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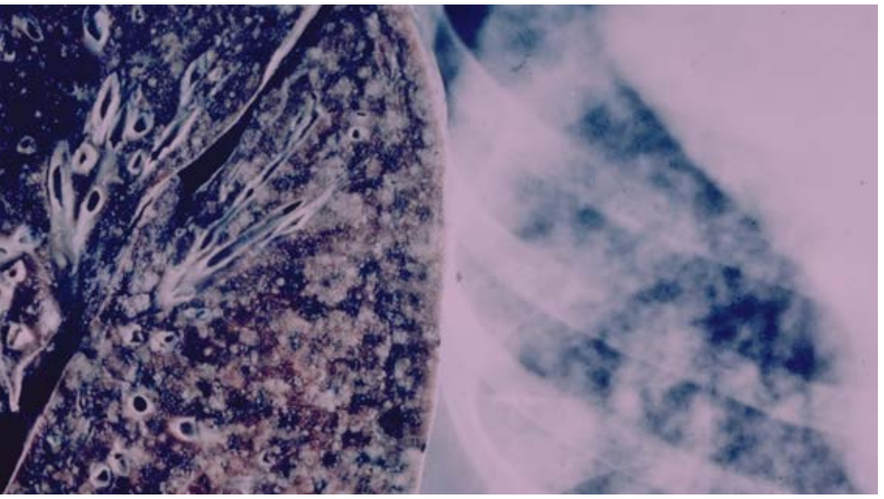
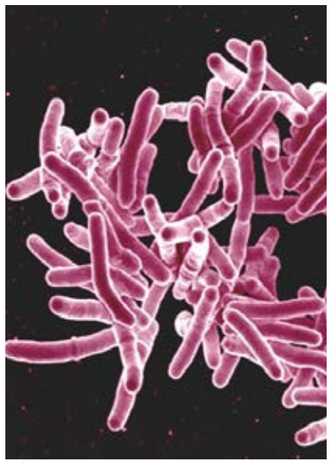
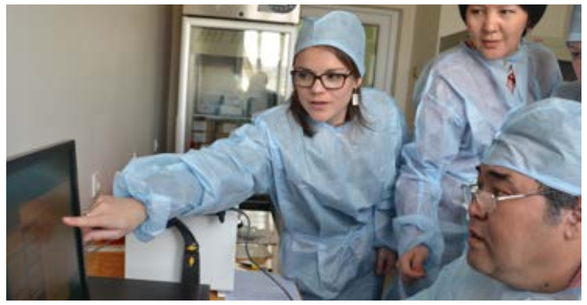
To eliminate TB

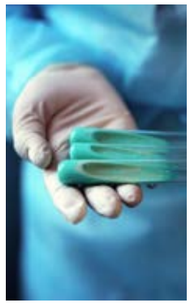
TUBERCULOSIS RESEARCH IN THE NETHERLANDS:

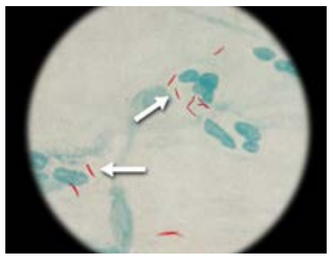
INNOVATION TO ACCELERATE GLOBAL TUBERCULOSIS ELIMINATION











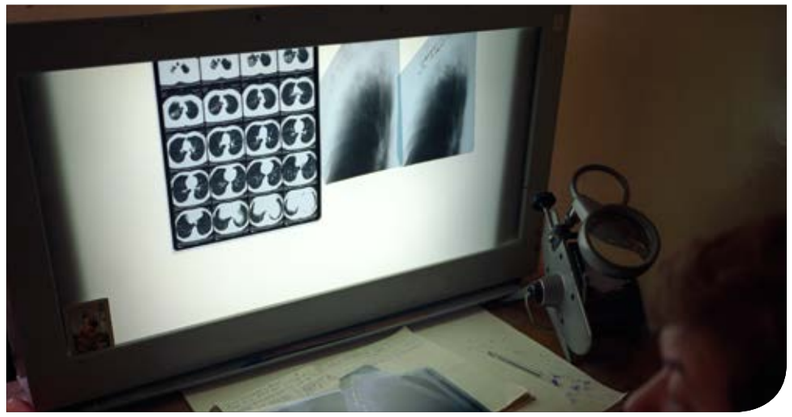


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TABLE OF CONTENTS

PREFACE: TUBERCULOSIS RESEARCH IN THE NETHERLANDS: INNOVATION TO ACCELERATE GLOBAL TUBERCULOSIS ELIMINATION

At the 67th World Health Assembly held in Geneva in May 2014, all WHO Member States approved a new strategy for tuberculosis (TB) control for the post-2015 time that follows the Millennium Development Goals (MDG) era. In that era, progress in TB control and research has been remarkable. Achieving the MDG-related TB target of reversing a per-capita incidence rate that was increasing during the 1990s is not something to be disregarded as little ambitious. Apprehension existed at the time among experts, especially because no easy solution could be put into practice to halt the co-epidemic of TB and HIV in the impoverished African continent and to limit the spread of multidrug-resistant TB (MDR-TB) in many parts of the world. Thanks to a number of favourable factors, including adoption and implementation of better strategies to care for and control TB, economic growth in many countries, introduction of new and unprecedented international financing mechanisms to support low- and middle-income countries, and wider adoption of antiretroviral drugs, the trend could be reversed and the damage, in terms of human lives and suffering, limited. However, the burden of TB remains enormous and this disease is today the top infectious killer with 1.5 million people dying every year and over 9 million developing new episodes of disease. Several challenges remain: how to handle the "missed" cases that are not captured by the national health statistics and programs, how to control MDR-TB, how to intensify efforts against HIV-associated TB, how to raise all necessary resources, and how to stimulate and accelerate research towards identification of better tools.

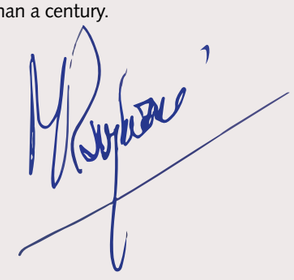
Acknowledging these issues, the World Health Assembly in 2014 adopted a new End TB Strategy targeting the "end of the epidemic" by 2035, defined as a global incidence of less than 10 cases per 100,000 people, similar to the situation of advanced economies of today. The strategy, besides proposing a patient-centred care approach that consists of the basics of TB control complemented by all modern technologies available and a bold health policy environment that emphasizes universal coverage and social protection, promotes rapid intensification of research efforts in a way that results in new means and their immediate application everywhere. To reach the targets set for 2035 – cutting mortality by 95% and incidence by 90%, and abolishing catastrophic expenditures to households affected – a simple model has been created that would break the trajectory of the TB epidemic by, in the first decade, accelerating the annual decline from the current 2% to 10% through optimization of use of the existing and foreseeable tools, and in the second decade by further accelerating to above 15% per year through new revolutionary technology including rapid simple diagnostics for infection and disease, shorter universal regimens for infection and disease, and eventually an effective vaccine. To achieve this, research in its broadest sense is necessary immediately, along a continuum that links logically and strategically the very upstream, fundamental research to discovery and new tool development, and ultimately to operational and implementation investigations.

To facilitate this effort, the World Health Organization, jointly with experts and partner agencies, has developed a new Global Action Framework for TB Research to set the principles for action and recommend roles and responsibilities of the major stakeholders at global and national levels. It consists of four main parts dealing with: (i) strengthening TB research in low and middle-income countries most affected by TB; (ii) supporting and facilitating research at global level; (iii) defining the role of WHO in promoting research; (iv) and describing milestones and deliverables at 1, 5 and 10 years.

Transforming this Framework into practice will require several steps including establishment or strengthening of a national TB research network, creating or updating a national strategy for TB research, developing a budgeted plan to build and maintain capacity for TB research, and ensuring national funding for TB research that can be complemented by non-state financing. This process, which may sound slow and tedious, will in fact be necessary for a radical transformation in, ultimately, the way TB is diagnosed, treated and prevented. To succeed, efforts have to be undertaken along the full spectrum of research. This implies, first, improving the understanding of basic science to prompt discovery and nurture pipelines for development of new diagnostics, drugs and vaccines. It also means amplifying and integrating research and development efforts for testing and validating new diagnostics, treatments and vaccines. Once new tools and technology are available, bringing together all fields of research towards innovative strategic approaches adapted to specific country needs will be the essential next step. This requires also building better comprehension of socio-behavioural factors influencing health-related practices of TB patients, peers, caregivers and health care workers, and transforming the larger policy and health system environment, through research towards full exploitation of universal health coverage, social protection, and whole-of-government actions on social and economic determinants of ill health.

For this vision to succeed, every country, starting with low- and middle-income and including high-resource countries, needs to ensure that the principles contained in the Framework supporting the research pillar of the End TB Strategy are rigorously implemented. In practical terms, this means mapping the existing research capacity and on-going projects, mobilizing all public and private institutions that can contribute, establishing a network of researchers and institutions, having consensus on the top priorities, building a national strategic plan for TB research, linking internationally as required, and eventually identifying the necessary human and financial resources.

With the White Paper, the Netherlands TB stakeholders have moved more quickly than most in immediately applying these principles and developing a national consensus agenda for TB Research. This historical document, which should be used as a model for other countries, highlights the needs to expand global and national TB research efforts and to contribute therefore to ending TB as a public health threat. By mapping the traditionally strong TB research capacity in the country and pondering on how to make it stronger, this White Paper should be a clear and loud call to the Government of the Netherlands across different ministries to recognize the key importance of research and support it for the very noble aim of ending suffering from a millennia-old disease such as TB. The document builds on a sound assessment of the major challenges to TB elimination internationally and domestically, and advocates for a clear agenda, capacity building, and financing. Conscious of the national expertise and skills, the authors focus on some priority areas of excellence, including host-pathogen interaction, transmission, treatment optimization, and improvement of the broad health system response. They acknowledge the links with top priorities in the global health research agenda, such as antimicrobial resistance, the solutions to which are necessarily similar for all diseases. Becoming very specific, the White Paper finally enlists all major institutions that can contribute to the joint effort describing how and in what research area. The document therefore becomes more than just a vision, and evolves finally into a first plan for expanding research in a country that, more than many others, has offered crucial contributions to the global fight against TB for more than a century.



By Mario C. Raviglione, Director Global TB Programme, WHO, Geneva

EXECUTIVE SUMMARY

Tuberculosis, often thought a disease from the past, is still rampant in large parts of the world. With 1.5 million deaths annually it is the most important global killer due to an infectious disease. In May, the United Nations World Health Assembly adopted the new post-2015 Global TB Strategy. This "End TB" strategy sets highly ambitious targets: to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035, and to ensure that no family is burdened with catastrophic expenses due to TB. For the first time, the global ambition is not just to control TB, but to eliminate it as a (public) health problem.

To reach these goals, research and development (R&D) is one of the three pillars in the "End TB"-strategy as to accelerate the level, volume and capacity of TB research on a global scale. Only this way, the world is able to eliminate TB in a scaled-up, low-cost and effective way. Investing in better TB diagnosis and treatment is a very effective way to attain high health and economic returns. TB has been identified as one of the best buys with a return of between $16 and $82 for each dollar invested in TB diagnosis and treatment, with highest returns for the poorest in the world. Specifically, the World Health Organization calls for fundamental research, new diagnostics, new drugs and treatment regimens, effective and safe vaccines, and optimized implementation.

The Netherlands has strong and broad capacity and infrastructure to contribute to this global R&D agenda for eliminating TB. KNCV Tuberculosis Foundation and the Netherlands Tuberculosis Research Platform (NTRP) took the initiative to map this Dutch R&D capacity, and to identify specific areas of excellence in TB research in which a collaborative Dutch effort could bring major, cutting-edge value. Identified through a consensus process based on existing research capacity, scientific track record, involvement in research networks, and innovation potential these areas of excellence are as follows:

Host-pathogen interaction.

Little is yet known about the interaction between host and pathogen in the various stages of infection and disease. Fundamental and (pre-) clinical research in this area is vital for developing an effective vaccine, and for discovering biomarkers for improving diagnosis, predicting treatment outcomes and shortening TB drug and vaccine trials. Several Dutch research groups are highly competitive in this field, and the capacity for large animal research offers unique opportunities. The Netherlands-based Tuberculosis Vaccine Initiative serves as a major catalyst of research activities.

Understanding and reducing tuberculosis transmission.

Better insights in what drives transmission is essential for targeting new TB interventions. The Netherlands boasts the largest, highest-coverage and most extensively researched TB molecular surveillance database in the world, and has parallel databases of veterinary cases. Together with a leading position globally in design and conduct of population surveys for TB and strong clinical collaborations throughout the world, this provides Dutch research groups with unique capacity and opportunities for studying transmission of TB and (multi-) drug resistant TB.

Tuberculosis treatment optimization.

This encompasses new drugs as well as more effective and efficient use of existing drugs. Dutch research groups play an important role in drug discovery, preclinical testing of new drug candidates, drug trials, pharmacovigilance and cost-effectiveness of new drug regimens, as well as in research on precision treatment based on drug resistance profiles and individual patient pharmacokinetics. A leading position in the PanACEA drug trial consortium, longstanding collaborations in TB high-incidence countries and access to (drug-resistant) M. tuberculosis strains from large parts of the world provide Dutch groups with excellent capacity for research in this field.

Improving the health system response.

The Netherlands has a solid history in operational and health systems research to drive policy change at local, national and global level, partly through intensive links with national TB control programs and international bodies such as the World Health Organization. An important niche for Dutch groups is implementation research to collect evidence for scale-up of new TB interventions, linking effectiveness to feasibility and cost-effectiveness and affordability in an integrated multidisciplinary disciplinary approach. Similarly, Dutch groups have been at the forefront of developing technological improvements in service delivery, including point-of-care diagnostics.

Linked to these thematic areas is a strong position in research capacity building in resource-poor settings, at infrastructural, individual, institutional and programmatic levels. The areas of excellence fit well into the Dutch future science ambitions laid down in the Dutch Science Policy Framework (*Wetenschapsvisie 2015: keuzes voor de toekomst*), other global health issues such as microbial resistance, One Health, and responsible use of medicines. This document outlines the unique position The Netherlands has in combating one of the major killers worldwide, by collating and presenting the available research capacity and ongoing cutting-edge research per area.

This unique position results in a call to action from our side. The Netherlands is the perfect place to address the research themes identified as areas of excellence, being the forerunner on global health issues and setting the agenda the first half of 2016 as the EU President. Therefore, we call upon the Dutch government to recognize these four areas of excellence within its new science policy framework, and incorporate them into the new Dutch Research Agenda. Furthermore, we ask The Netherlands to make use of the opportunities in international forums: issuing TB within the antimicrobial resistance agenda and including TB in the One Health Agenda during the Dutch EU Presidency, and looking further ahead putting forward TB at the during next Global Health Security Summit address.

1. RATIONALE AND JUSTIFICATION

Tuberculosis (TB), often thought of a disease from the past, is still rampant in large parts of the world. With 1.5 million deaths annually, it is the most important cause of death due to an infectious disease worldwide. The last decades, TB is on a solid course towards minimizing it as a health threat in The Netherlands thanks to years of knowledge and expertise in effective TB control. However, international travel, labour migration and influx of refugees from endemic countries pose a continued threat of importation of TB and spread within the community.

In addition, resistance to effective drugs is an increasing problem, in particular in Eastern Europe and Asia, which complicates treatment and increases mortality and long-term morbidity. In 2014, the World Health Organization (WHO) adopted the End TB Strategy, a policy of eliminating TB as a public health problem at the global level by 2050. The European Union (EU) has set the goal of eliminating of TB in Europe likewise.

These ambitions cannot be reached without major efforts and investments in research and innovation. There is a broad consented need for developing an effective vaccine, shorter and simpler treatment and better diagnostics as well as implementing these technologies in the health system in a cost-effective manner. This requires research along the entire R&D chain, including preclinical studies, clinical trials, public health and implementation research.

The Netherlands has strong and broad capacity and infrastructure to contribute to the global R&D agenda for eliminating TB. In order to realize this potential, KNCV Tuberculosis Foundation and the Netherlands Tuberculosis Research Platform (NTRP) took the initiative to map this Dutch R&D capacity, and to identify specific research themes for which a collaborative Dutch effort could bring scientific excellence (areas of excellence).

KNCV TUBERCULOSIS FOUNDATION is one of the leading organizations in tuberculosis control globally and a key partner of both the World Health Organization and USAID as ministries of health worldwide.

The Netherlands Tuberculosis Research Platform (NTRP) brings together researchers on human and animal tuberculosis of various disciplines, with the aim of stimulating exchange and collaboration between Dutch TB researchers and enhancing their involvement in international TB research projects.

Dutch researchers and research groups active in the field of tuberculosis were invited to an inventory meeting on 25 June 2015. Invitees included all NTRP members and additional researchers identified by screening publicly available scientific publication databases. This meeting was attended by representatives of 21 different research groups.
The global TB research agenda, as developed over the past years in a broad consultation of experts and stakeholders, was presented and discussed. Then through plenary discussion a limited number of areas of excellence were identified based on four sets of criteria:

1. **existing research** capacity, including specific research expertise, animal models, laboratory infrastructure and biosafety, clinical research infrastructure;
2. **scientific track record**, including publications, key findings and discoveries, potential for translating work in other disease areas to TB;
3. **networks**, including access to TB patients, clinical specimens and bacterial isolates, strategic collaborations with other research groups, access to public health data and relationships with policy makers, funders and product development partnerships at national, regional and global level; and
4. **Innovation potential**, including (contribution to) development of innovative products for TB (vaccines, drugs, diagnostics), innovativeness in R&D approaches, and innovativeness in research methodologies regarding implementation and health service delivery.

In addition, all invitees were requested to provide written summaries of their respective research groups and other key aspects for mapping purposes.

