

Accelerating TB Vaccine Research & Development Through Partnership



TBVI

TuBerculosis Vaccine Initiative

Annual Report 2014



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1. Foreword

Tuberculosis is one of the world's deadliest communicable diseases. In 2013, an estimated 9 million people developed TB and 1.5 million died from the disease. To meet global targets of reducing TB infection, it is essential to improve or replace the existing BCG vaccine with new safe and more effective TB vaccines that protect all people from infection and prevent transmission of the disease. New vaccines will also be essential to address the growing problem of multidrug-resistant TB.

TBVI continues its long-standing and effective collaboration with top European laboratories and new partners in TB vaccine research and development (R&D). In 2014, the TBVI consortium initiated a new project, TBVAC2020, with a grant of 24.6 million Euros from the European Commission and a number of governments outside the EU. TBVAC2020 brings together 40 leading research institutions with cutting-edge expertise from Europe, the USA, Asia, Africa and Australia to continue to innovate and diversify the TB vaccine and biomarker pipeline through a range of new approaches. By applying portfolio management strategies, the project identifies the most promising vaccine candidates as early as possible and advances them through early clinical development.

This report highlights the TBVI consortium's R&D achievements in the TB vaccine and biomarker fields and the essential services provided by TBVI to its consortium members and other partners. These services include project identification, development and management, resource mobilisation, and technical advice and support for product and clinical development. TBVI promotes knowledge development, exchange and synergies among the consortium partners to accelerate the discovery and development of new vaccine candidates. The report looks forward giving an overview of TBVI's R&D priorities for the years 2015-2017. The report shows how TBVI works to advance global R&D efforts by contributing to greater innovation, collaboration and coordination among key TB vaccine stakeholders.

The achievements of 2014 are the result of the efforts of many key partners and stakeholders. TBVI would like to thank the consortium partners for sharing their concepts and ideas, data and results; the funders for their confidence in TBVI to make a difference in delivering products and services; and its Governance Board and Advisory Committee members for their expert guidance and advice. Together we will continue our work to discover and develop new, safe, effective, affordable and accessible TB vaccines for all.

Onno Ruding, Chair of the Governance Board
Nick Drager, Executive Director



2. TBVI and the road to safe and effective vaccines for all

TuBerculosis Vaccine Initiative (TBVI) is a non-profit foundation that facilitates the discovery and development of new, safe and effective TB vaccines that are accessible and affordable for all people. As a Product Development Partnership (PDP), TBVI integrates, translates and prioritises R&D efforts to discover and develop new TB vaccines and biomarkers for global use. TBVI provides a range of key services that support the R&D efforts of its consortium partners. TBVI does not have its own commercial interests. Ownership of vaccine candidates and biomarkers and any intellectual property rights remain with researchers and vaccine developers.

The TBVI consortium includes more than 50 partners from academia, research institutes and private industry in the TB vaccine field. Key stakeholders include the European Commission (EC), the World Health Organization (WHO), Aeras, the Bill & Melinda Gates Foundation (BMGF), the European and Developing Countries Clinical Trials Partnership (EDCTP), the European Investment Bank (EIB), the governments of Norway, United Kingdom and vaccine industry companies. The governments of Switzerland, South Korea and Australia provide co-funding through the TBVAC2020 project.

Mission

To support, integrate, translate and prioritise R&D efforts to discover and develop new tuberculosis vaccines that are accessible and affordable for all

TBVI Supports

TBVI mobilises resources and identifies, develops and manages projects for TB vaccine R&D with a particular focus on discovery, preclinical and early clinical activities. In addition, it supports projects for the discovery, optimisation and validation of biomarkers. TBVI works with governments, foundations and the private sector to increase public funding as well as private sector investment opportunities for R&D of new vaccines.

TBVI Integrates

TBVI brings together the efforts of leading universities, government institutes, biotech and vaccine companies through TB vaccine and biomarker discovery and development projects. TBVI creates an enabling environment through its knowledge-sharing platform, including meetings, symposia and workshops, and through joint collaborative research that stimulates knowledge exchange and creates synergies among R&D partners and other stakeholders in the field.



TBVI Translates

TBVI supports translation from ideas to tangible products through the advisory services of its Product & Clinical Development Team (P&CDT). This team of independent vaccine R&D experts supports TBVI's R&D partners in moving their candidates from discovery to early clinical development.

TBVI Prioritises

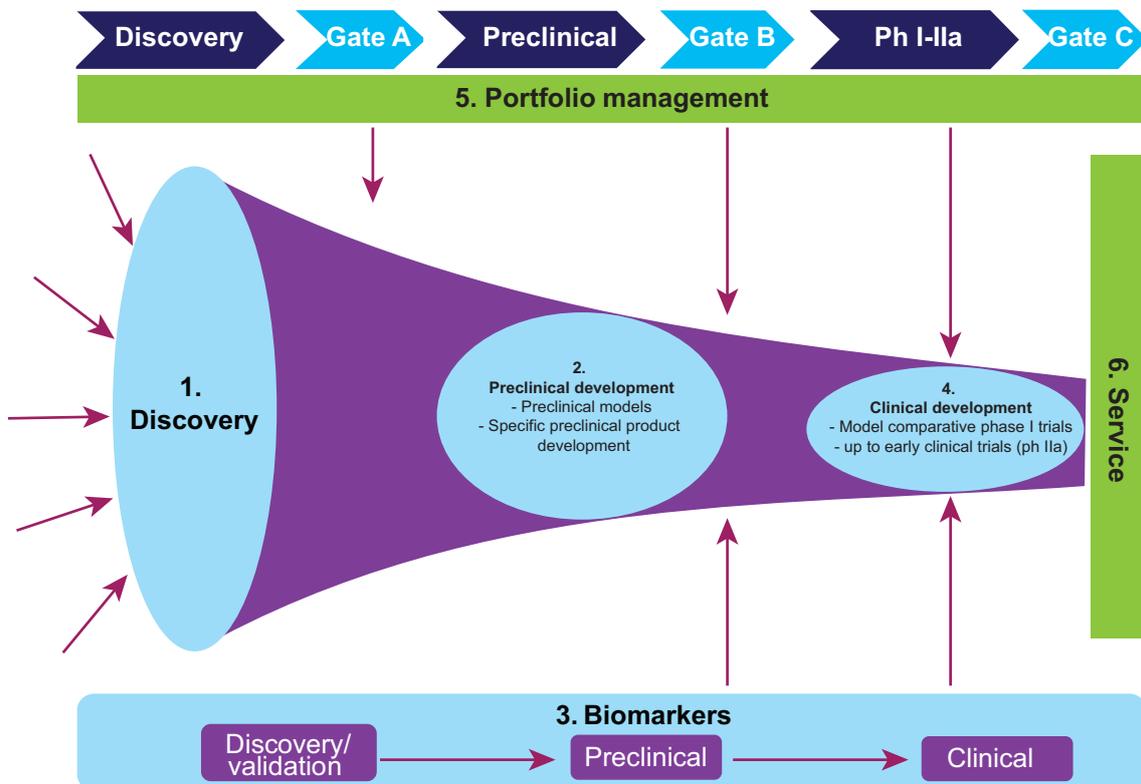
TBVI accelerates the most promising vaccine and biomarker candidates through the pipeline, applying portfolio management to support decision-making in an objective and transparent manner and to use the available financial resources effectively. It seeks to align its portfolio management approach with other global efforts, in particular with the portfolio management approach foreseen by the Global TB Vaccine Partnership (GTBVP).

