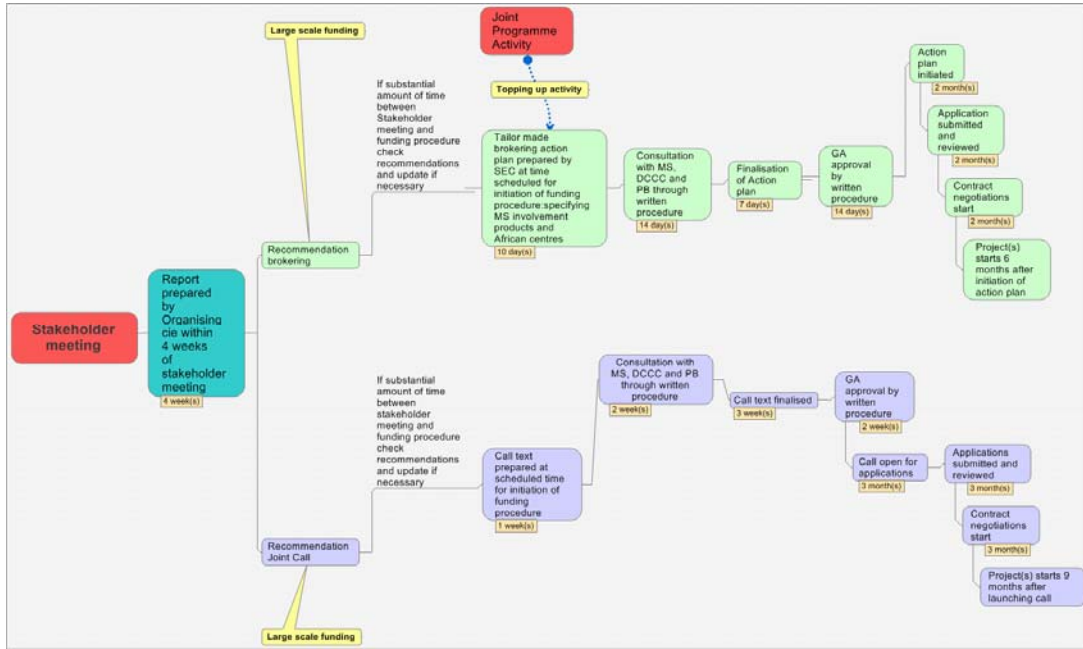
Outcome/follow up

The organising committee will produce a report of the meeting within 4 weeks. The report will be presented to EDCTP. EDCTP will initiate its funding procedures at the appropriate time after considering the report. The timing for launching calls or brokering initiatives can range from 2007-2009 depending on the on the availability of products and sites. A final list of expected dates for initiation of funding procedures will be prepared after all stakeholder meetings have taken place. The diagram below summarises both funding procedures. More information on the EDCTP funding procedures can be found at the website.

A summary of both procedures is described below:

- *Call for proposals*
A call text is drafted based on the recommendations that came out of the stakeholder meeting. After consultation of the various EDCTP constituencies and approval of the General Assembly the call will be published. An EDCTP call is normally open for applications for a period of 3 months. The applications are then checked against the eligibility criteria as defined in the call text and eligible applications will be reviewed by at least 2 external experts as well as the EDCTP Scientific Review Committee (SRC). The SRC ranks the applications and makes a recommendation for funding. This recommendation is examined by the PB which ensures the quality of the review procedure and also assess if the proposal is in line with the EDCTP strategy. The PB make the final recommendation for funding to the General Assembly who approve the application.
- *Brokering*
A brokering action plan is prepared by the EDCTP Secretariat and requires to be approved by the General Assembly after consultation with the EDCTP constituencies. The action plan will be initiated resulting in an application for funding. This application is checked for eligibility as described in the brokering action plan and reviewed by at least two external experts as well as the relevant EDCTP SRC. The SRC make a recommendation for funding or rejection which is examined by the PB which examines both the procedure as well as the alignment of the project with the EDCTP strategy. Upon recommendation of the PB the GA make the decision to fund the project or not.

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Annex 3: Instructions for presentations

Expected outcome of the meeting

The expected outcome of the EDCTP stakeholder meetings is to make recommendations to EDCTP for:

- The development of cooperative projects and coordination of efforts
- Priorities for EDCTP in terms of product and sites
- Expression of a willingness of the various stakeholders to contribute to the topic both in financial as well as practical terms.
- Establishment of trust in the EDCTP approach with our stakeholders

The stakeholder meeting is considered the start of a process that leads towards EDCTP funding of one or more projects through an open call or brokering.