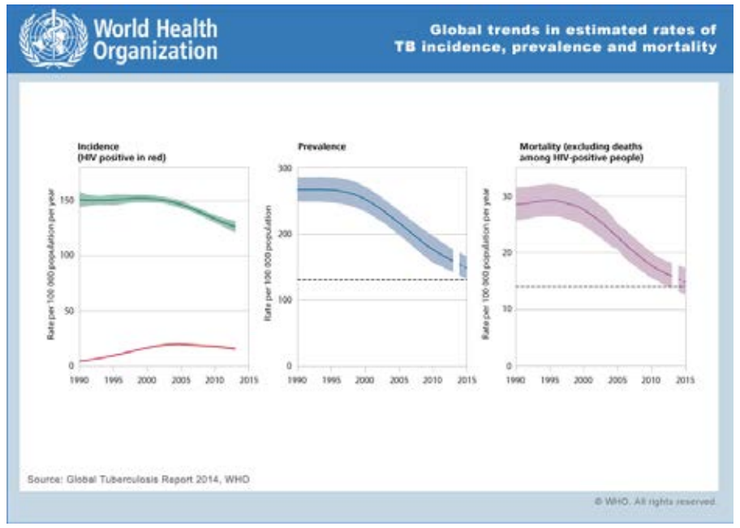
The four areas of excellence identified, explained in more detail in chapter 6, are:

1. **Host-pathogen interaction**
2. **Understanding and reducing transmission**
3. **Treatment optimization**
4. **Improving the health system response.**

Results of the inventory meeting were laid down in a consensus document, on which two rounds of comments were invited, again to all invitees to the meeting. The first round of comments focused on the areas of excellence identified, the second on the draft for the entire document. Here you find the completed, final version.

KEY FIGURES OF THE GLOBAL TB BURDEN[1]:

- **9 million** people fell ill with TB in 2013.
- The TB mortality rate has decreased by 45% since 1990. Still, 1.5 million people died from TB, including **360,000** among people who were HIV-positive, in 2013.
- TB is the **top killer** of people living with HIV/AIDS and one of the top killers of women of reproductive age.
- In 2013, **5.5 million** people enrolled in HIV care were screened for TB, up from 4.1 million in 2012.
- In the **African** region that has the highest TB/HIV burden, three out of four TB patients knew their HIV status.
- Globally, **70%** of the TB patients known to be living with HIV in 2013 were started on antiretroviral therapy.
- The number of people diagnosed with Multi-Drug Resistant (MDR)-TB tripled between 2009 and 2013, and reached **136,000**. Progress in the detection of drug-resistant TB has been facilitated by the use of new rapid diagnostics.
- There were an estimated **210,000** deaths from MDR-TB in 2013.
- A total of **97,000** patients were started on MDR-TB treatment in 2013, a three-fold increase compared with 2009.
- However, the gap between diagnosis and treatment widened between 2012 and 2013 in several countries.
- Between 2000 and 2013, **37 million** lives were saved through effective TB diagnosis and treatment.



[1] *World Health Organization, Global Tuberculosis Report 2014, http://apps.who.int/iris/bitstream/10665/137094/1/9789241564809_eng.pdf?ua=1*

2. MAJOR HURDLES IN TB CONTROL AND ELIMINATION

Looking at the key figures (panel at page 7), and achievements over the past decades notwithstanding, TB remains poorly controlled in many resource-limited settings while elimination is hard to achieve elsewhere in the world. Acceleration and more focused efforts in control practices are urgently needed. From an innovation perspective the major hurdles to be overcome include:

There is no effective vaccine against TB.

Although there has been a vaccine since the 1930s (BCG), it provides variable protection beyond early childhood age with limited impact on TB transmission. Several vaccine candidates are currently in the pipeline but their development and evaluation is hampered by the lack of validated correlates of protection. As a result, vaccine candidates that seem immunogenic in animals and humans may not prove effective in humans when it comes to protecting against TB disease. Consequently large expensive trials with lengthy follow-up are currently needed to establish protective efficacy. The availability of correlates of protection would greatly facilitate and accelerate TB vaccine development, as well as render savings in cost and time while moving and selecting vaccine candidates through the development stages.

Transmission of TB is difficult to interrupt.

The TB bacillus, Mycobacterium tuberculosis, is transmitted through aerosols, mainly as a result of coughing. This mode of transmission puts every close contact of a person with contagious TB at risk of infection. TB transmission has been difficult to interrupt at the population level in resource-poor settings, because of high contact rates, late diagnosis and possibly other poverty-related factors that increase susceptibility to infection. "Superspreaders" causing large numbers of TB infections would be a possible target for intervention but little is known about how these could be identified at an early stage.

Increasing drug resistance deeply affects patients, and is a major threat to TB control, especially in Europe.

MDR TB has the potential to reverse the gains of decades as evidenced in some countries in the eastern part of the WHO Europe region. Treatment is far from optimal when diagnosed with MDR-TB. Infections resistant to the two key first-line drugs isoniazid and rifampicin (as is the case with MDR-TB) require treatment for up to 24 months with toxic and expensive drug combinations for which dosing has not been optimized to balance efficacy and toxicity. Resistance to additional drug classes (extensively drug resistant TB, XDR-TB) is emerging quickly, with limited treatment options and high mortality. Europe, including some of the new EU countries, has among the highest proportions of MDR/XDR-TB in the world. Two new TB drugs have been approved lately (for the first time since 50 years) but based on limited data. This restricts their use to difficult-to-treat MDR/XDR-TB patients, leaving many patients infectious with highly resistant bacilli. Moreover, detection of MDR-TB and XDR-TB requires resistance testing of the infecting bacilli, which until recently was only possible in high-level biosafety labs with time-to-result of up to 4 months. New molecular assays have shortened this to less than one day, but are limited to key first-line drugs and the technology is still too expensive to be widely available.

TB is often diagnosed late

Resulting in poor treatment outcomes and continued transmission to others. Moreover, with delayed diagnosis, long-term effects of TB hamper and impair health post-TB treatment. The chronic nature of the disease, its insidious onset and non-typical signs and symptoms lead to poor clinical suspicion with patients, physicians and other health care workers. Until recently diagnosis in resource-poor settings was based on sputum smear microscopy, which though inexpensive has limited sensitivity. Novel molecular assays such as cartridge-based PCR systems (that also test for drug resistance) have better sensitivity but still miss TB in children and/or in other organs than the lungs, and are too expensive to be used at point-of-care.

Preventive treatment cannot be efficiently targeted.

Once infected, the lifetime risk of developing active TB disease is on average 10%, but increased by (in addition to HIV, see below) malnutrition, smoking, diabetes and alcohol abuse. Progression from latent infection to TB disease can be prevented with a 3 to 6 months course of one or two drugs ("prophylaxis"), but this present regimen of prophylaxis is too toxic, cumbersome and expensive to be used for mass prophylactic treatment. Currently available tests cannot identify those with clearly increased risk of disease progression, precluding targeted preventive treatment in a cost-effective way. Diagnostic biomarkers that identify latently infected persons at high risk of progression to disease are largely unknown.

All these problems are aggravated in patients co-infected with HIV.

HIV infection is the strongest risk factor for progression from latent TB infection to TB disease, increasing this risk by 10 to 100-fold depending on the level of immune impairment. Patients with TB-HIV co-infection, especially those with severe immune deficiency, are more difficult to diagnose and have high mortality if left untreated. Antiretroviral treatment reduces the risk of TB disease and improves survival, but not completely. Preventive treatment with isoniazid provides additional protection against TB disease but has limited effect beyond the time-span of the preventive treatment course, and limited application because of feasibility constraints. In addition, MDR/XDR-TB outbreaks among HIV-infected individuals occur in settings where nosocomial TB transmission is poorly controlled, and prophylactic treatment for MDR TB is not available.

Failing TB control = failing health systems.

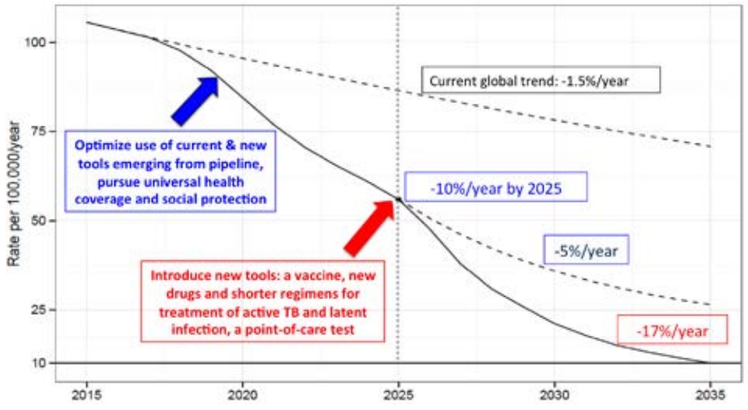
Finally, effective control of TB is hampered by poor health system responsiveness. TB is the archetypal disease of poverty, hitting hardest those with the poorest access to quality health care. TB patients and their families often face catastrophic expenditures for diagnosis and treatment, especially with MDR/XDR-TB. Public clinics and laboratories, in most countries responsible for managing TB, are often poorly staffed, poorly equipped and underfunded, while private care providers tend to delay diagnosis, provide substandard treatment and not notify TB cases. Also these problems are aggravated in TB-HIV co-infection, which requires integrated management by collaborating or integrated services that in practice often work in isolation.

3. ELIMINATION OF TB REQUIRES MASSIVE STEP-UP IN RESEARCH

Striving to overcome these hurdles, much needs to be done. That is why the United Nations (UN), WHO, researchers, and TB experts are stepping up their efforts and plea urgently for more research to be targeted to eliminate TB by 2050. Herein, The Netherlands play a key role, boasting a strong tradition, capacity and potential with regard to both TB control and TB research. The Dutch national TB program has proven to be very effective, and The Netherlands stand out in research for global health issues, including TB as a major area. Knowledge, expertise and know-how on TB control as well as TB research findings have been shared with experts around the world. However, in order to eliminate TB by 2050, research needs to be ramped up massively. The Netherlands science sector stands to contribute in significant and excelling ways in this specific niche which has strong spill over effects towards strengthening Dutch research engagement in the broader areas of Life Sciences and Health.

3.1 TOWARDS ELIMINATING TB

In May 2014, UN member states adopted the goal of eliminating TB as a public health problem by 2050. Similarly, the European Union is working towards TB elimination, defined as an incidence of less than one case per one million inhabitants. To reach this ambitious goal, the decline in TB incidence has to accelerate from an average 1.55% per year to an average 17% per year for the next twenty years (2015-2035).
This massive acceleration cannot be reached without major improvements in prevention, diagnosis and treatment of the disease. It requires transformative technological innovations to address the current major obstacles to control, let alone elimination, of TB. Mathematical modelling studies show that such acceleration can only partly be reached with optimizing current diagnostics and treatment and improving access to care through universal health coverage and social protection (see graph). The push needed to achieve the acceleration in TB decline requires introduction of a vaccine, new drugs and shorter regimens for treatment of active TB and latent infection, and point-of-care diagnostics.



Source: Global TB Program, WHO.

3.2 CAPACITY NEEDS

Expanding research capacity and strengthening existing capacity in both resource-rich and resource-poor settings are essential step up the research effort needed to eliminate TB. Major areas in which capacity should be expanded and strengthened in high-endemic (generally resource-poor) countries are clinical-epidemiological research, diagnostic evaluation, treatment trials and vaccine trials, as well as implementation and operational research, epidemiology and program evaluation. The WHO's End TB Strategy proposes models for local research capacity strengthening in high-endemic countries. Reason to strengthen in-country research capacity is that it is considered a key condition in enabling the level and required effectiveness of research activities and output.

In resource-rich countries, where knowledge and the economic infrastructure for advanced fundamental research and product development are available, capacity needs include several areas. These areas are development and expansion of animal models, 'omics'-approaches, in vitro M. tuberculosis and macrophage co-culture models, and innovative culture systems that accurately model the situation in patients and link bacterial phenotype with genotype. Finally, researchers in resource-rich countries should be stimulated and enabled to provide methodological and academic support for TB research in resource-poor settings.

3.3 FUNDING FOR TB RESEARCH

TB can be difficult to diagnose, but once it is detected, it is generally treatable. This makes the economic case for investment in TB control compelling, as treatment is low cost and highly effective. On average, a TB patient when treated gains 20 additional years of life, resulting in substantial economic and health return, be it in low- middle or high income settings. TB receives, however, less than 4% of total development assistance for health globally (compared to 25% of total development assistance for fighting HIV/AIDS).

The cost-effectiveness of screening and treatment of latent TB in those with HIV is long established, and treatment of drug-susceptible TB is one of the most cost-effective components of a basic package of health care. Also, while diagnosing and treating MDR-TB may be more costly than treating drug-susceptible TB, it has still been found to be cost-effective. Recently, Recently, the Copenhagen Consensus Centre estimated investments in accelerated TB control, including research, to have a social return of between US$ 16 and US$ 82 per dollar invested, with the highest benefit-cost ratios for the poorest globally.[2]

Despite effective treatment of TB patients being hugely cost-effective, major gaps exist between the funding levels required for realizing the global research agenda and the actual amounts available. The World Health Organization and the Global Fund to Fight AIDS, TB and Malaria estimate that there is an annual anticipated demand for at least US$ 1.6 billion in international support to bridge the funding gap over 2014- 2016, in 118 low and middle income countries which are eligible for financing from the Global Fund.

The total resource requirements to combat TB and multidrug-resistant TB (MDR-TB) equal US$ 4.8 billion each year. It is projected that domestic contributions could cover the bulk (over 65%) of financing required for TB care and control in these 118 countries, equivalent to US$ 3.2 billion. This will require that TB funding increases in line with economic growth and that there is increased political commitment especially in countries that currently underperform in comparison to their ability to pay.[3]

Although, investing in TB research is cost-effective, has a high social return and is of major importance for people living with HIV/AIDSAIDS, funding TB research is not as common as it seems. Funding depends highly on a small number of donors, such as the USA and UK governments and the Bill and Melinda Gates Foundation. The EU invests mainly in TB research through the Europe Developing Countries Clinical Trials Platform (EDCTP) for an amount of US$18.9 million (out of the total amount of US$32.3 million) for TB research. The largest single spending area of the EU was drug development (US$19.0 million, 59% of its spend).

The Netherlands, in certain niches, rank among global leaders in combating HIV/AIDS, TB and neglected tropical diseases. The Dutch government funded TB research with an amount of US$9.7 million. The vast majority of this amount, US$ 8.1 million, is invested in international product development partnerships in diagnostics and vaccines; most of this is spent outside The Netherlands. In November 2014, the Minister for Foreign Trade and Development Cooperation, Liliane Ploumen, announced her decision to renew, for the next 5-6 years the Ministry's funding for public-private partnerships that develop products in the battles against HIV, TB, malaria and neglected tropical diseases, pointing to the value of continued financial and scientific contributions from the Netherlands.

Global industry spending for TB research has been limited to a few candidate products including drug compounds. As private pharmaceutical companies are retreating from antimicrobial R&D, particularly for TB, there is an urgent need to increase and diversify sources for investment in TB research, and make optimal use of every euro spent on TB research.

[2] *The Copenhagen Consensus Centre, Post-2015 consensus: health perspective, http://www.copenhagenconsensus.com/publication/post-2015-consensus-health-perspective-tuberculosis-vassall*
[3] *http://www.who.int/tb/WHO_GF_TB_financing_factsheet.pdf*

4. THE GLOBAL TB RESEARCH AGENDA

The World Health Organization has developed a global TB research strategy to ensure that research is targeted and stepped up in the most effective directions worldwide. The strategy builds on the needs and potential to contribute knowledge in low- and middle-income countries, which bear the largest burden of human suffering due to TB. An important component is to ensure that appropriate technology is adopted promptly so that novel control tools become accessible and affordable to populations in the countries that need them most. These are critical steps for achieving elimination of TB as a public health problem by 2050. The research strategy builds on a global TB research agenda, developed through consensus and consultation of researchers and stakeholders from around the world. It is laid down in the International Roadmap for Tuberculosis Research [4] but is continually updated as new knowledge emerges. The global TB research agenda identifies priorities in the following areas:

1. Fundamental research.

Our understanding of the pathogenesis of TB and the contributions of host and pathogen is still limited. Much more insight is needed into the dynamics of host-pathogen interaction to explain failing natural and induced (vaccination) immune responses, as well asthe phenomenon of latency and determinants of progression along the continuum from exposure to the pathogen to, ultimately, disease. In parallel, stage-specific bacterial and host markers of this progression need to be determined to facilitate diagnostic and early treatment efficacy. This requires large-scale clinical-epidemiological studies integrated with basic research into immunology and microbiology. Various research strategies need to be applied, including genomics, transcriptomics, proteomics and metabolomics, in-vitro co-culture systems and animal studies that can overcome the limitations of current models.

A cross-cutting item in the global TB research agenda is the need for valid biomarkers: 1. to diagnose TB in general, and in children and extra pulmonary TB in particular (diagnostic biomarkers); 2. to distinguish those latently infected individuals who are at high risk of developing TB and should receive preventive treatment (prognostic biomarkers of TB risk); 3. to select and evaluate the most promising vaccine candidates at an early stage (correlates of immune protection; important for risk mitigation strategies in vaccine development); and 4. to monitor and triage for predicting treatment outcomes (prognostic biomarkers of cure).

2. New diagnostics.

Despite an encouraging increase in development of new tests, the ultimate goal of a single cheap point-of-care assay for all types of TB in all types of patients that also tests for resistance to major drugs is still beyond reach. Recently, four consensus target product profiles were identified for high-priority tests that could realistically be developed. Aimed at aligning the needs of end-users with the specifications that product developers require, these profiles include a highly accessible test to replace sputum smear microscopy, a biomarker-based test to diagnose forms of TB that cannot be detected through sputum (extra pulmonary TB, TB in children), a simple and cheap triage test to identify patients who have high probability of having TB, and an assay to rapidly detect resistance of M. tuberculosis against the most important first- and second-line drugs. Similar profiles for improved assays for latent TB infection are underway. The development of several of these assays requires intensified biomarker research, as well as transforming sophisticated laboratory technologies into robust, accurate and affordable point-of-care platforms.

