



THE ACCESS AND
DELIVERY PARTNERSHIP

New Health Technologies for TB, Malaria and NTDs

A PIPELINE ANALYSIS OF NEW PRODUCTS FOR MALARIA, TUBERCULOSIS AND NEGLECTED TROPICAL DISEASES

A WORKING PAPER



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Resilient nations.*



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ABOUT THE ACCESS AND DELIVERY PARTNERSHIP

The adverse impact of tuberculosis (TB), malaria and neglected tropic diseases (NTDs) on development outcomes has resulted in new approaches and partnerships to tackle the global deficiencies in research and development, and treatment access. One such initiative is the strategic partnership between the Government of Japan and UNDP, which promotes research and development, and expedites access to and delivery of health technologies used to address TB, malaria and NTDs. This partnership comprises two complementary components, which reflect the Government of Japan's and UNDP's strategic goals on global health:

The **Global Health Innovative Technology (GHIT) Fund**, which focuses on the promotion of innovation and research through the development of drugs, diagnostics and vaccines for TB, malaria and NTDs. The GHIT Fund stimulates research and development of new health technologies through funding research and product development partnerships between Japanese and non-Japanese organizations.

The **Access and Delivery Partnership (ADP)**, which aims at assisting low- and middle-income countries (LMICs) enhance their capacity to access, deliver and introduce new health technologies for TB, malaria and NTDs.

Led and coordinated by UNDP, the ADP is a unique collaboration between UNDP, TDR (The Special Programme for Research and Training in Tropical Diseases, which is co-sponsored by UNICEF, UNDP, the World Bank and WHO) and PATH. Working together, the project partners will leverage the expertise within each organization to provide the full range of technical skills necessary to strengthen capacity in LMICs. The ADP emphasizes consultation, collaboration and implementation with partner-country governments and stakeholders, working to develop LMICs' capacities to access and introduce new technologies.

New health technologies are broadly defined as drugs, diagnostic tools and vaccines that are relevant for the prevention, treatment or cure of TB, malaria and NTDs, but are not yet available for market introduction or have not been introduced in LMICs. The introduction of new health technologies can place burdens on existing health systems, including new requirements for drug regulation, supply and distribution and health personnel training. Accordingly, the ADP will focus on providing LMIC stakeholders with the necessary skills to develop the systems and processes required to effectively access new health technologies, and introduce them to populations in need.

The ADP is a five-year project, running from April 2013 until March 2018.

FOREWORD

In September 2015, United Nations Member States adopted the 2030 Agenda for Sustainable Development). In doing so, they committed themselves to ensuring the health and well-being of all people (SDG 3) and to a range of targets, which includes ending the epidemics of AIDS, TB, malaria and neglected tropical diseases as public health threats, and combating hepatitis, water-borne diseases and other communicable diseases. For these targets to be achieved, synergies must be built between efforts to incentivize innovation for new medicines, vaccines and diagnostics, on the one hand, and the access and delivery of these medicines, vaccines and diagnostics to the people in need, on the other. The partnership between the Government of Japan and UNDP seeks to bring together these two corresponding elements of global health response through two projects – the Global Health Innovative Technology (GHIT) Fund and the Access and Delivery Partnership (ADP).

This report provides a comprehensive overview of promising new medicines, vaccines and diagnostics that can improve the prevention and/or treatment of TB, malaria and selected NTDs. Hence, the product pipelines of biomedical companies and product development partnerships, such as the GHIT Fund, Medicines for Malaria Venture, Drugs for Neglected Diseases Initiative, are surveyed for new products that are likely to be available for use in the near future.

Such information can be a useful planning tool, because introducing new products into the health system can sometimes be a challenge for the over-stretched health systems in low- and middle-income countries (LMICs). New products may come with requirements for greater safety monitoring, or changes to the procurement and supply systems, as well as distribution considerations. Where relevant information is available, it can contribute to the planning and design of interventions to help health systems deliver the new products to the patients who need them. Thus, the basic premise of this report is to contribute towards better planning and informed decision-making for the adoption and introduction of new health products in LMICs.