Audience

The audience will be a mixture of experts in the field and people who represent funding agencies and may not have a scientific/medical background. Therefore we would like to suggest that your presentation should be aimed at a general audience.

Expected contents of your presentation

Given the expected outcome of the meeting and the composition of the audience EDCTP would like to provide you some points regarding the expected contents of your presentation.

If you talk about science and products

- A short introduction on the organisation you are representing
- Without going into too much scientific details basic information about the products in the pipeline:
 - Basic principles of the product
 - Status with respect to clinical testing: what has been done/what is ongoing and what is planned/needed
 - Availability of the product
 - Restrictions with respect to the use of the product: is it only available for persons associated with your organisation/is it for sale?

In addition to the presentation could you provide a short summary document on each product that should enable the participants to the meeting to assess its scientific validity and potential.

If you talk about sites in Africa

- A short introduction on the organisation you are representing
- Basic information about the sites you are representing:
 - Capacity and trial experience
 - Commitment to other trials/availability to do the trial
 - Local tuberculosis situation

Duration of your presentation

The time available per presentation is limited to 15 minutes. The presentations will be followed by an initial discussion of 1 hour.

Annex 4: Agenda**Agenda EDCTP Stakeholder Meeting
Tuberculosis vaccines**

The Hague, 11 April 2007

NWO, room 300 (3rd floor Java-building)

Laan van Nieuw Oost Indië 300, 2593 CE The Hague

10:00-16:45hrs

Aim of the meeting:

- Identify and prioritise potential products in the pipeline
- Identify potential suitable sites to do the trial
- Recommend if the funding procedure of EDCTP will be an open call, brokering or whether EDCTP should fund this topic at all
- Recommend EDCTP 's timeline concerning the initiation of funding for this topic

Agenda items	By	Timelines
<i>Coffee/Tea</i>	<i>All</i>	<i>10:00 – 10:15</i>
1.0 Welcome	Charles Mgone, Judith de Kroon and Marie Paule Kieny	10:15 – 10:30
2.0 Approval of the Agenda	All	10:30-10:40
3.0 Science and products		
3.1 Scientific overview of the field	Uli Fruth	10:45-11:00
3.2 Products in the pipeline: TBVAC	Paul Lambert	11:00-11:15
3.3 Products in the pipeline: AERAS	Larry Geiter	11:15-11:30
<i>Coffee break</i>	<i>All</i>	<i>11:30-11:50</i>
4.0 Discussion on products and science	All	11:50-12:30
5.0 Sites in Africa		
5.1 Needs in field of TB vaccines	Tumani Corrah	12:30-12:45
5.2 SATVI	Greg Hussey	12:45-13:00
5.3 Promising future sites for TB vaccines: EDCTP	Richard Adegbola	13:00-13:15
<i>Lunch</i>	<i>All</i>	<i>13:15-14:15</i>
6.0 Discussion on sites	All	14:15-14:45
7.0 Concluding remarks on sites	Chair	14:45-15:00
8.0 EDCTP procedures	Cynthia Naus	15:00-15:15

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9.0 Member States commitment	Member State representatives	15:15-15:30
10.0 Recommendations on how to proceed in terms of products, sites and funding procedure	all	15:30-16:00
11.0 Summary of recommendation	Chair	16:00-16:15
<i>Drinks</i>	<i>all</i>	<i>16:15-16:45</i>

Annex 5:List of participants**TB Vaccines Stakeholder Meeting****Wednesday 11 April 2007, The Hague, the Netherlands**

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Annex 6: Discussion paper

**Tuberculosis Vaccine Development
A brief background**

Contents

1. Introduction and background
2. TB pathogenesis and host response
3. Functional characteristics of new TB vaccines
4. Novel TB vaccine candidates
5. TB vaccine development strategy
6. Risks and challenges

by Uli Fruth, *Ph.D.*

World Health Organization

Initiative for Vaccine Research

April 2007

1. Introduction and background

Every year, about 1.7 million HIV negative individuals die as a consequence of pulmonary tuberculosis and many hundreds of thousands more succumb to tuberculosis as a direct consequence of the breakdown of immunity caused by HIV. These deaths occur despite the availability of efficient drugs and a vaccine, BCG, which is the most widely used of all childhood vaccines. The effectiveness of the BCG vaccine can be described at best as variable and drug treatment is long and burdensome, optimally requiring direct observation by a health worker. This and the fact that (a) diagnosis of infection with *Mycobacterium tuberculosis* (*Mtb*), at least in developing countries, is often made late, when bacteria already appear in the sputum and are being spread to previously uninfected contacts, (b) reinfection or reactivation of *Mtb* occurs in drug-cured TB patients, and (c) multi-drug resistant *Mtb* strains commonly result from improper adherence to chemotherapy regimens, justifies the need for an effective vaccine to help control the global epidemic of tuberculosis.

