Annex 1

What is in the TB pipeline?

November 2006

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Summary table of current TB products in the pipeline

by stage of development and by year (from 2006 to 2015)

❒ New TB Drugs

CLINICAL TESTING	**Gatifloxacin**	Phase II				Phase III[1]					
	Moxifloxacin	Phase II/III				Phase III					
	Diamine (SQ-109)	Phase I				Phase III					
	Nitrodihydro-imidazooxazole derivative OPC-67683	Phase II					Phase III				
	Pyrrole LL3858	Phase I					Phase III				
	Diarylquinoline (TMC 207)	Phase I						Phase III			
	Nitroimidazole (PA-824)	Phase I						Phase III			
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
PRECLINICAL	**Dipiperidines (SQ-609)**	Preclinical								Phase III	
	Synthase Inhibitor FAS200313	Preclinical								Phase III	
	Translocase I Inhibitors	Preclinical								Phase III	
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
DISCOVERY	**Nitroimidazole analogue program**	Discovery									Phase III
	Quinolones	Discovery									Phase III
	AstraZeneca Portfolio	Discovery									Phase III
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**

[1] "Phase III" means "Anticipated completion of Phase III"

❒ New TB Diagnostics

REFERENCE LABORATORY	**Liquid culture system and DST**	CU[2]		AA[3]							
	Speciation test	DP[4]		AA							
	Phage-based DST		DP	AA							
	Manual NAAT	EP[5]				AA					
	Automated NAAT					AA					
	Urinary Nucleic Acid Amplification	EP						AA			
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
PERIPHERAL LABORATORY	**Same day sputum smear microscopy**	EP		AA							
	Low-cost fluorescence	EP	DP	AA							
	Bleach digestion of sputum			DP	AA						
	LED Fluorescence Microscopy	DP			AA						
	First generation Nucleic Acid Amplification	DP				AA					
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
HEALTH POST											
	Urinary antigen detection	DP				AA					
	Antibody detection test	DP					AA				
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**

[2] Already in use in countries
[3] Earlier date for availability for adoption in the public sector
[4] Demonstration phase
[5] Evaluation Phase

❒ New TB Vaccines

VIRAL VECTORED VACCINES	**MVA85A**	Phase I									Phase III
	Aeras-402	Phase I									Phase III
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
MODIFIED-RECOMBINANT BCG	**Aeras-X03**	Preclinical development	Phase I								Phase III
	rBCG::ΔureC-llo	Preclinical development									Phase III
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
PROTEIN SUBUNITS VACCINES	**M72**	Phase I									Phase III
	HyVac 4	Preclinical development									Phase III
	Hybrid-1	Phase I									Phase III
	Bacteria-vectored vaccines	Evaluation phase									Phase III
		2006	**2007**	**2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**

Chapter 1 NEW TB DRUGS

Current short-course (6-month) combination therapy for TB is effective when administered reliably. However, TB control is hindered by the lengthy and complex treatment required by current drugs, and is further complicated by the disease's deadly interaction with HIV/AIDS and the rise of multi-drug resistance (MDR-TB). These factors underscore the urgent public health need for new TB therapies.

The Working Group on New TB Drugs established as its goal the development of new, affordable TB drugs that would: 1) simplify or reduce the necessary duration of treatment to 2 months or less; 2) effectively treat MDR-TB; and, 3) provide treatment for patients with latent TB infection. It must be recognized that drug development in general is a slow and careful process (8 to 12 years) that emphasizes safety and efficacy in a phased approach to the clinical development pipeline. Phase I is the first examination of a new chemical entity in humans, and is conducted under careful supervision on a small number of healthy volunteers with escalating doses of a new drug. Phase II is for continued safety plus efficacy testing in infected patients (20-50) and establishes an appropriate dose range for more expanded evaluations. For tuberculosis, Phase II may include an early bactericidal assay (EBA) to detect quantitative effects in reducing the number of sputum bacilli. Phase III is a large study of infected patients (> 300), is often conducted at multiple sites, determines efficacy with clinical outcomes, and may be the pivotal study for official registration of a new TB drug. It must be noted that throughout this course of evaluations, the attrition rate for drugs of all types is very high, on the order of 1/100 successfully completing safety testing.

For the first time in 40 years, there is a coordinated portfolio of promising new compounds in the pipeline, some of which have the potential to become the cornerstone drugs of the control and even contribute to the elimination of TB in the future

A. CLINICAL TESTING

1. Gatifloxacin

Sponsors
European Commission (EC) OFLUTOB Consortium, Lupin Ltd. and UNICEF/UNDP/World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO TDR)
Program Description
Fluoroquinolones have been shown to have bactericidal activity in vitro against M. tuberculosis, which has been confirmed in animal models (1-4). They are rapidly absorbed and have high oral bioavailability. They are highly concentrated in respiratory tract tissues, pulmonary secretions and inside lung macrophages. In humans, the fluoroquinolone class of drugs is well tolerated over extended periods, thus they have been proposed in the treatment of tuberculosis (5). Amongst the various fluoroquinolones, gatifloxacin is particularly active against Gram-positive organisms and achieves plasma concentrations higher than the minimal inhibitory concentration obtained with other fluoroquinolone. The phase II trial results of a gatifloxacin-containing regimen are demonstrating good potential. The phase II trial was conducted by the South African Medical Research Council in Durban, South Africa, in patients with newly diagnosed pulmonary tuberculosis with and without HIV co-infection. It was designed to measure the anti-tuberculosis activity of the treatment in the first two months of therapy when compared to standard WHO recommended treatment and two other similar regimens which contained either ofloxacin or moxifloxacin. Treatment with either the gatifloxacin or moxifloxacin containing regimen was shown to be significantly more active than either the standard regimen or the ofloxacin containing regimen after two months of treatment.