This report is intended to be the start of an on-going initiative. It is being published as a working document, with the aim of soliciting updates on pipeline products, so that information can be updated regularly to enable policy-makers and other actors to have access to key information on products that may be coming onto the market.



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EXECUTIVE SUMMARY

This report provides a comprehensive survey of the product pipeline for new health products that have promise in significantly improving current approaches towards the prevention, diagnosis and treatment of malaria, tuberculosis (TB) and selected neglected tropical diseases (NTDs). The aim is to identify the products with a high probability of market entry by 2020 that developing countries will likely introduce for use within their health systems. The objective is to highlight potential challenges to the introduction of new chemical entities (NCEs), diagnostics and vaccines and to assess whether proposed introduction of these new products can place additional requirements or burdens on the health systems in developing countries. The latter include the need for new regulations, increased capacity for pharmacovigilance, and/or changes to the procurement or supply systems. The analysis also examines a number of considerations related to supply and pricing, as well as the potential market and competition landscape for the products.

The basic premise of this report is that such analysis can contribute towards better planning and informed decision-making for the adoption and introduction of new health products in developing countries. The report is intended as a resource document, primarily for policymakers in disease programme implementation and product procurement. Information in this report should be considered in conjunction with the normative work of the World Health Organization (WHO) on the assessment, validation and recommendations on the introduction of new health products.

The analysis was compiled through a combination of a literature review and key informant interviews. Information in the public domain included publications from key actors in the field, including WHO, UNITAID, the Treatment Action Group (TAG), Médecins sans Frontières (MSF), Aeras, the Drugs for

Neglected Diseases Initiative (DNDi), Medicines for Malaria Venture (MMV), PATH and the Global Alliance for TB Drug Development (TB Alliance). Interviews and communications with technical experts in the various disease/product areas provided the substantial portion of the information that enabled the analysis for this report. Information on issues, such as the status of clinical trials for NTDs, is often not readily available in the public domain; thus, the contributions of researchers and product developers have been fundamental in compiling this report.

Analysis and findings

This report collates pipeline information across the product categories for each of the disease areas. Existing pipeline reports, including those for TB and malaria, typically review a single product category alone. It is hoped that this analysis across the product categories of medicines, diagnostics and vaccines within a disease can highlight common issues or problems. It is also hoped that an overview of the product pipeline across the diseases and product categories may also promote better planning and synergies for implementation research at the country level. One such finding of this analysis is to highlight the need to ensure that necessary linkages are made between product development with the basic research that is required to develop desired diagnostic tools, regimens and immunization strategies. For example, basic research for biomarkers is the basis for the development of point-of-care (POC) diagnostics, as well for ensuring more reliable measurement of efficacy in clinical trials. Consideration of the pipeline across diseases can also highlight the potential for cross-cutting areas of technology use (e.g. advancements in nucleic acid amplification (NAA) diagnostic technologies for deployment at the peripheral level and for multiple disease application).

The majority of products under development offer potential dispensing and supply advantages. The product pipeline for malaria includes a number of NCEs for treatment and prevention, as well as over 20 vaccines currently in clinical trials or advanced pre-clinical development. In July 2015, one of these vaccines received a positive scientific opinion on its quality, safety and efficacy from the European Medicines Agency for its use outside the European Union; it is the first malaria vaccine approved for such use. A WHO policy recommendation on the use of the vaccine is expected in late 2015. In the case of TB, two NCEs have been approved for marketing, representing the first TB medicines with novel mechanisms of action reaching the market in over 50 years. Clinical trials are underway to develop shorter, non-toxic TB regimens with these and other NCEs. Product development for NTDs is aimed primarily at fully oral administration of medicines, eliminating injectables and shortening treatment duration. Dosages are also being reviewed in order to reduce side effects while ensuring efficacy. Treatment will therefore be simpler to administer by health workers and easier to adhere to by patients. New diagnostic tools under development also present potential advantages for increasing diagnostic capacities within health systems. For example, rapid diagnostic tests (RDTs) under development for several diseases do not require cold chains, and more complex diagnostic technologies are under development in simplified platforms for decentralized use. Point-of-care and test-of-cure diagnostics are also sought to improve diagnostic and treatment algorithms for TB, Chagas disease and leishmaniasis.