The search for a new, improved TB vaccines is a relatively young field. No research activities aimed at development of a new vaccine worth-mentioning are recorded between the introduction of BCG vaccine in the 1920ies and the late 1980ies, when TB, in the wake of the rising HIV/AIDS pandemic, made a frightening comeback. Nevertheless, numerous promising new approaches have been developed during the last two decades. Advances in gene and antigen identification, availability of genome sequences, a greater understanding of immune mechanisms possibly able to control mycobacterial disease, the development of adjuvants and delivery systems to stimulate T-cell immunity, and increased funding from the public as well as the private sectors are some of the reasons for progress in this area. The most advanced of the new TB vaccine candidates are now entering clinical evaluation. The present paper will try to give an overview over this very dynamic field of research, but also highlight potential bottlenecks, both scientific and financial.

2. TB pathogenesis and host response

An understanding of the pathogenic mechanisms of *Mtb* infection and colonization of susceptible hosts and the role of the subsequent host immune response to the invading organism in the progression of tuberculosis is crucial to the development of better vaccines and treatments for this widespread disease. It is important to appreciate that the pathology of TB (particularly in the lung), although initiated by the invading bacterium, *Mtb*, is also a result of the complicated immune response to this intracellular organism. Our current understanding suggests that a cascade of host defense mechanisms is triggered when a relatively small number of inhaled *Mtb* reach the terminal airspaces of the lung and are ingested by alveolar macrophages. This initial event is followed by a phase of logarithmic growth of the bacilli at the site of infection, their spread to the proximal lymph nodes and eventual dissemination to other sites in the body. This process of replication and dissemination is commonly controlled by the onset of an effective immune response. The typical manifestation of cellular immunity against tuberculosis is the formation of immune-dependent granulomas (or tubercles), consisting of a core of *Mtb*-harboring macrophages and surrounded by a layer largely composed of lymphocytes. It is, however, important to understand that the bacteria walled off within the granuloma are almost never completely eliminated and infection may reactivate at a later date. The lifetime risk for immuno-competent individuals for this to happen is estimated at around 5 to 10 percent, whereas the risk of reactivation for an immuno-compromised, e.g. HIV infected individual is thought to be around 10 percent annually.

It is widely accepted that protective immunity against tuberculosis relies on the activation of T cells rather than B cells. Within the T cell 'family', it is the CD4+ T cell which are thought to be key in fending off TB. However, other T cell types such as CD8+ and $\gamma\delta$ T cells are known to participate in the anti-mycobacterial immune response, but their relative importance during the progressive stages of the disease remains elusive. T cells are known to exert their function at least partly through secretion of a number of hormone-like proteins, called cytokines. In particular the cytokines interferon-gamma (IFN γ) and interleukin-12 (IL-12) have been ascribed beneficial roles in protection against TB and exceptional susceptibility to TB has been described in human individuals who are genetically deficient for IFN γ receptor, the IL12 receptor or IL 12.

3. Functional characteristics of new TB vaccines

What is needed is probably not one, but more likely two or even three new TB vaccines with different profiles: one to replace or 'amplify' BCG early in life and before exposure to *Mtb*, another one to boost anti-mycobacterial immune responses later in life when latent TB is installed, and possibly a therapeutic vaccine against active TB. It may be possible that a vaccine can be identified which covers several of these functional profiles, but this will not be automatically the case for all vaccine candidates. Thus, it is known that live BCG does not boost anti-TB immunity in latently infected or previously BCG-immunized human individuals or animals.

Pre-exposure TB vaccines: This type of TB vaccine, of which BCG is the prime example, is intended for use in newborns or young infants, i.e. at a timepoint when the individual's immune system has not yet been exposed to natural infection with *Mtb* or other mycobacteria. All the vaccine candidates which are currently in preclinical or early clinical development were selected in protection studies in unexposed animal models, i.e. mimicking neonatal vaccination. Current thinking implies that live TB vaccines such as 'old' BCG, improved BCG or rationally attenuated *Mtb* would be used as 'first contact' pre-exposure vaccines, with or without additional booster doses of one of the new non-living products under development, e.g. adjuvanted subunit or virus-vectored vaccines.

