

Viewpoint

Achieving STOP TB Partnership goals: perspectives on development of new diagnostics, drugs and vaccines for tuberculosis

Peter Mwaba^{1,2}, Ruth McNerney³, Martin Peter Grobusch⁴, Justin O'Grady^{2,5}, Matthew Bates^{2,5}, Nathan Kapata^{1,5}, Markus Maeurer⁶ and Alimuddin Zumla^{2,5}

1 Ministry of Health, Lusaka, Zambia

2 University of Zambia-University College London Medical School Research and Training Project, Lusaka, Zambia

3 London School of Hygiene & Tropical Medicine, London, UK

4 Department of Infectious Diseases, Tropical Medicine and AIDS, University of Amsterdam, Amsterdam, The Netherlands

5 Department of Infection, University College London Medical School, London, UK

6 Karolinska Institutet, MTC, Laboratory Medicine and Karolinska Hospital, CAST, Stockholm, Sweden

Summary

Global eradication of tuberculosis (TB) depends on identification and treatment of all active TB cases and of the two billion people who are estimated to be latently infected with *Mycobacterium tuberculosis*. The past decade has seen a renaissance of scientific activities and funder investment into development of new TB drugs, diagnostics, biomarkers and vaccines. This viewpoint critically summarises the promising portfolio of more accurate TB diagnostics, new TB drugs and vaccines that have been endorsed by the STOP TB Partnership. Increasing numbers of Phase 2 and 3 drug, vaccine and diagnostic clinical trials in high-TB endemic areas reflect substantial progress towards attaining Global STOP-TB Partnership targets. Achievement of STOP-TB Partnership goals will crucially depend on political will and serious investment by funders and developing country governments into improving delivery of better health services and living conditions for their people. Long-term sustainability of any newer tools implemented at point of care is essential.

keywords tuberculosis, diagnostics, drugs, biomarkers, vaccines, WHO, STOP TB Partnership

Introduction

Global eradication of tuberculosis (TB) ultimately depends on identification and treatment of the all active TB cases and of the two billion people who, according to WHO estimates, are latently infected with *Mycobacterium tuberculosis* (*M. tuberculosis*) (Zumla *et al.* 2011; Sudre *et al.* 1992). The latter is seemingly impossible; thus, current WHO focus is on the former. Improvement of social factors driving the current TB pandemic (poverty, poor housing, poor nutrition, chronic liver diseases, smoking, diabetes, immunosuppression and poor health services) is crucial in curtailing the epidemic. They will need to be tackled in parallel with existing and newer diagnostics, drugs and vaccines, if the current global pandemic is to be controlled (Grange *et al.* 2001; Zumla &

Grange 2010). The progress made in these areas over the past decade is critically reviewed here in the light of the stated goals of the STOP TB Partnership.

Establishment of the STOP TB Partnership

In response to the global emergency of the TB pandemic, the Stop TB Partnership was established by the World Health Assembly (WHA) in May 2000; it comprises >1200 donors, national and international organisations, government and non-governmental organisations. The Partnership consists of a Partners' Forum, a Coordinating Board and a Partnership Secretariat currently hosted by WHO in Geneva, Switzerland (WHO, 2006). It has seven working groups (WG); three are focussed on new tools required to achieve TB control: TB diagnostics, drugs and

vaccines. A critical aspect of TB control is early accurate diagnosis and effective treatment of active TB disease to render patients non-infectious. An effective vaccine to prevent development of TB is an ideal, which has not been realised. Testing of new TB vaccine candidates is underway, and identification of clinically meaningful and robust biomarkers to gauge vaccine take and efficacy remains unavailable.

In 2006, the TB pandemic continued to kill 2 million people annually and was growing by 1% each year, despite WHO having declared it a 'Global Emergency' over a decade earlier. The Global Plan to Stop TB (2006–2015) (WHO, 2006) was launched in 2006 by the STOP TB Partnership, and this formed the basis of a universally accepted roadmap for substantially reducing the global burden of TB by 2015. This was updated in the 2010 WHO Report. The Research and Development (R&D) component of the Global Plan to Stop TB envisaged that fundamental basic research will allow discovery of new TB diagnostics, drugs and vaccines (Ma *et al.* 2010; Wallis *et al.* 2010; Kaufmann *et al.* 2010). The aims of the Global Plan to Stop TB, although ambitious, were clear, and a huge financial investment was required to achieve its aims.

For new TB diagnostics, a portfolio of new and improved diagnostic tests for the detection of active and latent TB, and drug-resistant forms of TB, in all age groups and in HIV-infected populations, was deemed a priority. Diagnostic test development was to aim for at least one simple, robust and affordable test that could be used as a rapid and accurate diagnosis of TB at points of care (POC) within all peripheral health systems, and a test for latent infection capable of identifying people at the greatest risk of progression to active TB disease.