3. New drugs and treatment regimens.

Shorter, simplified and safer treatment is needed along the entire spectrum of TB: for drug-susceptible TB, for MDR/XDR-TB and for latent (MDR-) TB infection, and applicable in all types of patients, including children and patients on antiretroviral treatment. This requires research into more effective use of existing drugs based on pharmacokinetic and pharmacodynamic parameters, combinations of recently approved drugs with existing drugs, and development of new drugs. In particular drugs are needed with sterilizing capacity that target persisting organisms during the continuation phase of treatment to reduce the unacceptably long treatment duration. Therapeutic vaccines can provide cure in patients with complex resistance patterns.

Clinical trials and trial capacity need to be massively expanded, as well as pharmacological studies on optimized dosing in relation to efficacy and toxicity including drug-drug interaction studies. The drug pipeline at present appears static with no compound in Phase I of clinical development. There is a major need for expanding this pipeline and getting promising compounds from the pre-clinical into the clinical stages of development, and for identifying early prognostic biomarkers of relapse-free cure that can accelerate clinical development by shortening clinical evaluation from 1-3 years to 1-3 months per patient.

4. An effective and safe vaccine.

At present 15 vaccine candidates of various types are in clinical development. Most candidates are designed for prevention of infection or of progression to disease in infected persons, and are currently in, or about to enter, Phase II or IIb trial stages. There are however still fundamental gaps in our understanding of protective immunity in TB, and there are no established immune correlates of protection, disease risk or infection. Therefore until tested in Phase III trials (which need to be large, of long duration and expensive) there is major uncertainty as to whether the current candidates will prove effective. The pipeline must be further expanded with vaccine candidates that are based on diverse strategies to elicit protection. This requires identification of new biomarkers, novel strategies for antigen selection and evaluation, development of vaccine delivery methods and early experimental trial designs for addressing fundamental questions about vaccine-induced protective immune responses as well as for evaluating these against biologically relevant endpoints. Novel trial designs and targeted study populations with high a priori chance of developing clinically meaningful endpoints should be considered to reduce costs and to allow for testing of multiple agents within a reasonable timeframe.

5. Optimized implementation.

Critical for eliminating TB is to not only develop new tools (diagnostics, drugs/treatment regimens, vaccines, biomarker assays), but also ensure that they are integrated in interventions in ways that maximize their uptake and access and quality of care. This requires implementation research to evaluate these tools and interventions for their effectiveness, feasibility, cost-effectiveness and affordability in the real world. Barriers to access to timely diagnosis and quality care need to be studied and addressed through operational research, including involvement of the private health sector and community organizations, and alleviating economic burden to patients. More epidemiological data are needed in order to target interventions to segments of the population that will benefit from them most. Finally bottlenecks to implementing established policies need to be to identified and addressed through systematic program evaluation, taking into account the perspective of the health system as well as patients and communities.

[4] *http://www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf.*

5. THE DUTCH TB RESEARCH POLICY, GLOBAL HEALTH THEMES AND RESEARCH AREAS

5.1 THE DUTCH TB RESEARCH AGENDA AND THE NETHERLANDS SCIENCE POLICY FRAMEWORK

As the WHO strives to increase and improve TB Research worldwide, the Dutch government has defined its ambitions in an overarching Dutch R&D and Science Policy Framework (*Wetenschapsvisie 2025: keuzes voor de toekomst*).[5] When considering the four themes of TB research proposed in this White Paper as harnessing Dutch areas of excellence with global relevance, the fit with the ambitions and approach proposed in the Dutch Science Policy Framework is evident:

1. **Key ambition is to develop and create world-leading science:**
The four areas of excellence identified in this document each represent areas in which Dutch TB researchers and research groups are among the world leaders in the field. This is illustrated by their scientific publications and achievements, their networks and the major funding sources they have been able to access (e.g. EU Framework Programs, EDCTP, NIH/NIAID, BMGF). This world-leading position is rooted in strong international competitiveness of some of the relevant research fields. For example, the cutting-edge Dutch research into host-pathogen interactions and TB biomarkers reflects the high level of basic and translational immunology in The Netherlands in general. Similarly, the high level of infectious disease and molecular epidemiology provides a strong basis for the competitiveness of Dutch research into TB transmission. There is certainly interest among other excellent researchers in these fields to expand their work to TB, provided that funding allows them.

2. **Key ambition is to link science to society and industry, with maximized impact:**
The TB research areas of excellence are uniquely linked to societal needs and application, informed as they are by a global research agenda meant to eliminate one of the major infectious killers in the world. This applies along the entire R&D spectrum: for example the upstream host-pathogen work is essential for vaccine development and biomarker discovery, which in turn are essential to provide the products highly needed to accelerate successes in TB control. The competitive position of Dutch TB knowledge has resulted in major contracts in (more downstream) implementation, such as the US government's selection of Dutch organizations to lead its principal technical assistance programs to countries most affected by TB.

   Since TB is often a disease of poverty, industry interest in product development has remained of modest dimension thus far. For Dutch companies this has largely been in diagnostics, in particular to improve access to care in resource-poor settings. However, novel mechanisms are being created to stimulate industry involvement in TB product development. Interestingly, among the first initiatives in health to link research funding with that of the European Investment Bank was the Global TB Vaccine Partnership, in which the Netherlands-based Tuberculosis Vaccine Initiative plays an important role. In addition, the Dutch TB research environment is not only strong at the upstream end of the R&D chain, i.e. in preclinical and early clinical research, but also at the downstream end of 'real world' product evaluation and implementation. Together with strong links of several Dutch groups with end users (e.g. TB control programs, patient groups), policy bodies (e.g. WHO) and international donors (e.g. GFATM) this allows product developers to optimize the chances of future uptake of their product. Therefore the expectation is that Dutch companies will become more interested in collaborating with Dutch TB research groups. All this will maximize the impact that Dutch research will have on the final goal, global elimination of TB as a public health problem.

3. **A breeding place for scientific talent, also by 2015:**
Dutch TB research has attracted, and is attracting, a lot of young research talent, as shown by the large numbers of PhDs taken on TB-related subjects in Dutch research institutes. Its strong international reputation has made Dutch TB research groups popular places for PhD and post-doc attachments, importantly also for foreign applicants. This broad supply of young talent has allowed several groups to pick and nurture the best among their peers. The opportunity to work both at the parent institute in The Netherlands and in the many collaborating institutes in high-incidence countries around the world contributes to this success. The major achievements needed over the coming decades and vitality and breadth of the Dutch TB research field, with regard to focus as well as scientific approaches, further ensure that TB research will remain a breeding place for scientific talent at least for the coming 10 years.

5.2 THE DUTCH TB RESEARCH AGENDA AND OTHER GLOBAL HEALTH PRIORITIES

In addition to the new science policy of The Netherlands, policies on other global health issues are being developed and discussed within the Dutch government as well as at European level. These global health priorities have a clear link to TB and to the areas of excellence for Dutch TB research:

1. Antimicrobial resistance

Increasing antimicrobial resistance is widely recognized as a global threat. Increasing drug resistance in tuberculosis, including MDR-TB and XDR-TB, is an integral part of this problem. Perhaps more than any other form of antimicrobial resistance, drug-resistant TB due its airborne transmission does not respect national boundaries. International travellers, labour migrants and refugees may import MDR-TB and XDR-TB unnoticed and they may transmit these resistant forms in resident community's months to years after entry. This clearly calls for a cross-boundary approach. Control of drug-resistant TB is among the international priorities in antimicrobial resistance and included in policy guidance such as the EC's Action Plan against the rising threats from Antimicrobial Resistance.[6] The measures proposed in this Action Plan for controlling antimicrobial resistance in general completely reflect the measures needed to combat drug-resistant TB: ensuring appropriate use of antimicrobials, promoting microbiological diagnosis, preventing microbial infection, developing effective antimicrobials, taking an international approach and reinforcing research. Each of the four areas of excellence identified in this document contributes to this agenda. Dutch research work on these research themes will yield biomarkers for improved microbial diagnosis, insights into preventing transmission of drug-resistant TB, effective drugs and improved treatment of drug-resistant TB and drug-susceptible TB (addressing the spread as well as the emergence of drug resistance), and scalable and effective health interventions that bring these elements together.

2. One Health

Tuberculosis of humans and animals are firmly interconnected. Human TB pathogens are found in various animal species, and mycobacteria of animals are pathogenic for humans. In the Netherlands research on animal and human tuberculosis is of high quality but not yet fully integrated. The One Health concept is based on the recognition that human and animal health are inextricably linked. Humans and animals have socio-economic interactions through direct physical contact, food chain and environment. Therefore, the health and well-being of all species can only be safeguarded by enhancing cooperation and collaboration between physicians, veterinarians, and other scientific health professionals. This must be achieved by effectively coupling the know-how and infrastructure available in the human and veterinary-agricultural domain. In this context, the area of excellence understanding and reducing transmission is of particular importance. In addition to M. tuberculosis, Mycobacterium bovis (>99% identical; similar pathogenesis and clinical signs) is an important cause of morbidity, both in man and in animals. The Veterinary Faculty of Medicine in Utrecht has invested in research capacity to understand the pathogenesis in view of vaccination/post infection treatment and diagnosis. Such information is critical for the reduction of transmission.

3. Responsible use of medicines

Promoting more effective, safer and cost-efficient use of medicines is an important area of (inter)national policy and research. This is much applicable to tuberculosis: the number of available effective drugs is limited, combination treatment is needed to prevent emergence of resistance, and treatment is for 6 to 24 months, posing challenges to adherence. Misuse of TB drugs is a likely cause of emergence of MDR/XDR-TB in many regions of the world. While the current one-size-fits-all paradigm of standard drug regimens has the advantage of simplicity and easy scalability, increasing drug resistance as well as increasing importance of co-morbidities and co-medication call for more personalized approaches. The area of excellence of treatment optimization proposed here is exactly about addressing this issue, through developing new drugs and rapid drug-resistance tests, improving our knowledge and the patient management-oriented use of pharmacokinetics of TB drugs, and treatment personalization (drugs, duration) based on prognostic markers. Also, innovative use of existing drugs (such as high-dose rifampicin) is an important area of research given the limited new TB drug pipeline, and ties in closely with this broader research and policy agenda. The other areas of excellence contribute to these aims, through identifying prognostic biomarkers, sequencing clinical strains to inform the design of molecular resistance assays, developing and evaluating interventions to implement these improvements and developing novel treatment strategies that combat also MDR/XDR-TB.

[5] *https://www.rijksoverheid.nl/documenten/rapporten/2014/11/25/wetenschapsvisie-2025-keuzes-voor-de-toekomst*
[6] *http://ec.europa.eu/dgs/health_food-safety/docs/communication_amr_2011_748_en.pdf*

6. THE DUTCH AREAS OF EXCELLENCE EXPLAINED

As said, Dutch research groups have made, and will continue to make, internationally highly recognized contributions to research for accelerating global elimination of TB. Based on unique capacity, track record, networks and product innovation, four research areas, the so-called areas of excellence, stand out that are outlined below. In addition, Dutch researchers have played important roles in research capacity building.

AREA OF EXCELLENCE 1: HOST-PATHOGEN INTERACTION

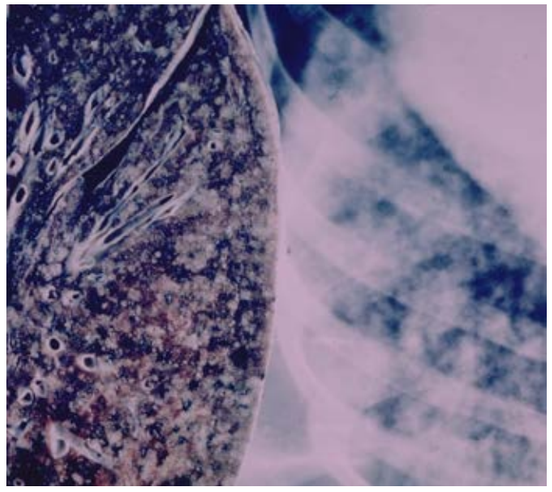
Various research groups in the Netherlands perform cutting-edge work on host-pathogen interactions in TB. There is strong complementary expertise in vaccine development and biomarker discovery, including but not restricted to genomics, transcriptomics, proteomics, lipidomics and other -omics technologies. Active participation in high-ranking international networks provides access to clinical material and latest data.

Fundamental work is done at Leiden UMC to understand the host cellular immune response during infection and disease, discover antigenic targets for vaccination, diagnosis and human biomarker profiling (protection, progression towards disease, response to intervention) and identify human genetic determinants and mechanisms that underlie susceptibility to mycobacterial infections. In Amsterdam research groups at VUMC and AMC, together with various international partners, work on fundamental questions such as the composition of the outermost part of M tuberculosis and its effects on bacterial virulence and immunogenicity, the role of bacterial protein secretion in vaccine responses, and mechanisms of granuloma formation. The unique capacities here are the use of high-resolution fluorescence and electron microscopy, the zebrafish model (developed by the VUMC group) for studying host-pathogen interactions, and granuloma biology in relation to immunology.

Humanised mouse models with the required BSL3 infrastructure are being used in several institutes, including Leiden UMC (vaccination and challenge models) and AMC (granuloma biology models). The Netherlands also boasts unique capacity for animal research in natural host models. These facilitate translation to the human situation and offer possibilities for longitudinal follow-up studies with high frequency repeated sampling, as well as anatomical site-specific host-pathogen interaction studies.

The Biomedical Primate Research Centre (BPRC) in Rijswijk, the largest of its kind in Europe, has extensive experience in infectious disease research in non-human primates, and been involved in several TB vaccine challenge studies. At the Central Veterinary Institute (CVI) in Lelystad there is expertise and BSL3 infrastructure for (vaccination) challenge models in large animal species (bovine, porcine). Bovine challenge models with M. bovis and non-tuberculous mycobacteria have been performed to improve diagnostic test systems, and to study the basis for cross-reactive immune responses based on protein and non-protein (glycolipid) antigens.

Dutch research groups, through their networks, have excellent access to clinical samples and technological platforms needed for such research. Important in this respect are the TBVAC2020/TBVI network for TB vaccines and TB Biomarkers; the PanACEA network for clinical trials of TB drugs and drug regimens; the European clinical research network TBnet, the BMGF-Grand Challenges TB Biomarker Research network and additional long-term clinical research collaborations with universities and hospitals in, among others, Indonesia, Vietnam, Tanzania, Uganda, South Africa, Gambia, Ethiopia, Gabon, Belarus and Romania.



Achievements and current projects: some examples

At the Netherlands Cancer Institute and AMC high resolution analysis of the subcellular localization of pathogenic mycobacteria and its vaccine strain caused a paradigm shift in the host-pathogen interaction field and importantly, opportunities to improve the vaccine BCG.

Leiden UMC together with other partners has identified host transcriptomic biomarker signatures, diagnostic of TB disease in adults as well as in children, including HIV infected individuals, and is identifying host transcriptomic biomarker signatures, prognostic of TB risk in adults. Faculty of Veterinary Medicine, Utrecht University and Stratingh Institute for Chemistry, University Groningen have developed reagents to detect mycobacterial lipid-specific human T cells. These are now being validated for their ability to distinguish latent from active TB and to monitor the effects of lipid immunizations using chemical synthesis which facilitates quality control and scale-up. The same group contributed to the recent discovery of the first chemical marker for TB.

Radboud UMC, Leiden UMC and their Indonesian collaborators have established large patient cohorts and identified genetic variation associated with TB, and M. tuberculosis genotypes associated with severity and treatment outcome. In a collaborative effort VUMC and AMC described the outermost part of mycobacteria to be an instable layer detectable with electron microscopy and mass spectrometry but absent using detergents. This finding caused a shift in the culture conditions used for BCG, the vaccine strain used worldwide.

KIT BR has been exploring the potential of a pragmatic Treat-to-Test approach, in which host-derived biomarkers are identified that show responses during the initial period of anti-TB treatment. This approach has potential use for diagnosing extra pulmonary tuberculosis, but also for treatment monitoring and prediction of treatment outcomes.

Opportunities for valorisation: some examples

Leiden UMC is developing low-cost robust user-friendly point of care lateral flow assays based biomarker tests for TB diagnosis, has tested several new TB vaccines in first-in-human trials, and is developing new multi-stage TB vaccines.

Under the One Diagnostics initiative KIT BR and Philips collaborate to develop and evaluate a biomarker identified by KIT using the simple hand-held Magnotech diagnostic device of Philips for TB diagnosis and treatment monitoring.

VFMU has been developing assays for the early diagnosis of TB in cattle and wild life species. American zoos are investing into the further development of these assays, as they are concerned about the zoonotic aspect of mycobacterial diseases in animal species. In addition, VFMU has been involved in developing a paratuberculosis vaccine for cattle in collaboration with MSD Animal Health.

AREA OF EXCELLENCE 2: UNDERSTANDING AND REDUCING TRANSMISSION

Dutch research groups have been at the forefront of population epidemiology and molecular epidemiology to understand TB transmission and develop and target interventions for its interruption. This is based on several unique research conditions in The Netherlands.

First, The Netherlands boasts a national surveillance and molecular epidemiology (molepi) database in which clinical, epidemiological, drug resistance and strain typing data have been collected for all TB patients notified in the country since 1994. Resulting from a longstanding and highly successful collaboration between RIVM and KNCV it is the largest, richest, highest-coverage and most extensively researched and publicized TB surveillance database in the world. It has provided the basis for development of several state-of-the-art DNA fingerprinting and genotyping methods (e.g. IS6110 RFLP; spoligotyping) as well as methodologies for studying TB transmission and population structure of M. tuberculosis. The cutting-edge molepi expertise stemming from this work has been applied in similar collaborative studies in the USA, South Africa, Vietnam, China, Indonesia and Uganda. Of recent the Netherlands surveillance and molepi database is being expanded with whole genome sequencing, allowing much more in-depth understanding of M. tuberculosis transmission, population changes and micro-evolution, in particular with regard to drug resistance and virulence. This makes the Netherlands database again one of the most valuable of its kind in the world.

Secondly, parallel research is being done in animals. The Central Veterinary Institute is National Reference Laboratory for

tuberculosis in all other animal species besides human subjects, and has a large collection of typed mycobacterial species (non-tuberculosis as well as tuberculosis complex bacteria) from a large variety of mammals, birds and fish species. Comparable molecular techniques for DNA fingerprinting and genotyping are operational and available for molecular epidemiology and other type of studies. Collaborative work is done on cattle, buffalo, lion and elephant at the Faculty of Veterinary Medicine, Utrecht University.