Post-exposure TB vaccines: 'Post-exposure vaccines' are vaccines that can be given at a post-infancy timepoint in life, typically to school children, adolescents or adults, when the individual has either been vaccinated, .e. g. with 'old' or 'improved' BCG, or latently infected with *Mtb* (or other mycobacteria) or both. Post-exposure TB vaccines to be used against firmly established latent TB may require a different set of antigens than the ones that are expected to be active against primary infection in newborns and the type of immune response induced may differ. Also, the fact that later in life TB can arise both from endogenous reactivation and from exogenous reinfection - with the latter representing up to 75% of all TB relapse cases in high burden countries - should be reflected in the antigenic composition of a potent post-exposure vaccine. The difficulty in reliably reproducing latency in animal models is an obstacle to the development of post-exposure TB vaccines as are safety concerns over potential immune exacerbation induced by vaccination of latently infected individuals, sometimes referred to as 'Koch's reaction'. It must be noted that post-exposure vaccines remain at present a hypothetical concept, for which no proof of principle exists. This is in contrast with pre-exposure vaccines, where the fact that neonatal BCG is protective in some populations or age groups is taken as an

indication that it should be possible to improve on whatever meagre protection BCG affords. While indeed at least one of the new TB vaccines has been shown to boost preexisting anti-mycobacterial T cell immune responses in a post-exposure situation, it is currently unknown if these booster responses will actually translate into improved protection against TB disease. Post-exposure vaccines may be the more difficult to develop, but they are also the ones that are most urgently needed in order to deal with those estimated two billion individuals who are thought to be already infected with *Mtb* and where an effective 'post-exposure' vaccine could make a huge impact in a short period of time. Obviously, a vaccine that could be used in mass vaccination campaigns would be particularly desirable in this context.

Therapeutic TB vaccines: Therapeutic vaccines, i.e. those that are to be given to individuals with active TB, represent a special case of the above-mentioned post-exposure vaccines. The general idea is not to use these vaccines as stand-alone agents, but rather as adjunct to antibiotic treatment, with the aim of shortening the duration of anti-TB chemotherapy. Inactivated mycobacteria as well as a DNA subunit vaccine encoding for a mycobacterial heat-shock protein are being proposed for this purpose.

4. Novel TB vaccine candidates

Genetically modified mycobacteria: An argument can be made that since BCG is widely used, has a good safety record and likely prevents complications caused by *Mtb* infection in infants, we should develop a better BCG. Three main approaches to genetically improve BCG are currently underway: (a) overexpression of highly immunogenic antigens, (b) reconstitution of genetic segments ('RD1') which were lost during the attenuation of *M. bovis* to create BCG and (c) introduction of secreted pore-forming proteins from other bacteria species such as *Listeria monocytogenes* or *Clostridium perfringens*, which facilitate an intracellular process called 'endosome-escape' and are thought to induce a broader type of immune response, including in particular higher CD8+ T cell frequencies. Attempts to combine some of the above approaches are ongoing, e.g. antigen overexpression plus 'endosome-escape'. The only recombinant BCG that has been tested in humans so far is the rBCG30, a live vaccine that is genetically engineered to produce large amounts of a 30kDa protein (Ag85B). A Phase 1 study of rBCG30 in the USA showed good safety of this candidate vaccine. Other recombinant BCGs are thought to enter clinical evaluation in 2007 or 2008. To this day, it is unknown which antigenic shortcomings render conventional BCG sub-optimal as a vaccine. The fact that BCG's 'parent' organism, *M. bovis* has primarily evolved in an adaptation to bovine rather than human hosts is cited as one possible reason. This assumption has sparked numerous efforts to attenuate the actual human pathogen, *Mtb*. All approaches to develop rationally attenuated live *Mtb* vaccines that are decreased in virulence but persistent enough to elicit effective immune responses are still in an early phase of vaccine development. Examples include both regulatory mutants such as the deletion of the *phoP* gene as well as introduction of metabolic mutations, e.g. pantothenate auxotrophy. An improved BCG or attenuated *Mtb* has an advantage in that it may be accepted more readily into the existing global BCG immunization program than the other new vaccines. It is indeed planned that such live mycobacteria would replace 'old' BCG as the neonatal 'pre-exposure' vaccine in the immunization schedules to be designed for the different combinations of new products.