3. TBVI's Research & Development strategy

In its strategy, TBVI considers the need to: discover and develop safe and effective vaccines for all; prevent infection and transmission of disease; build on the R&D comparative advantage of the TBVI consortium members; make the best use of limited resources and mobilise additional funding.

TBVI has prioritised the following R&D areas to meet its objectives (see Figure 1).

Figure 1: TBVI focus areas



1. Discovery

TBVI focuses on innovating, expanding and diversifying the TB vaccine pipeline. This is based on cutting-edge research addressing knowledge gaps in immune-mediated protection against TB infection and disease, and on new vaccine concepts targeting diverse immune mechanisms.

TBVI supports

- new antigen discovery, including protein and non-protein (e.g. glycolipid) targets
- novel formulations and delivery systems
- alternative routes and methods of vaccine administration
- development of safer and more effective live vaccines

2. Preclinical development

New priming and boosting vaccines

The BCG vaccine, available since 1921, can protect children from severe forms of tuberculosis. However, BCG has little to no efficacy in preventing pulmonary TB in adolescents and adults, the most common and most infectious form of tuberculosis. Therefore, efforts are being undertaken to improve or replace BCG with better vaccines. While appreciating that the greatest impact on transmission is by developing vaccines that target adolescents and adults, efforts to develop new and safer priming vaccines for infants will also be supported.

TBVI supports

- development of priming vaccines that perform better and/or are safer than BCG
- development of booster vaccines
- development of prime-boost strategies
- development of post-infection vaccine strategies for therapeutic use
- comparative testing of new vaccines in standardised (preclinical) models
- GMP manufacturing, and toxicity and safety studies

Preclinical models

The development of new vaccines is dependent upon robust preclinical animal models in order to select those vaccine candidates, which should progress to clinical development. These standardised animal models and their read-outs provide evidence of safety, immunogenicity and/or protective efficacy of new vaccine candidates. Preclinical data then support portfolio management and decision-making based on predefined gating and priority setting criteria.

To improve and extend beyond its current preclinical portfolio of models, TBVI supports the refinement of existing models and the development of others specifically fit-for-purpose in several species. Refined non-human primate experiments remain a valuable bridging tool between preclinical and clinical development. TBVI and its partners comply with the highest ethical standards for using animals in TB vaccine development, where no suitable alternatives are available.

TBVI supports

- standardisation, harmonisation and refinement of preclinical models
- comparative (head-to-head) testing and immunological evaluation
- post-exposure vaccination models
- exchange of (clinical and) preclinical data to support R&D into correlates of protection

3. Novel approaches to identify biomarkers

Better correlates of protection will help to identify relevant antigens, to develop improved vaccines and to allow the demonstration of their immunogenicity and potential efficacy at an early stage. Importantly, such correlates will facilitate the selection of candidate TB vaccines, and accelerate and reduce the cost of human efficacy trials. In addition, these correlates will permit optimisation of dose, vehicle, adjuvants, formulations and immunisation schedules for new candidate vaccines at an early stage, and thereby inform preclinical study design. Correlates of disease risk will be invaluable in the stratification of individuals in clinical studies, contributing to the optimisation of these studies.

TBVI supports

- biomarker discovery
- development and standardisation of biomarker assays
- translation and validation of biomarkers in TB vaccine trials

4. Clinical development

TBVI aims to support and accelerate promising candidates through early clinical development. TBVI aims to incorporate new developments in clinical trial design.

TBVI supports

- clinical experimental medicine studies
- development of a human challenge model for TB
- first-in-man (Phase I) clinical trials and Phase IIa trials
- the planning, guidance and evaluation of Phase IIb and Phase III trials

5. Portfolio management

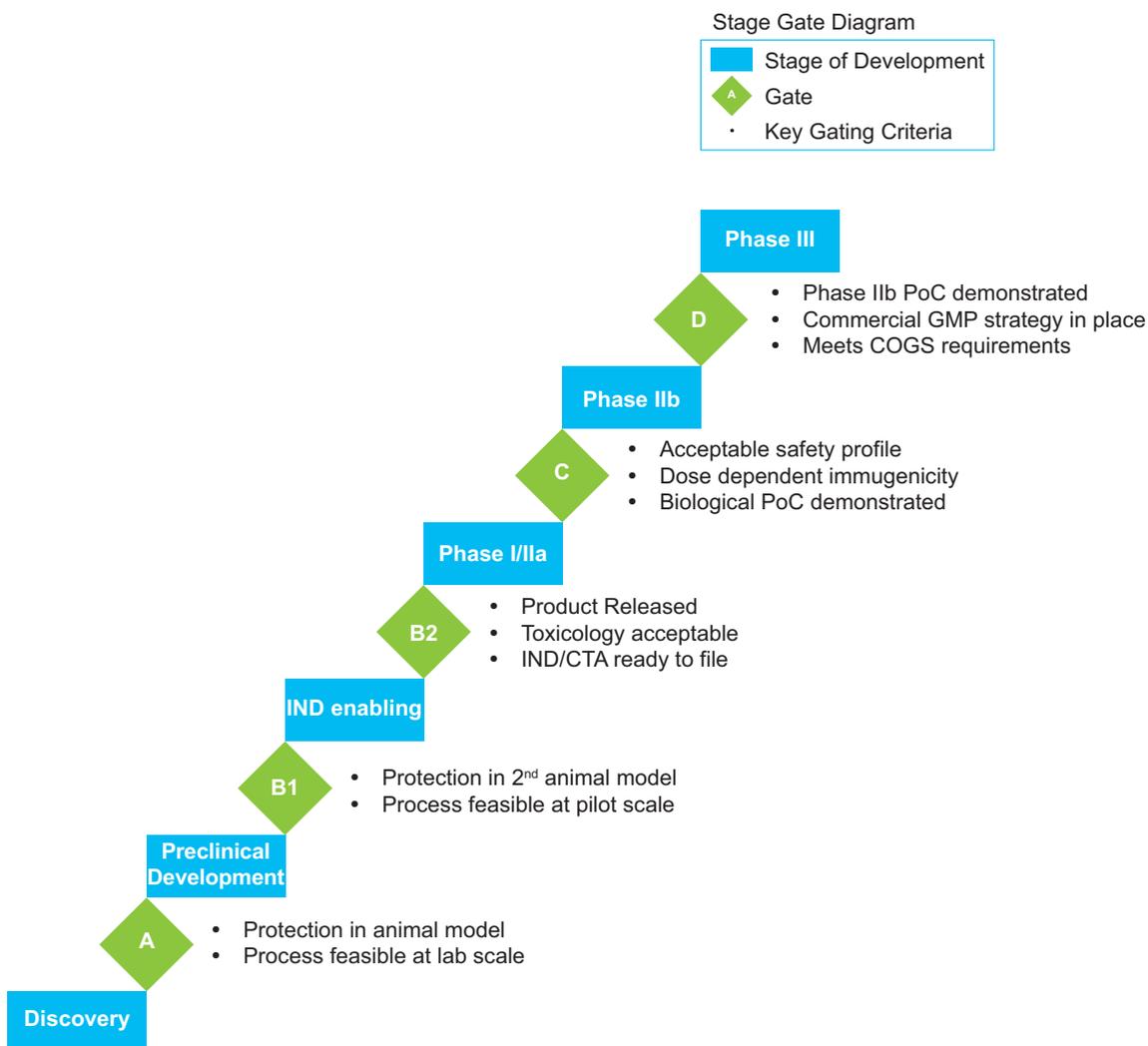
Portfolio management is considered to be an efficient and effective mechanism to advance a vaccine pipeline. It is a structured and evidence-based decision-making process that seeks to maximise the probability of success against acceptable cost and risk. It is built around agreed criteria for success at the various stages of vaccine development and an objective assessment of the data against those criteria. TBVI applies the portfolio management process at entry, stage gating and priority setting of candidates.

