



Position paper

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Summary

Worldwide an estimated 2 billion people, one third of the world's population, are infected with the bacterium that causes tuberculosis (TB), and are at risk of developing disease. Almost 14 million people have TB, which takes a toll of around 2 million lives each year. The global burden of TB, affecting economies all over the world, is estimated at hundreds of billions of dollars every year.

Current control measures are hampered by a lack of funding, the increasing appearance of drug resistant bacteria, and increased incidence in HIV co-infected individuals. Modeling studies prove that without new vaccines, drugs and diagnostics TB can never be eliminated. With respect to vaccines, we need new vaccines that boost the current BCG vaccine as well as new priming vaccines to replace BCG. These new vaccines should also prevent TB in latently infected people and be safe in people infected with HIV.

TuBerculosis Vaccine Initiative (TBVI) is an independent nonprofit organization that stimulates and coordinates the development of new, globally accessible and affordable vaccines. TBVI acts by supporting an integrated European network of over forty of the best universities, institutes and industries to develop more effective, safe vaccines against tuberculosis.

TBVI's unique network and outstanding track record shows that new effective, safe vaccines can be developed. To improve the current vaccine or develop new TB vaccines, we seek an additional support of 200 million euros in the coming ten years.

The global burden of tuberculosis

Tuberculosis (TB), caused by a bacterium called *Mycobacterium tuberculosis*, is contagious and spreads through the air. Around two billion people, or one third of the world's population, are estimated to be infected with the bacterium (Dye et al, 1999). About five per cent gets sick with tuberculosis in the first two years after infection. The other 95 per cent develops a latent or 'sleeping' infection, which is not contagious, but can still develop into TB later in life. The overall lifetime risk for developing TB following infection is estimated to be approximately ten per cent (Comstock, 1982).

According to the latest data of the World Health Organization (WHO), there were 9.27 million new cases of TB in 2007, bringing the total number to 13.7 million people with TB worldwide (WHO report, 2009). That same year, 1.77 million people died from this infectious disease, equaling about 4800 deaths a day, or one death every 18 seconds.

TB is a special threat to people with HIV, because of their weakened immune system. They are twenty to forty times more likely to suffer from TB once they are infected with the bacteria than people without HIV. The HIV/AIDS epidemic has fuelled a dramatic resurgence of TB. Of the 9.27 million new cases of TB in 2007, an estimated 1.37 million people (15%) were HIV-positive. The 1.77 million TB-deaths included 456 000 people with HIV, making TB a leading killer of HIV-infected people (WHO report, 2009).

Multidrug-resistant TB (MDR-TB), resistant to front-line drugs, and extensively drug-resistant TB (XDR-TB), resistant to front-line and second-line drugs, are a growing and worrying problem. These forms of TB are expensive and extremely difficult or virtually impossible to treat.

There were 0.5 million new cases of MDR-TB in 2007, but less than 1 per cent of them were receiving treatment based on WHO's recommended standards. 27 countries account for 85% of all MDR-TB cases. The top three countries with the largest number of cases are India, China and the former Soviet Union. Some 50,000 new cases of XDR-TB occurred in 2007; these were reported in an increasing number of both developing and developed countries (WHO report, 2009).

The increased mobility of the world's population, with more people traveling across borders, intensifies the spread of the airborne infectious disease. If not treated, each person with active TB infects on average 10 to 15 people every year. The disease mostly affects young adults in their most productive years. People in the prime of their lives who - because of the long, burdensome, complicated and possibly even fatal course of the disease - often are no longer able to (financially) support themselves and their families or help build up the economy of their country.

In a 2007 World Bank paper (Laxminarayan et al, 2007) the global burden of TB is estimated at hundreds of billions of dollars every year. The economic loss because of the almost 2 million deaths a year is 0.52% of the world's gross national income. Thus, TB undermines the capacity of countries to escape poverty and is an enormous drain on the worldwide economy.

Although poverty-related and mostly affecting developing countries (Africa and Asia), the developed world is not free from the disease: TB is prevalent in all continents. The situation is turning serious in Europe, is alarming in Africa and extremely worrisome in Russia, China and India.