General observations

While not possible nor desirable to make generalized conclusions across the different diseases covered in this report, a number of generally applicable observations may however be highlighted.

The pipeline analysis shows that significant gaps exist in terms of the interventions for prevention, treatment and diagnosis. For malaria and TB, there

is considerable potential to sustain a vaccination strategy for the prevention of these diseases. Similarly, the value of immunotherapeutic vaccines for cutaneous and mucosal leishmaniasis and possibly, visceral leishmaniasis (VL), warrants a funding and development strategy to take full advantage of research undertaken to date. But, much depends on whether the particular product market is regarded sufficiently attractive for investments in product development. For diagnostics, while the market for RDTs – particularly for HAT, VL and Chagas disease – is characterized by competition and relatively low prices, the situation is different for other diagnostics. For example, the production and supply of the best confirmatory test for human African trypanosomiasis (HAT), the mAECT (also known as the “Minicolumn” test), production and supply has yet to be secured at affordable prices. For medicines, where detection rates for a specific disease are low and the potential market is consequently small, problems may be encountered with securing production and supply of sufficient medicines, as has been the case for Chagas disease, leishmaniasis and drug-resistant TB. In this context, the development and introduction of NCEs and new regimens can similarly face supply and market challenges.

Defining research priorities and the target product profiles (TPPs) – as has been done by WHO in the case of medicines, vaccines and diagnostics for malaria – can promote targeted use of resources to respond to public health needs. This work can also help to guide and channel global community and industry efforts towards the appropriate products for optimal public health impact. In addition, the basic research needs can also be identified and defined. Within the TB field, WHO developed a roadmap for TB diagnostics and the corresponding TPPs that will channel investments towards the desired diagnostics. WHO is also monitoring the pipeline for NCEs and new regimens, as well as developing the policy guidance for the introduction of NCEs. There is, however, no formal WHO mechanism to coordinate the research agenda for new TB regimens, which should necessarily take account of resistance surveillance data. In the TB vaccines arena, the coordination is led

by a global partnership of TB vaccine public-private partnerships (PPPs). In the case of NTDs, efforts have been more limited. For HAT, a WHO task force aims to define the elimination strategy as well as the essential innovation needs. While research priorities were set for post-kala-azar dermal leishmaniasis, there has yet to be a comprehensive exercise undertaken to define research priorities, TPPs or milestones for improved cutaneous and mucosal leishmaniasis treatments and diagnostics. For Chagas disease, the need for a priority-setting exercise and definition of TPPs for vaccines, diagnostics and treatments is acute.

The role and impact of intellectual property rights (IPRs) vary across the product/disease categories, depending on the actors involved in the research and development. It can be expected that pharmaceutical companies will seek IPR protection, while PPPs and product development partnerships may be guided by considerations of ensuring availability and affordability of their products. Research is also carried by academic groups and smaller companies, especially in the area of biomarkers and diagnostics, which may seek IPR protection. A patent landscape report for TB NCEs developed by the industry and by PPPs is available, while the IPR landscape for malaria NCEs has not been investigated. The impact of IPRs should be investigated for NAA-based technologies, biomarker-based POC tests, and tests of cure, which are sought for a number of diseases, including TB, leishmaniasis and Chagas disease.

A key aspect of the development and delivery of health products is the regulatory framework. There is a need for regulatory reform and harmonization, with regard to the processes of review and approval of NCEs and novel regimens in the developing countries. For example, accelerated marketing approval based on Phase IIb data and compassionate use has been adopted to expedite the roll-out of two NCEs for multidrug resistant-TB, but regulatory frameworks in developing countries typically do not permit approval on grounds of compassionate use or introduction of medicines approved on Phase IIb data. The need for pharmacovigilance should also be foreseen in the introduction of NCEs. For example, WHO has

recommended establishing active pharmacovigilance in countries using bedaquiline and delamanid. In the case of diagnostics, there is a concern that commercialization is taking place in a largely unregulated market. The need for the evaluation of field use of these technologies has been highlighted across all diseases.