For improved drug treatment outcomes, it was planned that development of new drugs with a new shorter 4-month TB regimen including at least one new TB drug would be approved by regulatory authorities for drug sensitive TB, recommended by WHO, and available for use globally. Other drug development targets were at least one new drug for the treatment of multidrug-resistant TB (MDR-TB) available; a 9-month regimen for treatment of MDR-TB (including at least one new drug) in a Phase III trial; and a safer, shorter duration, higher-efficacy regimen available for treatment of latent TB infection.

For new TB vaccine development, the Global Plan aimed for four new TB vaccine candidates to have entered Phase III clinical trials for safety and efficacy; with assays to determine biomarkers and correlates of immunity incorporated into clinical trials; and sufficient manufacturing capacity and licensing agreements in place to ensure an ample, affordable supply of new TB vaccines.

It has been a decade since the formation of the STOP TB Partnership, and the time is ripe to take stock of progress and reflect on the future. Since the launch of the Global Plan to Stop TB in WHO, (2006), an increased, but not optimal, investment for development of new TB diagnostics, biomarkers, drugs and vaccines has led to several promising new technologies and a number of high-quality product potential candidates (Ma *et al.* 2010; Wallis *et al.* 2010; Kaufmann *et al.* 2010). A renaissance of research activities and funder investment has led to development of a pipeline of new TB diagnostics, drugs and vaccines. Biomarker discovery has lagged behind.

Progress in development of new TB diagnostics

A number of important new developments in TB diagnostics give hope for the future of TB control (Table 1) (Wallis *et al.* 2010; WHO/TDR, 2008; McNerney & Daley 2011; World Health Organization, 2009a,b). The WHO Stop TB Partnership's New Diagnostics Working Group and Foundation for Innovative New Diagnostics (FIND) has classified tools for the diagnosis of active TB as the following: 'WHO-endorsed' tools in 'late-stage development or evaluation' and tools in 'early-stage development'. New WHO-endorsed tools include molecular line probe assays (LPAs) MDR-TB diagnosis and a rapid detection and speciation assay Capilia TB-Neo to assist culture. Light-emitting diode (LED) fluorescence microscopy was recommended to WHO by the Strategic and Technical Advisory Group for Tuberculosis (STAG-TB) in 2009 as an alternative to conventional microscopy. Three non-commercial culture and drug susceptibility methods were recommended by STAG-TB in 2010: the colorimetric redox indicator method, the microscopic observation drug susceptibility assay (MODS) and the nitrate reductase assay. Other diagnostic tools (WHO/TDR, 2008; McNerney & Daley 2011) in development include a breathalyser screening test (Jassal *et al.* 2010), isothermal nucleic acid amplification assays (Aryan *et al.* 2010), phage-based tests for rapid diagnosis of MDR-TB (Yzquierdo *et al.* 2009), MPT64 skin patch (TB Patch backgrounder. Sequella, Inc. Rockville, MD. Transrenal urinary DNA detection and LAM antigen detection (Peter *et al.* 2010), among others (McNerney & Daley 2011).

Not all new TB diagnostic tests have proved advantageous, and in 2010, STAG TB made negative recommendations for two recent technologies: commercial serological tests and interferon gamma release assays (IGRAs), to discourage their use in TB endemic countries (WHO Report, 2010). A similar comment has recently been made by the ECDC (http://ecdc.europa.eu/en/publications/Publications/1103_GUI_IGRA.pdf).

Table 1 Summary of WHO tuberculosis new diagnostic recommendations (adapted from references Wallis *et al.* 2010; World Health Organization, 2009a,b)

New diagnostic test	Year	Recommendations
Liquid media for culture and DST	2007	WHO recommends, as a stepwise approach: The use of liquid medium for culture and DST in middle- and low-income countries. The rapid species identification to address the needs for culture and drug susceptibility testing (DST).
Molecular line probe assays for rapid screening of MDR-TB	2008	The guiding principles for use of line probe assays: Adoption of line probe assays for rapid detection of multidrug-resistant tuberculosis (MDR-TB) should be decided by Ministries of Health within the context of country plans for appropriate management of MDR-TB patients, including the development of country-specific screening algorithms and timely access to quality-assured second-line anti-TB drugs.
LED-microscopy	2009	Conventional fluorescence microscopy to be replaced by LED microscopy in all settings and that LED microscopy be phased in as an alternative for conventional ZN microscopy in both high- and low-volume laboratories.
Non-commercial culture and drug-susceptibility testing (DST) methods	2009	WHO recommends that of selected non-commercial culture and DST methods be used as an <i>interim solution</i> in resource-constrained settings, in reference laboratories or those with sufficient culture capacity, whilst capacity for genotypic and/or automated liquid culture and DST are built. Microscopically observed drug susceptibility (MODS) The nitrate reductase assay (NRA) for screening of patients suspected of having MDR-TB Colorimetric redox indicator (CRI) methods, as indirect tests on <i>Mycobacterium tuberculosis</i> isolates from patients suspected of having MDR-TB
MTB/RIF assay	2010	WHO Expert Group and STAG-TB recommendations Xpert MTB/RIF should be used as the <i>initial diagnostic test</i> in individuals suspected of MDR-TB or HIV-associated TB Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens Xpert MTB/RIF is suitable for use at district and sub-district level, outside of conventional laboratory settings, compared to conventional culture and DST which are suitable only at national or regional level in reference laboratory settings. Xpert MTB/RIF technology does not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

MDR-TB, multidrug-resistant TB; RIF, resistance to rifampin; STAG-TB, Strategic and Technical Advisory Group for Tuberculosis.