The global fight against tuberculosis

Targets for global TB control have been set in the Millennium Development Goals (MDG), the international goals that 192 United Nations member states and the world's leading development institutions have agreed to achieve by the year 2015. MDG 6 Target 6C is to halt and reverse incidence of TB by 2015.

The Stop TB Partnership has translated the MDG 6C into two specific goals: to halve TB prevalence and to halve TB mortality by 2015 compared with their levels in 1990. As a longer term goal, Stop TB targets to eliminate TB as a global public health problem by 2050 (a global incidence of less than 1 per million population). The Stop TB Partnership is a global network of international organizations, countries, donors from the public and private sectors, governmental and nongovernmental organizations and individuals launched by the World Health Organization (WHO).

The WHO-recommended strategy to control TB is primarily based on efforts to reduce transmission by prompt diagnosis and treatment of infectious cases using the DOTS strategy (Direct Observed Treatment, Short-course). This treatment generally involves daily treatment with various medicines for a minimum of 6 months under observation of a health care worker. The worldwide costs of TB control are estimated to be \$4.2 billion for 2009, with \$3 billion available (mostly government funding) (WHO report, 2009), leaving a funding gap of more than \$1 billion.

Epidemiological modeling indicates that - if the increased budget funding outlined in the Global Plan to Stop TB is made available - the targets of 50% reduction in prevalence and mortality by 2015 will be achieved at global level. However, these goals will not be met in Africa or Eastern Europe, regions especially challenged by the global difficulties in case detection, increased incidence of TB in association with HIV co-infection and the spread of MDR- and XDR-TB strains.

Even if the 2015 goals of halving prevalence and mortality would be achieved, then still about one million people a year would die of TB. The more ambitious goal of eliminating TB as a global public health problem by 2050 can only be achieved with the development of new and more effective drugs, diagnostics and vaccines.

New vaccines needed

Next to improved diagnostics and drugs, new vaccines are crucial to achieve effective and sustainable control of TB. Mathematical modeling shows the

impact of vaccination on the reduction of TB incidence and mortality will be significant (Abu-Raddad et al., 2009 ; Young & Dye, 2006). More effective, safe vaccines would save tens of millions of lives. Vaccination will also be particularly important in combating MDR- and XDR-TB.

Bacille Calmette-Guérin (BCG), the only available vaccine against TB, is widely used and is effective in preventing severe forms of TB in children. The vaccine is administered to over 100 million babies every year. However, its efficacy against pulmonary TB in (young) adults – the most common form of TB worldwide – is poor or variable at best.

Studies prove that the effectiveness of the BCG-vaccine varies from giving no protection at all to reducing the incidence of pulmonary TB by around 80 per cent (Rodrigues & Smith, 1990 ; WHO discussion document, 1999). Moreover, recent data show that the risk of BCG vaccination resulting in disseminated BCG disease in HIV-infected infants is considerably higher than previously estimated (Hesseling et al., 2009). The Global Advisory Committee on Vaccine Safety (GACVS) therefore advised the WHO to change its recommendation such that children who are known to be HIV-infected should no longer be immunized with the BCG vaccine.

For effective and sustainable control of TB and the costs related to it, finding more effective, safe vaccines is of extreme importance. Over the past years, significant coordinated research and development has been carried out in Europe to find better solutions for preventing TB. Two so-called Framework Program (FP) projects funded by the European Union (EU) – namely Tuberculosis Vaccine Cluster (2000-2003) and TBVAC (2004-2009) - have been particularly successful in the search for TB vaccines. Both programs brought together many partners in Europe and Africa with complementary expertise, creating a unique, ambitious and expanding network of universities, research institutes and private industries.

TBVAC has resulted in four new vaccine candidates in preclinical and non clinical stages, four new vaccine candidates in clinical phase I to II (testing safety and immunogenicity), fifteen candidate biomarkers (used to monitor the effectiveness of new vaccines) with potential to be used in monitoring of clinical trials and three adjuvant molecules (used to enhance the immunogenicity and therefore the efficacy of vaccines), one of which in clinical phase I studies. The most advanced vaccine candidate is currently being tested for efficacy in a Phase IIb study. If successfully tested in further clinical stages this vaccine could hopefully be licensed by 2017.