TBVI, together with Aeras, developed and applies this transparent quality decision-making process that allows for fact-based, data-driven and strategy-oriented management decisions. This process is built on four pillars to ensure strategic alignment of vaccine candidates and resources, and an optimal balance between them:

- filling the pipeline with new vaccine candidates and regimes, governed by a set of entry criteria: to encourage entry of new candidates into the inventory and to ensure diversity and complementarity
- stage gating: a framework to aid decision-making in advancing and investing further in candidates through the R&D pipeline (see Figure 2)

- priority setting: a matrix process to prioritise candidates competing for available resources
- resource mobilisation and fund management

Figure 2: Stage gate criteria (work in progress)



To illustrate the process of priority setting, Figure 3 gives a hypothetical example of the comparison of four similar vaccine candidates (P1-P4), in the same stage of development, across 13 key criteria. The process shown here provides a transparent framework for decision-making. Results are shown by green = criteria have been satisfactorily met, orange = partially met and can be met if appropriate measures are taken, red = criteria not met and very difficult to meet. In this example, P1 & P2 would be given the highest priority.

Figure 3: Priority setting (work in progress)

	Criteria	P1	P2	P3	P4
1. Innovation & diversity	1a. Scientific concept	Green	Orange	Green	Orange
	1b. Mechanism / delivery	Orange	Green	Green	Orange
	1c. Technology	Green	Orange	Red	Green
2. Feasibility	2a. Laboratory	Green	Green	Orange	Green
	2b. Industrial	Orange	Green	Green	Red
	2c. Development	Green	Orange	Green	Green
	2d. Regulatory pathway	Green	Orange	Orange	Orange
3. Relevance	3a. Strategy	Green	Green	Green	Green
	3b. Public health need	Green	Orange	Orange	Green
4. Business environment	4a. Intellectual property	Green	Orange	Green	Orange
	4b. Budget	Orange	Orange	Green	Orange
	4c. Partnership	Orange	Green	Green	Red
	4d. Market	Green	Green	Orange	Green

To implement its portfolio management, TBVI has established a Portfolio Management Committee (PMC) composed of independent experts from relevant vaccine R&D fields. The PMC provides advice to the Executive Director and the TBVI Governance Board on the following portfolio management items and decisions:

- prioritisation of TB vaccine candidates and other related TB vaccine R&D activities for support
- scope of calls for proposals
- monitoring of new TB vaccine developments
- refinement and updating the portfolio management process including the stage gating and prioritisation criteria

4. TBVI services

TBVI provides a range of key services to support the R&D efforts of its consortium members and other partners. These include:

- project identification, design and development
- project management
- resource mobilisation
- knowledge development, exchange, and networking
- technical support for product and clinical development

Project identification, design and development

TBVI initiates new projects when new funding opportunities arise. In line with its R&D strategy, TBVI sets the main parameters for the design of the project and actively reaches out to partners and links them to relevant key stakeholders to initiate new collaboration. It then works closely with partners to develop full project proposals.

Project management

TBVI manages and coordinates projects supporting partners with all administrative, financial and legal requirements for a grant or project.

Resource mobilisation

TBVI mobilises resources for the TBVI consortium, for its individual members and for other partner vaccine developers. Resource mobilisation activities are focused on traditional as well as innovative funding sources involving governments, foundations and private sector partners.

Knowledge development, exchange and networking

To optimise the discovery and development of new TB vaccines and biomarkers, TBVI facilitates and supports the generation of new knowledge and exchange among R&D partners. TBVI creates an enabling environment for consortium members to promote knowledge sharing through scientific meetings and workshops, publication in scientific and non-scientific journals, formal and informal networking.

Technical support for product and clinical development

To move a good scientific idea or novel concept into a useful product, TBVI provides technical support for product and clinical development. TBVI's Product & Clinical Development Team (P&CDT), comprised of independent, top vaccine R&D experts, is charged with furthering the development of the candidates prioritised by the TBVI portfolio management process. P&CDT advises and guides vaccine researchers and developers while they move their candidates from concept to clinical development. P&CDT supports the definition of a final target product profile (TPP) and the development of subsequent plans for product development, characterisation and clinical testing.

P&CDT experts provide the following services to support, advise and guide vaccine researchers and developers:

- identifying vaccine candidates and the needs to enter into focused preclinical development
- addressing production issues, cGMP requirements, product specifications
- advising on animal studies and specific preclinical development requirements to move the candidates forward
- assisting in the preparation of vaccine candidates for the subsequent phases of clinical trials
- assisting in meeting regulatory requirements
- planning and preparation of clinical studies
- providing expertise to evaluate clinical test sites
- establishing partnerships with clinical investigators
- guidance during Phase I, II or III clinical trials

Prof. Charles Mgone, Executive Director EDCTP

“In the past decade, TBVI has been a global key player in bringing forward innovative and promising candidates from discovery to clinical trials. This work, which TBVI conducts in collaboration with various partners from all over the world, paves the way for collaborative clinical trials in Africa under the auspices of the EDCTP programme.”

5. The impact of TBVI's strategy

Innovating and diversifying the pipeline

Operationalising TBVI's strategy in the coming four years is expected to result in support for 20 new discovery approaches, up to 6 candidates at preclinical stages and up to 6 candidates at early clinical stages. In addition, it will identify, optimise and evaluate 15 innovative approaches on biomarkers.

Reducing TB disease burden and the cost to the global community

The vast majority of TB cases occur in developing countries, especially in adolescents and adults between 15 and 45 years of age, the economically most active segment of the population. Modeling studies show that more effective TB vaccines will have a significant impact on the TB disease burden, including drug resistant TB. The development of a new vaccine by means of a preclinical and clinical portfolio management approach is estimated to cost approximately €600 million over the next ten years. This investment seems relatively small when compared to the estimated costs of TB disease in Europe or globally over this period, which are estimated to be €5.9 and €58 billion respectively.

Maintaining excellence

TBVI's strategy and activities contribute to maintaining and extending European and global partners' leadership and excellence in discovery and development of new TB vaccines and biomarkers.

Dr Olivier Neyrolles, CNRS Toulouse

"TBVI is key to TB research in Europe. Under TBVI's leadership, a number of novel antigens, viral carriers, adjuvants and live vaccine candidates have been discovered and are now being tested in clinical trials. The main driver for these outstanding results was the open, transparent and collaborative atmosphere in which TBVI leads its projects. Huge progress has been made thanks to TBVI support; in particular, an unprecedented strong pan-European network has been established, ready to generate even more promising results in the future."

6. TBVI consortium key achievements

Discovery

Over the past four years, 40 different novel vaccine strategies have been pursued and 22 have moved from research to discovery. These strategies have included genome-wide protein and glycolipid antigen discovery, development and testing of novel delivery systems, adjuvants and improved live vaccines.

Preclinical development

Over the past four years, TBVI projects have delivered 6 vaccine candidates moving from discovery to the preclinical phase, and 4 vaccine candidates going to Phase I clinical trials.