Organization of report

The report is organized into four main sections. Section 1 presents the introduction, followed by sections 2, 3 and 4, which set out the analysis of the product pipeline for malaria, TB and NTDs, respectively. In section 4, the focus is on the NTDs caused by kinetoplastid parasites: human African trypanosomiasis (HAT), leishmaniasis and Chagas disease, given the available information on the product pipeline for these diseases. Each section presents the analysis of the products within three categories: namely, medicines, diagnostics and vaccines that are advanced in the pipeline. Sections 2, 3 and 4 are supplemented by annexes, which provide detailed descriptions of the identified pipeline products. Section 5 concludes the report with a number of observations arising out of the analysis.

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ABBREVIATIONS AND ACRONYMS

ACT	artemisinin combination therapy	GSK	GlaxoSmithKline
ACTG	AIDS Clinical Trial Group	HAT	human African trypanosomiasis
API	active pharmaceutical ingredient	ICGEB	International Centre for Genetic Engineering and Biotechnology
BCG	bacille Calmette-Guérin	ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
BMGF	Bill and Melinda Gates Foundation	IDRI	Infectious Disease Research Institute
BRICS	Brazil, People's Republic of China, India, the Russian Federation and South Africa	IED	Institute of Endemic Diseases (Sudan)
CATT	card agglutination test for trypanosomiasis	INRB	Institut National de Recherche Biomédicale (Kinshasa, Democratic Republic of the Congo)
CDC	Centers for Disease Control (United States)	IPR	intellectual property right
CEM	cohort event monitoring	ITG	Instituut voor Tropische Geneeskunde/ Institute of Tropical Medicine (Antwerp, Belgium)
CL	cutaneous leishmaniasis	IVD	<i>In vitro</i> diagnostic
CRESIB	Barcelona Centre for International Health Research (Spain)	LAMP	loop-mediated isothermal amplification
DFID	Department for International Development (United Kingdom)	LED	light-emitting diode
DNA	deoxyribonucleic acid	LPA	line probe assay
DNDi	Drugs for Neglected Diseases Initiative	LSHTM	London School of Hygiene and Tropical Medicine (United Kingdom)
DR-TB	drug-resistant tuberculosis	MA	meglumine antimoniate
DS-TB	drug-sensitive TB	mAECT	mini Anion Exchange Centrifugation Technique
DST	drug susceptibility testing	µl	microlitre (one millionth of a litre)
EBA	early bactericidal activity	MDR-TB	multidrug-resistant TB
EC	European Commission	ML	mucosal leishmaniasis
EDCTP	European & Developing Countries Clinical Trials Partnership	MMV	Medicines for Malaria Venture
EIB	European Investment Bank	MSF	Médecins sans Frontières
EMA	European Medicines Agency	MVI	Malaria Vaccine Initiative
EU	European Union	NAA	nucleic acid amplification
EVI	European Vaccine Initiative	NCE	new chemical entity
FDC	fixed-dose combination	NECT	nifurtimox–eflornithine combination therapy
FIND	Foundation for Innovative New Diagnostics	NIAID	National Institute of Allergy and Infectious Diseases (United States)
G6PD	glucose-6-phosphate dehydrogenase		
GDF	Global Drug Facility		
Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria		

NIH	National Institutes of Health (United States)
NTD	neglected tropical disease
NWCL	New World cutaneous leishmaniasis
OWCL	Old World cutaneous leishmaniasis
PCR	polymerase chain reaction
PDP	product development partnership
PECET	Programa de Estudio y Control de Enfermedades Tropicales (Colombia)
PKDL	post-kala-azar dermal leishmaniasis
POC	point-of-care
PPP	public-private partnership
qPCR	quantitative polymerase chain reaction
RCT	randomized controlled trial
RDT	rapid diagnostic test
SbV	pentavalent antimony
SRA	stringent regulatory agencies
SSG	sodium stibogluconate
STAND	Shortening Treatment by Advancing Novel Drugs
TAG	Treatment Action Group
TB	tuberculosis
TB Alliance	Global Alliance for TB Drug Development
TBTC	Tuberculosis Trials Consortium (Centres for Disease Control)
TBVI	Tuberculosis Vaccine Initiative
TDR	Special Programme for Research and Training in Tropical Diseases
TPP	target product profiles
US FDA	United States Food and Drug Administration
USAID	United States Agency for International Development
USAMRMC	United States Army Medical Research and Material Command
VL	visceral leishmaniasis
WGS	whole genome sequencing
WHO	World Health Organization
WRAIR	Walter Reed Army Institute of Research
XDR-TB	extensively drug-resistant tuberculosis