TBVI: a unique network and approach

Although extremely valuable and essential, investments done by EU institutions and research partners alone are not enough to continue research and develop the urgently needed TB vaccines. Therefore, on suggestion of the European Commission, TuBerculosis Vaccine Initiative (TBVI) was founded to collect additional funds from governments, non-governmental organizations, foundations, private industry and other private funders. So that

we can sustain and accelerate current vaccine and vaccine related developments of TBVAC (and its future successors, such as the already approved NEWTBVAC (2010-2014)) and maintain the integrated creativity, excellence and synergy of over 40 leading institutions and industries in the area of TB vaccine discovery. Their intense cooperation created a solid base for ongoing, even closer and more constructive collaboration. By supporting the best and most renowned researchers and research institutes, TBVI increases the chances and likelihood of finding the best results and solutions to TB.

Furthermore, TBVI aims to raise awareness among policy makers, opinion leaders and other decision makers as well as the general public and international media about the global health threat TB poses in general and the need for (more research into) new vaccines in particular. A \$3 million grant of the Bill & Melinda Gates Foundation enables us to conduct our advocacy and fundraising activities for the next three years (2009-2012).

Many people remain unaware of the resurgence of TB as a global public health threat. Most still believe TB is a disease of the past and that sufficient ways of prevention and treatment exist. TBVI aims to improve general knowledge of the TB-situation in the world by reaching out to politicians, decision makers and international, opinion-leading media. Doing so, we will emphasize the need for new vaccines, as we are convinced that without new vaccines the global fight against TB can never be won.

Where appropriate, TBVI will seek cooperation with other organizations to put TB back on the world's agenda through e.g. conferences, other events, media exposure and advocacy.

TBVI

Vision statement:

TBVI wants to develop new vaccines to protect future generations against Tuberculosis

Mission statement:

TBVI stimulates integrated European efforts to develop more effective, safe vaccines against tuberculosis, that will be globally accessible and affordable.

The objectives of TBVI are:

1. Stimulate research and discovery on TB vaccines
2. Assure preclinical and early phase clinical development
3. Guarantee that promising projects result in affordable vaccines as soon as possible
4. Develop biomarkers that will increase performance and speed of vaccine development
5. Increase capacity of existing clinical trial sites in developing countries
6. Raise political and public awareness on the global health threat of TB and the need for new vaccines

Our strategy

The search for a new TB vaccine currently mostly centers around finding preventive vaccines to improve, boost or replace the current BCG vaccine. TBVI encourages this, but we also believe a wider range of vaccines is necessary to make TB a disease of the past. Next to initial protection, vaccines should also protect those with latent TB from developing the disease.

TBVI's vaccine strategy is based on two pillars:

- 1) developing priming vaccines that could be given to newborns, which are also protective in latently infected persons and safe in persons with HIV.
- 2) developing boosting vaccines to be used in infants, adolescents or young adults, protecting both non-infected as well as latently infected persons from developing TB.

By facilitating an integrated group of the best TB research institutes and industries, and having demonstrated an ability to translate research and discovery into clinical product development, TBVI is in a unique position to focus on developing these new types of vaccines.

TBVI also supports the development of biomarkers to increase performance and speed of vaccine development. Biomarkers can provide early insight into the likely effect of a vaccine in different populations and as such can be used as a selection tool before starting long and costly clinical trials. Biomarkers can be useful tools to monitor vaccine trials.

Currently there is a lack of sufficient trial capacity for evaluating TB vaccines. TBVI wants to contribute to improvement of this situation by selecting one to three sites with existing TB research capacity and providing support to make these sites suitable for carrying out Phase I trials (testing safety). This will include support for the establishment of state of the art technologies and tools to enable evaluation of the human immune response in a well defined clinical setting.

TBVI aims to create an overall portfolio structured around four programs: two vaccine programs, one program for biomarkers and one program for infrastructure support activities. The vaccine programs aim primarily to support discovery, preclinical and early clinical development (Phase I). TBVI would link with other partners to move promising candidates into costly Phase II/Phase III efficacy trials.