MTB/RIF assay for TB diagnosis – a significant new development?

The development of a commercially available tool, the Xpert[®] MTB/RIF assay (Cepheid, California, USA), (Helb *et al.* 2010; Watts, 2010; Boehme *et al.* 2010) has been deemed a significant development for TB diagnostics by the WHO (MTB/RIF assay recommendations: http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf). The performance of Xpert MTB/RIF automated real-time PCR molecular test for simultaneously identifying *M. tuberculosis* DNA, and RIF, with fully integrated sample processing, was performed in 1730 patients with suspected drug-sensitive or multidrug-resistant pulmonary TB in a multicountry study (Peru, Azerbaijan, South Africa and India) (Boehme *et al.* 2010). Among culture-positive patients, a single, direct MTB/RIF test identified 551 of 561 patients with smear-positive TB (98.2%) and

124 of 171 with smear-negative TB (72.5%). The test was specific in 604 of 609 patients without TB (99.2%). Among patients with smear-negative, culture-positive test results, the addition of a second MTB/RIF assay increased sensitivity by 12.6% and the addition of a third by 5.1% to a total of 90.2%. Compared to phenotypic drug susceptibility testing, MTB/RIF testing correctly identified 200 of 205 patients (97.6%) with rifampicin-resistant bacteria and 504 of 514 (98.1%) with rifampicin-sensitive bacteria. Sequencing resolved all but two cases in favour of the MTB/RIF assay. Based on this and supporting as yet unpublished data, MTB/RIF assay has recently been endorsed by WHO Stop TB Partnership for use and adoption at POC globally (MTB/RIF assay recommendations: http://www.who.int/tb/laboratory/roadmap_xpert_mtb-rif.pdf). The assay sensitivity is higher than that of smear microscopy (10 000 cfu/ml) and close to that of liquid culture (10–100 cfu/ml) (Helb

P. Mwaba *et al.* **Achieving STOP TB Partnership goals**

et al. 2010). The assay is also said to be highly specific with no cross-reaction with non-tuberculous mycobacteria and normal flora of the respiratory tract.

MTB/RIF assay – point of care test or not is the question?

The characteristics of Xpert MTB/RIF assay meet some of the minimum POC specifications by the STOP TB Working Group on New Diagnostics (Helb *et al.* 2010). The assay is said to be robust, could be performed by low-skilled technicians and detects both *M. tuberculosis* and rifampicin resistance in sputum samples collected from adults within 2 h, of which only a few minutes hands-on attendance is required by the operator. The instrument operates at a wide range of room temperatures (15–30 °C) and in humid conditions. The Xpert MTB/RIF assay is said not to be associated with a measurable infection risk and results in a lower biohazard compared with conventional smear microscopy. The Xpert MTB/RIF assay was developed and evaluated in collaboration with the FIND, and a reduced pricing structure has been established for non-commercial health providers in countries where TB is endemic.

Rate-limiting steps of the MTB/RIF assay

Whilst the Xpert MTB/RIF assay appears to be a long-awaited breakthrough for TB diagnostics, the rate-limiting steps of this new technology are that this device does not appear to fulfil the need for a POC diagnostic test aimed for by the STOP TB Partnership: a test that can be implemented in the most peripheral settings in high TB endemic areas (Van Rie *et al.* 2010) that often have highly limited infrastructure and resources and are not suited for operating and maintaining computer-driven real-time PCR-based equipment. POC specifications that are not yet met are reagent shelf-life of approximately 1 year compared with the required 2 years; required annual instrument maintenance; high cost of the machine and cartridges; and need for continuous electrical power. Time of the assay is also at the upper limit, and some clinics will not be able to deliver same day treatment for those found positive with the test. Safe disposal recycling of large volumes of plastic cartridges remains an environmental concern.

MTB/RIF assay and rifampicin resistance

Doubts have been raised about the usefulness of the MTB/RIF assay in detection and surveillance for drug-resistant TB (Van Rie *et al.* 2010; Bhanot 2011; Zbinden

et al. 2011; Mohapatra 2011). There are also issues about the interpretation of a positive rifampicin resistance result and its usefulness for management in settings that do not have capacity for DOTS-Plus and treatment of MDR-TB (Zbinden *et al.* 2011; Mohapatra 2011). False-positive test for rifampicin resistance (Bhanot 2011; Zbinden *et al.* 2011) is being reported, which in clinical practice may be deleterious to patients. Other concerns have been expressed about the quality assurance for rifampicin resistance for the assay in resource-poor countries (Boehme *et al.* 2010).