A multi-centre phase III clinical trial is planned to definitely assess whether the four month gatifloxacin containing regimen is equivalent to the current standard six month short course regimen. Study sites are in Benin, Guinea, Kenya, Senegal and South Africa.

Anticipated Completion of Phase III

2010

2. Moxifloxacin

Sponsors

Bayer Healthcare AG; Centers for Disease Control TB Trials Consortium; European and Developing Countries Clinical Trials Partnership (EDCTP); Food and Drug Administration (FDA) Orphan Products Division; Johns Hopkins University, Medical Research Council, United Kingdom (MRC); TB Alliance; University College London

Program Description

Moxifloxacin is a fluoroquinolone – a subset of the quinolone class of antibiotics. Developed by Bayer Pharmaceuticals, moxifloxacin has demonstrated efficacy for the treatment of several acute respiratory infections. It also has an excellent safety record, having been used more than 42 million times, in 104 countries.

Moxifloxacin's mechanism of action differs from those of the drugs currently used to treat tuberculosis. It acts by inhibiting an enzyme called DNA gyrase, which is essential for bacterial survival. At the same time, moxifloxacin has little interaction with the cytochrome P450 enzyme system. Cytochrome P450 is heavily involved in the metabolism of some of the antiretroviral drugs (ARVs) used to treat HIV/AIDS. Rifampin, a cornerstone of the current TB regimen, induces certain cytochrome P450 enzymes, causing some ARVs to be metabolized too quickly. This drug-drug interaction can complicate the treatment of people co-infected with TB/HIV. Moxifloxacin avoids this interaction, making it easier to use when patients are also receiving drugs which are affected by the cytochrome enzyme systems.

Several animal studies have shown that moxifloxacin may be effective against *M. tuberculosis*. Results indicate that substituting moxifloxacin for one of the current standard TB drugs may eliminate TB infection faster than today's standard treatment protocol. In preclinical studies commissioned by the TB Alliance in 2002-03, investigators at Johns Hopkins University found that substituting moxifloxacin for isoniazid in a mouse model system decreased the amount of time needed to eradicate TB infection by two months.

On August 25 2005, the TB Alliance and Bayer Pharmaceuticals signed an historic agreement: to conduct a global clinical development program, seeking to register moxifloxacin for a TB indication. Should these trials prove successful, the agreement includes a joint commitment to ensuring the drug's affordability for TB patients in the developing world. Bayer is donating moxifloxacin for each trial site and will sponsor regulatory filings. With Bayer, the TB Alliance is managing the overall clinical trial program, ensuring the coordination of information and results towards the goal of registration. Financial support for the program comes from the TB Alliance, and from the CDC, the U.S. Food and Drug Administration Orphan Products Development Center, and the European and Developing Countries Clinical Trials Partnership.

Moxifloxacin is currently in clinical trials for the treatment of pulmonary tuberculosis. The clinical development program includes four late stage clinical trials that together will enroll more than 2,000 TB patients. Sites are in Africa, Europe, and the Americas, including 10 U.S. States (see Table). Two drug regimens are being evaluated, each substituting moxifloxacin for one of the drugs in the standard four drug treatment. The first substitutes moxifloxacin for ethambutol, and the second substitutes moxifloxacin for isoniazid.

The goal of this program is to register moxifloxacin for a TB indication. The initial focus is the treatment of drug-sensitive, adult, pulmonary TB. Successful trials will allow moxifloxacin to contribute to an optimized first-line TB treatment regimen. Supplementary studies will be carried out as appropriate, based on the results of these initial investigations.
Anticipated Completion of Phase III
2010

3. Diamine (SQ-109)

Sponsors
Sequella Inc, NIH
Program Description
Developed in partnership with the NIH, SQ109 is a new diamine anti-TB drug. It could replace one or more drugs of the existing first-line TB drugs in intensive phase regimen. With a mechanism of action distinct from other antibiotics used in TB therapy (including Isoniazid, Ethambutol, and Ethionamide), SQ109 inhibits cell wall synthesis in a select group of microorganisms with excellent in vitro activity against both drug susceptible and drug resistant TB bacteria, including XDR-TB. SQ109 also enhances, both in vitro and in vivo, the activity of the anti-tubercular drugs Isoniazid and Rifampin, thereby shortening the time required to cure mice of experimental TB by 25%. The Phase 1 dose-escalation study is enrolling 46 healthy normal volunteers. The patients will be divided into five ascending dose groups of eight, plus an additional group of six in an effect of food group, to evaluate the safety and pharmacokinetics of SQ109. Increased dose levels will be administered approximately ten days apart to allow for clinical safety measurements. The trial will run for approximately three to four months. SQ109 has completed all IND-directed preclinical toxicology, pharmacology, and safety studies in two animal species. The IND was filed with the U.S. FDA in August 2006.
Anticipated Completion of Phase III
2010