Preclinical models

The TBVI consortium has established a novel pre-clinical prime-boost model to evaluate innovative prime-boost strategies.

Biomarkers

A series of new TB biomarker signatures has been identified through candidate testing as well as through unbiased biomic approaches. Assays suitable for use in large-scale monitoring studies (e.g. in TB endemic areas) have been developed.

Clinical development

The Phase I trial of vaccine candidate MTBVAC, conducted at the University of Lausanne, was completed in 2014. The safety and immunogenicity results of this trial were satisfactory. MTBVAC is planned to move forward to a Phase Ib trial in South Africa in 2015.

Prof. Oswaldo Álvarez, Biofabri

"In such a complex area as the investigation and research of vaccines against tuberculosis, it is a vital necessity to be able to count on an organisation that provides resources and efforts, coordinates, plans and mobilises resources, all whilst applying scientific criteria in an objective way. Thanks to TBVI's advice and support, during the product development as well as in planning the preclinical and clinical trials, Biofabri has been able to adequately conduct the MTBVAC vaccine development project from the preclinical up to the current stage. Without continuous help from TBVI and its scientific and technical network, MTBVAC would not be at the point of starting the second clinical trial (Ph1b) in humans in an endemic country."



Resource mobilisation

The TBVI consortium was awarded a €24.6 million grant from the EC and from several institutions as well as national governments outside the EU, among others Switzerland, South Korea and Australia in 2014. TBVI also received a \$1,500,000 (approx. €1,200,000) grant from the UK government (DFID) through Aeras.

Knowledge sharing

TBVI held its 10th annual meeting in February 2014, where over 100 leading scientists shared data and results on ongoing TB vaccine and biomarker R&D projects. In May 2014, inaugurated by Queen Sophia of Spain, TBVI organised an international high level scientific symposium in Madrid. The consortium published 30 articles in peer reviewed journals.

7. TBVI consortium vaccine candidates

MTBVAC/MTBVAC+

MTBVAC, developed by the University of Zaragoza, Institut Pasteur and Biofabri, is a live attenuated Mtb strain currently in early clinical development. Its primary target population is newborns, with a view to its use as a replacement for BCG. The safety and immunogenicity results of the Phase I trial conducted at the University of Lausanne were satisfactory. In 2015, MTBVAC will move forward to Phase Ib testing within the South African Tuberculosis Vaccine Initiative (SATVI).

MTBVAC+ is an inactivated MTBVAC strain in the preclinical stage of development. This candidate expresses the whole antigen repertoire of live MTBVAC, including the antigens absent in BCG. Currently, non-human primate experiments are being performed to address its tolerability, immunogenicity and efficacy.

rBCG Δ ais1/zmp1

rBCG Δ ais1/zmp1 is a recombinant BCG developed by the University of Zürich. Its primary target is global boosting. On the basis of its attenuated profile, it also aims to safely replace BCG in the (HIV-exposed) newborn. Proof of concept studies on immunogenicity, safety and protective efficacy were successfully performed in mice, guinea pigs and cattle. Currently, protection experiments in non-human primates are being performed; results are pending. Upon success, a Phase I clinical trial is intended to be initiated soon, in 2015/2016.

HBHA

Recombinant heparin-binding haemagglutinin (HBHA), developed by Institut Pasteur Lille, is a surface antigen-based subunit vaccine. The primary target is particularly to function as a booster vaccine, also preventing reactivation of latent infection. Prime-boost protection studies in mice and guinea pigs have shown improved protection and good safety and immunogenicity when HBHA boosts previous BCG administration. Currently, formulations of HBHA in clinically tested adjuvants are assessed in preclinical studies, and in 2015, studies in non-human primates will be performed. The aim is to go into clinical development in 2016.

H64 + CAF01

H64 is a protein fusion vaccine developed by Statens Serum Institut. H64 consists of six highly expressed and immunogenic proteins and is administered in CAF01, an adjuvant that has recently demonstrated induction of CMI responses in humans. The primary target of the H64 vaccine is to boost BCG. In 2014, H64/CAF01 was evaluated in the TBVI centralised head-to-head NHP model, data of which will become available in 2015. Ongoing experiments are continuing to investigate which epitopes are immunodominant during Mtb infection and whether removal of the immunodominant epitopes will improve protection.



ChAdOx1.85A-MVA.85A

ChAdOx1 is a recombinant, replication deficient chimpanzee adenovirus. MVA is a replication deficient vaccinia virus. Both express antigen 85A. A prime-boost regimen including these viral vectors is being developed by the University of Oxford. In mice, vaccination with BCG followed by ChAdOx1.85A and MVA.85A significantly improved protection against Mtb infection. Currently, other candidate antigens are also being evaluated in mice and guinea pigs using these vectors. The ChAdOx1.85A-MVA.85A prime-boost combination is currently being evaluated in a Phase I clinical trial in Oxford.

8. Looking forward - priorities for 2015-2017

In 2015-2017, TBVI will continue to support consortium partners to innovate and diversify the vaccine and biomarker pipelines and to move promising candidates through preclinical and early clinical development. TBVI will strengthen its knowledge-sharing platform, expand its research and strategic partner network and diversify its funding sources. TBVI will continue to support global efforts to accelerate TB vaccine discovery and development through increasing innovation, collaboration and coordination.

Figure 4: Current TBVI vaccine pipeline, to be further developed and expanded

Discovery	Preclinical	Phase I	Phase IIa	Phase IIb
Approximately 20 novel TB vaccine strategies in development, several R&D partners, TBVI	HBHA Institut Pasteur Lille, Aeras, TBVI	ChAdOx1.85A-MVA.85A University of Oxford, TBVI	VPM1002* VPM, Germany	MVA85A / Aeras-485 University of Oxford, Aeras
	rBCGΔais1/zmp1 University of Zurich, Aeras, TBVI	MTBVAC Biofabri, University of Zaragoza, TBVI	H1 + 1C31 SSI, Valneva, EDCTP	M72 + ASO1E GSK, Aeras
	H64 + CAF01 SSI, TBVI	Aerosolised MVA85A* University of Oxford, Aeras, TBVI	H56 : IC31 SSI, Valneva, Aeras	
	ChAdOx PPE15 * University of Oxford, TBVI	Ad5 Ag85A McMaster University, Can Sino	H4 : IC31 SSI, Sanofi Pasteur, Aeras	
	MTBVAC+ Biofabri, University of Zaragoza, TBVI	ID93 + GLA-SE IDRI, Aeras	Crucell Ad35 / Aeras402 Crucell, Aeras	
		DAR-901 Dartmouth University, Aeras	RUTI Archivel Pharma	
	Crucell Ad35 – MVA85A University of Oxford, Aeras, Crucell			

- Vaccine candidates currently supported by TBVI
- Vaccine candidates formerly supported by TBVI
- Other global vaccine candidates

*new candidates (re-)entered TBVI pipeline end 2014/beginning 2015

Research & Development

1. Discovery

To fill and diversify the pipeline of vaccine candidates and strategies, TBVI aims to support 20 approaches, focusing on:

- discovery of new vaccine targets by innovative approaches that allow the identification of non-classical vaccine antigens like non-protein antigens and subdominant epitopes and novel protein candidates
- exploration and implementation of innovative immunisation strategies and vaccine delivery platforms
- optimisation of promising sub-unit and live vaccine candidates by, inter alia, the use of novel delivery and adjuvant platforms

Total estimated cost: €10.5 million

Available funding: €9 million

Additional funding required: €1.5 million (projects identified through TBVI's bottom-up approach with consortium partners).