Population groups unlikely to benefit from MTB/RIF assay

Tools that predict disease progression, screen for multidrug and extensive drug resistance (MDR and XDR respectively), extrapulmonary TB, sputum-negative TB and paediatric TB are still lacking and need further investment and research. Up to 30% of cases of TB cases occur in children who mostly do not produce sputum and where the diagnosis of TB is challenging (Hesseling *et al.* 2011). Furthermore, the usefulness of the MTB/RIF assay in people living with HIV/AIDS, who are either unable to produce sputum specimens, or are likely to produce paucibacillary specimens, needs evaluation. As a result, these patient populations will continue to have access to diagnostics of suboptimal performance, and significant number of active TB cases will remain undiagnosed.

Practicalities of implementation at POC

Importantly, discovery of new diagnostic tools like the MTB/RIF assay does not necessarily ensure their adoption and use in high TB endemic areas. Translation of new tools to POC requires a better understanding of barriers to implementation. For example, two decades, a large investment has gone into developing appropriate low-cost CD4 count testing for patients on antiretroviral therapy (ART) in Africa (Janosy 2008). Despite these attempts at developing a point of care tool, CD4 counting remains restricted to centralised services and not POC (MacLennan *et al.* 2008). Many African countries have upgraded their laboratory services with these flow cytometers. Many of these machines have become redundant within a few years of usage because of unavailability of regular servicing, quality control and sustained funding. Lessons must be learnt here. The true programmatic impact of the implementation of MTB/RIF assay will only be feasible through political commitment and substantial collateral funder investment. Several ‘point of care’ studies evaluating the MTB/RIF assay in a variety of clinical situations in

different geographical regions are underway. The need to standardise the designs of new studies is crucial so that valid comparisons can be made. The final verdict on the practical application of this MTB/RIF assay at POC is awaited.

Progress in the development of new TB Drugs

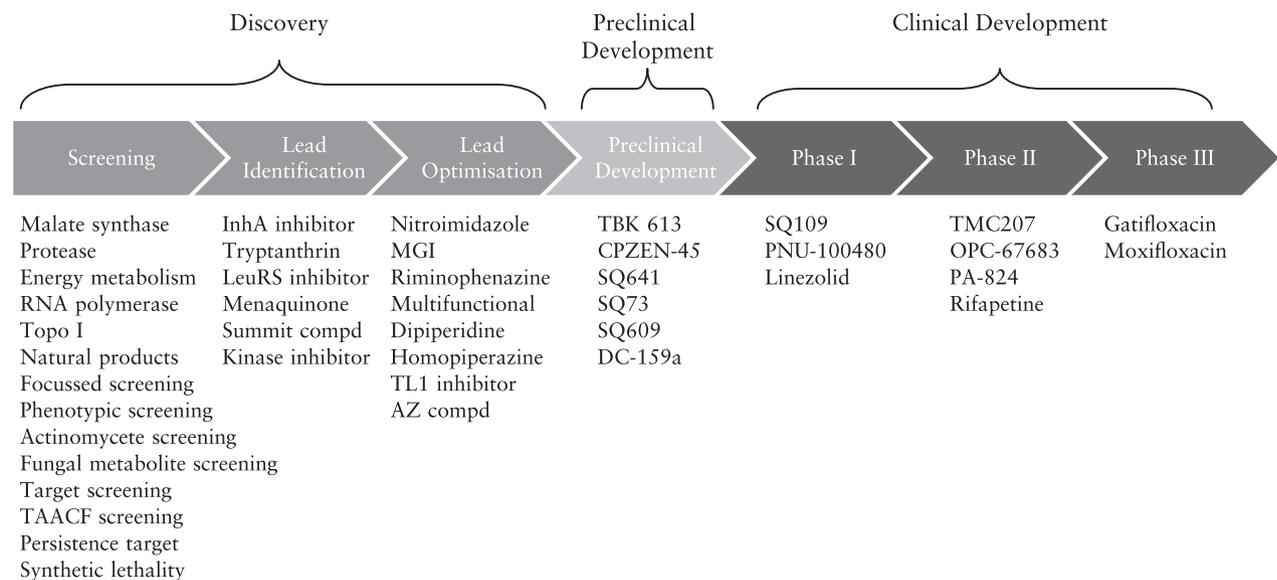
There have also been important advances in new TB drug development (Ma *et al.* 2010; Lienhardt *et al.* 2010) (Table 2). Despite the demonstrated efficacy in clinical trial of the standard 6-month chemotherapy of active drug-susceptible TB, it requires direct supervision to ensure adequate treatment adherence and prevention of drug resistance (Lienhardt *et al.* 2010). In addition, TB remains a leading cause of death in HIV-infected people in the developing countries, and treatment of TB in HIV-infected populations is difficult, because of potentially severe drug-drug interactions between rifampicin and some antiretroviral drugs (Ma *et al.* 2010; Lienhardt *et al.* 2010). Drugs that are active against drug-resistant forms of TB are less potent, more toxic and need to be taken for at least 18 months. Shorter and simpler regimens that are safe, well tolerated, effective against drug-susceptible and drug-