4. Nitrodihydro-imidazooxazole derivative OPC-67683

Sponsor
Otsuka Pharmaceutical Company
Program Description
OPC 67683 has potent in vitro activity against MTB, may shorter duration of therapy in active TB/MDR-TB and is more effective than current drugs for ATT. A mycolic acid biosynthesis inhibitor found to be free of mutagenicity and to possess highly potent activity against TB, including MDR TB. In comparison with R, H, E, streptomycin (S), Z, and PA-824, OPC showed an exceptionally low minimum inhibitory concentration (MIC) range (0.006 to 0.024 ug/mL) in culture experiments and highly

effective therapeutic activity at low doses in animal studies. In a mouse model of TB, OPC did not produce antagonistic effects in combination with other TB drugs, and the combination of OPC with R and Z exhibited the strongest effect, showing at least a 2 month quicker eradication of viable TB bacilli in the lung than seen with the existing standard TB regimen. Other in vitro experiments have shown that OPC was not affected by, nor did it affect, the activity of liver microsome enzymes, suggesting that OPC may possibly be used in combination with drugs (including ARVs) that induce or are metabolized by cytochrome P450 enzymes. OPC was also found to be highly active in mice with SCID, which mimics the immune deficiency seen in AIDS patients. OPC is currently in phase II clinical development in TB patients, but no results have been published to date.

Additionally, Otsuka has initated a back up

Anticipated Completion of Phase III

2011

5. Pyrrole LL3858 (Sudoterb)

Sponsors

Lupin Ltd.

Program Description

SUDOTERB has demonstrated in-vitro and in-vivo anti-mycobactericidal activity against both sensitive and resistant strains of M.Tuberculosis. Complete killing of M.Tuberculosis has been observed to occur as early as 19 days when combined with INH, Rifampicin and Pyrazinamide. The molecule is also expected to have post anti-biotic effect. Preclinical toxicology studies have established the safety of the molecule.

Phase I clinical development of the molecule is being undertaken. Randomized, double-blind, placebo controlled single, dose escalation studies conducted in healthy adult male volunteers have so far proven to be safe, well tolerated and well absorbed following oral administration. Randomized, double-blind, placebo controlled, multiple, dose escalation studies are in progress.

Phase II clinical development for the novel drug, administered alone or in combination with INH, Rifampicin and Pyrazinamide may be conducted in patients suffering from tuberculosis to establish efficacy and safety.

Anticipated Completion of Phase III

2011

6. Diarylquinoline (TMC 207)

Sponsors

Tibotec Pharmaceuticals Limited

Program Description

The diarylquinolines specifically inhibit adenosine triphosphate (ATP) synthesis in M. tuberculosis, thus blocking its energy producing mechanism. The drug's unique mechanism of action explains the lack of cross-resistance observed in preclinical studies to any of the current TB drugs, including moxifloxacin. In cell culture and mice studies, TMC has extremely potent anti-TB activity, more active than the combination of rifampicin, isoniazid, and pyrazinamide even when used as monotherapy. When substituted for either rifampicin or isoniazid in combination therapy, TMC207 halved

treatment time, leading to complete TB sterilisation within two months.

Preliminary studies in healthy human volunteers suggest that the drug may be safe and has a half-life of more than 24 hours, which may permit intermittent dosing. The drug is currently in early clinical activity studies in patients with tuberculosis. A phase II trial focusing on MDR TB will commence in mid 2007. Based on the available non clinical safety assessment, the initial treatment duration will be 2 months. A solid dosage form is available for this trial. No recent published peer-reviewed data are available on clinical trials of TMC207 (6-11), however results from a 7-day EBA trial are being presented at the 2006 IUATLD Conference (Diacon A et al).

Anticipated Completion of Phase III

2012

7. Nitroimidazole (PA-824)

Sponsors

TB Alliance, Novartis, and National Institute for Allergy and Infectious Diseases (National Institutes for Health)

Nitroimidazole Analogs: TB Alliance, University of Auckland, University of Illinois, Chicago

Program Description

PA-824 is a nitroimidazole, a class of novel anti-bacterial agents. As a potential tuberculosis therapy, it has many attractive characteristics – most notably its novel mechanism of action, its activity in vitro against all tested drug-resistant clinical isolates, and its activity as both a potent bactericidal and a sterilizing agent in mice. In addition, the compound shows no evidence of mutagenicity in a standard battery of genotoxicity studies, no significant cytochrome P450 interactions, and no significant activity against a broad range of Gram-positive and Gram-negative bacteria.

In 2002, the TB Alliance and Chiron Corporation, a biotechnology company based in California, signed a landmark agreement to develop PA-824 and, potentially, other nitroimidazole derivatives for TB. PA-824 became the first compound in the TB Alliance portfolio. The TB Alliance received worldwide exclusive rights to PA-824 and its analogs for the treatment of TB, and Chiron pledged to make the technology royalty-free in endemic countries. Chiron retained the right to develop and commercialize the compounds for non-TB indications.

The TB Alliance immediately outlined plans to advance the development of this class of compounds. With support from the U.S. National Institute of Allergy and Infectious Diseases, the TB Alliance engaged Research Triangle Institute, to assist in the management of the development project. In its first two years of development, PA-824 successfully passed all major preclinical milestones. In June 2005, the compound entered Phase I clinical trials, to evaluate its safety, tolerability, and pharmacokinetics in healthy volunteers.