Thirdly, the Netherlands has been uniquely positioned for collection and analysis of large-scale epidemiological TB data in high-incidence countries, among others through applied research work at KNCV in the context of technical assistance to National TB Control Programs that, among others, lead to the globally accepted DOTS approach to TB treatment. One area of world-leading expertise is TB surveys. Started with tuberculin surveys this evolved into scientific supervision of TB prevalence surveys and drug resistance surveys in a large number of countries. A related area of expertise is spatial analysis of TB data (at KIT BR), which can be applied to study TB transmission by e.g. analysing the spatial links between phylogenetic lineages of M. tuberculosis. Complementary work on innovative methods for antimicrobial resistance surveillance, including for TB, is done at AIGHD.

Finally, there are longstanding collaborations with clinical research institutes in high-incidence settings with a broad and intensive collaboration in the field of clinical, operational, immunological and genetic studies in which TB transmission and TB control are being studied from a biological as well as a public health point of view. These include collaborations with Padjajaran University in Bandung, Indonesia and with Kilimanjaro Medical Research Centre in Moshi, Tanzania (both Radboud UMC, Leiden UMC), Makerere University in Kampala, Uganda (AIGHD) and the Albert Schweitzer Medical Research Unit in Lambaréné, Gabon (AMC). There are in addition more recent clinical research collaborations with the Universities of Yogyakarta (Indonesia), Iasi (Romania) and Minsk (Belarus) (Groningen UMC).

Together with a broad expertise in clinical research these conditions and capacities provide a unique basis for also addressing questions about the "biology of TB transmission" in humans and non-human species. Such questions relate to determinants of individual and collective susceptibility to infection (such as the role of innate immunity and effects of vitamin and other micronutrient deficiencies as well as other biological correlates of poverty) and options for reducing that susceptibility, but also the role and early identification of "TB superspeaders" and places in specific communities where the bulk of transmission takes place.

Achievements and current projects: some examples

The Netherlands molecular epidemiology database and the related work of RIVM, KNCV and AIGHD have been highly important for discovering the Beijing genotype, a globally emerging genotype associated with (multi)drug resistance, and for understanding development and transmission of TB drug resistance in Europe, Asia and Africa. It has also been invaluable for discovering and understanding trans-border "migration" of MDR-TB, in particular between Eastern and Western Europe.

The work by KNCV on TB population data and surveillance has yielded, and continues to yield, invaluable knowledge about the burden of TB and drug-resistant TB around the world and its epidemiological and economic determinants. The unique expertise built through this work provided opportunities and input data for epidemiological and economic modelling to inform TB control worldwide. treatment outcomes.

Valorisation: examples of successes and opportunities

RIVM developed methods (IS6110 RFLP typing, spoligotyping) that for two decades have been global the standard of DNA fingerprinting and genotyping of M. tuberculosis.
KIT in collaboration with the Dutch company MRC-Holland has developed a high-throughput SNP typing assay combining detection of drug resistance and strain identification, suitable for use on site by reference labs in endemic countries for surveillance and control purposes. The assay is now commercially available and being distributed by the French start up Beamedex.

AREA OF EXCELLENCE 3: TREATMENT OPTIMIZATION

The Netherlands boasts a wide array of experimental, translational and applied research activities around TB treatment. Work on new drugs and drug regimens spans the entire R&D chain, from drug discovery, preclinical testing of new drug candidates and Phase I, II and III drug trials to pharmacovigilance and cost-effectiveness of new drug regimens. Complementary to this focus is that of precision treatment: selection of drugs and drug doses based on drug resistance profiles and individual-patient pharmacokinetics. There have been important achievements and there is ongoing leading work, by Dutch groups, on identification of genetic resistance markers, development of rapid resistance assays and therapeutic drug monitoring. A new area is that of host-directed therapy, which aims at improving host defence against mycobacterial infection, including metabolic reprogramming.

Also here the strength of this research area in The Netherlands is defined by unique expertise and capacities, as well as fruitful national and international collaborations and networks. Several Dutch research institutes are active in discovery, preclinical and early clinical research into novel treatment options - highly important given the scarcity of newly available antibiotics and the rapid emerging of MDR/XDR-TB strains.

At VUMC work is done on antibiotic-related stress in M. tuberculosis, identification of new compounds active against the bacillus, and in vivo testing of combinations of new and existing antibiotics using the zebrafish model. Leiden UMC is screening libraries of selected molecules for repurposing and/or discovery, which impact on intracellular infection, both in humans and in zebrafish models. Groningen UCM, RIVM and Erasmus UMC jointly work on newly synthesized compounds. Screening for activity against M. tuberculosis is done at RIVM and subsequently pharmacokinetics are studied in animal models at Groningen UMC, followed by studies in infection models at Erasmus UMC.

Essential for clinical research and phase II-III drug trials are longstanding collaborations with institutes in TB high-incidence countries, and capacity building for these institutes to function as clinical research/trial sites. For drug-susceptible TB, the PanACEA consortium is among the largest TB drug clinical trial partnerships in the world. With Radboud UMC as the co-lead, it operates trial sites in 6 African countries and has been involved in several non-proprietary TB drug trials. Other clinical research collaborations mentioned under Area of excellence 2 are also important as potential drug trial sites.

For drug-resistant TB there is access to MDR/XDR-TB patients through the treatment unit in Beatrixoord, Haren. There are multiple direct collaborations between Dutch groups and MDR/DRX-DR-TB treatment institutes in Eastern Europe, including Romania, Belarus, Georgia and Kazakhstan. In addition, Dutch groups actively participate in TBnet, a network of European researchers and TB treatment centres, including several with high MDR/DRXDR-TB rates; the TBnet MDR/XDR-TB clinical database is managed in The Netherlands by AIGHD. The group at Groningen UMC also has an intensive collaboration in clinical research on second-line drugs and therapeutic drug monitoring with specialist institutes in Italy, including the WHO Collaborating Centre for TB and Lung Disease, Tradate.
Equally important is the opportunity for Dutch research groups to work with M. tuberculosis strains with a broad range of resistance patterns and geographic origin. Foremost this is through the unique, extensively profiled and genotyped strain collection from the Netherlands that, with complete national coverage, spans over 20 years. In addition various Dutch groups (RIVM, KNCV, AIGHD, Radboud UMC, Groningen UMC, KIT BR) have access, through research collaborations, to data and M. tuberculosis strains from drug resistance surveillance programs in other parts of the world, including Eastern Europe (see above), Asia (China, Vietnam, Indonesia) and Africa (several countries - there is close collaboration with the newly established Supranational Reference Laboratory for the African region in Kampala, Uganda).

Dutch research on precision treatment is spearheaded by Groningen UMC that is among the world leading groups in pharmacokinetics and pharmacodynamics of second-line TB drugs. Technology development by this group, including a dried blot spot method for sample collection and preservation, allows application in resource-poor settings. Groningen UMC also works on therapeutic vaccination strategies to augment the treatment response in patients with MDR/XDR-TB.

Finally, Dutch groups are well positioned for implementation research on new drugs and drug regimens. KNCV, as major global player in scale-up of TB interventions, is closely involved in the introduction of new second-line drugs, including the establishment in resource-poor settings of pharmacovigilance systems – a new development of wider significance in the context of antimicrobial resistance which will increasingly see introduction of conditionally approved antibiotics for which the safety profile is not completely determined. Moreover, there is a solid base of existing collaborations on modelling of economic and epidemiological impact of new TB drugs of Dutch groups (AIGHD, KNCV) with major funders and stakeholders in this field, such as BMGF, the TB Alliance and the Critical Path Institute, as well as international research partners. Similar work is being done by Erasmus UMC for the Dutch and European setting, focusing on prophylactic treatment of latent TB infection.

Achievements and current projects: some examples

KIT BR in collaboration with RIVM and Radboud UMC has used highly innovative and sensitive culture systems to study micro colony responses to transient drug exposure. These investigations have resulted in a deeper understanding of the ability of certain strains to generate resistance and may lead to further optimization of treatment regimens.

Radboud UMC, with Indonesian collaborators, was responsible for the first randomized-controlled trial evaluating high-dose rifampicin treatment in TB meningitis, showing a 45% survival benefit. Radboud UMC is also leading clinical trials evaluating high-dose rifampicin in pulmonary TB in Africa.

AIHGD in the context of the BMGF-funded TBMAC network is developing and validating models for economic evaluation of new treatment regimens and drug resistance testing, meant to steer global R&D investments in treatment combinations and rapid resistance assays, as well as their future implementation in public health programs.

Opportunities for valorisation: some examples

Groningen UMC has developed and validated a range of dried blood spot assays for monitoring TB drug blood concentrations in resource-poor settings. This procedure combines an easy sampling procedure (finger prick) with high sample stability. In addition the UMCG developed limited sampling procedures enabling accurate drug exposure assessment without the need of intensive blood sampling.

KIT BR is in the process of valorising its micro colony monitoring system with two Dutch companies.

TB drug repurposing and discovery at Leiden UMC has identified several FDA approved compounds as hits, suggesting rapid paths towards clinical testing.

AREA OF EXCELLENCE 4: IMPROVING THE HEALTH SYSTEM RESPONSE

Research to improve the health system response to the TB epidemic has for long time been an important niche for Dutch research groups.

There are numerous examples of successful operational and health systems research collaborations and projects that have driven policy change at local, national and even global level. Several of these studies have been done, or supported, by KNCV as part of their close collaboration with National TB Control Programs. Various other groups contribute to this area of work, e.g. as part of longstanding clinical research collaborations (see above: Radboud UMC, AIGHD, AMC) or evaluations of intervention programs (e.g. TB REACH – by KIT BR). Important in this respect are studies into improvement of service delivery, e.g. focusing on high-risk patients for more active diagnostic approaches such as for people living with HIV, diabetes mellitus or other chronic conditions. Operational research is also an important area for local capacity building (see below).

An area of growing importance is implementation research to collect evidence for policy decisions about scale-up of new TB interventions, linking effectiveness to feasibility and cost-effectiveness and affordability in an integrated approach. Dutch groups are at the forefront of this area of multidisciplinary TB research, and play an important role in agenda setting and methodology development in this field in close collaboration with global players such as the WHO, the GFATM and the BMGF (AIGHD, KNCV). The epidemiological and economic impact modelling mentioned earlier has also been important in other areas of implementation, such as for new diagnostics and diagnostic algorithms (AIGHD, Erasmus UMC).

This area of excellence also includes development and evaluation of methods for improving access to TB diagnosis and care, an important area for technological innovation. These may be low-tech solutions, but also technologically complex solutions that can nonetheless have significant positive impact on cost-effectiveness and affordability of TB interventions. An example of the former is the use of Light Emitting Diode (LED) illumination for TB smear microscopy that was invented by KIT BR and has now been adopted worldwide as standard WHO policy for TB smear microscopy and is developed by the main microscopy manufacturers. An example of the latter is computer-assisted reading of digital chest X-rays, a method developed for TB by Radboud UMC in collaboration with Delft Imaging Systems.

Achievements and current projects: some examples

AIGHD and KNCV, in collaboration with international research groups recently completed comprehensive multidisciplinary implementation research projects on patient-centred TB treatment in Tanzania (step-wise development pilot) and rapid molecular TB diagnosis in Brazil (phased implementation trial). Both resulted in major changes in national TB control policies and scale-up of the intervention at country level.

Radboud UMC leads an international consortium on TB and Diabetes mellitus, with field sites in 4 countries and basic sciences in leading laboratories in Europe and South Africa. This project is yielding important insights to guide service delivery for TB patients who have diabetes.

Opportunities for valorisation: some examples

Radboud UMC with Dutch companies Thirona and Delft Imaging Systems develops software for computer-assisted reading of digital chest X-rays. This software is now being used in several countries, and being evaluated for endorsement for global use by the WHO.

Groningen UMC and Radboud UMC work on the evaluation of a TB-specific handheld exhaled breath analyser developed by the Dutch eNose Company. This technology could potentially identify patients with high probability of having TB (triaging) at very low cost, allowing much more cost-effective and affordable use of existing molecular diagnostics.

7. ADDED-VALUE OF THE DUTCH TB RESEARCH: CAPACITY STRENGTHENING FOR TB RESEARCH

Locally and globally relevant TB research in settings with high incidence of TB and drug-resistant TB requires strengthening of local research capacity. The Netherlands has a long and successful track record in building up and sustaining research capacity for TB in various countries. In their collaborations and projects Dutch groups have been rather unique in combining the four essential elements of research capacity building: infrastructural capacity (building and equipping labs and clinics), individual capacity (training researchers), institutional capacity (creating a research-conducive and supportive environment) and programmatic capacity (setting national priorities and resource mobilization).

Research infrastructure capacity

KIT BR, as WHO Collaborating Centre on Laboratory Strengthening, has a program for laboratory capacity building including Good Laboratory Practice, biosafety and lab accreditation that has been applied in several countries in Africa, Eastern Europe and Central Asia. RIVM has provided support to several research labs around the world in the field of M. tuberculosis drug susceptibility testing and genotyping.

Clinical and immunological capacity has been built by several groups in clinical research collaborations in Indonesia, Tanzania, Uganda, Gabon, and more recently Belarus and Romania. Groningen UMC in collaboration with Radboud UMC is supporting pharmacology laboratory activities, dried blood spot analysis and a pharmacokinetics proficiency testing program for TB drugs. Various Dutch researchers have been part of the European TBNET network form the start, including its steering committee. As such, they have shaped and influenced clinical TB research in Europe, and contributed to research capacity building in European member states.

Individual research capacity

Dutch collaborative projects have created opportunities for research training of numerous local staff. Highly successful examples have been the NACCAP projects. For example the INTERACT program in Uganda and Rwanda (by AMC/AIGHD and KIT BR) resulted in 4 completed PhD's for local researchers on TB on clinical, epidemiological and operational research topics. In addition INTERACT provided MSc training and short-course training in various aspects of research (e.g. GCP and ethics; interview techniques, data management and monitoring) for numerous local staff at various levels.
Also the NACCAP APRIORI program has been very successful in training multiple MSc's and PhD's from Africa and Indonesia at Radboud UMC and Leiden UMC. Pharmacology projects at Groningen UMC include PhD training in Vietnam and Indonesia, and KNCV's work on population epidemiology and operational research has resulted in several PhDs in Vietnam, Tanzania and Bangladesh (with AMC/AIGHD). Other projects with significant capacity building have been the BMGF Grand Challenges Biomarker Research network, various EDCTP projects and TBVAC2020/TBVI.

An important asset in this respect is the Dutch PhD system that allows fellows to complete their work in a sandwich format, i.e. they remain in service in their jobs but receive on-the-job supervision and visit the PhD awarding institute in The Netherlands regularly for scientific mentoring, data analysis and write-up. This prevents brain drain and enhances embedding of the project in the host institute and country and sustainment of the institutional capacity. Before the re-orientation of Netherlands policy, funding mechanisms such as NUFFIC PhD grants had been very important in supporting such individual capacity building.

Institutional research capacity

Dutch programs such as CONMAL, INTERACT and its follow-on ARISE (all NACCAP funded, with involvement of AIGHD, AMC and KIT BR) have helped building institutional capacity for clinical and operational research for TB, HIV and malaria through establishing locally owned Research Support and Training Centres at African academic institutes. These centres combine support functions (such as grant writing and management, statistical and epidemiological support, and data monitoring and management) and training (short course and intensive training in various aspects of research) with strengthening of institutional ethical review, research strategy development and coordination of research activities. APRIORI (Radboud and Leiden UMCs) has provided similar support to collaborating centres in Tanzania and Indonesia.
Another example of institutional research capacity building by Dutch groups is the joint research program and master education program in TB between VFMU and the University of Pretoria, South-Africa (Veterinary Faculty Onderstepoort). This program, devoted to global health problems arising at the human/animal/ecosystem interface, aims to design, implement, and evaluate practical, cost-effective, and sustainable solutions in collaboration with local and regional stakeholders and global partners.

Programmatic research capacity

The End TB Strategy's approach to building research capacity at country levels has been modelled on Dutch initiatives that centre on three elements: creating a national TB research network, developing a national TB research agenda, and building capacity within National TB Control Programs to perform a coordinating role. National TB research networks involve local academia and other research institutes, the National TB Control Program and other stakeholders (e.g. local NGO's, international research groups) to plan, execute and report locally relevant research projects. National research agendas to prioritize research questions and projects are established through this network, and feed into National TB Strategic Plans, among other to mobilize funding for research from domestic sources and the GFATM. Key staff of National TB Control Programs is trained for research coordination tasks through operational research courses and collaborating programs. This model has been successfully piloted by KNCV in Vietnam, Indonesia and Ethiopia, and is now being promoted by WHO and further expanded in several countries in Asia and Africa with GFATM support.
It offers ample opportunities for other Dutch research groups to be engaged in collaboration and scientific support and supervision.

8. WAY FORWARD: INTEGRATING DUTCH TB RESEARCH

In this White Paper, four areas of Dutch scientific excellence in TB research are proposed. Collectively they can be regarded as a Dutch TB research agenda in the spirit of the Dutch Science Policy Framework (*Wetenschapsvisie 2025, keuzes voor de toekomst*). This Framework describes three key ambitions towards 2025. By linking these ambitions to the Dutch TB research agenda for the future, Dutch TB science finds itself at a defining stage:

- The Dutch TB research agenda is set against the background of the existing global societal needs, in particular the global research agenda set by the WHO in the context of the End TB Strategy adopted by the World Health Assembly. This Dutch agenda was defined in a joint endeavour, linking diverse research capacities and disciplines present in the Netherlands. Each of the research themes, identified as areas of excellence for Dutch TB research, contribute to tackling the global challenges in TB control, working towards TB elimination.
- Clearly, the areas of excellence emerged from a participatory and engaged process and are built on scientific track record as well as specific capacities and opportunities for cutting-edge research in efficient and relevant ways. This niche in Dutch science has a long history of linking research and practice both in the Netherlands and in the countries most affected by this deadly and persistent disease.
- The Netherlands has been and continues to be on the forefront globally in several areas of TB research. A strong and interlinked eco-system of research, know-how and global network has evolved amongst academics and practitioners based in the Netherlands. In addition, TB research continues to be highly relevant for global foals as TB research has a major impact on the fight against HIV/AIDS as well.