How we work

The vaccine programs are divided into one program for candidate vaccines to boost the current BCG vaccine (or future vaccines replacing BCG) and one program for live attenuated vaccines (containing weakened forms of the

organism that causes the disease) that could replace BCG. Both kinds of vaccines should prevent TB in healthy individuals as well as prevent latently infected persons from developing the disease..

The vaccine and biomarker programs will each be dissected into various stages of research and development. The Steering Committee (SC) of TBVI, which consists of top TB researchers from all over Europe, decides on the funding of projects and makes a go/no go decision before a vaccine/biomarker candidate moves to the next stage. In case of potential conflicts of interest, e.g. when discussing a project involving (institutes of) one or more steering committee members, the relevant persons are obliged to leave the discussion.

At the late discovery stage, product development teams (PDT) and clinical development teams (CDT) will be involved with each vaccine development. PDT and CDT are teams of international experts in vaccine research and development. They help bridge the gap from discovery to development. The product development teams support researchers in getting their product from discovery to the preclinical phase. From there, the clinical development teams take over to bring the vaccine candidate further towards clinical evaluation.

PDTs and CDTs hold regular meetings with the researchers to review progress, to advise and bring in expertise that is lacking. The teams submit their findings in a report to the TBVI Steering Committee. On basis of this information, the Steering Committee decides on funding for the subsequent stages of development. Criteria for moving candidates to preclinical and clinical stages will be developed by the PDTs and CDTs. Product development teams play the same role in the late discovery stage of biomarkers.

As part of our unique approach, the responsibility and ownership of vaccines and biomarker candidates always remain with the individual partners. TBVI does not claim any rights, but rather serves as an honest broker to turn scientific potential into industrial reality and facilitate the development of more effective, safe vaccines against TB.

Included in each agreement for support from TBVI is a commitment from its partners to aim for vaccines that are accessible and affordable to the developing world. We want those people around the world who need the vaccines most to have them as soon as possible, without (financial) barriers.

What we need

For the several programs we want to support, TBVI aims to raise €200 million over the next 10 years (2009-2018). Or an average €20 million a year. To calculate this budget, we used the standard costs for development of vaccines and biomarkers, mostly based on previous experiences within TBVAC.

The following table shows the goals and costs:

Program	Starting point	Includes (approximate)	Expected output	Costs (in million €)
1. Boosting vaccines	January 1, 2009	18 vaccines	5 vaccines ready for Phase II between 2009-2020	71.4
2. Priming vaccines that could replace BCG	January 1, 2009	19 vaccines	3 vaccines ready for Phase II between 2009-2020	64.95
3. Biomarkers	January 1, 2009	30 biomarkers/correlates	3 assays between 2015-2020	34.2
4. Infrastructure supporting activities	January 1, 2009	1-3 existing clinical trial sites		30
TOTAL				200.55

TBVI wants to raise funds from governments, non-governmental organizations, foundations, private industry and other private funders.

We are partnering with Aeras Global TB Vaccine Foundation, private industry and EDCTP (European and Developing Countries Clinical Trials Partnership) to diminish barriers to entry of the market and increase the chances of scientific discoveries truly becoming industrial products: TB vaccines that will – while saving lives – generate a return on investment. TBVI offers industrial partners access to its impressive network of research institutes.

Why invest in TBVI?

Investing in TB vaccines is a real investment in the future with tangible results. Not only will it save lives, prevent health disasters, strengthen countries in their fight against TB and relieve poverty, but investment in TB vaccines can also contribute to building knowledge-based economies, creating jobs and sustainable growth. With that, TBVI and its goals also help contribute to international plans and policies, such as those of the Lisbon Agenda, the Millennium Development Goals (MDG) and the Stop TB partnership.

The Lisbon Agenda aims to establish a European Area of Research and Innovation, making the European Union the most competitive and dynamic knowledge-based economy in the world. TBVI contributes to this by supporting and stimulating research and development, and strengthening its unique consortium of research institutes. We work with the best researchers, research institutes and universities in Europe and beyond, who and which are

especially capable of giving research and innovation a tremendous boost. TBVI's outstanding track record has proven so.

In the coming years, TBVI will continue to support research and development in institutes all over Europe and the rest of the world. If we can generate sufficient resources, we might see the dawn of an era in which TB really is a disease of the past.

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