resistant TB, appropriate for joint treatment with ART, children-friendly and amenable to routine programmatic conditions are all needed urgently. Robust patient support systems are required to ensure high levels of adherence to treatment are achieved. The Global Plan to STOP TB (WHO, 2006) calls for a more concerted action to develop and introduce new drugs, preferably with novel mechanisms of action.

New TB drug pipeline

Significant progress has been made over the last 5 years, and there is a coordinated portfolio of promising new compounds on the horizon (Table 2) (Ma *et al.* 2010; Lienhardt *et al.* 2010). There are at present eleven new drugs in clinical development, which will likely lead to two newly approved drugs by 2015 (Ma *et al.* 2010; Lienhardt *et al.* 2010). Of these, three are in Phase I (safety) trials, six are in Phase II (early bactericidal activity and sputum conversion) trials, and two are in Phase III (efficacy) trials. At least five TB drug candidates are presently in pre-clinical development, and at least 23 additional candidates to identify new compounds are in the discovery phases.

Table 2 Current global TB drug research and development portfolio based on information compiled by the Stop TB Partnership. Working Group on New Drugs (from references Ma *et al.* 2010; Lienhardt *et al.* 2010)



TB, tuberculosis.

Fluoroquinolones

Gatifloxacin and moxifloxacin, recently developed fluoroquinolones, have shown better *in vitro* activity against *M. tuberculosis* than have ofloxacin and ciprofloxacin. On the basis of results from a mouse model of tuberculosis infection, moxifloxacin-containing regimens have the potential to shorten treatment of drug-susceptible TB from the present 6 months to 4 months. Rates of 2-month sputum culture conversion seemed better in Phase 2 trials in which gatifloxacin or moxifloxacin was substituted for ethambutol or isoniazid in the control regimen. Phase 3 trials are in progress for investigation of whether treatment of drug-susceptible TB can be shortened to 4 months by substitution of gatifloxacin for ethambutol or moxifloxacin for ethambutol or isoniazid.

Other classes of drugs

Two nitroimidazoles are in clinical development, PA-824 and OPC-67683. OPC-67683 Phase 1 is being assessed in a Phase 2 trial for the treatment of MDR-TB. A Phase II, stage 1 double-blind, placebo-controlled study with TMC207 in patients with MDR tuberculosis has been performed (Diacon *et al.* 2009). Clinical studies are in progress to assess the effects of high doses of rifampentine once or twice per week given with moxifloxacin and daily rifampentine in the first-line regimen to shorten treatment. The ethylenediamine, SQ-109, is a derivative of ethambutol and interacts synergistically with isoniazid and rifampicin. Phase 1 studies of SQ109 are complete, and Phase 2 studies are to start soon (http://www.edctp.org/uploads/tx_viprojects/Project_Profile_IP_TB_32011_Michael_Hoelscher.pdf Accessed February 28th 2011). No new drug or treatment regimen is yet available for treatment of latent TB infection.

Better planning for new TB drug evaluation is required

Despite this progress, the drug pipeline for TB is still insufficient for global needs. The Global Alliance for TB Drug Development initially estimated that one new TB drug would be introduced into clinical practice by 2010. This has not yet happened. One of the main challenges in TB drug development is the lack of global clinical trial capacity to conduct late-stage controlled trials necessary for product registration. Multiple trial sites are required to assess the safety and efficacy of new compounds and regimens and to take into account regional variations. Product registration trials for FDA approval are burdensome, and protracted affairs and results of evaluation of

new drugs will be slow in coming. An expansion in the numbers of sites TB endemic countries capable of conducting trials compliant with international good clinical practice (GCP) and good clinical laboratory practice (GCLP) standards is required. The European Developing Countries Clinical Trials Partnerships (EDCTP) is leading the way for African capacity development (Zumla *et al.* 2010). Other funding agencies need to follow suit, and the Global alliance needs to include capacity development into its investment portfolio.

Progress in development of new TB vaccines

New TB vaccines are urgently needed if the goal of substantially reducing the incidence of TB by 2050 is to be reached. According to recent modelling studies, the introduction of new effective TB vaccines and vaccination strategies will make a crucial contribution to achieve the STOP TB Partnership's goal to reduce the global incidence of TB disease to less than one case per million population by 2050. Research and Development of new vaccines for protection against TB is gaining momentum as reviewed by Kaufmann *et al.* (2010). The past 5 years has increased the pipeline of TB vaccine candidates (Table 3). Over the past decade, 12 vaccine candidates have left the laboratory stage and entered clinical trials. These vaccines are either aimed at replacing the present vaccine, Bacille Calmette-Guérin (BCG), or at enhancing immunity induced by BCG. However, these pre-exposure candidates are designed for the prevention of disease and will therefore neither eradicate the pathogen nor prevent stable infection.