NOW WE CALL ON DUTCH POLICY MAKERS TO LEND THEIR EFFORTS TOWARDS THE REALIZATION OF OUR AMBITIONS BY:

1. **Explicitly recognizing and addressing TB research as an area of excellence:**
   Dutch government endorsement and acknowledgement of TB research as an area of excellence will foster an environment in which Dutch TB science can continue to excel. This acknowledgement will lead to more scientific talent (The Netherlands as a breeding ground for talent), significant cutting-edge research and enables Dutch science to gain global impact on relevant societal needs. In addition, the Dutch Research Agenda, now being drafted for the years to come, should take into account, and make explicit mention of, the Dutch TB research agenda laid down in this document.

2. **Actively positioning Dutch TB research in diplomatic and trade engagement:**
   The Netherlands continues to have a strong say in global health forums, such as the recent Global Health meeting in seoul cannnot take place in the Netherlands next year.

   Also, The Netherlands are preparing AIDS2018, wherein TB will be part of the focal areas of the conference on fighting the AIDS epidemic. This voice offers the opportunity to position Dutch TB research more strongly. TB research is of increasing relevance, e.g. in addressing antimicrobial resistance and formulating the One Health approach. Considering trade-related issues, the BRICS countries - Brazil, the Russian Federation, India, China and South Africa - account for 46% of all incident cases of tuberculosis and 40% of all tuberculosis-related mortality. There is more than ever an increasing scope for marketing Dutch TB knowledge, TB research capacity and capacity building regarding TB control and elimination.

3. **Strategically positioning TB research in the EU research agenda (Horizon 2020):**
   the Dutch EU Presidency during the first half of 2016 offers an initial opportunity to profile TB as a Dutch area of excellence within the priorities of Minister Schippers, of which antimicrobial resistance is one. Furthermore, EU Member State Slovakia has made the fight against TB a focal point in their EU Presidency second half of 2016. In this perspective, we would like to ask for more research openings in the Horizon 2020 agenda on global health issues, such as TB.

ANNEXES

1. OVERVIEW OF TUBERCULOSIS RESEARCH IN THE NETHERLANDS

The Netherlands is an internationally important player in TB research. It has a long and renown history in this field, based on its strong civil society involvement in domestic TB control, a rich past in mycobacteria research driven by a strong interest in leprosy (another mycobacterial disease) and a strong community of basic TB researchers with a medical background and cutting-edge facilities, a well-developed TB laboratory network lead by the RIVM, an interest in control of bovine TB and later paratuberculosis in cattle, and historically strong ties with research and public health institutes in developing countries.

Landmark achievements include transmission studies in the pre-chemotherapy era, worldwide tuberculin studies to map the epidemic, the development in an iterative process of the DOTS Strategy, the invention of mass radiography technologies, and more recently the development of standardized genotyping and molecular epidemiology methods, the discovery of genotype variation in drug resistance, the description of mechanisms by which M. tuberculosis survives in immune cells and the discovery and clinical testing of various TB biomarker signatures.

Currently several Dutch research groups have unique expertise, technical capacity and important networks and collaborations in TB research.

a. Unique expertise and capacities

Dutch research groups boast expertise and capacities that are unique in the world. A complete overview per group is given in the annexes.

World-leading expertise

Human immunity to mycobacteria (Leiden UMC, VFMU)
TB biomarker research (Leiden UMC)
Pharmacokinetics of TB drugs (Groningen UMC)
Epidemiological and economic (mathematical) modelling in TB (AIGHD, Erasmus MC)
Computer-assisted X-ray analysis (Radboud UMC)
Population and molecular epidemiology (RIVM, KNCV, AIGHD)
Lipid chemistry of mycobacteria (SIC-UG)
Development of point-of-care assays (KIT BR)

Unique capacity

Non-human primate research, possibly PET-scanning (BPRC)
Large animal models, high BSL (3+) (CVI)
Electron microscopy of mycobacteria (AMC)
Dried blot spot assays for pharmacokinetic testing (Groningen UMC)
DNA fingerprint database (RIVM)
"First in man" vaccine testing (Leiden UMC)
Knock-out and transgenic animal models for studying granuloma biology (AMC)
Microcolony monitoring of M. tuberculosis (KIT BR)
Spatial analyses (GIS) of TB data (KIT BR)

b. Networks

Major international networks and consortia in which Dutch TB research groups participate (alphabetical order):

Challenge TB (www.challengetb.org): USAID's flagship program for TB control, currently working in 21 countries worldwide and executed by an international coalition of technical agencies with KNCV as the lead partner. In this program, technical assistance is combined with operational research into deficiencies and improvements in TB service delivery, implementation research of new interventions and epidemiological studies.

EMIDA-ERANET (http://www.era-platform.eu/era-nets/emida): Platform for European Research on Emerging and Major Infectious Diseases of Livestock, consisting of 29 partner organisations from 18 European countries. Several funded projects are on animal TB and mycobacterioses. EMIDA is coordinated by CVI, Wageningen University.

OneDiagnostics (http://onediagnostics.org/): A not-for-profit initiative by KIT BR for the development and accessibility of simple, affordable and high quality rapid diagnostic tests for poverty-related diseases under its own brand name to patients in low-resource health settings. By establishing its own quality, not-for-profit brand of diagnostics, OneDiagnostics aims to become a confident label guaranteeing assured diagnostics.
PanACEA (http://panacea-tb.net): one of the largest TB drug trial consortia, bringing together scientists from more than 14 countries with skills in clinical trials design and implementation, pulmonology, mycobacteriology, pharmacokinetics, statistics and delivery of clinical service. Its mission is to shorten and simplify treatment of uncomplicated pulmonary TB, to increase the TB clinical trial capacity in Africa and to develop sustainable TB clinical trials network in Africa. Radboud UMC-Dekkerswald is constituting and co-lead partner.

PreDiCT-TB (http://www.predict-tb.eu): A public-private partnership funded by the EU Innovative Medicines Initiative, comprising three major pharmaceutical partners, two biotechnology firms and 15 academic partners. The multidisciplinary consortium brings together experts in microbiology, pharmacology, engineering, mathematical modelling and clinical trials to create a new integrated framework for TB drug development, making optimal use of preclinical information to design the most efficient clinical trials. Erasmus UMC and VUMC are among the academic partners.

TANDEM (www.tandem-fp7.eu): International EU 7th Framework-funded consortium leadled by Radboud UMC addressing the interaction of TB and diabetes mellitus, with field sites in Peru, South Africa, Romania and Indonesia.

TB Biomarker networks – several high quality international networks have been developed for TB biomarker research and validation in well-defined cohorts, including the BMGF-funded Grand Challenges network. Leiden UMC is an important partner.

TBMAC (http://tb-mac.org/): BMGF-funded TB modelling and analysis consortium. TBMAC aims to improve global TB control by coordinating and promoting mathematical modelling and other quantitative research activities to provide scientific support for policy decisions and implementation. AIGHD is one of the partners.

TBnet (http://www.tb-net.org/): largest European network of clinicians, public health specialists, epidemiologists, and laboratory specialists interested in combating TB, with currently 641 members covering all member states (MS) of the European Union, 12 other countries within the WHO European Region and 20 non-European countries. Various Dutch groups are active participants. The clinical database for MDR/XDR-TB is managed by AIGHD.

TB REACH (www.stoptb.org): initiative including 142 projects in 46 countries focusing on innovative approaches to early and increased TB case detection. KIT is part of the independent external evaluation team, contributing to obtaining evidence on which strategy works under which circumstances.

TBVI (TuBerculosis Vaccine Initiative, www.tbvi.eu): 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. TBVI is based in The Netherlands, and plays an important role in the global TB vaccine research and development. As a Product Development Partnership it integrates, translates and prioritises R&D efforts to discover and develop new TB vaccines and biomarkers for global use. TBVI provides essential services that support the R&D efforts of its 50 consortium partners including academia, research institutes and private industry in the TB vaccine field.

c. Collaborations

TB research collaborations of Dutch groups with institutes in high TB incidence countries:

Bangladesh (KNCV, Radboud UMC, AIGHD)
Brazil (AIGHD, KNCV)
China (RIVM, AIGHD, KNCV)
Ethiopia (KIT BR, KNCV, Leiden UMC)
Gabon (AMC)
Gambia (Leiden UMC)
Georgia (KIT BR)
Indonesia (Radboud UMC, Leiden UMC, KNCV)
Kazakhstan (KNCV)
Kenya (KNCV)
Malawi (Leiden UMC)
Mozambique (KNCV, AIGHD, KIT BR)
Pakistan (Radboud UMC)
Paraguay (Radboud UMC)
Peru (VFMU)
Romania (Groningen UMC)
Rwanda (AIGHD)
South Africa (KNCV, AMC, AIGHD, VUMC, Leiden UMC, Radboud UMC)
Tanzania (Radboud UMC, Leiden UMC, AIGHD, KNCV)
Uganda (AIGHD, Radboud UMC, Leiden UMC)
Vietnam (KNCV, AIGHD)
Zambia (KNCV, AMC)

d. Funding

Dutch research groups have been successful in attracting funding for TB research from a wide variety of sources. These include Netherlands government (ZON-MW, WOTRO Life Sciences for Health, STW), EU funding mechanisms (7th Framework, Horizon2020, EDCTP, Marie Curie, Erasmus Mundus, DG Santé, ECDC, EMIDA), US Government grants (USAID, NIH/NIAID), UK grants (DFID), Bill and Melinda Gates Foundation, Product Development Partnerships such as TBVI, Aeras, FIND and TB Alliance, GFATM, WHO, the Stop TB Partnership and various others. These grants have been acquired either with a Dutch group as the main applicant or as collaborators in research consortia.

Radboud UMC, Nijmegen, Department of Internal Medicine

Main Researchers
Dr. Reinout van Crevel, Prof. Andre van der Ven, Prof. Mihai Netea

Focus of Research
We combine: (1) patient studies (mainly in Indonesia), integrating basic, clinical, epidemiological, pharmacokinetic and operational research; (2) experimental studies focusing on innate host defense mechanisms and their interaction with particular M. tuberculosis genotypes.

Achievements
First; significant contributions to knowledge about:
- TB susceptibility and innate defense against M. tuberculosis
- The 'clinical phenotype' of Beijing strains; interaction of host and mycobacterial genotype
- Intensified (high-dose rifampicin) TB treatment
- Diagnosis and management of TB meningitis
- The interaction of TB and diabetes mellitus (DM)
- TB case-contact management and household transmission in Indonesia
- Second; significant contribution to Indonesian field site for clinical and immunological TB research.

Top-3 publications
1. Ruslami R, Ganiem AR, Dian S, Apriani A, Hanggono Ahmed T, van der Ven AJ, Borm G, Aarnoutse R, van Crevel R. A randomized trial evaluating pharmacokinetics, safety and clinical response to intensified antibiotic treatment for TB meningitis. Lancet Inf Dis 2013;13:27-35.
2. Riza AL, Pearson F, Ugarte-Gil C, Alisjahbana B, van de Vijver S, Hill PC, Ruslami R, Moore D, Aarnoutse R, Critchley JA, van Crevel R. Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. Lancet Diabet Endocrinol. 2014;2:740-53.
3. Van Laarhoven A, Mandemakers JJ, Kleinnijenhuis J, Ottenhoff TH, Netea MG, van Soolingen D, van Crevel R. Low induction of proinflammatory cytokines parallels evolutionary success of modern strains within M. tuberculosis Beijing genotype. Infect Immun. 2013;8:3750-6.

Capacity
- The Dept of Medicine at Radboud UMC focuses on innate immunity and host-pathogen interaction, with state-of-the art functional immunology, systems biology, experimental models. Research focused on TB / mycobacteria is one of the focus areas of our department.
- In Indonesia, since 2000 we have helped establish a site for clinical and translational TB research at Padjadjaran University, Bandung. This site now recruits approx. 500 pulmonary TB patients, 800 TB case contacts, and 50 TB meningitis patients per year in prospective studies. Capacity includes: a solid multidisciplinary team (incl. 5 Indonesian with international PhDs in TB); strong connections with the West Java Reference laboratory, national TB program, city health council, 33 primary health clinics; strong diagnostic facilities; digital data capture and bioarchiving; immunology and pharmacology lab; HIV clinic; constant exchange of PhD and MSc from RUMC and Indonesia; collaboration with other international groups. This has led to >75 joint international publications.

Collaborations and networks
- RUMC leads a consortium on TB and DM with 11 institutes from 7 countries (www.tandem-fp7.eu). - We have longstanding collaboration in TB with centres in Indonesia (Padjadjaran Univ, Bandung) and Tanzania (Tumaini Univ, Moshi). This was expanded through NWO-WOTRO 'PRIOR' program (2003-2008); an EU-funded HIV program (2006-2011); an EU-funded FP7 program on TB and DM (2013-2017). TB research in Indonesia is done in collaboration with Otago university, New Zealand (Prof PC Hill) and McGill university, Canada (Prof Menzies). We have ongoing collaboration on TB disease and the mycobacterium pathogen with groups in the USA, Sweden, UK, and Denmark.

Key figures
- 3 senior clinician-researchers involved in TB research
- 9 PhDs currently working on TB or mycobacteria/BCG (of whom 6 are women)
- 10 international PhDs on TB completed in the last 10 years
- 90 peer-reviewed publications on mycobacteria or TB last 10 years; 9 more on BCG

Biomedical Primate Research Centre (BPRC), Section of TB Research & Immunology

Main Researchers
Dr. Frank Verreck

Focus of Research
Tuberculosis research at the BPRC primarily focusses on the preclinical evaluation of new vaccine strategies in the non-human primate (NHP) host as well as on the investigation of mechanisms/correlates of disease and protective immunity.

Achievements
- BPRC – as a relatively unique facility – is a leading expert in studying experimental tuberculosis in non-human primate models as the closest proxy to man. In collaboration with European and global partners, several vaccine candidates have been evaluated for their immunogenicity, tolerability and protective efficacy in the primate host. Prototypes and product candidates are pushed ahead in a global effort to develop improved strategies for vaccination against TB.

Top-3 publications
1. Verreck FAW, Vervenne RAW, Kondova I, van Kralingen KW, Remarque EJ, Braskamp G, van der Werff NM, Kersbergen A, Ottenhoff THM, Heidt PJ, Gilbert SC, Gicquel B, Hill AV, Martin C, McShane H, Thomas AW. MVA.85A boosting of BCG and an attenuated, phoP deficient M.tuberculosis vaccine both show protective efficacy against tuberculosis in rhesus macaques. PLoS One 2009;4: e5264.
2. Young D and Verreck FAW. Creativity in tuberculosis research and discovery. Tuberculosis 2010;92: S14-16.
3. Lastrucci C, Bénard A, Balboa L, Pingris K, Souriant S, Poincloux R, Al Saati T, Rasolofo V, González-Montaner P, Inwentarz S, Moranā E, Kondova I, Verreck FAW, Sasiain M, Neyrolles O, Maridonneau-Parini I, Lugo-Villarino G, and Cougoule C. Tuberculosis is associated with expansion of a motile, permissive and immunomodulatory CD16+ monocyte population via the IL-10/STAT3 axis. (accepted for publication in Cell Research, 2015).

Capacity
BPRC has self-sufficient NHP breeding colonies. TB models are established in macaque (rhesus and cynomolgus) and marmoset species, that are not only relevant for vaccine studies but also hold potential for TB drug or combination therapy research. Experimental animal and lab facilities for containment of TB (biosafety level 3) are fully equipped and on site. Research and infrastructural modalities support readout of TB immunology, pathology, clinical chemistry & hematology, bacteriology, molecular biology and radiology. BPRC is implementing advanced PET-CT imaging for refined readout of NHP TB.

Collaborations and networks
BPRC has collaborated/collaborates as an independent expert research centre in European consortia under Framework Programmes 5, 6, 7 and the latest Horizon2020 on preclinical vaccine evaluation in particular. Outside Europe, BPRC has partnered with Aeras (Rockville, MA, USA) and most recently joined the Collaboration for TB Vaccine Development (CTVD, at the initiative of the Bill & Melinda Gates Foundation) as a NHP Central Service Facility.

Other information
BPRC is AAALAC (Association for Assessment and Accreditation of Laboratory Care International) accredited.

Key figures
- 1 senior researchers (dedicated full-time) working on TB
- currently 1 PhD working on TB (a woman)
- 14 peer-reviewed publications on TB last 10 years

Radboud UMC - Diagnostic Image Analysis Group, Department of Radiology and Nuclear Medicine

Main Researchers

Prof. Bram van Ginneken, dr. C.I. Sanchez

Focus of Research

The research of the group is focused on automated computer analysis of chest radiographs to detect signs of tuberculosis (CAD4TB). Currently, with digital radiography rapidly spreading throughout the world, a lack of human expertise to interpret chest radiographs in countries with a high TB burden is the main limiting factor for using radiography as a diagnostic for TB. Automated reading could alleviate that. Besides software development, the last few years validation studies have been carried out, including studies to elucidate the optimal role of chest radiography with automated reading within diagnostic algorithms. We aim to expand to other quantifications (e.g. TB lesion load for treatment monitoring, temporal analysis in case multiple X-rays over time have been acquired) and other application areas (e.g pediatric X-ray analysis).

Achievements

- The CAD4TB software has developed from a research prototype into a CE certified medical device and is now operational in 8 countries in Africa and Asia. Funding by NWO (STW), EDCTP, RVO.

Top-3 publications

1. R. Philipsen, C.I. Sánchez, P. Maduskar, J. Melendez, L. Peters-Bax, J. Peter, R. Dawson, G. Theron, K. Dheda and B. van Ginneken. Automated digital chest radiography as a triage for Xpert MTB/RIF testing in resource-constrained settings: a prospective study of diagnostic accuracy and cost. Sci Rep 2015;5:12215.
2. M. Breuninger, B. van Ginneken, R.H.H.M. Philipsen, F. Mhimbira, J.J. Hella, F. Lwilla, J. van den Hombergh, A. Ross, L. Jugheli, D. Wagner and K. Reither. Diagnostic accuracy of computer-aided detection of pulmonary tuberculosis in chest radiographs: a validation study from sub-saharan Africa. PLoS One 2014;9:e106381.
3. J. Melendez, B. van Ginneken, P. Maduskar, R.H.H.M. Philipsen, K. Reither, M. Breuninger, I.M.O. Adetifa, R. Maane, H. Ayles and C.I. Sánchez. A Novel Multiple-Instance Learning-Based Approach to Computer-Aided Detection of Tuberculosis on Chest X-Rays. IEEE Trans Med Imaging 2015;34:179-192.