As PA-824 moved through its preclinical phases, 15 Contract Research Organizations (CROs) conducted a full range of toxicology, pharmacokinetic, and production assessments, all the while managed by TB Alliance staff and Research Triangle Institute. Preclinical development was designed to assess both the efficacy and safety of PA-824. While early data indicated PA-824's efficacy against both drug-sensitive and MDR-TB, the preclinical phase of development assessed PA-824's efficacy compared to, and in combination with, current TB drugs. This phase was designed to assess the compound's non-clinical pharmacokinetic and safety profile to determine its suitability for entry into clinical trials.

PA-824 completed its preclinical milestones in approximately two years, and is now in Phase I clinical development. The Phase I program is evaluating the safety, tolerability,

pharmacokinetics and ADME (absorption, distribution, metabolism and excretion) properties of single and multiple doses of PA-824 in healthy male and female volunteers.

To date, three Phase I studies have been conducted. These include: a randomized, double blind, single ascending dose study in healthy male volunteers; a randomized, double-blind multiple ascending dose study in healthy male and female volunteers; and a single dose study with radio-labeled PA-824 to assess its absorption, distribution, metabolism and excretion in healthy volunteers of both genders.

Once Phase I studies have been successfully completed, PA-824 will be subjected to a Phase II Early Bactericidal Activity study, conducted in TB patients. This will provide proof-of-concept of the efficacy of PA-824 in adult patients with sputum smear-positive, pulmonary TB. The TB Alliance has also initiated an investigation of PA-824 nitroimidazole analogs, currently in the discovery phase of development. [link]

Nitroimidazole Analog Program
Any drug candidate is likely to encounter some difficulties during clinical development. Therefore, in addition to its work with PA-824, the TB Alliance has instituted an analog program on several tracks, seeking to maximize the potential of the novel nitroimidazole class. Working with researchers at the University of Auckland in New Zealand and the University of Illinois at Chicago, the TB Alliance aims to discover new nitroimidazopyrans that may have improved profiles over PA-824. This program has two conceptual purposes:

With the assumption that PA-824 will ultimately prove to be clinically useful, second generation compounds may be even better.
If PA-824 fails to develop into a commercial drug, there may be superior nitroimidazole compounds capable of overcoming any difficulties that precluded PA-824's regulatory approval.

The chemistry group, led by Prof. Bill Denny at the University of Auckland, has synthesized many new pharmacophores, several of which have demonstrated potent anti-tuberculosis activity. Further optimization of these pharmacophores may lead to new nitroimidazoles that have *in vitro* activity better than PA-824. In addition, some of these compounds have been scaled up for *in vivo* proof of principle studies in mice. A new, commercially viable synthesis has also been developed.

The project team will focus on the development of structure-activity relationships to address both mutagenicity and QT prolongation issues. Compounds that meet the *in vitro* potency criteria, and are free of mutagenicity and hERG inhibitory activity, will be advanced to *in vivo* efficacy and pharmacokinetic studies.

Anticipated Completion of Phase III

- For PA-824: 2012
- For Nitroimidazole Analog Program: 2015

B. PRECLINICAL

1. Dipiperidine (SQ-609)

Sponsors

Sequella Inc.

Program Description

This new class of antibiotic compounds, dipiperidines has promising in vitro and in vivo anti-TB activity. SQ609 was identified as a lead candidate in this series.
Product Profile Attributes:

Potent in vitro activity against M. tuberculosis; Kills M. tuberculosis by interfering with cell wall biosynthesis; Low in vitro toxicity in cultured mammalian cells; Orally bioavailable Antimicrobial activity in vivo in two different mouse models of TB; Significantly prolongs therapeutic effect after the withdrawal of drug therapy in mice; Favorable in vitro safety pharmacology profile
Anticipated Completion of Phase III
2014

2. Synthase Inhibitor FAS200313

Sponsors
FASgen Inc.
Rationale & Product profile
FASgen has designed and synthesized a series of novel compounds that not only inhibit the biosynthesis of the tubercle bacillus' waxy outer coating but also interfere with a vital step in the organism's energy-generating metabolic pathways.
Anticipated Completion of Phase III
2014

3. Translocase I Inhibitors

Sponsors
Sequella Inc, Sankyo Ltd
Program Description
Sequella licensed the Translocase I inhibitors from Sankyo, Ltd (November 2004). Sankyo identified the compound class and performed extensive research and preliminary preclinical development on three selected inhibitors. Sequella has exclusive worldwide rights to the series of Translocase I inhibitors for the treatment of TB and all other indications.
Anticipated Completion of Phase III
2014

C. DISCOVERY STAGE

1. Quinolones

Sponsors
TB Alliance in collaboration with the Korea Research Institute of Chemical Technology (KRICT) and Yonsei University
Program Description
Quinolones are one of the few classes of antimicrobial agents that are totally synthetic in origin. The first quinolone, nalidixic acid, was introduced in the 1960's as a narrow spectrum agent used primarily for the treatment of urinary tract infections.

