

### **10.3.3 Working Group on New TB Vaccines: summary strategic plan, 2006–2015**

The Working Group on Vaccine Development was established in 2000. Its aim is to foster and coordinate collaborative efforts to develop novel vaccination approaches that are effective in reducing TB disease.

#### **Strategic vision**

Development of new vaccines to protect against tuberculosis is gaining substantial momentum. Encouraging and consistent scientific results from the laboratory and from early field trials indicate that introduction of new effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis by 2050. New TB vaccines to prevent childhood and adult forms of tuberculosis, to reduce tuberculosis in persons coinfecting with HIV, and to shorten drug treatment regimens will fundamentally alter our approach to TB control.

It is probable that the next generation of vaccines will work by complementing the immune response induced by the current BCG vaccine. New vaccines could be delivered together with BCG at an early age before exposure to *M. tuberculosis* has occurred, as a separate booster to young adults, or as an adjunct to chemotherapy. The Working Group is promoting research and development on several approaches to the development of new candidate vaccines and new delivery strategies. The timetable for vaccine development is driven by the availability of suitable candidates and the need for extensive clinical trials to establish their safety and confirm their efficacy in human populations. It is anticipated that a new vaccine will be available by 2015.

It is difficult to predict the exact contributions to TB control that such a new vaccine will have. However, the impact of new vaccines can be simulated by introducing vaccine-related parameters into existing epidemiological models of the TB pandemic. One such simulation suggests that introducing a new vaccine between 2014 and 2018 that can be given to everybody could reduce TB incidence in Africa and South-East Asia by over 20% during the first 10 years of use and up to 40% by 2050.<sup>45</sup>

The strategic vision of the Working Group is that improved vaccines and vaccination strategies will make a crucial contribution to achieving the Stop TB Partnership's target for 2050 of reducing the global incidence of TB disease to less than 1 case per million population.

#### **Achievements to date**

In 2000, the Working Group took note of the historic opportunities for development of new TB vaccines that resulted from the availability of techniques for the genetic manipulation of mycobacteria, and completion of the genome sequence of *M. tuberculosis*. These advances facilitated production of new vaccine candidates in the form of live recombinant mycobacteria or mycobacterial genes, expressed in a variety of immunogenic forms. In parallel, advances were being made in our understanding of the cellular and molecular mechanisms underlying protective immunity, in humans as well as in experimental laboratory

animals. In the first Global Plan, the Working Group objective was to have five promising vaccine candidates in phase I trials in 2005. With four candidates in phase I trials in 2005 and three more lined up to follow by early 2006, this objective can be considered as largely achieved.

Important factors included major strategic investments by the European Community and the US National Institutes of Health. These donors established consortia of vaccine researchers and centralized facilities for preclinical evaluation, which have allowed comparative testing and selection of optimal candidates for progression to clinical trials. In addition, progress towards clinical trials has been promoted by major awards from the Bill and Melinda Gates Foundation to support the Aeras Global TB Vaccine Foundation and its predecessor, the Sequella Global TB Foundation.

#### **Objectives**

The overall objective of the Working Group for 2006–15 is to have **a safe, effective, licensed vaccine available at reasonable cost by 2015.**

##### ***Objective 1: Maintain and improve BCG vaccination programmes***

It is anticipated that BCG will remain the cornerstone of TB vaccination programmes over the period covered by the Global Plan, with the next generation of new vaccines introduced as an addition to BCG vaccine, which is commonly given at birth in many countries. Important issues include sustaining BCG production by a diminishing number of international suppliers, analysis of possible variations in vaccine efficacy as a result of genetic changes in BCG substrains, and establishment of a rational system for deciding when and how different substrains should be used.

##### ***Objective 2: Discovery and translation research ("keeping the pipeline filled")***

There is a need to expand discovery and translational research on vaccines. Progress with current clinical candidates does not signal an end of discovery research, but rather provides opportunities to link fundamental research to human studies. It is likely that experience gained as current candidates move through clinical trials will contribute to development of new candidates in an iterative process of refinement. In parallel, there is a well recognized need for further research in immunology to support development of evaluation criteria for vaccines in phase II/IIb trials and for the identification of correlates of immunity in phase III trials. The Working Group anticipates that scientists from high-burden countries will make a growing contribution in this area, particularly in the areas of epidemiology and human immune assay development.

##### ***Objective 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.

**Objective 4: Build capacity at vaccine trial sites**

Carrying out vaccine trials requires local expertise as well as baseline data for the populations that will participate. 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 diagnostic procedures, and infrastructure for vaccine delivery. These activities provide important opportunities for training and capacity strengthening, and require interaction with other working groups in the Stop TB Partnership.

**Objective 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 multicentre, 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 to resource-poor countries. It is likely that demands will exceed the capacity of existing vaccine production facilities and investment will be needed in one or more dedicated GMP-quality production facilities. This activity will require the establishment of innovative partnerships with manufacturers in developing and developed countries.

**Objective 6: Perform clinical trials**

Evaluation of vaccine candidates requires a series of clinical trials of increasing size, complexity and cost, to progressively evaluate safety, immunogenicity and, finally, efficacy. Ensuring investments by collaborators in developed and developing nations is a major challenge for the Partnership at this juncture.