The main target for vaccine development in the Global Plan to Stop TB 2006–2015 was that two vaccines would be in proof-of-concept trials by 2010 and that one new and safe vaccine would be available by 2015. As of 2009, TB vaccine candidates had entered clinical trials (Kaufmann *et al.* 2010) (Table 3). Of these, nine are still being tested: five are in Phase I (safety) clinical trials, two are in Phase II trials, and two are in Phase IIb 'proof-of-concept' trials. One vaccine has produced estimates of safety and effectiveness in a targeted HIV-infected population. At least six TB vaccine candidates are in preclinical development, and at least 21 additional next-generation candidates are in the vaccine discovery phase. Research into the development of new TB vaccine candidates is also underway to evaluate new delivery platforms that would be affordable and suitable for resource-limited settings, including needle-free delivery. There remains an urgent need for modern, safe and effective vaccines that prevent all forms of TB, in all age groups, in all geographical areas and among people living with HIV.

Table 3 New TB vaccines in various stages of clinical trials [from Kaufmann *et al.* (2010)]

Name	Description	Developmental stage
MVA85A	Attenuated strain of vaccinia expressing Ag85A	Phase I completed and Phase II ongoing. Phase IIb in infants commenced.
rBCG30	BCG overexpressing Ag85B	Phase I completed.
Aeras 402	Non-replicating Ad35 expressing Ag85A, Ag85B and TB10.4	Phases I and II ongoing.
AdAg85A	Non-replicating Ad5 expressing Ag85A	Phase I
M72	Recombinant fusion (Mtb39 and Mtb32) in AS02A and AS01B adjuvants	Phases I and II completed; additional trials ongoing.
Hybrid-1	Recombinant fusion of Ag85B-ESAT-6 in IC31 adjuvant	Phase I completed.
SSI HyVac-4 (Aeras 404)	Recombinant fusion of Ag85B-TB10.4 in IC31 adjuvant	Phase I commenced.
rBCGAUreC:Hly	BCG with an endosome escape mechanism	Phase I commenced.
RUTI	Detoxified <i>Mycobacterium tuberculosis</i> in liposomes	Phase I completed.
<i>M. vaccae</i>	Inactivated <i>M. vaccae</i>	Phase III completed.

TB, tuberculosis.

Progress in development of new TB biomarkers

In contrast to advances made in the development of TB diagnostics, drugs and vaccines, progress in discovery of new TB biomarkers for monitoring TB disease activity, relapse and cure has been slow. Recent advances in technology now allow for multiple markers to be studied (Doherty & Robert 2009; Kaufmann & Parida 2008; Jacobsen *et al.* 2007; Kunnath-Velayudhan *et al.* 2010; Maertzdorf *et al.* 2011; Banchereau *et al.* 2010). In an attempt to identify new biomarkers, several ambitious projects are now using highly multiplexed assays to compare gene expression between patients with TB, healthy persons with latent TB and healthy controls with no exposure to *M. tuberculosis*. It is now thought that multiple biomarkers, when combined, may perform substantially better than any single marker, and a small number of studies suggest that specificity and higher predictive values can be achieved by measuring multiple parameters by proteomics, transcriptomics and metabolomics. Most of the studies aim to visualise new marker patterns, identified by these platforms, by comparing clinically well-defined cohorts. A challenge will certainly be to define the correlates of immune protection in individuals with latent TB and in those individuals that fail to effectively eradicate or contain *M. tuberculosis*. The development of new 'marker test-beds' may aid to differentiate TB from other infectious and inflammatory conditions. These emerging technologies may further shed light on pathogenesis and may lead to discovery of potential new biomarkers and diagnostics for monitoring drug efficacy in clinical trials.

A recent study of South African patients (Banchereau *et al.* 2010) with active and latent TB infection LTBI

identified a whole blood 393 transcript signature for active TB in intermediate and high-burden settings, correlating with radiological extent of disease and reverting to that of healthy controls after treatment. A subset of patients with latent TB had signatures similar to those in patients with active TB. It has become clear that multiparameter assays generate associations, which may not be totally spurious, but which are specific to the precise population under test and may not necessarily be broadly applicable. It is important and that tests must be developed and adapted for easy use at POC in resource-poor settings.