Quinolones possess many desirable attributes for a first-line therapeutic agent against tuberculosis. These include potent bactericidal activity against both replicating and non-replicating *M. tuberculosis*, favorable long-term safety indicators, oral bioavailability, and an ability to penetrate macrophages. Moxifloxacin, a proven and effective antibiotic developed by BayerHealthcare AG, is a third generation quinolone compound, and has demonstrated effective sterilizing activities against *M. tuberculosis*. The TB Alliance, in collaboration with Bayer, is currently conducting Moxifloxacin clinical trials, evaluating the drug as a potential agent to treat TB (Link to Moxi). However, the quinolone class has not been extensively optimized for a TB indication.

In 2003, the TB Alliance initiated a lead identification and optimization project with the goal of identifying a new generation of quinolones with enhanced efficacy against tuberculosis. Based on data from animal models and the preliminary clinical evaluation of quinolones marketed for other antimicrobial indications, this class of compounds has the potential to both shorten the time required to treat TB, and to increase the effectiveness of widely spaced, intermittent therapy.

The objective of the quinolone project is to develop a new generation of DNA gyrase inhibitors that will be effective in shortening TB therapy, while maintaining an excellent safety and tolerability profile. The new agents should also be suitable for the treatment of MDR-TB and TB/HIV co-infections without prohibitive drug-drug interactions with ARVs. To achieve these goals, the TB Alliance is collaborating with the Korea Research Institute of Chemical Technology (KRICT) and Yonsei University. Scientists at KRICT and Yonsei University are synthesizing and testing novel quinolones, and have discovered several promising compounds that are being evaluated for their potential to be further developed as drug candidates.

This collaboration seeks to achieve the following profile:

- Potent activity against both replicating and non-replicating Mycobacterium tuberculosis (*M. tb.*);
- Efficacy in both acute and chronic animal models of tuberculosis;
- Pharmacokinetics that would support once-daily dosing;
- Acceptable safety; and
- Low cost of goods

Researchers at KRICT have synthesized more than 600 quinolone analogs; these analogs have then been tested for activity against *M. tuberculosis* in the laboratories of Professor Sang-Nae Cho at the Yonsei University Department of Microbiology. As a result of this effort, several promising leads have been identified, including compounds of the sub-class of quinolones known as quinolizinones. These lead compounds are highly active against mycobacteria, and have desirable solubility and pharmacokinetic properties. Such traits are the result of chemical modifications, focused on a key position in the quinolone molecule known for its important effects on antimicrobial potency, pharmacokinetics, and safety profiles.

Compounds that have acceptable potency in the *in vitro* screens will be scaled up and further evaluated in second and third-tier biological assays to determine whether or not they meet the criteria for development as candidates for clinical evaluation.

Anticipated Completion of Phase III
2015

2. AstraZeneca Portfolio

Sponsors
AstraZeneca

Program Description
This is a preclinical portfolio of projects with programmes in different phases including lead identification and optimization. AstraZeneca's research is focused on finding new therapies for TB that will either act in drug resistant disease and/or reduce the complexity or the duration of treatment. Thus the programme has three specific goals: 1. Shortening the duration of therapy to improve patient compliance 2. Eradication of disease, even latent disease, and therefore reducing the chances of relapse 3. New agents, which act on drug resistant strains and have no adverse drug-drug interactions. The portfolio of projects covers Lead identification and Lead optimization. Preclinical evaluation of compounds is a continuing activity. Development phase for successful compounds is targeted by 2010.
Anticipated Completion of Phase III
2015

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Chapter 2 NEW TB DIAGNOSTICS

We have divided the health services in three levels based on consideration of the intended level of the health system where the new tools are to be used: reference, peripheral laboratory and primary health care.

A. **Reference laboratory** is defined as a regional, tertiary or national level laboratory with mycobacterial culture capability.

B. **Peripheral laboratory** is defined as a laboratory at health center or higher level where sputum smear microscopy is conducted, and where auxiliary equipment such as biosafety cabinets, centrifuges, and incubators is unlikely to be present.

C. **Health post** is defined as a primary health care facility with no on-site access to microscopy or other laboratory testing.

Technologies described below are grouped according to their intended level of implementation.

In general, the highest impact on case finding will accrue from implementation at the lowest level of health services.

Some of the diagnostic tools expected to be introduced into control programs will be incremental improvements on existing technologies, while others will be radically new. The speed and extent of adoption of new technologies will depend on the balance between the benefits they bring and the degree of disruption their implementation causes. For instance, the a simplified microscopy method may see greater adoption than a novel alternative that necessitates changes in the way testing or case notification are carried out. On the other hand, a new method that rapidly identifies all smear-positive and many smear-negative cases might, if suitably robust and specific, see widespread use and substantially replace microscopy.

A. REFERENCE LABORATORY

1. Liquid culture system for case detection and Drug Susceptibility Testing

Type of product
Liquid culture system
Product
Mycobacterium Growth Indicator Tube (MGIT-TB) and MGIT-DST
Developers
FIND and Becton, Dickinson and Company (BD)
Rationale
It is recognized that direct smear microscopy has limited sensitivity, especially some patient groups such as children and individuals co-infected with HIV. Culture is substantially more sensitive than microscopy. Liquid culture systems are more rapid and more sensitive than solid culture.
Product profile
The MGIT-TB culture system allows for the rapid growth and detection of *M. tuberculosis*. The average time to detection is 10-14 days as opposed to three to four weeks with traditional solid egg or agar based culture. MGIT can also be used to diagnose multidrug-resistant tuberculosis (MGIT–DST). FIND, together with BD, is evaluating MGIT-DST to determine the feasibility and impact of its wider use in disease endemic settings.
Stage of Development
Both of these products are already in use in wealthier country and in the private sector of some developing countries. Currently MGIT-TB culture and MGIT-DST are being evaluated in demonstration projects to assess their effectiveness, efficiency and impact in the field situation in national control programs of low-income countries with

high TB prevalence settings.