2. Preclinical development

TBVI aims to support at least 6 vaccine candidates in preclinical development. Preclinical activities include:

- optimising immunogenicity and adjuvant combinations of vaccine candidates
- GMP manufacturing
- formulation and toxicology studies of novel candidates
- testing candidates in standardised preclinical models
- developing and implementing new or improved preclinical models with greater relevance to the target product profile (TPP) and clinical vaccine efficacy

Total estimated cost: €10.6 million

Available funding: €7.1 million

Additional funding required: €3.5 million

3. Biomarkers

TBVI aims to support 15 innovative approaches. This will be done through the following activities:

- identification of biomarkers
- development of corresponding correlate tests
- evaluation of correlates in a comprehensive series of human TB cohorts from genetically and geographically diverse populations
- study of correlates of risk of TB disease and infection in human cohorts
- building a TB biomarker database for tailor-made biomarker selection

Total estimated cost: €6.3 million

Available funding: €5.3 million

Additional funding required: €1 million

4. Clinical development

TBVI aims to accelerate and support promising candidates to early clinical development (up to and including Phase IIa):

- 2-6 candidates in early clinical experimental medicine studies, including comparative first-in-man trials
- development of a safe and controlled human challenge model for TB
- 2 candidates in Phase I
- 1 candidate in Phase IIa trial

Total estimated cost: €15.9 million

Available funding: €2.6 million

Additional funding required: €13.3 million

5. Portfolio management

Portfolio management will be continued to evaluate and advise during the development process, and to prioritise vaccine candidates. TBVI will continuously work with its partners to refine the portfolio management criteria and build consensus. TBVI will coordinate with stakeholders to expand the use of its portfolio management process in a global context.

Total estimated cost: €0.8 million

Available funding: €0.4 million

Additional funding required: €0.4 million

6. Services

TBVI will continue to provide a range of key services to support the R&D efforts of its current and new partners. The TBVI services include:

- project identification, design and development
- project management
- resource mobilisation
- knowledge development, exchange and networking
- technical support for product and clinical development

Total estimated cost: €4.5 million

Available funding: €3.0 million

Additional funding required: €1.5 million

Table 1: Total funding overview (in million €)

	Total estimated cost	Available funding	Additional funding required
Discovery	10.5	9	1.5
Preclinical	10.6	7.1	3.5
Biomarkers	6.3	5.3	1
Clinical	15.9	2.6	13.3
Portfolio management	0.8	0.4	0.4
Services	4.5	3	1.5
Total	48.6	27.4	21.2

9. TBVI – Accelerating TB vaccine development through partnership

The philosophy and spirit of TBVI and its consortium is one of true partnership and collaborative research efforts. The TBVI R&D strategic directions and priorities are based on the scientific and strategic inputs of its consortium members, its Advisory Committee, its P&CDT experts and other partners. This active, ongoing dialogue enables TBVI to stay at the cutting edge of TB vaccine and biomarker R&D.

A continuous dialogue with consortium partners

TBVI encourages and enables scientists and researchers to bring forward their innovative ideas, concepts, technologies and strategies for a creative ‘bottom up’ approach to vaccine and biomarker discovery and development.

TBVI does not have its own commercial interests. Ownership of vaccine candidates and biomarkers and intellectual property rights stay with researchers and vaccine developers. TBVI supports individual research organisations and developers to manage IP issues in accordance with their strategic interests and the need to provide affordable and accessible products for the end user.

Prof. Helen McShane, University of Oxford

“TBVI could be considered as some very powerful ‘glue’ that holds together a consortium of TB vaccine researchers. The principles of transparency, open and honest data sharing and collaborative discussions are the hallmark of this consortium. Through joint collaborative working with open sharing of data prior to publication, a network of trust and respect has been established between TB groups throughout Europe and throughout the world.”

Active networking for knowledge generation and exchange

TBVI provides project management and oversight but more importantly, uses its best practices and platforms to facilitate knowledge exchange, promote synergies and supports collaborative research.

TBVI brings R&D organisations, scientists and industry partners together in one network through organising scientific meetings where knowledge sharing is promoted and incentivised. It links research organisations and universities to SMEs and the vaccine industry in order to facilitate optimal development of vaccine candidates in clinical settings.

Prof. Tom Ottenhoff, Leiden University Medical Centre

“TBVI provides the unique opportunity to join forces with international researchers from five continents (EU, Africa, USA, Australia, and Asia), who together aim to design and develop better vaccines and biomarkers for TB. Particularly impressive, is the mutual support and collaboration. This is vital to the success of the TBVI endeavour, as the problem of TB is far too complex to be resolved by single researchers or even small groups of researchers.”

Transparency and confidentiality

Transparency underpins the work of TBVI. The Articles of Association, policies and rules of procedure, audited financial statements and governance-related documentation are published on the TBVI website (www.tbvi.eu).

Safeguards are in place to manage possible conflicts of interest or any perception of conflicts of interest. Any professional working with TBVI is asked to declare her/his conflicts of interest related to TBVI or the vaccine candidates. Similarly, external experts who advise TBVI are required to comply with TBVI's conflict of interest policy.

TBVI treats data received from its collaborators with strict confidentiality.

TBVI requires that all clinical trials funded by TBVI or in which TBVI experts are advisers are to be performed in accordance with the standards and codes of conduct accepted by the International Conference on Harmonisation (ICH) guidelines and in compliance with the local ethical and regulatory requirements.

The process of calling for project proposals

Depending on the nature of a project or the conditions of funding, TBVI calls for proposals from its network partners for the funding of specific activities by the following modalities:

- open call: a call for any relevant type of activity without limitation on the number of applicants
- a targeted call: a call addressing two or more pre-identified partners that will be invited to respond in the context of a specific activity
- dedicated individual call: in case of a project opportunity or activity that is highly specific and well-defined, TBVI may call upon a network partner that is best capable of delivering on the specific activity

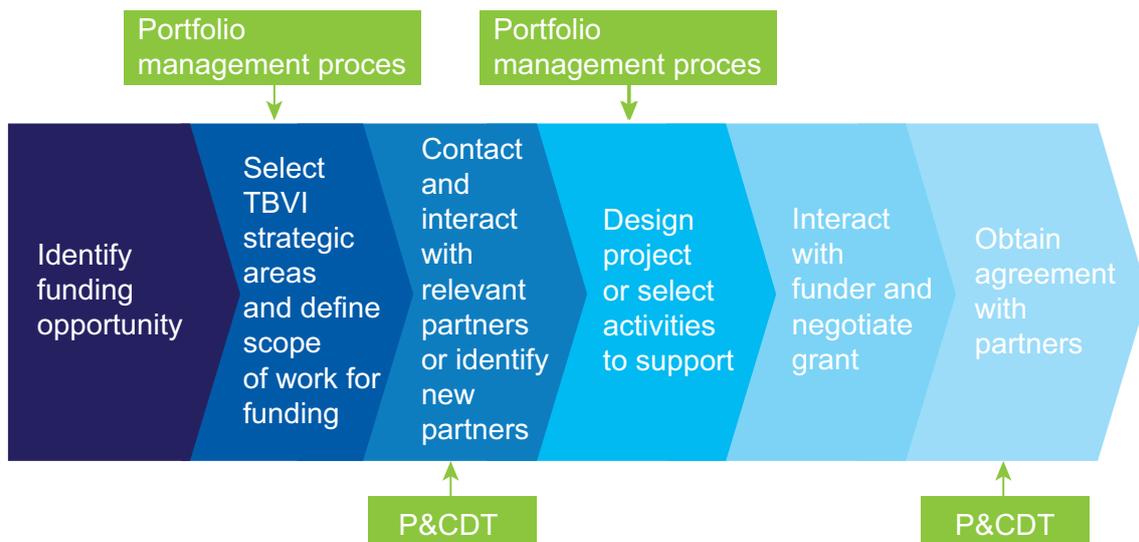
Project identification, design and development in steps