Adjuvanted subunit vaccines: Protein subunit vaccines have shown to be powerful vaccines against other diseases, e.g. hepatitis B or human papillomavirus and, due to their stability, ease of standardization and safety in the immunocompromised host are certainly the first choice of vaccine industry. In this context, proteins secreted by *Mtb* have received special attention as subunit vaccines (but also as 'add-ons' in new live vaccines) because such antigens are among the first molecules of the pathogen to be encountered by the human immune system after infection. There are two adjuvanted protein subunit vaccines currently in clinical trials: M72 is a recombinant fusion construct composed of the Mtb39a PPE protein and a 32kDA protease. The M72 vaccine in AS01A adjuvant is currently in phase 1 clinical trials, as is the second example, a TB subunit vaccine based on a fusion protein consisting of two immunodominant antigens: ESAT-6 and 85B, together with a mixture of the DDA and MPL adjuvants. Both vaccines were selected based on good immunogenicity and protection data from animal models and have in the meantime been shown to be safe and immunogenic in early human trials. While still in a rather upstream phase of development, it should be mentioned that proteins that which are differentially expressed by *Mtb* under low oxygen pressure, i.e. the exact conditions that the bacteria find during the latent phase inside their human host cell, are now being tested as antigens to protect against reactivation of TB. A mycobacterial protein termed α -crystalline homologue is the 'flagship' representative of that most interesting group of experimental latency or dormancy antigens.

Virus-vectored vaccines: Two vectored vaccine approaches are receiving current attention, both of which employ constructs that have already been used for development of HIV/AIDS and malaria vaccines. The first is an MVA (Modified Vaccinia Ankara) vector expressing *M. tuberculosis* antigen 85A (M85A). In mice and humans, M85A strongly boosts BCG-induced CD4+ and CD8+ T cell responses specific for M85A. The product has completed phase 1 trials in both the UK and the Gambia with promising results and, with ongoing phase II clinical trials in South Africa, is the new TB vaccine furthest along in clinical testing. The second vectored vaccine approach uses an adenovirus vector to express several mycobacterial proteins and that has entered phase I clinical evaluation in late 2006. The current plans for virus-vectored - as well as the above-mentioned adjuvanted subunit vaccines - imply their clinical evaluation and eventual use as either 'early' boosters of a neonatal vaccination with live mycobacteria at one to 6 months of age or as 'late' boosters in a post-exposure situation in school children, adolescents or adults.

Other approaches: Since the protective mechanism against TB are not fully elucidated, numerous other, largely empirical approaches are currently in the vaccine discovery pipeline. None of the concepts described below has so far been tested in human clinical trials. Lipid-containing non-protein antigens, known to be recognized by so-called non-classical T cells are tested in animal models. Conjugate vaccines against carbohydrate-containing cell-wall components of *Mtb* are being developed to stimulate antibody production against the pathogen, although a protective role of antibodies against TB remains to be proven. Finally, as mentioned above, killed mycobacteria and DNA subunit vaccines are being considered as therapeutic vaccines. The most recent products include killed *Mtb* organisms that were grown under conditions of oxygen starvation for enrichment in latency antigens (RUTI) and an adjuvanted DNA subunit vaccine that encodes a mycobacterial heat shock protein, hsp65.

5. TB vaccine development strategy

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TB vaccine development is an integral element of the Global Partnership to Stop TB, an network of international organizations, countries, public and private sector donors, governmental and non-governmental organizations and individuals that aims to accelerate social and political action to stop the spread of TB. The Stop TB Partnership has recently developed a Global Plan to Stop TB (2006-2015), which contains strategic plans of all 7 Working Groups of the Stop TB Partnership, one of which is on TB vaccine development. The overall objective of the Working Group is to have a safe, effective, licensed vaccine available at reasonable cost by 2015. The strategic plan details 7 key actions to achieve this goal:

Key Action 1 Maintain and improve BCG vaccination programmes: It is anticipated that BCG will remain the cornerstone of TB vaccination programmes, with the next generation of new vaccines being introduced as an addition to existing or new BCG vaccines. The better the implementing infrastructure will be set up, the easier and faster it will be to introduce new TB vaccine into an existing system rather than having to create one from scratch.

Key Action 2 Keep the pipeline filled - discovery and translation research: There is a need to expand discovery and translational research on vaccines. The success of the current clinical candidates does not signal an end of discovery research, but rather provides novel opportunities to link fundamental research to human studies. Current candidates are based on a very limited number out of potentially hundreds of antigens. It is likely that experience gained as current candidates move through clinical trials will contribute to development of new sets of candidates in an iterative process of refinement.