SECTION 1

INTRODUCTION

SECTION 1

INTRODUCTION

1.1 Aim and objective

The aim of this report is to identify new health products with a high probability of market entry in the next five years (2015–2020) that developing countries will likely introduce for use within national health systems. The focus is to identify products that have promise in significantly improving current approaches towards the prevention, diagnosis and treatment of malaria, tuberculosis (TB) and selected neglected tropical diseases (NTDs) caused by kinetoplastid parasites: human African trypanosomiasis (HAT), leishmaniasis and Chagas disease.

The report seeks to highlight potential challenges to the introduction and use of new chemical entities (NCEs), regimens, diagnostics and vaccines in developing countries. It analyses whether introduction of these new products can place additional requirements or burdens on the health systems in developing countries; this would include the need for new regulations, increased capacity for pharmacovigilance, and/or changes to the procurement or supply systems. In this context, key global policy issues, such as recommendations, endorsements, prequalification and monitoring of newly-introduced innovations, are outlined. Factors related to supply, and pricing, as well as the potential market and competition landscape of the products, are examined.

The analysis also aims to highlight the key developments and gaps, in terms of the current product pipeline, as well as in the basic research field. In this context, the relevant actors undertaking research and product development are also

identified. While it is not the main focus of the report, the analysis highlights specific instances of funding gaps in product development, as identified in published reports and by interviewees. In this context, the report considers how the availability of funds has impacted priority-setting for product development, which in some cases, may have left potential tools unfunded.

The basic premise of this report is that such analysis of the product pipeline can contribute towards better and informed decision-making on the adoption and introduction of new health products in developing countries. Hence, this report is intended as a resource document primarily for policymakers in disease programme implementation and product procurement.

Only one out of ten medicines that enter clinical development ultimately receives regulatory approval, with even lower rates for vaccines.¹ Commercialization of new products however, does not imply their suitability for use in all health systems or in varied geographical areas. The information provided in this report on pipeline products should therefore be used only in conjunction with the relevant policy recommendations by the World Health Organization (WHO).

1.2 Scope and methodology

A review of information available in the public domain – including published reports, meeting presentations, and databases of clinical trials – was undertaken to collect information on pipeline products for malaria, TB, HAT, leishmaniasis and

Chagas disease. The review included information made available by key actors in the field, including WHO, UNITAID, the Treatment Action Group (TAG), Médecins sans Frontières (MSF), Aeras, the Drugs for Neglected Diseases Initiative (DNDi), Medicines for Malaria Venture (MMV), PATH, the Global Alliance for TB Drug Development (TB Alliance) and other relevant public–private partnerships (PPPs) and product development partnerships (PDPs). Information on the status of clinical trials for NCEs, vaccines and devices – verified with the database service provided by the United States National Institutes of Health (<https://clinicaltrials.gov>) – was also used to determine the product pipeline.

Interviews and communications with key informants, including technical experts in the various disease/product areas, as well as from PPPs and PDPs, provided the substantial portion of the information that enabled the analysis for this report. A review of public domain information alone would have resulted in a much less complete analysis of the product pipeline. In particular, very little information related to NTDs is currently available in the public domain.

1.3 Criteria for selection of products

The analysis is based on available information on medicines, diagnostic tests and vaccines that are expected to be ready for market introduction by 2020. This report focuses on NCEs, vaccines, immunomodulators and new diagnostics as well as new shorter regimens and new non-pharmacological treatments under study.