Capacity

The research group is embedded in one of the largest groups on computer-aided diagnosis worldwide and has access to extensive databases and computational infrastructure.

Collaborations and networks

We have collaborated with research institutes, universities, and national TB programs in 15 countries. In particular the Lung Institute (South Africa), The London School of Tropical Medicine (UK), AIGHD, Swiss Tropical and Public Health Institute, Interactive Research & Development (Pakistan), Zambart (Lusaka, Zambia), CIDRZ (Zambia), icddr.b (Bangladesh), World Health Organization Regional Office for the Western Pacific (Philippines).

Other information

CAD4TB is an excellent example of a successful public/private collaboration. The research project has received long term support in cash and in kind by Delft Imaging Systems (DIS), and has resulted in technology licensing.

Key figures

- 1 senior researcher working on TB
- currently 1 PhD working on TB (of whom 0 are women)
- 3 PhDs on TB completed in the last 10 years
- 15 peer-reviewed publications on TB last 10 years

Koninklijk Instituut voor de Tropen, KIT Biomedical Research

Main Researchers

Dr. Richard Anthony, Dr. Mirjam Bakker, Prof. Paul Klatser

Focus of Research

Developing/simplifying diagnostic methods; developing and implementing near patient treatment monitoring to support treatment provision including serum cytokine kinetics; mechanisms of drug resistance, acquisition and transmission of resistance; molecular TB epidemiology; ecological studies understanding heterogeneity of TB burden.

Achievements

- First (in 1989) to describe PCR for mycobacteria
- First to invent LED FM microscopy for TB
- Established TB genotyping in Bulgaria and Georgia
- Characterization of over 1000 cultured clinical isolates collected from TB patients all over the world used for epidemiological surveillance and to understand mechanisms of drug resistance development.

Top-3 publications

1. Den Hertog AL, Menting S, van Soolingen D, Anthony RM. Mycobacterium tuberculosis Beijing Genotype Resistance to Transient Rifampin Exposure. Emerg Infect Dis 2014;20:1932-3.
2. den Hertog AL, de Vos AF, Klatser PR, Anthony RM. Early specific host response associated with starting effective tuberculosis treatment in an infection controlled placebo controlled mouse study. PLoS One 2013;8:e57997.
3. den Hertog AL, Mayboroda OA, Klatser PR, Anthony RM. Simple rapid near-patient diagnostics for tuberculosis remain elusive--is a “treat-to-test” strategy more realistic? PLoS Pathog 2011;7:e1002207.

Capacity

Geographic Information Systems (GIS) for visualizing and analyzing geographic heterogeneity of TB burden
System and methodology for the high throughput microcolony growth monitoring developed within the NanoNextNL programme.
Fully equipped (BSL3) laboratories.

Collaborations and networks

Collaborations with FIND; Centro de Investigação em Saúde de Manhiça (Mozambique); Infection Genetics Emerging Pathogens Evolution (IGEPE) research team, Université Paris-Saclay, France; National Center for Biotechnology, of the Republic of Kazakhstan; National Mycobacteriology Reference Laboratory, Georgia; Philips B.V.

Other information

KIT’s TB activities focus on an integrated package of services supporting detection, management and intervention: the development of new diagnostics, the validation or improvement of diagnostic methods, (molecular) epidemiology, impact assessment and evaluation of trials and interventions, capacity building, and performing genetic and microbiological studies on drug resistance.

Key figures

- Six senior researchers (4 female)
- Six PhDs on TB completed in the last 10 years
- 30 peer-reviewed publications on TB last 10 years
- Four patents related to TB

Erasmus MC, University Medical Center Rotterdam, Department of Public Health

Main Researchers
Prof. Jan Hendrik Richardus, Dr. Sake de Vlas, Dr. Rui Cai

Focus of Research
Mathematical modelling of infectious disease transmission and cost-effectiveness, including TB.
A mathematical simulation model for TB is being used and further developed to an individual based model to assess the impact of different components of the Dutch TB control policy on their cost-effectiveness in an integrated manner, and will provide a strong basis for modelling of introducing programmatic latent TB control in the European Union.

Achievements
- Consecutive screening of immigrants for TB (CXR) in the Netherlands for a number of years after entry is not cost-effective and the national policy was adjusted to one entry screening only.
- Screening of immigrants for TB and latent TB in the Netherlands has an unfavourable cost-effectiveness ratio. Only for screening at entry of immigrants from very high-risk countries such as many African countries the screening on TB (CXR) is reasonably favourable, but screening on LTB is not. Policy implications are still under debate.

Top-3 publications

1. Verdier JE, de Vlas SJ, Baltussen R, Richardus JH. A systematic review of economic evaluation studies of tuberculosis control in high-income countries. Int J Tuberc Lung Dis 2011;15: 1587-98.
2. Alvarez JL, Kunst AE, Leinsalu M, Bopp M, Strand BH, Menvielle G, Lundberg O, Martikainen P, Deboosere P, Kalediene R, Artnik B, Mackenbach JP, Richardus JH. Educational inequalities in tuberculosis mortality in sixteen European populations. Int J Tuberc Lung Dis 2011;15:1461-8.
3. De Vries G, van Hest RA, Richardus JH. Impact of Mobile Radiographic Screening on Tuberculosis among Drug Users and Homeless Persons. Am J Respir Crit Care Med 2007;176:201-7.

Capacity
Extensive experience with mathematical modelling of infectious diseases, including TB and its control.

Collaborations and networks
Gadja Mada University and University of Indonesia, in Indonesia. European Centre for Disease Prevention and Control (ECDC), Sweden

Key figures
- 3 senior researchers and postdocs working on TB
- currently 2 PhDs working on TB (male)
- 3 PhDs on TB completed in the last 10 years
- 10 peer-reviewed publications on TB last 10 years

Amsterdam Institute for Global Health and Development (AIGHD)

Main Researchers
Prof. Frank Cobelens, Dr. Frank van Leth

Focus of Research
The research of the group focuses on three areas, taking a multidisciplinary (clinical, epidemiological, economic) approach to: 1. Improving diagnosis and treatment of TB, a.o. by modeling (cost)-effectiveness of new diagnostics and new treatment regimens, 2. Causes, spread and control of TB drug resistance, 3. Susceptibility to infection and disease, in particular the role of poverty, 4. Analysis of routinely collected data to inform decision makers and public health experts.

Achievements
- AIGHD is among the foremost groups internationally in evaluation of new TB diagnostics. Its work has supported several international guidelines for improving TB diagnosis. The research on drug resistance has provided new insights in its global epidemiology, the role of genotype and novel approaches to surveillance. The strong epidemiological/ methodological expertise steered in-depth studies of clinical and surveillance data, providing new insights in care delivery.

Top publications

1. Vassall A, van Kampen S, Sohn H, Michael JS, John KR, den Boon S, Davis JL, Whitelaw A, Nicol MP, Gler MT, Khaliqov A, Zamudio C, Perkins MD, Boehme CC, Cobelens F. The rapid diagnosis of tuberculosis with Xpert MTB-RIF assay in high burden countries: a cost-effectiveness analysis. PLoS Med 2011;8: e1001120.
2. Cobelens F, van Kampen S, Ochodo E, Atun R, Lienhardt C. Research on Implementation of Interventions in Tuberculosis Control in Low- and Middle-Income Countries: A Systematic Review. PLoS Med 2012;9:e1001358.
3. Sester M, van Leth F, Bruchfeld J, et al. Risk assessment of tuberculosis in immune-compromised patients. A TBNET study. Am J Respir Crit Care Med 2014;190:1168-76.

Capacity
AIGHD brings together various disciplines in global health, including clinical research, epidemiology, microbiology, health economy, development economics and social science. Strong capacity in economic evaluation, antimicrobial resistance surveillance and (pragmatic) trials. AIGHD has satellite clinical research support capacity in Africa and Asia.

Collaborations and networks
AIGHD links research to implementation of health care interventions, working closely with NGOs such as KNCV (TB control) and PharmAccess International (innovative health financing). Long-term collaborations exist with research groups in high-incidence settings (Uganda, Tanzania, South Africa, China, Vietnam, Brazil) as well as in Europe (e.g. Institute of Tropical Medicine, Belgium; London School of Hygiene Medicine, UK; and TB Research Center Borstel, Germany) and the USA (e.g. Harvard, Yale, and Hopkins universities). AIGHD is a leading constituent of the TBNET network for European TB research.

Other information
AIGHD is affiliated with the Academic Medical center/ University of Amsterdam and through joint appointments collaborates closely with KNCV Tuberculosis Foundation.

Key figures
- 5 senior researchers and postdocs working on TB
- currently 9 PhDs working on TB (of whom 3 are women)
- 10 PhDs on TB completed in the last 10 years
- 182 peer-reviewed publications on TB last 10 years, including joint publications with KNCV

Leiden University Medical Center, Department of Infectious Diseases

Main Researchers

Prof. Tom HM Ottenhoff, Prof A Geluk, Dr SA Joosten, Dr MC Haks

Focus of Research

Primary objectives of the research work are: 1. To understand the host cellular immune response during human infection and disease in mycobacterial infections. 2. To discover antigenic targets for vaccination, diagnosis and human biomarker profiling (protection, progression towards disease, response to intervention). 3. To identify human genetic determinants and mechanisms that underlie susceptibility to mycobacterial infections.

Specific recent focus has been on: 1. Dissecting key hubs in the intracellular networks involved in controlling intracellular pathogens (Salmonella, Mtb), using chemical genetics and genetic knock down, and test candidate lead compounds for efficacy in human cells, zebrafish and mice. 2. Developing Host Directed Therapies for multi-drug resistant mycobacterial infections 3. Understanding the human transcriptomic response during co-infection, particularly helminth and HIV co-infections. 4. Developing next generation diagnostic tools for early detection of mycobacterial infection.

Achievements

- execution of various first in man clinical vaccine studies with new TB vaccines
- description of novel biomarker profiles with diagnostic potential
- description of novel biomarker profiles correlating with the curative response to TB treatment

Top-3 publications in 2015

1. (See http://www.ncbi.nlm.nih.gov/pubmed/?term=ottenhoff+t* for all publications)
2. N Caccamo, G Pietra, LC Sullivan, AG Brooks, T Prezzemolo, MP La Manna, D Di Liberto, SA Joosten, KE van Meijgaarden, P Di Carlo, L Titone, L Moretta, MC Mingari*, THM Ottenhoff*, F Dieli* (*: equal contributions). Human CD8 T lymphocytes recognize Mycobacterium tuberculosis antigens presented by HLA-E during active tuberculosis and express type 2 cytokines. Eur J Immunol 2015;45:1069-81.
3. KE van Meijgaarden, MC Haks, N Caccamo, F Dieli, THM Ottenhoff*, SA Joosten* (*: equal contributions). Human CD8+ T-cells recognizing peptides from Mycobacterium tuberculosis (Mtb) presented by HLA-E have an unorthodox Th2-like, multifunctional, Mtb inhibitory phenotype and represent a novel human T-cell subset. PLoS Pathog 2015;11:e1004671.
4. Ronacher K, Joosten SA, van Crevel R, Dockrell, HM, Walzl, G, Ottenhoff THM. Acquired immunodeficiencies and tuberculosis: focus on HIV/AIDS and diabetes mellitus. Immunol Rev 2015;264:121-37.

Capacity

LUMC has a world-leading role in immunological and host-genetic research related to tuberculosis and leprosy.

Collaborations and networks

We collaborate in several large, international consortia including with African and Asian partners.

Other information

Our mission is to dissect host immunological and host-genetic mechanisms of (protective or pathologic) immunity to mycobacterial infections (TB, leprosy), in order to design more effective intervention strategies and diagnostic tools for early detection of infection.

Key figures

- 4 senior researchers and postdocs working on TB
- Currently 6 PhDs working on TB (of whom 3 are women)
- 4 PhDs on TB completed in the last 10 years
- >200 peer-reviewed publications on TB last 10 years
- 2 patents related to TB

Maastricht University, Faculty of Health, Medicine and Life Sciences

Main Researchers

Dr. Nora Engel

Focus of Research

Qualitative research and social science insights for diagnostic test development

Achievements

- Insights generated during PhD: TB control in India does not offer a conducive environment for innovation, the potential remains underused; innovation shapes and is being shaped by existing control practices of for instance standards, supervision and entire control cultures; rich analysis of innovation dynamics for TB control in India including cases on innovation in organizational set-up (public-private-mix), technology (new diagnostics), strategy (policy responses to MDR-TB) and service delivery (new treatment guidelines)
- Insights generated during project Barriers to Point-of-Care testing, India & South Africa, funded by Bill & Melinda Gates Foundation (2012-2014): understanding of where point of care testing is successful and why (not) across different health system settings and major infectious diseases; rich insights into major barriers to testing at point of care; showed potential of qualitative research for diagnostics development
- Future insights expected related to ongoing VENI grant (2015-2018): Will provide knowledge about how to take contexts, users and local settings seriously when innovating TB diagnostics; compilation of innovation strategies for point of care TB & HIV diagnostics; development of a training course on qualitative STS methodologies for innovation in diagnostics

Top-3 publications

1. Engel N, Ganesh G, Patil M, Yellappa V, Pai NP, Vadnais C, Pai M. Barriers to Point-of-Care Testing in India: Results from Qualitative Research across Different Settings, Users and Major Diseases. PLoS ONE 2015;10:e0135112.
2. Engel N, Pai M. Tuberculosis diagnostics: Why we need more qualitative research. Journal of Epidemiology and Global Health 2013;3:119-21.
3. Pai NP, Vadnais C, Denkinger C, Engel N, Pai M. Point-of-Care Testing for Infectious Diseases: Diversity, Complexity, and Barriers in Low- And Middle-Income Countries, PLOS Medicine 2012; 9, e1001306.

Capacity

Specific expertise of developing better point of care tests for TB & HIV

Collaborations and networks

Joint research project with McGill University (Montreal, Canada) on Barriers to Point-of-Care testing in India and South Africa, funded by Bill & Melinda Gates Foundation including collaborations with University of Cape Town and Institute of Public Health Bangalore. As part of the qualitative fieldwork, extensive networks of practitioners, policymakers, NGOs, researchers and donors have been generated across India and South Africa.

Key figures

- 1 senior researcher working on TB
- 1 PhD on TB completed in the last 10 years
- 12 peer-reviewed publications on TB last 10 years

Central Veterinary Institute, Wageningen University

Main Researchers

Dr. Ad Koets, Dr. Norbert Stockhofe-Zurwieden

Focus of Research

Current focus of research includes:
Antigen discovery (protein and non-protein antigens) for use in diagnostics or vaccine development
Guinea pig model tuberculin potency assay improvement
Large animal TB models for vaccine evaluation and new diagnostics (porcine, bovine)
Molecular genetics and molecular epidemiology of TB complex and NTM mycobacteria
Host response to mycobacterial infection (wide host range, translational knowledge base for TB diagnostics and vaccine development), miRNA, microarray technology and bioinformatic approaches.

Achievements

- The Central Veterinary Institute has developed a production line and quality control for producing high quality tuberculins for the veterinary market. This has been developed into a business unit which was acquired by a commercial partner.

Top-3 publications

1. Bruffaerts N, Pedersen LE, Vandermeulen G, Préat V, Stockhofe-Zurwieden N, Huygen K, Romano M. Increased B and T Cell Responses in M. bovis Bacille Calmette-Guérin Vaccinated Pigs Co-Immunized with Plasmid DNA Encoding a Prototype Tuberculosis Antigen. PLoS One 2015;10: e0132288.
2. Santema W, Rutten V, Segers R, Poot J, Hensen S, Heesterbeek H, Koets A. Postexposure subunit vaccination against chronic enteric mycobacterial infection in a natural host. Infect Immun 2013;81:1990-5.
3. Stevenson K, Alvarez J, Bakker D, Biet F, de Juan L, Denham S, Dimareli Z,Dohmann K, Gerlach GF, Heron I, Kopecna M, May L, Pavlik I, Sharp JM, Thibault VC, Willemsen P, Zadoks RN, Greig A. Occurrence of Mycobacterium avium subspecies paratuberculosis across host species and European countries with evidence for transmission between wildlife and domestic ruminants. BMC Microbiol 2009;9:212.

Capacity

Expertise in use of large animal model for TB research to look into host- pathogen interaction, immune modulation, vaccine immunogenicity and efficacy. Aiming for innovative diagnostic and antigen discovery (lipid, glycolipids and proteins).

Collaborations and networks

TB Vaccine Initiative (TBVI), Coordination of European Research on Emerging and Major Infectious Diseases of Livestock (EMIDA-ERANET, http://www.era-platform.eu/era-nets/emida/), European reference laboratories for bovine tuberculosis

Other information

Large animal models for TB research for vaccine development and immune modulation.

Key figures

- 3 senior researchers and postdocs working on TB, 3 technicians
- 14 peer-reviewed publications on TB last 10 years

Free University Amsterdam, Department of Molecular Cell Biology

Main Researchers

Dr. Dirk Bald and Dr. Rob van Spanning

Focus of Research

Dr. Dirk Bald and Dr. Rob van Spanning work together on tuberculosis research with a major interest in energy metabolism and other aspects of central metabolism in mycobacteria. The projects aims both at basic understanding of the biochemistry/ microbiology involved, as well on the suitability of central metabolism as drug target. This research line made an important contribution to understanding the mechanism of action of bedaquiline, the first anti-TB drug approved in 40 years.