Historical reflections on TB control

The persistence of TB as a major killer disease today despite effective treatment being available informs us of the multifactorial aetiology of TB. TB will continue to outwit the human race until we tackle the social, economic, political conditions that allow a treatable disease to thrive. During the 19th century, the white plague, as TB was named (because of the loss of skin colour seen in London patients with TB), continued to ravage Europe where up to 25% of deaths were caused by this disease (Zumla 2011). The death toll from TB began to fall in Europe at the start of the 20th century, as living standards (better housing, nutrition and economic status) improved; subsequent TB control was achieved following the introduction in the 1950s of antituberculosis drugs, mass screening programmes and BCG vaccination. Investments in the development and implementation of new diagnostics, drugs, vaccines and biomarkers should be paralleled by efforts to improve living standards of the poor peoples of this world.

Conclusions

The past decade has seen a renaissance of scientific activities and funder investment into development of new TB drugs, diagnostics, biomarkers and vaccines. A promising and important portfolio of new TB diagnostics, new TB drugs and vaccines has been endorsed by the STOP TB Partnership. The increasing numbers of Phase 2 and 3 drug, vaccine and diagnostic clinical trials in high-TB endemic areas reflect good progress towards attaining STOP TB targets. The challenge now is to complete development and validation of these in high-TB and high-TB/HIV burden countries and then translate them to clinical practice at peripheral points of health care. Achievement of these goals will depend largely on political will and serious investment by funders and developing country governments into improving delivery of better health services and living conditions for their people and sustaining them long term.

Acknowledgements

AZ, JOG and PM receive support from the EU-FW7, EDCTP, UK-MRC and EuropeAid. AZ also receives support from the NIHR, UCLH-CBRC. MM receives funding from Vinnova, HLF and VR, Sweden. RM receives funding from Technology Strategy Board, UK. MPG receives support from EDCTP, UBS Optimus Foundation and the SA National Research Foundation (NRF).

References

- Aryan E, Makvandi M, Farajzadeh A *et al.* (2010) A novel and more sensitive loop-mediated isothermal amplification assay targeting IS6110 for detection of *Mycobacterium tuberculosis* complex. *Microbiological Research* **165**, 211–220.
- Banchereau J, Chaussabel D & O'Garra A (2010) An interferon-inducible neutrophil-driven blood transcriptional signature in human tuberculosis. *Nature* **466**, 973–977. PMID: 20725040.
- Bhanot N (2011) Rapid molecular detection of tuberculosis. *New England Journal of Medicine* **364**, 183.
- Boehme CC, Nabeta P, Hillemann D *et al.* (2010) Rapid molecular detection of tuberculosis and rifampin resistance. *New England Journal of Medicine* **363**, 1005–1015.
- Diacon AH, Pym A, Grobusch MP *et al.* (2009) A phase II, stage 1 double-blind, placebo-controlled study with TMC207 in patients with multi-drug resistant (MDR) tuberculosis. *New England Journal of Medicine*. **360**, 2397–2405.
- Doherty M, Wallis RS, Zumla A & WHO–Tropical Disease Research/European Commission joint expert consultation group (2009) Biomarkers for tuberculosis disease status and diagnosis. *Current Opinion in Pulmonary Medicine* **15**, 181–187.
- Grange JM, Gandy M, Farmer P & Zumla A (2001) Historical declines in tuberculosis: nature, nurture and the biosocial model. *International Journal of Tuberculosis and Lung Disease* **5**, 208–212.
- Helb D, Jones M, Story E *et al.* (2010) Rapid detection of *Mycobacterium tuberculosis* and rifampin resistance by use of on-demand, near-patient technology. *Journal of Clinical Microbiology* **48**, 229–237.
- Hesseling AC, Graham SM & Cuevas LE (2011) Rapid molecular detection of tuberculosis. *New England Journal of Medicine* **364**, 183–184.
- Jacobsen M, Repsilber D, Gutschmidt A *et al.* (2007) Candidate biomarkers for discrimination between infection and disease caused by *Mycobacterium tuberculosis*. *Journal of Molecular Medicine* **85**, 613–662.
- Janossy G (2008) The changing pattern of “smart” flow cytometry (S-FC) to assist the cost-effective diagnosis of HIV, tuberculosis, and leukemias in resource-restricted conditions. *Biotechnology Journal* **3**, 32–42.
- Jassal MS, Nedeltchev GG, Lee JH *et al.* (2010) 13[C]-urea breath test as a novel point-of-care biomarker for tuberculosis treatment and diagnosis. *PLoS One* **5**, e12451.
- Kaufmann SH & Parida SK (2008) Tuberculosis in Africa: learning from pathogenesis for biomarker identification. *Cell Host & Microbe* **4**, 219–228.
- Kaufmann SH, Hussey G & Lambert PH (2010) New vaccines for tuberculosis. *Lancet* **375**, 2110–2119.
- Kunnath-Velayudhan S, Salamon H, Wang HY *et al.* (2010) Dynamic antibody responses to the *Mycobacterium tuberculosis* proteome. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 14703–14708. Epub 2010 Jul 28. PMID: 20668240.
- Lienhardt C, Vernon A & Raviglione MC (2010) New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. *Current Opinion in Pulmonary Medicine* **16**, 186–193.
- Ma Z, Lienhardt C, McIlleron H, Nunn AJ & Wang X (2010) Global tuberculosis drug development pipeline: the need and the reality. *Lancet* **375**, 2100–2109.
- MacLennan CA, Dzumani F, Namarika A *et al.* (2008) Affordable pediatric CD4 counting by flow cytometry in Malawi. *Cytometry Part B: Clinical cytometry* **74** (Suppl. 1), S90–S97.
- Maertzdorf J, Repsilber D, Parida SK *et al.* (2011) Human gene expression profiles of susceptibility and resistance in tuberculosis. *Genes and Immunity* **12**, 15–22.
- McNerney R & Daley P (2011) Towards a point of care test for active tuberculosis: obstacles and opportunities. *Nature Reviews Microbiology* **9**, 204–213.
- Mohapatra PR (2011) Rapid molecular detection of tuberculosis. *New England Journal of Medicine* **364**, 184.
- Peter J, Green C, Hoelscher M, Mwaba P, Zumla A & Dheda K (2010) Urine for the diagnosis of tuberculosis: current approaches, clinical applicability, and new developments. *Current Opinion in Pulmonary Medicine* **16**, 262–270.