Considerations

Limitations: tests intended for use where culture and biosafety facilities exist or can be built. Additional care is required to minimize contamination of culture.

Earlier date for availability for adoption in public sector

Beginning of 2008

2. Speciation test

Type of products

Test for confirming *M.tuberculosis* grown in culture

Product

Capilia TB

Developers

FIND and TAUNS

Rationale

Not all AFB grown in culture are *M. tuberculosis*. Existing tests for confirming identification of *M. tuberculosis* are time consuming and complex. The Capilia TB test is a simple and fast lateral flow technology that allows the confirmation of *M. tuberculosis* in cultures in 15 minutes

Product profile

Capilia test is lateral flow (strip test) detecting a TB-specific antigen.

Stage of Development

The test is in the demonstration phase to assess effectiveness in real-life disease control programs.

Considerations

Limitations: tests intended for use where culture facilities exist or can be built.

Earliest date for availability for adoption in the public sector

Late 2008.

3. Phage-based drug susceptibility test

Type of product

Phage-based test

Products

FastPlaque-Response test

Developers

FIND and Biotec Laboratories

Rationale

Conventional detection of multidrug-resistance requires isolation of *M. tuberculosis* in culture prior to drug susceptibility testing. This leads to a long around time of weeks to months. The *FastPlaque Response* assay is applied directly to sputum smear positive samples with rifampin susceptibility results obtained in just 2 days.

Product profile

FastPlaque assay is bacteriophage-based and allows detection of rifampicin resistance directly from smear positive sputum or indirectly from culture. Rifampicin resistance in most settings serves as marker for multi-drug resistance.

Stage of Development

The test is entering the demonstration phase at the start of 2007 where its efficiency and effectiveness are to be assessed

Considerations

Limitations: tests intended for use where culture and biosafety facilities exist or can be built.

Earliest date for availability for adoption in the public sector

End of 2008.

4. Manual Nucleic Acid Amplification DST

Type of product
Molecular technique
Products
PCR based assay
Developers
FIND and HAIN Lifescience
Rationale
The rapid detection of multidrug-resistance could facilitate early initiation of correct treatment or appropriate measures to prevent transmission. The manual based nucleic acid amplification DST detects rifampicin and isoniazid resistance in 1 day.
Product profile
PCR-based line-probe assay
Stage of Development
The test is entering evaluation phase
Considerations
Limitations: tests intended for use where culture, biosafety and PCR capabilities exist or can be built. Requirement for specialized equipment (Thermocycler) and training. The sensitivity of the assay for INH resistance is only 60-70%.
Earliest date for availability for adoption in public sector
2008

5. Automated Nucleic Acid Amplification Test DST

Type of product
Molecular technique
Products
PCR based
Developers
FIND and CEPHEID
Rationale
Molecular amplification is a proven technology for the detection of *M. tuberculosis*. Current test methods however are too complex for routine widespread implementation in developing countries. Sample processing and DNA extraction adds significantly to this complexity. An assay that automates all of these steps could make NAAT much simpler to implement. Molecular detection of rifampin resistance could speed targeted treatment and other measures for controlling MDR-TB.
Product profile
FIND and Cepheid are working to develop an automated method to integrate sputum processing, DNA extraction and amplification and detection of TB DNA and rifampin-resistance-encoding mutations..
Stage of Development
Under development
Considerations
Limitations: Requirement for specialized equipment and limited training. Security. Electricity.
Earliest date for availability for adoption in the public sector
2010

6. Urinary Nucleic Acid Amplification

Type of product
Molecular technology
Products
PCR-based test for *M. tuberculosis* DNA in urine
Developers
FIND, University College London, Spaxen.
Rationale
Fragments of *M. tuberculosis* DNA have been shown to be excreted in urine. Urine is a less variable and easier to collect than sputum and may be safer to handle.. These characteristics may make this method applicable in less complex settings if paired with an appropriately simple amplification method.
Product profile
This is a method, not a product, and will need to be applied to an existing molecular amplification platform.
Stage of Development
It is in development
Considerations
Limitations: tests intended for use where PCR capabilities exist or can be built. Requirement for specialized equipment (Thermocycler) and training.
Earliest date for availability for adoption in the public sector
2011

B. PERIPHERAL LABORATORY

1. Same day sputum smear microscopy

Type of product
Optimising sputum microscopy
Product
Same day 2-smear strategy
Developers
WHO/TDR
Rationale
Current sputum smear microscopy strategy requires direct examination of 3 sputum specimen obtained on two-three different days. This strategy delays the diagnosis and leads to patient drop out during diagnostic process.
Product profile
The same-day approach reduces requires a patient to produce two separate sputum samples to curtail patient drop out thereby increase case detection.
Stage of Development
Under evaluation in operation setting, moving towards demonstration.
Considerations
More cases require links with treatment centre/drugs Possible cost saving/consumables. Reorganization of the lab workflow to maximize benefit
Earliest date for availability for adoption in the public sector
End of 2008