- Phase I trials include initial assessment of safety, typically in groups of about 30 healthy adults.
- Phase II trials require expanded safety studies with larger groups, testing different vaccine doses and delivery protocols, and including specific target populations (people previously exposed to *M. tuberculosis*, those coinfecting with HIV, adolescents, children and infants, etc.). Measurement of immunogenicity in phase II trials provides key data for deciding on future development.
- Phase IIB trials necessitate a further expansion from phase II, to test whether the candidate meets performance criteria set for entry into full-scale phase III efficacy trials.
- Phase III trials, which are substantially larger and require extensive resources, test the efficacy of the vaccine. Decision criteria for moving into phase III trials include: the availability of a suitable clinical site to access target populations; a facility for “scaled-up” manufacturing of reproducible vaccine lots; a clinical development plan that ensures that successful trials will produce data that can be used in licensing applications; potential to develop correlates of immunity (or surrogates) from the trial; a country willing to license the vaccine; a regulatory process to license the vaccine; and discussion with local TB care programmes to facilitate integration with TB drugs and diagnostics for trials. In order to ensure the availability of sufficient numbers of trial participants and geographically representative trial

results, multiple phase III trials sites in different parts of the world will be needed.

- Phase IV trials are post-licensing studies, using in-country infrastructure to monitor safety and determine the effectiveness of the vaccine through epidemiological studies.

**Objective 7: Provide an enabling infrastructure**

The Working Group will act as a focal point for discussion of vaccine development issues, serving as an honest and impartial broker among different stakeholder communities, and facilitating the development of consensus protocols and criteria for vaccine assessment. Specific initiatives include preparation of a scientific blueprint, assessment of the economic impact of vaccines with different performance characteristics, facilitation of international regulatory harmonization for TB vaccines, 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. The Working Group also serves as a centralized mechanism for integrating these activities with the development of vaccines for other diseases

**Targets and indicators**

In the overall workplan for 2006–2015, the first target is that at least 20 vaccine candidates will have entered phase I clinical trials by 2015. It is anticipated that multiple candidates will progress through clinical trials in parallel and that unsuccessful candidates will be continually replaced by new entrants.

It is anticipated that phase II trials of the first candidates will be well under way in 2006. Initial phase II trials will take approximately 3 years, with an expected reduction to 2 years following development and refinement of trial protocols and immunological assays. The second target is that nine candidates will be evaluated in phase II trials. Furthermore, by 2008 there will be at least two vaccines in phase IIb or “proof of concept” trials, which will provide some early indication of efficacy and therefore significantly reduce the risk of failure in phase III.

The first phase III trials could begin as early as 2010. They will test the ability of vaccine candidates to act as pre-exposure vaccines and will take 4 years to complete. Post-infection trial protocols will be available from 2011 and are expected to take 3 years to complete. The third target for the Global Plan is to carry out a total of four phase III efficacy trials.

Approximately two years will be required to complete licensing procedures and to begin to distribute a successful vaccine. The final target is to have a safe, effective, licensed vaccine available at reasonable cost by 2015.

*See Figure 36: Timelines for TB vaccine development 2006–2015*

**Monitoring and evaluation**

Progress towards the overall goal of producing an effective vaccine by 2015 will be reviewed against the targets and timelines set out above at annual meetings of the Working Group. Dedicated secretariat staff will monitor progress on a continuous basis and highlight bottlenecks and problems at the annual meeting of the full Working Group, or to appropriate individuals or subgroups. The development of international monitoring standards and increased global monitoring ability are needed to ensure that promising agents are not impeded in their progress towards registration and use.

**Risks and challenges**

**Scientific challenges.**

The major factor that could prevent 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. In spite of recent advances in our understanding of host responses to M. tuberculosis 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 of developing an effective vaccine.

Additionally, we may identify a promising preclinical candidate that confers enhanced immune response but displays unacceptable adverse events, for example, exacerbating other underlying disease symptoms. We may be able to develop a vaccine that is effective in immunocompetent individuals, but that fails at a population level in areas with high rates of HIV coinfection. It is conceivable that a successful vaccine could promote selection of strains of M. tuberculosis with altered pathogenicity that allows them to escape from vaccine control.

**Financial uncertainties.**

Vaccine development is expensive. Despite impressive commitments by the public sector and philanthropic organizations, a funding gap remains of at least 60% of the total required to achieve the objectives of the TB vaccine development plan on time.

The problem largely lies in insufficient commercial investment in TB vaccine development. As with the development of many new vaccines and drugs against diseases of poverty, this is related to the small size of the market for these innovative, but expensive, products. Diverse mechanisms have been put in place or are being considered to overcome this, including direct research funding and provision of disease burden information.

However, experts agree that such “push” initiatives, valuable as they are, are not enough and that “pull” efforts are needed to create a market in developing countries, in order to achieve the same level of involvement of the pharmaceutical industry that is typically observed for diseases prevalent in affluent countries. Mechanisms that ensure market take-up of new products are also essential and advanced purchasing agreements may be advantageous in this regard. Such advance market commitments are unlikely to materialize for TB vaccines alone, but rather as part of a comprehensive package to provide new tools against a whole range of major communicable diseases, including HIV and malaria.