Achievements

- Understanding of the delayed onset of kill displayed by energy metabolism inhibitors
- Insight into the working of mycobacterial energy metabolism and the mechanism of drugs acting on this pathway
- Identification of cytochrome bd as a key factor in the mycobacterial response to antibacterials

Top-3 publications

1. Lu P, Heineke MH, Koul A, Andries K, Cook GM, Lill H, van Spanning R, & Bald D. The cytochrome bd-type quinol oxidase is important for survival of Mycobacterium smegmatis under peroxide and antibiotic-induced stress. Sci Rep 2015;5:10333.
2. Koul A, Vranckx L, Dhar N, Göhlmann H, Özdemir E, Neefs JM, Schulz M, Lu P, Mørtz E, McKinney JD, Andries K and Bald D. Delayed bactericidal response to bedaquiline involves extensive remodeling of metabolic pathways in Mycobacterium tuberculosis. Nat Commun 2014;5:3369.
3. Koul A, Dendouga N, Vergauwen K, Molenberghs B, Vranckx L, Willebrords R, Ristic Z, Lill H, Dorange I, Guillemont J, Bald D, and Andries K. Diarylquinolines target subunit-c of mycobacterial ATP synthase. Nat Chem Biol 2007;3:323-4.

Capacity

Expertise on mycobacterial (energy/central) metabolism.

Collaborations and networks

Dr. Anil Koul / Dr. Koen Andries, Janssen Pharmaceuticals, J&J, Beerse Belgium
Prof. Gregory Cook, University of Otago at Dunedin, New Zealand

Key figures

- 3 Senior researchers involved in TB research, 2 technicians
- 14 peer-reviewed publications on mycobacteria or TB last 10 years

KNCV Tuberculosis Foundation

Main Researchers

Dr. Susan van den Hof, Dr. Michael Kimerling,
Prof. Frank Cobelens

Focus of Research

KNCV's research focuses on policy-relevant research in three major areas:
Implementation research: stimulate innovations in TB control by gathering evidence about new interventions for their implementation at programmatic scale.
Operational research: assess deficiencies in TB control and identify causes that are amenable to improvement using technical or managerial interventions.
Population epidemiology: surveys and surveillance data analysis to measure the extent and course of the TB epidemic, including drug resistance, at the population level.

Achievements

- KNCV has a long history of generating the necessary evidence base for national and international policy development and for programmatic implementation strategies. This is achieved through focused and prioritized implementation of quality research in the above key result areas.

Top-3 publications

1. Durovni B, Saraceni V, van den Hof S, Trajman A, Cordeiro-Santos M, Cavalcante S, Menezes A, Cobelens F. Impact of Replacing Smear Microscopy with Xpert MTB/RIF for Diagnosing Tuberculosis in Brazil: A Stepped-Wedge Cluster-Randomized Trial. PLoS Med 2014;11:e1001766.
2. He GX, Wang HY, Borgdorff MW, van Soolingen D, van der Werf MJ, Liu ZM, Li XZ, Guo H, Zhao YL, Varma JK, Tostado CP, van den Hof S. Multidrug-resistant tuberculosis, People's Republic of China, 2007-2009. Emerg Infect Dis 2011;17:1831-8.
3. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJ. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. Plos One 2011;6:e17601.

Capacity

KNCV has a diverse group of epidemiologists with various specializations. We have extensive experience with population surveys (TB prevalence, drug resistance), implementation studies of diagnostic tools and other innovations, and operational research. KNCV researchers work closely with the TB control programs and KNCV consultants providing technical support to these programs, to assess the most relevant research questions and to incorporate implications from results into policy and practice. We combine our research implementation with training of local researchers.

Collaborations and networks

KNCV Tuberculosis Foundation has long-standing collaborations with national TB control programs and associated research groups in all regions of the world (including Brazil, China, Ethiopia, Indonesia, South Africa, Tanzania and Vietnam). We work closely together with research groups from the Aurum Institute, the University of California, San Francisco (UCSF), the London School of Hygiene and Tropical Medicine (LSHTM), the World Health Organization, and The Union.

Other information

KNCV is the largest NGO specialized in technical assistance for TB worldwide, working in 24 countries in Africa, Asia and Europe. Research to support TB control is an integral aspect of its activities. KNCV's researchers through joint appointments closely collaborate with the Amsterdam Institute for Global Health and Development (AIGHD).

Key figures

- 7 senior researchers and postdocs working on TB
- 350 peer-reviewed publications on TB last 10 years, including joint publications with AIGHD
- 13 PhDs on TB completed in the last 10 years

National Institute for Public Health and the Environment (RIVM)

Main Researchers

Prof. Dick van Soolingen, MSc. Jessica de Beer

Focus of Research

The research of the group focuses on identification (taxonomy) of mycobacteria, (molecular) drug susceptibility testing, epidemiological typing, evolutionary development of Mycobacterium tuberculosis. New is the research on the protein expression of Mycobacterium tuberculosis in relation to resistance development.

Achievements

- Multiple publications on molecular typing of M. tuberculosis and the molecular epidemiology of tuberculosis, pioneer studies in the introduction of Whole Genome Sequencing of M. tuberculosis, introduction of new (sub) species, validation of molecular detection of resistance, introduction of protein expression of M. tuberculosis to study development of resistance.

Top-3 publications

1. De Keijzer J, de Haas PE, de Ru AH, van Veelen PA, van Soolingen D. Disclosure of selective advantages in the modern sublineage of the Mycobacterium tuberculosis Beijing genotype family by quantitive proteomics. Mol Cell Proteomics 2014; 13:2632-45.
2. Nebenzahl-Guimaraes H, Verhagen LM, Borgdorff MW, van Soolingen D. Transmission and progression to disease of Mycobacterium tuberculosis phylogenetic lineages in The Netherlands. J Clin Microbiol 2015 [epub ahead of print].
3. De Beer JL, Kodmon C, van der Werf MJ, van Ingen J, van Soolingen D; ECDC MDR-TB Molecular Surveillance Project Participants. Molecular surveillance of multi- and extensively drug-resistant tuberculosis transmission in the European Union from 2003 to 2011. Euro Surveill 2014;19(11).

Capacity

The RIVM is the national mycobacteria reference laboratory for the Netherlands and is in the position to combine microbiology, patient information and the latest scientific developments like Whole genome sequencing and analysis of protein expression.
Collaborations and networks
The RIVM has links with all relevant partners in the field of TB control in the Netherlands. The main researcher is associate professor at the Microbiology of the Radboud University Medical Center in Nijmegen. There is also a strong collaboration with the TB referral center Beatrixoord in Haren, the Netherlands on improvement of treatment of (resistant) TB. The RIVM is involved in the ECDC network for mycobacteria reference laboratories in Europe and organizes quality control of molecular typing for worldwide TB laboratories. There is an ongoing governmental collaboration with China.

Other information

RIVM works closely together with KNCV Tuberculosis Foundation on the surveillance of TB in The Netherlands and translational research.

Key figures

- 1 senior researcher working on TB
- 200 peer-reviewed publications on TB last 10 years
- 10 PhDs on TB completed in the last 10 years
- currently 6 PhDs working on TB (of whom 4 are women)

Stratingh Institute for Chemistry, University of Groningen

Main Researchers
Prof. Adriaan Minnaard

Focus of Research
The group focuses on chemical synthesis of known and newly discovered M. tuberculosis lipid antigens, and on development of chemical markers of M. tuberculosis infection.

Achievements
- We have shown that the recently identified compound tuberculosinyl adenosine accumulates to comprise >1% of all M. tuberculosis lipids; tuberculosinyl adenosine and an isomer have been proposed as infection markers.
- In addition the group has started to work also on modification of kanamycin and related aminoglycosides to fight multi-drug resistant tuberculosis. We developed synthesis technology to selectively modify aminoglycoside antibiotics (neomycin, kanamycin, amikacin etc.) in such a way that bacterial enzymes are probably not able to inactivate these drugs. This could be a way to rejuvenate these broad-spectrum antibiotics that are used as second-line treatment of TB.

Top-3 publications

1. Geerdink, D, Minnaard AJ. Total synthesis of Sulfolipid-1. Chem Comm 2014; 50:2286-8.
2. Layre E, Lee HJ, Young DC, Martinot AJ, Buter J, Minnaard AJ, Annand, J W, Fortune SM, Snider BB, Matsunaga I, Rubin E J, Alber T, Moody DB. Molecular profiling of M. tuberculosis identifies tuberculosinyl nucleoside products of the virulence-associated enzyme Rv3378c. Proc Nat Ac Sci 2014;111:2978-83.
3. Ly D, Kasmar AG, Cheng T-Y, de Jong A, Huang S, Roy S, Bhatt A, van Summeren RP, Altman, JD, Jacobs Jr WR, Adams EJ, Minnaard AJ, Porcelli SA, Moody DB. CD1c tetramers detect ex vivo T-cell responses to processed phosphomycoketide antigens. J Exp Med 2013;210: 729-741.

Capacity
Our specific research capacity resides in the chemical synthesis and structure elucidation of (glyco)lipids. We provide pure, that is devoid of biological contaminations, compounds in sufficient amounts. Infrastructure comprises fully equipped synthesis labs, spectroscopy equipment (NMR, X-ray, UV and IR) and chromatography (GC-MS, HPLC-MS).

Collaborations and networks
The group is involved in a Bill & Melinda Gates funded project within the "Vaccine Accelerator", together with the groups of Branch Moody (Brigham & Women's Hospital, Harvard Med School, USA), Martine Gilleron, (CNRS, Institut de Pharmacologie et de Biologie Structurale, Toulouse, France), Ann Rawkins and Simon Clark, (Public Health England, Porton Down, Salisbury), Ildiko van Rhijn, (University of Utrecht), and Nathalie Cadieux (Aeras).

Key figures
- 2 senior researchers and postdocs working on TB
- currently 2 PhDs working on TB (of whom 1 are women)
- 5 PhDs on TB completed in the last 10 years
- 21 peer-reviewed publications on TB last 10 years
- 0 patents related to TB

Radboud UMC - Department of Medical Microbiology

Main Researchers
Dr. Jakko van Ingen, Dr. Johan Mouton, Dr. Dick van Soolingen

Focus of Research
To improve the outcome of antibiotic treatment for pulmonary disease caused by nontuberculous mycobacteria, we have set up a pipeline of static (minimum inhibitory concentration determination, time-kill kinetics assays) as well as dynamic models (hollow fiber pharmacodynamic model) to evaluate the possible contributions of single (new) drugs and drug combinations. New drugs or combinations that do well in this pipeline are selected for further analysis in mouse models and ultimately clinical trials.

Achievements
- We have shown, that currently recommended regimens for Mycobacterium avium complex lead to low serum concentrations and thus likely to low efficacy. This has generated strong discussion in the field and sparked investigations into alternative regimens. Our in vitro evaluation pipeline has proven useful and successful in this matter. The first compound that was evaluated in our in vitro pipeline, clofazimine, is now tested in a clinical trial.

Top-3 publications

1. van Ingen J, Egelund EF, Levin A, Totten SE, Boeree MJ, Mouton JW, Aarnoutse R, Heifets LB, Peloquin CA, Daley CL. The pharmacokinetics and pharmacodynamics of pulmonary Mycobacterium avium complex disease treatment. Am J Respir Crit Care Med 2012; 186: 559-65.
2. López-Varela E, García-Basteiro AL, Santiago B, Wagner D, van Ingen J, Kampmann B. Non-tuberculous mycobacteria in children: muddying the waters of tuberculosis diagnosis. Lancet Respir Med 2015;3:244-56.
3. Ferro BE, van Ingen J, Wattenberg M, van Soolingen D, Mouton JW. Time-kill kinetics of antibiotics active against rapidly growing mycobacteria. J Antimicrob Chemother 2015;70:811-7.

Capacity
Our specific expertise is the analysis of the antimycobacterial activity of drugs and drug combinations. For this goal we have set up the pipeline of static (minimum inhibitory concentration determination, time-kill kinetics assays) as well as dynamic models (hollow fiber pharmacodynamic model).

Collaborations and networks
We have close collaborations within Radboud UMC with the internal medicine (Reinout van Crevel) and pulmonology (Martin Boeree) departments. With ErasmusMC, we collaborate to bring new drugs that proved active in our in vitro models into mouse models. Jakko van Ingen is the coordinator of the NTM-NET network that connects >150 clinicians and researchers in 26 different countries, to perform joint studies on nontuberculous mycobacterial disease (NTM) . We collaborations with National Jewish Health/University of Colorado (Charles Daley), Baylor Institute for Immunology Research (Tawanda Gumbo), the Stellenbosch University, Cape Town, South Africa (Andreas Diacon), Kilimanjaro Christian Medical Center (Gibson Kibiki). We are clinical trial laboratory serving all European participants for 2 industry-supported clinical trials in NTM.

Key figures
- 3 senior researchers and postdocs working on TB
- currently 2 PhDs working on TB (of whom 1 is a woman)
- 2 PhDs on TB completed in the last 10 years
- 106 peer-reviewed publications on TB last 10 years

Academic Medical Center, Amsterdam, Electron Microscopy Centre Amsterdam (EMCA)

Main Researchers

Nicole van der Wel

Focus of Research

EMCA uses high resolution microscopes to visualize chemically incorporated tags on mycobacteria,, study mutants and the regeneration of the capsular layer of mycobacteria. Furthermore, we are determining the subcellular localization in granulomas of various conditions. Currently we are working on 2 lines of investigation: 1). Capsular layer of mycobacteria; specifically BCG and mutants as culturing conditions affects this outer layer of mycobacteria, 2). Localisation of mycobacteria in vivo to understand why the BCG-vaccine is ineffective and investigate the localisation in tissues.

Achievements

- We showed: (1) Direct Visualization by Cryo-EM of the Mycobacterial Capsular Layer: A Labile Structure Containing ESX-1-Secreted Proteins; (2) Mycobacterial secretion systems ESX-1 and ESX-5 play distinct roles in host cell death and inflammasome activation; (3) why the current vaccine is ineffective through subcellular localization of Mycobacteria, and how we can improve it.

Top-3 publications

1. Van der Wel NN, Hava D, Sugita M, Fluitsma DM, Brenner MB and Peters PJ. M. tuberculosis and M. leprae are sequential phagolysomal – cytosolic pathogens in human myeloid cells. Cell. 2007;129:1287-98.
2. Sani M, Houben EN, Geurtsen J, Pierson J, de Punder K, van Zon M, Wever B, Piersma SR, Jiménez CR, Daffé M, Appelmelk BJ, Bitter W, van der Wel N, Peters PJ. Direct Visualization by Cryo-EM of the Mycobacterial Capsular Layer: A Labile Structure Containing ESX-1-Secreted Proteins. PLoS Pathog 2010;6:e1000794.
3. Houben D, Demangel C, van Ingen J, Perez J, Baldeón L, Abdallah AM, Caleechurn L, Bottai D, van Zon M, de Punder K, van der Laan T, Kant A, Bossers-de Vries R, Willemsen P, Bitter W, van Soolingen D, Brosch R, van der Wel N, Peters PJ. ESX-1-mediated translocation to the cytosol controls virulence of mycobacteria. Cell Microbiol 2012;8:1287-98.

Capacity

The EMCA is a collaboration between 5 Amsterdam research institutes. We are setting up a grant for a trial for leprosy in collaboration with Jan Hendrik Richardus Erasmus, MC Rotterdam and Stefan Kaufmann Max Planck Institute Germany. For the clinical trial on the application of a new rBCG for bladder cancer purposes in collaboration with VPM, Berlin, Dr Bas van Rhijn, NKI Amsterdam and Dr Cyrill Rentsch, Basel we are seeking funding for a research project.

Collaborations and networks

National:

KIT (Dr. Rene Lutter, Dr. Alice den Hertog), Erasmus MC Rotterdam (JH Richardus), LUMC (S van Kasteren), LUMC (T Ottenhof), VU (W Bitter, J Luirink), RIVM (D van Soolingen), A v Leeuwenhoek hospital (B van Rhijn)

International:

Harvard USA (B Moody), Institute Pasteur France (R Brosch), Stellenbosch University South Africa (G Walzl), Ohio State University USA (L Schlesinger), New York USA (W Jacobs), Max Planck Germany (S Kaufmann), Cornell University USA (D Russell), VPM Germany (L Grode), National Hansen's Disease Program USA (R Truman), Univ de Zaragoza Spain (C Martin), University Hospital Swiss (C Rentsch).

Key figures

- 4 technicians working on TB
- current 0 PhDs working on TB and 3 students (of whom 1 is women)
- 1 PhDs on TB completed in the last 10 years
- 16 peer-reviewed publications on TB last 10 years

Academic Medical Center/ University of Amsterdam, Center for Experimental and Molecular Medicine (CEMM) and Depts. of Respiratory Medicine and Experimental Immunology.

Main Researchers

Dr. Jeroen van Heijst, Prof. Tom van der Poll and Dr. René Lutter

Focus of Research

Mechanisms of T cell protection against tuberculosis (TB). Towards this goal, the group utilizes a unique adoptive transfer model of transgenic M. tuberculosis-specific CD4 T cells, which confers substantial protection against bacterial growth.
The immunomodulatory enzyme indoleamine 2,3-dioxygenase (IDO) is markedly expressed in granuloma, but its role in granuloma biology is unknown. We employ IDO knock-out mice and our unique conditional IDO transgenic mice to study the role of IDO in tuberculoid granuloma.

Achievements

- Dr. van Heijst has contributed to the development of T cell receptor transgenic mice that are specific for the immunodominant M. tuberculosis antigen ESAT6. Using these mice, it was found that ESAT6-specific CD4 T cells can reduce M. tuberculosis growth by more than 100-fold, which is 10-fold greater protection than standard BCG vaccination. We are now exploring the mechanisms behind this protective effect using functional genomics approaches, aiming to identify novel biomarkers of T cell immunity against TB. We also have shown that granulomatous IDO in murine TB affects anti-mycobacterial responses and controls dissemination of M. tuberculosis.