TBVI has a transparent process in place to connect new funding opportunities to R&D priorities in the field. Decisions on the design of a project and allocation of funding are based on close interaction with relevant partners and on the bottom-up process of calling for proposals from partners in the network. The following steps are applied:

- TBVI identifies funds for TB vaccine, biomarker R&D projects
- R&D areas are selected on the basis of appropriateness of funding conditions and complementarity with TBVI strategies and identified R&D priorities. The Portfolio Management Committee (PMC) provides advice and guidance in this process
- network partners are invited to apply via a call for proposals (see box above)
- the PMC reviews the applications, prepares a decision matrix based pre-established criteria, and advises on prioritisation for funding
- the TBVI Executive Director makes the final decision
- TBVI, together with the selected partners, elaborates the specific R&D content of the project. If needed, advice is sought from the PMC or specific P&CDT members
- when applicable an ethical review of the approved proposal is carried out by independent reviewers

- TBVI interacts closely with the funders to ensure the project meets the aims and prerequisites of their funding conditions
- a grant agreement with each partner is negotiated. In principle, TBVI expects partners to provide for co-funding when they are selected for funding through TBVI
- P&CDT proactively manages and supports the progress of activities of the project partners

Figure 5: TBVI's funding and prioritisation process



The TBVAC2020 example

- TBVI identified the European Commission Horizon 2020 call on new TB vaccines with a maximum available budget of €25 million
- TBVI, in consultation with leading experts in the field, identified the following areas and scope of work to be included in the project proposal: discovery, preclinical, biomarkers, early clinical development and portfolio management
- to enable the involvement of new partners and to receive the best new ideas, TBVI launched an open call for Expression of Interest (EoI)
- the call was published on the TBVI website and sent out to all 2,500 contacts and newsletter subscribers all over the world. Over 100 EoI letters were received
- a project selection committee – comprised of a selection of TBVI's P&CDT, TBVI staff and experts – selected the best project proposals based on pre-determined selection criteria. A total of 54 proposals were selected and included in the grant proposal that was submitted to the EC Horizon 2020 programme
- the EC selected TBVI's project for further negotiation and offered a contribution of €18.2 million for the project
- a round of consultation with the anticipated project partners resulted in a final proposal and agreement with the EC for a budget of €18.2 million. Additional funds from the Swiss, Korean and Australian governments complemented the project budget for a total of €24.6 million

10. Finances

The TBVI consortium receives funding from the European Commission, government agencies, private foundations and industry. Over the past seven years, a total of €46.5 million has been received to support ongoing and anticipated activities until 2017. These activities include R&D activities and the services that TBVI provides to the consortium partners (see Figure 6).

Figure 6: Donations and pledges 2010-2017 (in € x 1000)

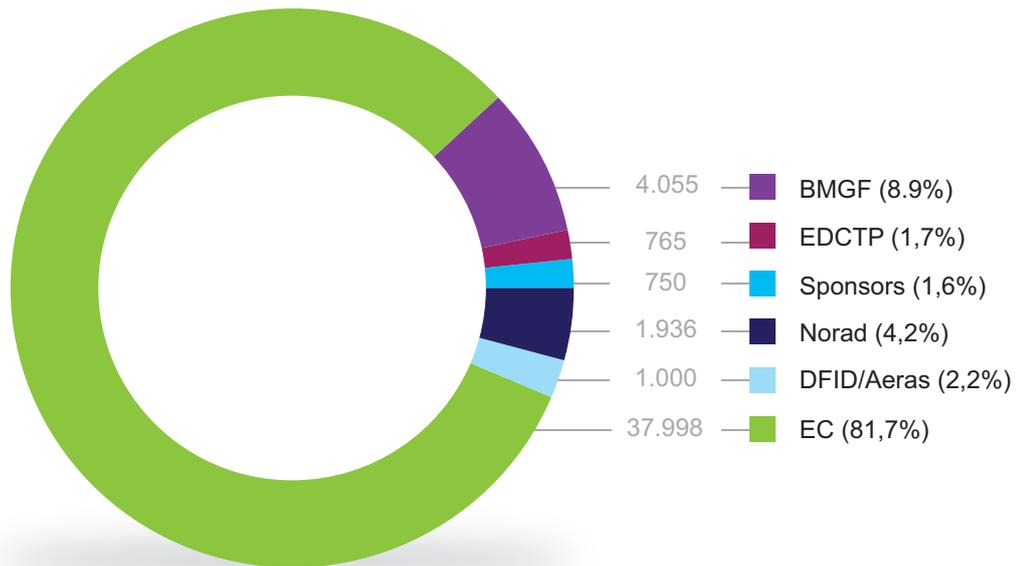
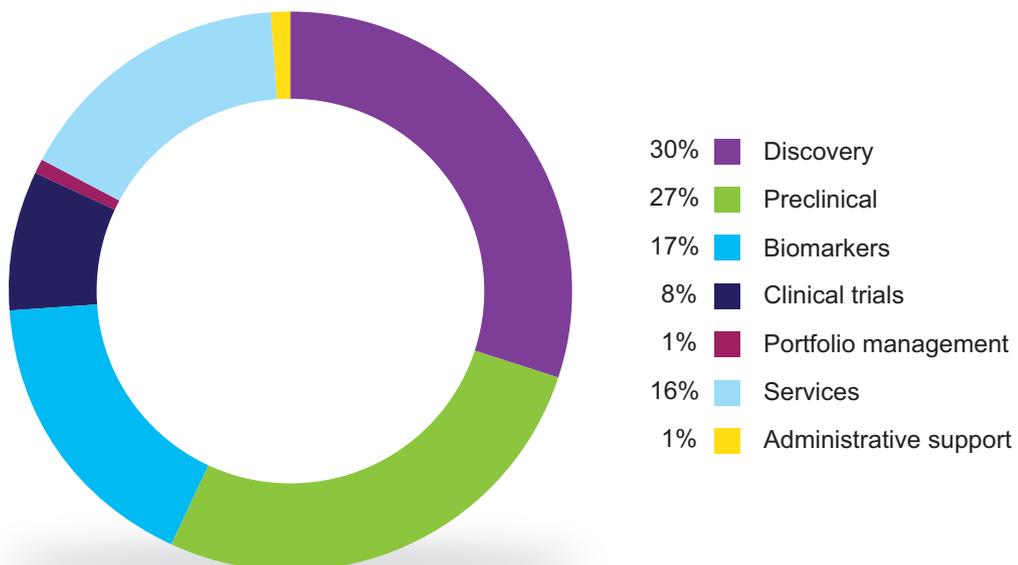


Figure 7 shows the allocation of these funds to R&D activities (broken down into 5 strategic areas) and to TBVI services and administration.