2. Low-cost Fluorescence Microscopy

Type of products
Sputum microscopy
Product

Fiber-optic based fluorescence microscopy system
Developers
WHO/TDR
Rationale
Fluorescence microscopy increases the sensitivity of direct smear microscopy. The expense of conventional fluorescence microscopy system precludes the wide spread use at peripheral level. This system offers a cheaper alternative. Potential exists for further optimisation of smear microscopy by combining low-cost fluorescence microscopy with bleach digestion and/or same day approaches.
Product profile
A simple objective with light filters that can be fitted to most standard makes of microscopes and is connected by fiber-optic cable to a halogen light source.
Stage of Development
Already available and used by some organizations in the field. Evaluation in operational settings and move to demonstration projects planned for 2007.
Considerations
Requires training. As yet no guidelines for EQA. Fluorescence microscopy may represent a broad platform with advantages in the diagnosis of other diseases. Considerable time will be saved in microscopic examination of smears.
Earliest date for availability for adoption in the public sector
End of 2008

3. Bleach digestion of sputum

Type of product
Sputum smear microscopy
Product
Bleach
Developers
WHO/TDR
Rationale
Digestion of sputum with bleach (sodium hypochlorite) prior to the preparation of smears has been shown to increase sensitivity of smear microscopy.
Product profile
Bleach digestion of sputum. Various methods of bleach digestion have been described involving different digestion times and supplementary processes.
Stage of Development
Developing a standardised bleach digestion method to be put into demonstration projects in 2008.
Considerations
The expected reduction in biohazard resulting from bleach digestion will be evaluated prior to demonstration projects
Earliest date for availability for adoption in the public sector
End of 2009

4. LED Fluorescence Microscopy

Type of products
Fluorescent microscope
Product
LED Microscope
Developers
FIND
Rationale

Existing conventional fluorescence systems increase the sensitivity of direct smear microscopy. The LED microscope lamp is inexpensive in comparison to mercury vapour or halogen lamp used in the regular fluorescent microscope and may have a life span of more than 50,000 hours.
Product profile
Simple binocular microscope incorporating LED light source
Stage of Development
Microscope in development phase.
Considerations
Training. As yet no EQA system for fluorescence microscopy. May represent a broad platform with advantages in the diagnosis of other diseases. Considerable time-savings in microscopic examination.
Earliest date for availability for adoption in the public sector
2009

5. First generation isothermal Nucleic Acid Amplification

Type of product
Molecular technique
Product
First generation LAMP-based assay (Loop mediated isothermal amplification technology platform)
Developers
FIND and EIKEN Chemical Company
Rationale
A simple DNA amplification method which does not require an expensive thermocycler or detection system and which allows visual detection of amplification could allow sensitive molecular methods to be used at lower levels of the health system.
Product profile
Preliminary data suggest high sensitivity and specificity. Modifications of the assay may be suitable for implementation at microscopy level. It is envisaged that the method may be applied to sputum, urine and blood specimens.
Stage of Development
This is in the development phase
Considerations
Cross-disease platform. Training required. Somewhat more complex than microscopy, but with potential for further simplification and implementation at peripheral laboratory.
Earliest date for availability for adoption in the public sector
2010

C. HEALTH POST

At present no tests are available for use at this level of the health system. Bringing diagnostics to this level of the health system would be a tremendous achievement with great implications for the ability of a control program to increase case detection. In general the technology best suited for this level is lateral flow or other immunochromatographic strip test.

1. Urinary antigen detection

Type of product
Antigen detection test
Product
LAM (mycobacterial lipoarabinomannin) antigen detection in urine.

Sponsors
FIND and partners
Rationale
M. tuberculosis LAM has been shown to be excreted in the urine of TB patients. Urine is an easier specimen to collect than sputum, and may be less variable in quality and safer to handle..
Product profile
There are several versions of this assay in development, including in-tube ELISA and dipstick methods. Urinary antigen detection may be of particular value in diagnosing TB in HIV co-infected patients. There is potential for further development and simplification resulting in a lateral flow test.
Stage of Development
Development.
Considerations
Lateral Flow Test – implementation could significantly increase case-finding through improving access to testing. The ELISA format has potential to increase case-finding if combined with smear microscopy and/or culture in high HIV prevalence areas. Possible improvements in the diagnosis of paediatric and extra-pulmonary TB.
Earliest date for availability for adoption in the public sector
2010

2. Antibody detection tests

Type of products
Antibody detection tests
Product
-
Sponsors
FIND, and other partners.
Rationale
TB patients often have detectable antibodies to a variety of *M. tuberculosis* antigens. Currently the commercially-available serological tests have been shown to perform poorly. A limited number of potential diagnostic antigens have been evaluated. FIND is systematically interrogating the proteome of *M. tuberculosis* for potential diagnostic antigens.
Product profile
Likely final product would be an immunochromatographic lateral flow or flow-through test.
Stage of Development
Antigen identification stage
WHO guidance on adoption and recommendations
Performance dossier STAG May 2011
Considerations
Antibody detection may not perform well in patients with HIV-mediated immunosuppression.
Earliest date for availability for adoption in the public sector
2011