In terms of NCEs, the focus is on those medicines undergoing Phase III and Phase IIb/IIa clinical trials, which, if successful throughout the clinical development process, are likely to be submitted for regulatory approval and/or enter the market by 2020. On vaccines and immunomodulators, an overview of the pipeline is presented, along with information on the research aimed at accelerating progress for the

introduction of such interventions. For diagnostics, the report presents an overview of new diagnostic tools and technologies that constitute a novel approach (i.e. point-of-care (POC) diagnostics) that are being evaluated and introduced in countries, as well as those that are under development to meet additional public health needs.

This report does not cover the range of products that represent incremental innovations, such as fixed-dose combinations (FDC) of already known or recommended products, or paediatric formulations. While the importance of incremental innovation and product optimization is fundamental to health systems in the context of disease control and access to treatment, such products are not the focus of this report, as these products will likely not require new or major changes to implementation steps for health systems. Nevertheless, a number of treatments that are not based on NCEs or new technologies have been included in the section on NTDs, as these represent key developments in the product pipeline for these diseases. Emphasis is given to improvement of existing diagnostics for which a costing and/or supply issue still exists, as well as new diagnostic tools that are in a relatively early stage of roll-out in countries.

1.4 Organization of the report

The document is organized as follows: section 1 presents the introduction, followed by sections 2, 3 and 4, which present the analysis of the product pipeline for malaria, TB and NTDs, respectively. In each of these sections, the pipeline analysis is undertaken within three product categories: medicines, diagnostics and vaccines. section 5 concludes the report with a number of observations arising out of the analysis.

Products that are advanced in the pipeline are identified and analysed: medicines that are under Phase III and Phase II; clinical trials for new regimens in Phase III; vaccines in Phase III that are under registration or planned for registration in stringent

regulatory agencies (SRAs); and diagnostics, which are recently WHO-endorsed (or are in the pipeline for WHO endorsement). These sections are complemented by several annexes that provide detailed descriptions of the products.

Considerations on diagnostics developmental stage

In the case of diagnostics, it is more difficult to have a clear distinction and a sequence of developmental phases because information is not clearly maintained in any repository during the development phase, as it is for clinical trials. In addition, the development phases for diagnostic tools are also not defined within an international classification system.

Level of intended use within health systems

While the health system setting in which a product under development is intended for use (i.e. referral, district or peripheral level) has been indicated for diagnostics, this is more difficult to establish for NCEs. The technological aspects of each diagnostic tool are included either in the narrative of the annexes or summarized in the tables. For medicines under development, it is not possible in all instances to indicate the health system level at which they will be used, as this will depend on results of Phase III/IV trials and on related WHO policy recommendations. Controlled temperature and/or cold chain requirements for medicines are disclosed only once a given product has received regulatory approval.

SECTION 2

MALARIA



SECTION 2

MALARIA

2.1 Background/context

The past decade has seen major achievements in malaria vector control, prevention, diagnosis and treatment. While challenges remain in the use of existing tools – such as rapid diagnostic tests (RDTs) and effective artemisinin combination therapy (ACT) and chemoprophylaxis – there has been great momentum towards implementation of these interventions. In parallel, there is significant investment in interventions and innovations to support malaria elimination. Efforts are focused on development of treatments that can be effective against ACT resistance and latent malaria infection; in the design and application of diagnostic strategies for confirmation of clinical malaria cases; and the pursuit of vaccination strategies to prevent malaria and also reduce onward malaria transmission in support of elimination efforts.^{2,3,4,5}

2.2 Medicines

In identifying NCEs for malaria prevention and treatment, the following criteria have been used:

- Novel mechanisms of action (i.e. in anticipation of artemisinin drug resistance).
- Single dose to improve patient compliance and increase drug effectiveness.
- Transmission-blocking drugs to reduce disease burden.
- Prophylactic activity to prevent infection.
- Parasite radical cure to prevent disease relapse.