Figure 7: Allocation of funding to strategic areas

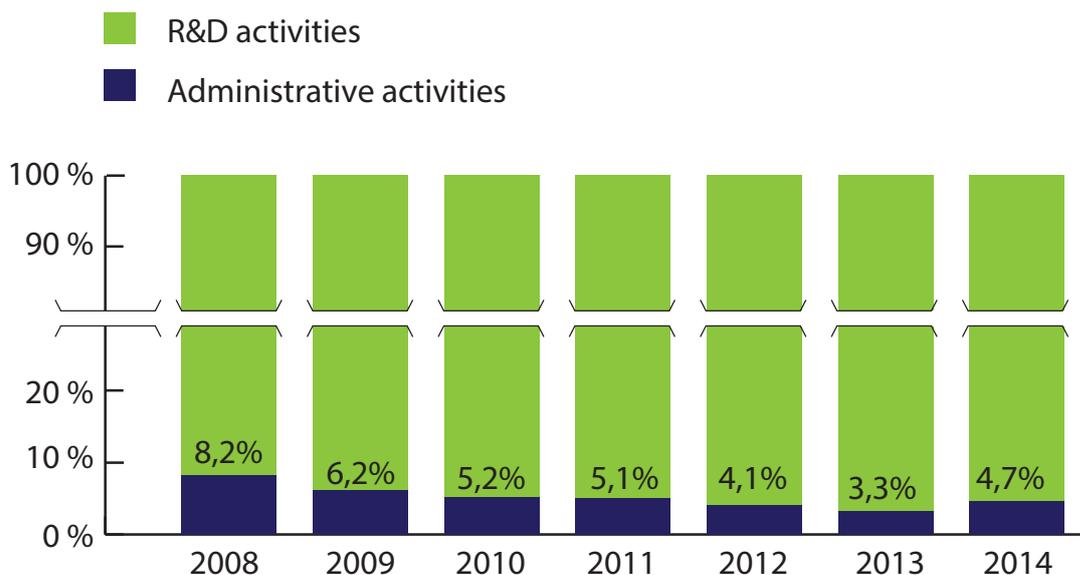


In terms of its funding, 2014 was a year of transition for TBVI. The funding from the European Commission (EC) for the NEWTBVAC project came to an end in 2014 and EC funds for the new TBVAC2020 project were awarded. Funds from the Bill & Melinda Gates Foundation plus new funding from Norad (Norwegian government) and DFID (UK government) provided some bridging funding to consortium partners between the two EC projects.

2015 will be the first year of the new TBVAC2020 project and enables the consortium to effectively continue its R&D activities and TBVI to provide its essential services to consortium partners. In January 2015, TBVI will have a budget of €8,070,000, including a €6,250,000 R&D budget for its consortium partners. TBVI will build on this new programme by broadening and diversifying its funding sources, to seek additional funding for the planned activities until 2017 and beyond.

TBVI's financial management is underpinned by efficiency and effectiveness, with a drive to deliver results and impact. TBVI's management and administration costs were kept at below 5% of all expenditures in 2014.

Figure 8: R&D and administrative spending



Reporting standards

As a Dutch non-profit foundation, TBVI meets the criteria set for 'Algemeen Nut Beogende Instellingen' (ANBI), or Public Benefit Organisations, which are applicable for charity fundraising. TBVI works according to the applicable audit standard RJ 650 (RvJ). Auditing of TBVI accounts is conducted annually by PricewaterhouseCoopers Accountants NV. The books over the financial year 2014 were closed with a surplus of €52,682 which has been added as a reserve to the TBVI contingency fund.

Table 2: Statement of activities and balance sheet 2014 (all amounts in Euro)

Statement of Activities	Financial report 2014	Financial report 2013
Revenues		
Contributions	1,491,216	1,371,411
• Foundations: BMGF, Gulbenkian	797,753	972,117
• Governments: EDCTP, Norad	693,463	399,294
Grants EC	226,736	460,727
Interest	27,682	23,303
Other	-	32,185
Total	1,745,634	1,887,626
Expenses		
Research and development support	1,613,872	1,766,866
Administrative and programme support	79,080	65,272
Total	1,692,952	1,832,138
Surplus	52,682	55,488
Balance sheet	31-12-2014	31-12-2013
Non current assets		
• Tangible fixed assets	8,632	11,795
	8,632	11,795
Current assets		
• Receivables	47,989	63,008
• Banks	7,003,980	1,993,987
	7,051,969	2,056,995
Total	7,060,601	2,068,790
Reserves		
• Contingency (unrestricted)	155,374	102,692
	155,374	102,692
Liabilities		
• Restricted project operating funds	6,780,861	1,757,109
• Provisions	16,844	30,908
• Payables	107,522	178,081
	6,905,227	1,966,098
Total	7,060,601	2,068,790

Auditors' report

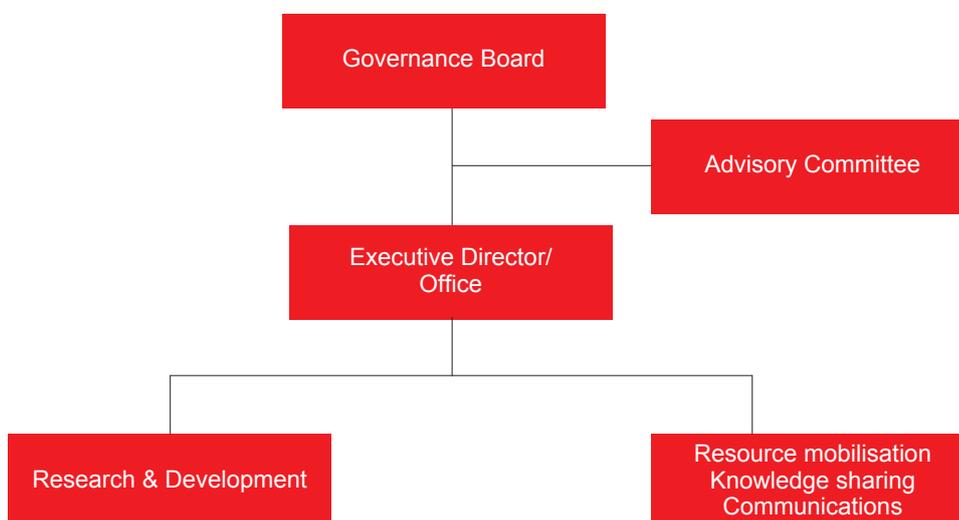
The 2014 financial statements have been audited by PricewaterhouseCoopers Accountants NV. The financial report, as stated above, has been derived from the 2014 financial statements. More detailed information can be found on the TBVI website.