Chapter 3 NEW TB VACCINES

A. VIRAL VECTORED VACCINES

1. MVA85A

Type of products
Modified vaccina virus expressing AG85a Ankara
Sponsors
MVA85A was developed in Adrian Hill's laboratory at the University of Oxfordwith funding from the Wellcome Trust and the European Commission.
Rationale
Product description
MVA is a highly attenuated strain of vaccinia virus MVA has been used to immunise some 120,000 humans during the smallpox eradication campaign and has an excellent safety record.
Stage of Development
MVA85A has been evaluated in multiple phase I trials in the United Kingdom, The Gambia and South Africa, in unexposed and exposed healthy adults, as well as in HIV infected adults.
Considerations
As judged by the number of trials as well as pardigms tested, MVA85A can be considered the most advanced of the new TB Vaccine candidates
Expected date for completion of phase III trials

2. Aeras-402

Type of products
Replication-incompetent adenovirus 35 vector expressing *M.tuberculosis* antigens Ag85A, Ag85B and TB10.4
Sponsors
Aeras-402 is being developed by the Aeras Global TB Vaccine Foundation through contract with Crucell Holland BV
Rationale
Product description
Adfenovirus 35 an advanced adenovirus delivery system for the induction of antigen-specific $CD8^+$ T cell responses
Stage of Development
Aeras-402 is currently being evaluated in phase I safety trials in the USA.
Considerations
Expected date for completion of phase III trials

B. MODIFIED-RECOMBINANT BCG

1. Aeras-X03

Type of products
Recombinant BCG, overexpressing *M.tuberculosis* antigens Ag85A, Ag85B and TB10.4 as well as perfringolysin from *Clostridium perfringens*
Sponsors
Aeras-402 is being developed by the Aeras Global TB Vaccine Foundation.
Rationale
Product description
Aeras-X03 is a recombinant BCG expressing perfringolysin as a mechanism to induce antigens-specific CD8+ T cells via escape of mycobacterial antigens from the endosome.
Stage of Development
Aeras-X03 is currently in late-stage pereclinical development and is scheduled to enter phase I clinical trials in 2007.
Considerations
Expected date for completion of phase III trials

2. rBCG::ΔureC-llo

Type of products
Recombinant BCG, expressing M.tuberculosis antign rv3407 and listeriolysin, as well as carrying a urease deletion mutation.
Sponsors
rBCG::ΔureC-llo^{+}is being developed by VPM under license from the Max-Planck Socieity. It was initially developed by the group of Professor S. Kaufmann from the Max-Planck-Institute for Infection Biology (Berlin, Germany).
Rationale
Product description
rBCG::ΔureC-llo^{+} a recombinant BCG expressing listeriolysin as a mechanism to induce antigens-specific CD8+ T cells via escape of mycobacterial antigens from the endosome. Urease has been deleted as a means to provide the optimal pH for listeriolysin function.
Stage of Development
rBCG::ΔureC-llo^{+} has completed preclinical development and is currently under GMP production. Phase I clinical trials are planned for 2007.
Consideration rBCG::ΔureC-llo^{+}**s**
Expected date for completion of phase III trials

C. PROTEIN SUBUNITS VACCINES

1. M72

Type of products
Recombinant protein, composed of a fusion of *M.tuberculosis* antigens Rv1196 and Rv0125.
Sponsors
Aeras-402 is being developed by GlaxoSmithKline under contract from the Aeras Global TB Vaccine Foundation.
Rationale
Product description
M72 is a fusion protein of separate *M.tuberculosis* delivered in GSK proprietary adjuvant AS02
Stage of Development
M72 is currently in clinical phase I trials in the USA and in Europe.
Considerations
Expected date for completion of phase III trials

2. HyVac 4

Type of products
Adjuvanted, recombinant protein, composed of a fusion of *M.tuberculosis* antigens Ag85B and TB10.4
Sponsors
HyVac 4 is being developed by the Aeras Global TB Vaccine Foundation through contract with Crucell Holland BV
Rationale
-
Product description
HyVac 4 is a fusion protein of separate *M.tuberculosis* delivered in Intercell proprietary adjuvant IC31
Stage of Development
HyVac 4 is currently in late-stage preclinical development (non-human primates). Phase I clinical trials are scheduled being evaluated in phase I safety trials in the USA.
Considerations
Expected date for completion of phase III trials

3. Hybrid-1

Type of products
Adjuvanted recombinant protein, composed of *M.tuberculosis* antigens Ag85B and ESAT-6
Sponsors
Hybrid-1 is being developed by the Statens Serum Institute (Copenhagen, Denmark) and the European TB vaccine project, TBVAC.
Rationale
Product description
Hybrid-1 is a fusion protein of separate *M.tuberculosis* antigens delivered in the Intercell proprietary adjuvant IC31
Stage of Development
Hybrid-1 is currently being evaluated in phase I safety trials in The Netherlands.
Considerations
Expected date for completion of phase III trials

4. Bacteria-vectored vaccines

Aeras-X05
Type of products
Shigella-delivered recombinant double-stranded RNA nucleocapsid encoding M.tuberculosis antigens Ag85A, Ag85B and TB10.4
Sponsors
Aeras-X05 is being developed by the Aeras Global TB Vaccine Foundation.
Rationale
Product description
Shigella-delivered nucleocapsids represent an inexpensive means to manufacture TB antigens, capable of delivering multiple TB antigens an d induce high levels of $CD8^+$ T cells.
Stage of Development
Aeras-X05 is currently being evaluated in animal studies.
Considerations
Expected date for completion of phase III trials

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