A prime objective for the TB community must therefore be to advocate to ensure that development of tools against TB is part of any initiative to create an enlarged market for innovative new pharmaceuticals for developing countries.

**Budget requirements for the Working Group on New TB Vaccines: 2006–2015**

*See Table 27: Working Group budget, 2006–2015 (US\$millions)*

The total funding necessary is US\$3,641 million; the funding available is US\$2,065 million, leaving a total funding gap of US\$1,576 million.

**FIGURE 36: TIMELINES FOR TB VACCINE DEVELOPMENT 2006–2015**

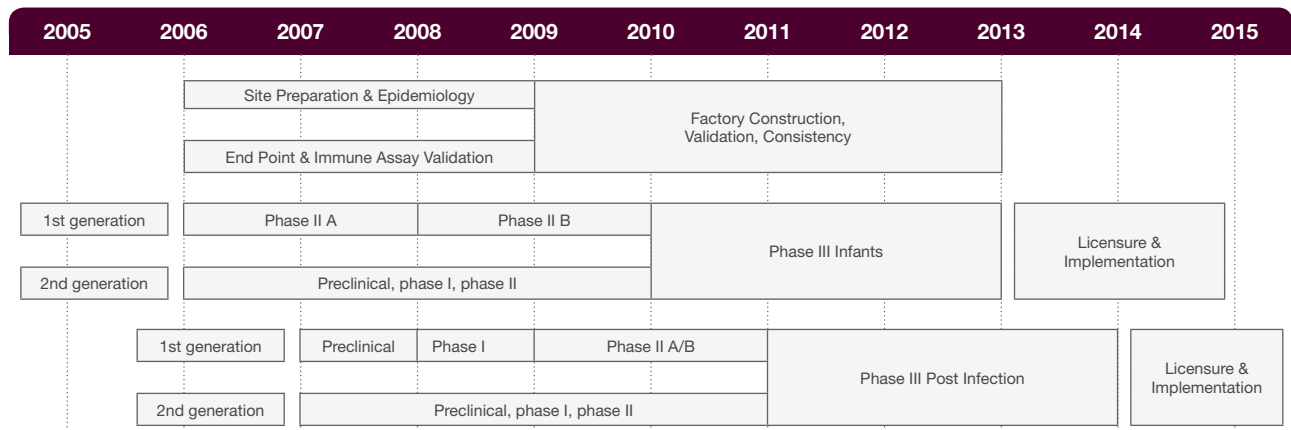


TABLE 27: BUDGET REQUIREMENTS FOR THE WORKING GROUP ON NEW TB VACCINES, 2006-2015 (US\$ MILLIONS)

	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	All years	% total
<b>PROGRAMME NEEDS (a)</b>	130	134	138	142	146	151	155	160	165	170	1,490	41%
Objective 1: Maintain and improve BCG programmes Estimated cost of US\$0.10 per dose with an annual production of 400 million doses per year, plus US\$0.90 per dose distribution costs for an annual cohort of 100 million children.	130	134	138	142	146	151	155	160	165	170	1,490	41%
<b>RESEARCH NEEDS (a)</b>	155	163	168	184	230	237	244	252	221	228	2,082	57%
Objective 2: Discovery and translation research («keeping the pipeline filled») <sup>19</sup>	120	124	127	131	135	139	143	148	152	157	1,376	38%
Objective 3: Facilitate preclinical development Preclinical development (including toxicology, safety, regulatory, IP) estimated at US\$725 000 per candidate (20 candidates)	5	5	5								15	0.4%
Objective 4: Build capacity at vaccine trial sites Estimated as 10% of total trial costs for phase I and II trials	3	4	4	4	0	0	0	0	0	0	16	0.4%
Objective 5: Ensure availability of vaccine production capacity/ scale-up Phase I lots (US\$5 million); phase II/III lots (US\$76.5 million); manufacturing facility (US\$100 million).	12	15	16	33	34	35	36	37	0	0	217	6%
Objective 6: Perform clinical trials and prepare access to new vaccines Phase I: 20 candidates/6 permutations/30 subjects – US\$45 million. Phase II: 9 candidates/6 permutations/300 subjects – US\$100 million. Phase II: 4 trials/40 000 subjects – US\$240 million.	15	15	15	16	61	63	65	67	69	71	457	13%
<b>WORKING GROUP OPERATIONS (a)</b>	6	6	6	7	7	7	7	7	8	8	69	2%
Objective 7: Providing an enabling infrastructure Critical items include staff and communications (US\$225 000 per year); economic analysis and blueprint (US\$850 000 per year); meetings (US\$100 000 per year), consultancy (US\$45 000 per year), scientific outreach activities (US\$50 000 per year).	6	6	6	7	7	7	7	7	8	8	69	2%
<b>TOTAL</b>	291	303	312	333	383	395	407	419	393	405	3,641	

(a) Unit costs in column 1 are in 2006 prices. Total budgets after 2006 do not exactly correspond to these unit prices since they have been adjusted for inflation.