11. Governance and Organisation

TBVI's highest decision-making body is its Governance Board. TBVI's Advisory Committee gives advice to the Governance Board and to the Executive Director on strategic issues related to R&D, resource mobilisation and external affairs. Day-to-day business is carried out by the Operational Office, which comprises:

- The Executive Director's office: policy and strategy development, scientific leadership, oversight, legal, finance and management
- Research & Development: project management, product and clinical development team (P&CDT), portfolio management committee (PMC)
- Resource mobilisation, Knowledge sharing and Communications

Figure 9: Organisation structure



January 2015

Governance Board

Dr Onno Ruding (chair)
 Chairman of CEPS
 Retired Vice Chairman of Citibank
 Former Dutch Minister of Finance
 The Hague, The Netherlands

Ms Michèle Boccoz
 French Ambassador to Croatia
 Zagreb, Croatia

Prof. Michel Goldman
 Professor at the Université Libre de Bruxelles
 Past Executive Director of IMI
 Brussels, Belgium



Prof. Paul-Henri Lambert

Director of the International Advanced Course of Vaccinology
University of Geneva
Geneva, Switzerland

Prof. Fritz Melchers

Professor of Immunology at the University of Basel
Senior Research Group Leader at the Max Planck Institute for Infection Biology
Co-founder of 4-Antibody
Berlin, Germany

Mr Dick Pouwels

Chairman of the Board of the HAS University of Applied Sciences
Den Bosch, The Netherlands

Prof. Douglas Young

Fleming Professor of Medical Microbiology at Imperial College London
Head of Division of Mycobacterial Research at the National Institute for Medical Research
London, United Kingdom

Advisory Committee

Prof. Helen McShane (chair)

Professor of Vaccinology
University of Oxford
Oxford, United Kingdom

Prof. Oswaldo Álvarez

General Manager
Biofabri
Porriño, Spain

Prof. Peter Andersen

Vice President of Vaccine Research and Development
Statens Serum Institut
Copenhagen, Denmark

Mr John Bowis OBE

Former member of the European Parliament
Former Minister of Health and Transport of the UK
London, United Kingdom

Prof. Willem Hanekom

Deputy Director Tuberculosis
Bill & Melinda Gates Foundation
Seattle, United States of America



Dr Carol Holm-Hansen
Senior Scientist
Norwegian Institute of Public Health
Oslo, Norway

Prof. Stefan Kaufmann
Founding Director
Max Planck Institute for Infection Biology
Berlin, Germany

Prof. Michel Kazatchkine
Special Envoy of the UN Secretary General on HIV/AIDS in Eastern Europe and Central Asia
Representative of the Board of Directors of Aeras
Geneva, Switzerland

Dr Camille Locht
Research Director, French National Institute of Health and Medical Research (Inserm)
Head of the Center for Infection and Immunity of Institut Pasteur de Lille
Lille, France

Prof. Carlos Martin
Professor of Microbiology
University of Zaragoza
Zaragoza, Spain

Dr Olivier Neyrolles
CNRS Research Director
Institute of Pharmacology & Structural Biology
Toulouse, France

Prof. Tom Ottenhoff
Professor of Immunology, Head group Immunology and Immunogenetics of Bacterial Infectious Diseases
Leiden University Medical Center
Leiden, The Netherlands

Dr Frank Verreck
Head TB Research, Department of Parasitology
Biomedical Primate Research Centre
Rijswijk, The Netherlands

Dr Gérald Voss
Director of the Disease Area Programme for Emerging Diseases and HIV
GSK Biologicals
Rixensart, Belgium



Dr Gerd Zettlmeissl
Representative of the Board of Directors of Aeras
Former CEO Valneva SE (formerly Intercell AG)
Vienna, Austria

Office

Senior Leadership Team:

Dr Nick Drager
Executive Director

The TBVI Scientific Team is composed of Prof. Tom Ottenhoff, Professor of Immunology, Head group Immunology and Immunogenetics of Bacterial Infectious Diseases, Leiden University Medical Center; Dr Jelle Thole, Chief Scientific Officer at Intravacc; and Dr Frank Verreck, Head TB Research, Department of Parasitology, Biomedical Primate Research Centre. These team members will maintain their current institutional affiliations.

Operational Office:

Dr Nick Drager
Executive Director

Ms Cora Agterdenbosch
Sr. Management Assistant

Ms Erna Balk
Director Advocacy and Communications

Mr René Coppens MSc
Director Resource Mobilisation

Mr Koen de Lange
General Legal Counsel

Mr Anne Meinema
Director Finance and Administration

Ms Daniëlle Roordink MSc
Project Manager

Product & Clinical Development Team

Dr Jelle Thole (chair)
Chief Scientific Officer
Intravacc
Bilthoven, The Netherlands



Dr Bernard Fritzell

Former Vice-President, International Scientific & Clinical Affairs, Pfizer Vaccines Research
Former Chairman of the clinical working group of the European Vaccines Manufacturers
(EVM)
Paris, France

Dr Emmanuèle Gerdil

Former Executive Director, Regulatory Affairs Europe
Sanofi Pasteur MSD
Lyon, France

Dr Luc Hessel

Independent expert, Former Executive Director, Medical and Public Affairs, Europe
Sanofi Pasteur MSD
Lyon, France

Dr Mei Mei Ho

Principal Scientist
National Institute for Biological Standards and Control
Potters Bar, United Kingdom

Dr Brijesh Patel

Former Deputy Manager and Senior Assessor Biologicals and Biotechnology Unit
MHRA (Medicines and Healthcare products Regulatory Agency)
London, United Kingdom

Dr Eddy Rommel

Managing Director
Rommel Consulting Partners
Jodoigne, Belgium

Dr François Spertini

Associate Professor of Medicine, University of Lausanne
Chief Physician, Centre Hospitalier Universitaire Vaudois
Lausanne, Switzerland

Research Partners

Australia

University of Sydney

Belgium

Ghent University
GSK-Biologicals
Scientific Institute of Public Health
Université Libre de Bruxelles

Denmark

Statens Serum Institut



France

Centre National de la Recherche Scientifique
Institut National de la Santé et de la Recherche Médicale
Institut Pasteur de Lille
Institut Pasteur
Institut Mérieux

Germany

Max Planck Institute for Infection Biology
Paul Ehrlich Institut
University of Ulm
Vakzine Projekt Management GmbH

Ireland

University College Dublin

Italy

IRCCS Lazzaro Spallanzani
Istituto Superiore Di Sanità
Università Degli Studi Di Padova
University of Palermo

Norway

Norwegian University of Life Sciences

Republic of Korea

Educational Foundation Yonsei University
International Tuberculosis Research Center

Senegal

Centre Hospitalier Universitaire Le Dantec
Espoir Pour La Santé (EPLS)

South Africa

K-Rith Kwazulu-Natal Research Institute for Tuberculosis
SATVI/University of Cape Town
Stellenbosch University

Spain

Biofabri/CZ Veterinaria
Fundació Institut d' Investigació en Ciències de la Salut Germans Trias i Pujol
Universidad de Zaragoza

Switzerland

Centre Hospital Universitaire Vaudois
ETH Zürich
University Hospital of Basel
University of Basel
University of Geneva
University of Lausanne
University of Zürich



The Gambia
Medical Research Council

The Netherlands
Biomedical Primate Research Centre
VU University Medical Center Amsterdam
Intravacc
Leiden University Medical Center

United Kingdom
Aston University
Bangor University
Imperial College of Science Technology and Medicine
London School of Hygiene and Tropical Medicine
National Institute for Biological Standards (NIBSC-MHRA)
Public Health England at Porton Down
University of Oxford
Veterinary Laboratory Agencies DEFRA

United States of America
Aeras

Funding Partners

European Commission
FP7 and Horizon 2020 Programmes
Brussels, Belgium

European Investment Bank (advisor to the EC and stakeholder in GTBVP)
Luxembourg

Bill & Melinda Gates Foundation
Seattle, USA

Government of Norway (Norad)
Oslo, Norway

Government of the UK (DFID)
Through Aeras

Governments of Switzerland, Australia and South Korea
Through TBVAC2020

Biofabri
Porriño, Spain

GSK Biologicals
Rixensart, Belgium



TBVI

TuBerculosis Vaccine Initiative

TuBerculosis Vaccine Initiative (TBVI)

Runderweg 6

8219 PK Lelystad

The Netherlands

T +31 320 277550

E info@tbvi.eu

www.tbvi.eu

www.twitter.com/TBVI_EU

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