P. Mwaba *et al.* **Achieving STOP TB Partnership goals**

- Sudre P, ten Dam G & Kochi A (1992) Tuberculosis: a global overview of the situation today. *Bulletin of the World Health Organization* **70**, 149–159.
- Van Rie A, Page-Shipp L, Scott L, Sanne I & Stevens W (2010) Novel and improved techniques for TB diagnosis HIV burden, resource-limited countries: hype or hope? *Expert Review of Molecular Diagnostics* **10**, 937–946.
- Wallis RS, Pai M, Menzies D *et al.* (2010) Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. *Lancet* **375**, 1920–1937.
- Watts G (2010) Immediate treatment for drug resistant tuberculosis possible with “while you wait” test. *British Medical Journal* **341**, 7132.
- WHO (2006) The Global Plan to Stop TB, 2006–2015: Actions for life: towards a world free of tuberculosis. WHO, Geneva; (WHO/HTM/STB/2006.35). Available at: http://whqlibdoc.who.int/publications/2006/9241593997_eng.pdf.
- WHO Report (2010a) The Global Plan to STOP TB 2011–2015. Transforming the fight towards elimination of tuberculosis.
- WHO Report (2010b) Strategic And Technical Advisory Group for Tuberculosis (STAG-TB) Report of the tenth meeting. WHO, Geneva.
- WHO/TDR: Diagnostics Evaluation Series No. 2. Laboratory-based evaluation of 19 commercially available rapid diagnostic tests for tuberculosis. 2008. [<http://apps.who.int/tdr/publications/tdr-research-publications/diagnostics-evaluation-2/pdf/diagnostic-evaluation-2.pdf>].
- World Health Organization (2009a) Report of the 9th Meeting of the Strategic and Technical Advisory Group on Tuberculosis (STAG-TB) World Health Organization, Geneva.
- World Health Organization (2009b) Stop TB Partnership’s New Diagnostics Working Group and World Health Organization. Pathways to Better Diagnostics for Tuberculosis: A blueprint for the development of TB diagnostics. World Health Organization, Geneva.
- Yzquierdo SL, Kumar V, Lemus D, Montoro E & McNerney R (2009) Mycobacteriophage and control of tuberculosis. In: *Contemporary Trends in Bacteriophage Research* (ed Horace T Adams) Nova Science Publishers, Inc., New York. 353–373 ISBN: 978-1-60692-181-4.
- Zbinden A, Keller PM & Bloemberg GV (2011) Rapid molecular detection of tuberculosis. *New England Journal of Medicine* **364**, 183.
- Zumla A (2011) The white plague returns to London – with a vengeance. *Lancet* **377**, 10–11. Epub 2010 Dec 16.
- Zumla A & Grange JM (2010) Is the eradication of tuberculosis ‘yesterday’s ambition’ or ‘tomorrow’s triumph’? *Clinical Medicine, Journal of the Royal College of Physicians* **10**, 450–453.
- Zumla A, Huggett J, Green C, Kapata N & Mwaba P (2010) Trials and tribulations of an African-led research and capacity development programme: the case for EDCTP investments. *Tropical Medicine and International Health* **15**, 489–494.
- Zumla A, Atun R, Maeurer M *et al.* (2011) Viewpoint: scientific dogmas, paradoxes and mysteries of latent *Mycobacterium tuberculosis* infection. *Tropical Medicine and International Health* **16**, 79–83. doi: 10.1111/j.1365-3156.2010.02665.x.

Corresponding Author Alimuddin Zumla, Department of Infection, Windeyer Institute of Medical Sciences, University College London Medical School, London, UK. E-mail: a.zumla@ucl.ac.uk