Top-3 publications

1. Wieland CW, Koppel EA, den Dunnen J, Florquin S, McKenzie AN, van Kooyk Y, van der Poll T, Geijtenbeek TB. Mice lacking SIGNR1 have stronger T helper 1 responses to Mycobacterium tuberculosis. Microbes Infect 2007;9:134-41.
2. Gallegos AM, van Heijst JW, Samstein M, Su X, Pamer EG, Glickman MS. A gamma interferon independent mechanism of CD4 T cell mediated control of M. tuberculosis infection in vivo. PLoS Pathog 2011;7:e1002052.
3. van der Sluijs KF, van de Pol MA, Kulik W, Dijkhuis A, Smids BS, van Eijk HW, Karlas JA, Molenkamp R, Wolthers KC, Johnston SL, van der Zee JS, Sterk PJ, Lutter R; RESOLVE research team. Systemic tryptophan and kynurenine catabolite levels relate to severity of rhinovirus-induced asthma exacerbation: a prospective study with a parallel-group design. Thorax 2013;68:1122-30.

Capacity

AMC has unique tools to address the profound immunomodulatory functions of IDO; using mice with conditional expression of human IDO, as well as unique mouse models to study T cell protection against TB. The AMC possesses a state-of-the-art Biosafety level 3 laboratory in which both wild type and genetically-modified M. tuberculosis can be cultured, in addition to a matching animal facility in which in vivo experiments with these bacteria can be performed.

Collaborations and networks

Several international collaborations, including with Prof. Michael Glickman (MSKCC New York) and with Prof. Roland Brosch (Pasteur Institute Paris).

Key figures

- 3 senior researchers and postdocs working on TB.
- 1 current PhD working on TB (of whom 0 are women).
- 2 PhDs on TB completed in the last 10 years.
- 22 peer-reviewed publications on TB last 10 years.

KIDS2KIDSAFRICA at Vrije Universiteit Medical Center in Amsterdam, Department of Pediatric Infectious Diseases and Immunology, and at Tijgerberg Hospital, Cape Town, South Africa

Main Researchers

Prof. AM van Furth, Dr. M van der Kuip, Dr. D Visser, Dr. R van Toorn, Dr. R Solomons

Focus of Research

The main focus is on tuberculous meningitis in children, in the Western Cape in South-Africa. The research is form organized from "bench to bedsite" meaning that fundamental immunological studies are performed, metabolomics studies, clinical studies and home treatment studies.

Achievements

- Our group has developed a unique adherence tool for children with tuberculous meningitis (TBM) which made it possible to treat these children safely in their home environment. We identified specific immunological makers in the cerebrospinal fluid which can be used as a diagnostic test for TBM.

Top-3 publications

1. Visser DH, Solomons RS, Ronacher K, van Well GT, Heymans MW, Walz G, Chegou N, Schoeman JF, van Furth AM. Host immune response to tuberculous meningitis. Clin Infect Dis 2015;60:177-87.
2. Solomons RS, Wessels M, Visser DH, Donald PR, Marais BJ, Schoeman JF, van Furth AM. Uniform research case definition criteria differentiate tuberculous and bacterial meningitis in children. Clin Infect Dis 2014;59:1574-8.
3. Solomons RS, Visser DH, Donald PR, Marais BJ, Schoeman JF, van Furth AM. The diagnostic value of cerebrospinal fluid chemistry results in childhood tuberculous meningitis. Childs Nerv Syst 2015;31:1335-40.

Capacity

We have very specific expertise on the granuloma formation in the brain of children with TBM (human material, computer modeling, and in a zebrafish model).

Collaborations and networks

We work in several national and international networks, including with University of Stellenbosch and Centre for Human Metabolomics (South Africa), University of Michigan Medical School (USA), within VUMC and with UMC St Radboud, Nijmegen

Other information

The VU has a Desmond Tutu program together with the South African National Research Foundation; it gives Desmond Tutu Professors (van Furth is one of them) the possibility to train South-African PhDs, who will get a PhD degree from the VU and from the partner University in South-Africa. The next 3 years there will be another 100 PhDs.

Key figures

- 4 senior researchers and 1 postdocs working on TB
- currently 4 PhDs working on TB (of whom 3 are women)
- 4 PhDs on TB completed in the last 10 years
- 18 peer-reviewed publications on TB last 10 years

Academic Medical Center, Center of Tropical Medicine and Travel Medicine, University of Amsterdam

Main Researchers

Prof. dr. Martin Peter Grobusch

Focus of Research

Current research foci are tuberculosis (TB)/HIV co-pathophysiology (TB bacteremia and sepsis, TB Immune Reconstitution Inflammatory Syndrome (IRIS)) and the diagnosis of childhood TB; therapy development and optimization of HIV/TB co-therapy and shortening of therapy for drug-resistant TB); behavioral and socio-economic determinants of TB treatment-seeking and outcome.

Achievements

- TB research activities date back to MPG's working period in South Africa in 2005-2010 when he oversaw the building of TB clinical and research capacity with a 268 bed MDR- and XDR-TB clinical and research facility. Main research achievement was the contribution to bedaquiline phase II trials for treatment of MDR/XDR-TB. Currently research activities in South Africa are shifted to pathophysiological and diagnostic studies, gearing up towards starting HIV/TB co-treatment trials. At the CERMEL research facility in Lambaréné, Gabon, the group initiated the building of TB diagnostic and therapeutic capacity and led the first large TB epidemiology study in the country.

Top-3 publications

1. Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, Leimane V, Andries K, Bakare N, De Marez T, Haxaire-Theeuwes M, Lounis N, Meyvisch P, De Paepe E, van Heeswijk RP, Dannemann B. Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med 2014;371:723-32.
2. Dheda K,Shean K, Zumla A, Badri M, Streicher EM, Page-Shipp L, Willcox P, John MA, Reubenson G, Govindasamy D, Wong M, Padanilam X, Dziwiecki A, van Helden PD, Siwendu S, Jarand J, Menezes CN, Burns A, Victor T, Warren R, Grobusch MP, van der Walt M, Kvasnovsky C. Early treatment outcomes and HIV status of patients with extensively drug-resistant tuberculosis in South Africa: a retrospective cohort study. Lancet 2010; 375:1798-1807.
3. Diacon AH, Pym A, Grobusch MP, Patientia R, Rustomjee R, Page-sHipp L, Pistorius C, Krause R, Bogoshi M, Churchyard G, Venter A, Allen J, Palomino JC, De Marez T, van Heeswijk RP, Lounis N, Meyvisch P, Verbeeck J, Parys W, de Beule K, Andries K, McNeeley DF. The diarylquinoline TMC207 for multidrug-resistant tuberculosis. N Engl J Med 2009; 360: 2397-2405.

Capacity

At the Amsterdam site, the research activities across the African network are coordinated, and PhDs supervised. At the Lambaréné site, a fully-fledged TB laboratory has been set up, as well as a MDR-TB treatment unit at the Georges Rawiri Hospital with 8 staff members. At the Cape Town site, collaborative work is conducted at Khayelitsha Hospital, the Red Cross Hospital and in Prof. Graeme Meintjes' laboratory at IIDMM (with currently 2 Amsterdam PhDs in place).

Collaborations and networks

University of Cape Town; CERMEL Lambaréné; Ministry of Health, Lusaka, Zambia; PANACEA consortium (EDCTP-funded), Host-Directed Therapies Network (HD-NET); and a wide range of collaborative partners across Africa, the USA and Europe. MPG has recently been appointed lead investigator for the TB activities of the University of Tübingen, Germany for DEZIF, the German Center of Infectious Diseases Research.

Other information

In the Netherlands, the Center of Tropical Medicine and Travel Medicine works closely together on TB with the AIGHD, the KIT, and the University of Groningen.

Key figures

- 1 senior researcher, 6 PhDs (5 women) and a group of local staff and collaborators in the partner sites Cape Town and Lambaréné constitute the core group.

University Medical Center Groningen (UMCG); departments of pulmonary diseases and tuberculosis and clinical pharmacy and pharmacology, TB Center Beatrixoord

Main Researchers

Prof. Tjip van der Werf, Dr. Jan-Willem Alffenaar

Focus of Research

The research of the group focuses on four areas, taking a multidisciplinary approach (clinical, pharmacokinetic/pharmacodynamics (PK/PD), immunological) to: 1. Improving diagnosis and treatment of TB, e.g. by evaluating new diagnostic and therapeutic strategies. 2. Evaluation of PK/PD based dosing strategies to increase efficacy, reduce toxicity and prevent development of drug resistance. 3. Evaluation of therapeutic vaccines on top of optimal care. 4. Exploration of newly synthesized compounds and available drugs with other indications for activity against M. tuberculosis.

Achievements

- UMCG group is internationally well known for its multidisciplinary treatment approach with outstanding treatment results. Members of the group have participated in several international guidelines for improving TB diagnosis and treatment. The research on clinical pharmacology of TB drugs has provided new insights. Exploration of moxifloxacin for TB meningitis, blood level guided dosing of linezolid and aminoglycosides proved to be successful. The group has world leading expertise on dried blood spot analysis.

Top-3 publications

1. Alffenaar JW, Gumbo T, Aarnoutse R. Shorter moxifloxacin-based regimens for drug-sensitive tuberculosis. N Engl J Med 2015;372:576.
2. Alffenaar JW, van Altena R, Bökkerink HJ, Luijckx GJ, van Soolingen D, Aarnoutse RE, van der Werf TS. Pharmacokinetics of moxifloxacin in cerebrospinal fluid and plasma in patients with tuberculous meningitis. Clin Infect Dis 2009;49:1080-2.
3. van Altena R, de Vries G, Haar CH, de Lange WC, Magis-Escurra C, van den Hof S, van Soolingen D, Boeree MJ, van der Werf TS. Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000-2009. Int J Tuberc Lung Dis 2015;19:406-12.

Capacity

UMCG brings together various disciplines in TB treatment, including treatment standard of excellence, clinical research, pharmacology, analytical chemistry and microbiology. The laboratory of the UMCG is one of the largest in the world with dedicated capacity for TB pharmacology research. Implementation research is done across a wide range of infectious diseases and settings.

Collaborations and networks

UMCG links research and treatment optimization; collaborations exist with research groups in high-incidence settings (Belarus, Romania, South Africa, China, Vietnam, Bangladesh, Ghana) as well as in Europe (e.g. Karolinska Institute, Sweden; WHO Collaborating Centre for TB and Lung Disease, Italy; TB Research Center Borstel, Germany) and the USA (e.g. Baylor University, Dallas Tx; University of Florida, Gainesville Fl; Johns Hopkins Medical Center, Baltimore MD).

Key figures

- 4 senior researchers and postdocs working on TB
- currently 12 PhDs working on TB (of whom 4 are women)
- 4 PhDs on TB completed in the last 10 years
- 80 peer-reviewed publications on TB last 10 years

Utrecht University, Faculty of Veterinary Medicine, Department of Infectious Diseases & Immunology

Main Researchers

Prof. Victor Rutten, Prof. Willem van Eden, Dr. Alice Sijts and Dr. Ildiko van Rhijn

Focus of Research

Current research is focused on determining the effect of non-tuberculous mycobacteria on diagnostic assays and efficacy of vaccination for tuberculosis, and developing and validating diagnostic tools for the diagnosis of tuberculosis in free-roaming as well as captive wildlife species.
Using tuberculosis in cattle as a model for the disease in humans, experimental exposure followed by preventive or therapeutic vaccination is underway. In addition detailed analyses of the amino acid composition of shared (homologous) antigens, especially those known to be immunogenic, in relation to immune responsiveness are conducted.

Achievements

- The group has a long track record in (para)tuberculosis research. Major projects led by the group include "The impact of non-tuberculous mycobacteria and host genetics on immunological responsiveness of Cattle and African Buffaloes to BCG vaccination and Mycobacterium bovis infection in South Africa and Elephant Health and reproduction". We recently discovered T cells that recognize Mycobacterium tuberculosis lipids presented by CD1b. This research may open up new possibilities for diagnostics and vaccines in TB.

Top-3 publications

1. Santema W, van Kooten P, Hoek A, Leeflang M, Overdijk M, Rutten V, Koets A. Hsp70 vaccination-induced antibodies recognize B cell epitopes in the cell wall of Mycobacterium avium subspecies paratuberculosis. Vaccine 2011;29:1364-73.
2. Van Rhijn I, Kasmar A, de Jong A, Gras S, Bhati M, Doorenspleet ME, de Vries N, Godfrey DI, Altman JD, de Jager W, Rossjohn J, Moody DB. A conserved human T cell population targets mycobacterial antigens presented by CD1b. Nat Immunol 2013;14:706-13.
3. Eisenberg SW, Rutten VP, Koets AP. Dam Mycobacterium avium subspecies paratuberculosis (MAP) infection status does not predetermine calves for future shedding when raised in a contaminated environment: a cohort study. Vet Res 2015;46:70.

Capacity

The group has decades of experience performing research pertaining to pathogenesis, diagnosis and vaccination in the field of paratuberculosis and tuberculosis in large animals.
Collaborations and networks
Apart from work in the Netherlands, the majority of the research is conducted in a WOTRO project in South Africa (currently 4 PhD students) and Thailand (1 PhD student). We collaborate with universities of Utrecht and Groningen, and Harvard university (USA).

Other information

Tuberculosis in cattle may be considered as a good model for tuberculosis in humans. Increasing occurrence of tuberculosis in captive wildlife species, is a health threat for neighbouring species, including humans.

Key figures

- 4 senior researchers and postdocs working on TB
- Currently 2 PhD students working on TB (of whom 1 are women)
- 5 PhDs on TB completed in the last 10 years
- 20 peer-reviewed publications on TB last 10 years
- 2 patents related to TB

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List of contributors
Research groups

LIST OF ABBREVIATIONS

AIGHD	Amsterdam Institute for Global Health and Development, University of Amsterdam
AMC	Academic Medical Center, University of Amsterdam
BCG	Bacille Calmette-Guérin, the currently used TB vaccine
BMGF	Bill and Melinda Gates Foundation
BPRC	Biomedical Primate Research Center
BSL	biosafety level
CVI	Central Veterinary Institute, University of Wageningen
EDCTP	European & Developing Countries Clinical Trials Partnership
GFATM	Global Fund to fight AIDS, Malaria and TB
GIS	Geographic Information Systems
KIT (BR)	Koninklijk Instituut voor de Tropen/Royal Tropical Institute, (Biomedical Research)
MDR-TB	Multidrug-resistant tuberculosis
Molepi	molecular epidemiology, i.e. related to microbial DNA typing
NIH	National Institutes of Health (USA)
NIAID	National Institute of Allergic and Infectious Diseases (USA)
NTRP	Netherlands Tuberculosis Research Platform
R&D	research and development
RIVM	Rijksinstituut voor Volksgezondheid en Milieuhygiëne/National Institute of Public Health and The Environment
SIC-UG	Stratingh Institute for Chemistry, University Groningen
TB	tuberculosis
TBVI	Tuberculosis Vaccine Initiative
UMC	University Medical Center - Groningen, Leiden, Radboud (Nijmegen)
USAID	US Agency for International Development
VFMU	Faculty of Veterinary Medicine, Utrecht University
VUMC	Free University Medical Center (Amsterdam)
WHO	World Health Organization
XDR-TB	Extensively resistant tuberculosis

Tuberculosis Referral Hospital Dekkerswald, Radboud University Medical Center (UMC) Nijmegen

Main Researchers
Prof. Martin Boeree, Dr. Cecil Magis-Escurra, Dr. Wouter Hoefsloot

Focus of Research
TB research in Dekkerswald is intensively interwoven with other research groups within the Radboud UMC and through its KCMI (Knowledge Centre Mycobacterial Infections). Martin Boeree is one of the chief investigators in the EDCTP funded PanACEA consortium. PanACEA's research portfolio ranges from two-center early Phase II studies through to large-scale Phase III studies in a multitude of sites and countries. While initially individual development programs were conducted for each of the drugs in the portfolio (moxifloxacin, rifampicin and SQ109), these programs have grown together and has set a new standard in TB combination therapy research, investigating all three drugs in different regimes in a single trial.

Achievements
- The development of the concept of higher dosages of rifampicine in the treatment of tuberculosis, the contribution to alternative approaches in the treatment of NTM infections.

Top-3 publications
1. Boeree MJ, Diacon AH, Dawson R, Narunsky K, du Bois J, Venter A, Phillips PP, Gillespie SH, McHugh TD, Hoelscher M, Heinrich N, Rehal S, van Soolingen D, van Ingen J, Magis-Escurra C, Burger D, Plemper van Balen G, Aarnoutse RE; PanACEA Consortium. A dose-ranging trial to optimize the dose of rifampin in the treatment of tuberculosis. Am J Respir Crit Care Med 2015;191:1058-65.
2. van Ingen J, Aarnoutse RE, Donald PR, Diacon AH, Dawson R, Plemper van Balen G, Gillespie SH, Boeree MJ. Why Do We Use 600 mg of Rifampicin in Tuberculosis Treatment? Clin Infect Dis. 2011; 52: e194-9
3. de Steenwinkel JE, Aarnoutse RE, de Knegt GJ, ten Kate MT, Teulen M, Verbrugh HA, Boeree MJ, van Soolingen D, Bakker-Woudenberg IA. Optimization of the rifampin dosage to improve the therapeutic efficacy in tuberculosis treatment using a murine model. Am J Respir Crit Care Med. 2013;187:1127-34.

Capacity
Dekkerswald and the KCMI have extensive expertise in the execution of clinical trials both in tuberculosis as in NTM. There are laboratories for pharmacokinetics, pharmacodynamics, medical microbiology, including molecular techniques such as the hollow fiber model as whole genome sequencing. The PanACEA consortium is a group of scientists from more than 14 countries with skills in clinical trials design and implementation, pulmonology, mycobacteriology, pharmacokinetics, statistics and delivery of clinical service. PanACEA has accumulated vast experience in the field of tuberculosis research.

Collaborations and networks
Dekkerswald has networks within the Netherlands within Radboud UMC (KCMI), LUMC, EMC and the UMCG. The PanACEA consortium operates trial sites in Tanzania (KCRI, IHI, Mbeya) South Africa (UCT, University of Stellenbosch, Aurum Institute, University of Witwatersrand), Malawi (COM), Mozambique, Gabon and Uganda. Major research partners include the EDCTP, TBTC, ACTG, St Andrews University, ULC London, University of Munich (LMU).

Key figures
- 3 senior researchers and postdocs working on TB and NTM
- currently 7 PhDs working on TB and NTM (of whom 2 are women)
- 12 PhDs on TB and NTM completed in the last 10 years
- 147 peer-reviewed publications on TB last 10 years

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