Key Action 3 Facilitate preclinical development: There is a need to identify and assist in the development of facilities for production of pilot lots of vaccine candidates suitable for human trials, and to ensure that these candidates are subject to appropriate tests to confirm biological potency and lack of toxicity in experimental systems.

Key Action 4 Build capacity at vaccine trial sites: Carrying out vaccine trials requires the availability of local expertise as well as baseline data in the populations who will participate in these trials. Prerequisites include baseline epidemiological information, development of community interaction programmes, development of protocols that comply with legal and ethical requirements, coordination with national regulatory authorities, local proficiency in immunological assays and optimized diagnostic procedures, and infrastructure through which the developmental vaccine will be delivered. These activities provide important opportunities for training and capacity strengthening, and require interactions with national TB control and vaccine implementation programmes.

Key Action 5 Ensure availability of vaccine production capacity/scale-up: The potential to scale up production of experimental vaccines to a level suitable for widespread distribution in multi-center, multinational studies is an essential factor in the selection of candidates for clinical trials. Also, it is anticipated that a new licensed vaccine would be made available at a cost that is affordable for resource-poor countries. It is likely that these demands will exceed the capacity of existing vaccine production facilities and will necessitate investment in one or more dedicated GMP-quality production facilities. This activity will require the development of innovative partnerships with manufacturers in developing and developed countries.

Key Action 6 Perform clinical trials: Evaluation of vaccine candidates requires transition through a series of clinical trials of increasing size, complexity and cost to progressively evaluate their safety, immunogenicity and finally efficacy. Assuring commitment of investments by collaborators in developed and developing nations is a major challenge for the global TB vaccine development community at this juncture.

Key Action 7 Provide an enabling infrastructure: Targeted support actions need to include assessment of the economic impact of vaccines with different performance characteristics, facilitation of international regulatory harmonization for TB vaccines and strengthening of regulatory capacity in high burden countries, identification of standard reagents and protocols to produce comparable preclinical and clinical data, identification of facilities for timely vaccine production, and preparation for accelerated access to licensed vaccines for high-burden countries.

6. Challenges

Scientific and operational challenges: The major factor that could preclude achievement of the 2015 target relates to the scientific uncertainty about protective immunity to TB and our current lack of experience with new TB vaccines in human populations. Vaccine induced immune parameters, such as antibody threshold levels which are sometimes used as a surrogate read-out of vaccine-induced protection (surrogate or correlate of protection) against other diseases are not defined for vaccine-mediated protection against TB. Moreover, our knowledge of the relevance of protection experiments in animals - which are used to select antigens for clinical evaluation - for humans is very limited in pre-exposure situations and completely absent for animal models of latent TB. In spite of recent advances in our understanding of host responses to *Mtb* infection and TB disease, we may nevertheless be unable to identify vaccine candidates that provide consistent protection against TB. The dual strategy of maintaining support for relevant activities in vaccine discovery research while maximizing the number of candidates introduced into clinical trials, provides the optimal means of increasing our chances for developing an effective vaccine. At a more operational level, diagnosis in infants and children, main targets for new vaccines and therefore indispensable in clinical testing, is demanding. Definitive diagnosis may be possible in no more than 50% of suspect cases. This will have a major influence on where an efficacy trial in that population can be organized, how many individuals will have to be enrolled and eventually, how expensive the performance of the trial will be.

Financial uncertainties: Vaccine development is expensive. Despite impressive commitments by the public sector and philanthropy, a funding gap remains of at least 60% of the total R& D fund required to achieve the objectives of the TB vaccine development plan in time. The three areas, in which the Global Plan to Stop TB has identified the most pressing resource mobilization needs is the in the areas of (a) maintenance of the vaccine discovery pipeline, (b) performance of clinical trials, in particular phase IIb and III trials and (c) the creation of an enabling infrastructure. The reasons are different for each category. Maintenance of a broad basic research infrastructure is per se very expensive. Advanced clinical trials are usually financed by the pharmaceutical industry. However, as with the development of many new vaccines and drugs against diseases of poverty, commercial investment is negligible due to the estimated small size of the market for these innovative, but expensive-to-develop products. Finally and paradoxically, the elements of an enabling

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infrastructure are usually inexpensive and therefore, donors often shy back from the administrative burden of funding these modestly sized but generally high impact activities.