The landscape of NCEs for malaria comprises a number of candidate medicines undergoing Phase II trial for the treatment of uncomplicated malaria (see table 1). One NCE, tafenoquine, has entered a Phase III trial for radical cure of *Plasmodium vivax*. KAE609,

KAF156 and DSM265 have new mechanisms of action. Other NCEs are reported to be in Phase II trials, but apart from SAR97276, which has a novel mechanism of action but for which development has been halted, all other compounds in the pipeline belong to known substance classes.^{6,7} Work is ongoing to commercialize artesunate suppositories for pre-treatment of severe malaria at the community level. It should be noted that there is currently no precedent for malaria medicines to be approved based only on Phase IIb trials data, as recently took place with the TB medicines bedaquiline and delamanid. In order to register any alternative single medicine or FDC for malaria, Phase III trials will be required. See annex 1 for a summary of information on malaria product innovations.

Table 1. New chemical entities and combinations under clinical development for malaria

Drug(s)	Developer(s)	Developmental stage
Tafenoquine	GlaxoSmithKline, with United States Army Medical Research and Materiel Command (USAMRMC) and MMV	Phase III
OZ439 (artefenomel)/ferroquine	Sanofi S.A., France	Phase IIb
OZ439 (artefenomel)/piperazine	Sanofi S.A., France	Phase IIb
Arterolane/piperazine	Ranbaxy Laboratories, Ltd., India	Phase IIb
KAE609 (formerly NITD609)	Novartis AG, Switzerland	Phase IIa
KAF156	Novartis AG, Switzerland	Phase IIa
DSM265	Takeda Pharmaceutical Company, Japan, Global Health Innovative Technology and MMV	Phase IIa
AQ13	Immtech, United States, with Tulane University (New Orleans, US)	Phase IIa

2.3 Diagnostics

Several RDTs have been developed to test the presence of malaria parasites in blood samples. A major remaining challenge is to ensure that RDTs marketed and/or distributed in countries have acceptable quality assurance. The capacity to perform regulatory functions for diagnostic tools is extremely weak in many low- and middle-income countries. This increases the importance of assessing and guaranteeing RDT quality through the WHO prequalification scheme. Alongside RDTs, diagnostic microscopy also continues to be widely used. The RDTs support the surveillance of confirmed clinical cases but do not allow detection of infected individuals without clinical symptoms. In moving towards malaria elimination, the need for new diagnostic tools has been identified and development of new technologies based mainly on nucleic acid amplification (NAA) techniques is ongoing (see section 2.3.1).

Concurrently, the malaria community has taken a broader approach to malaria diagnosis by viewing it as a central facet of improving broader febrile illness management. This view has catalysed work to improve the management of fever more generally – at a normative level in WHO and at the country level – through appropriate scaling up of diagnostic testing and quality of laboratory services to manage malaria and other illnesses appropriately (see section 2.3.2). In addition, the potential introduction of new medicines belonging to the class of 8-aminoquinolines for the radical cure of *Plasmodium vivax* infection has renewed interest in developing a POC test for detecting glucose-6-phosphate dehydrogenase (G6PD) deficiency (see section 2.3.3).

2.3.1 Diagnostic capacity for malaria elimination

With increasing coverage of malaria interventions, a growing number of countries have achieved regional shifts from high to low transmission levels in less than five years. Identifying and successfully treating remaining malaria infections in low

transmission areas is critical to further reducing transmission towards elimination. The WHO began defining policy recommendations and developing the necessary guidance on diagnostics for the elimination of malaria, with a 2013 report from the WHO Evidence Review Group on Malaria Diagnosis in Low Transmission Settings. Elimination programmes will require additional diagnostic tools for research and surveillance, to screen and detect asymptomatic infection cases on a large scale, and to be operated at reference/district levels.

The new technologies under development to support malaria elimination are based on NAA techniques, and are more sensitive and specific than RDTs or microscopy in the identification of low-parasite load in individuals. A few products have already been commercialized, although WHO does not recommend their large-scale use until evidence is generated on their utility in low transmission areas. An initial review of the new technologies, their operational characteristics, their expected performance and cost has been completed. The 2013 report of the WHO Evidence Review Group on Malaria Diagnosis in Low Transmission Settings recognized the need to establish a robust framework to coordinate research and product development towards defined targeted product profiles, in order to ensure, compare and monitor the quality of developed diagnostics.^{8,9}

Preferred product characteristics for malaria elimination diagnostics: The 2013 report of the WHO Evidence Review Group on Malaria Diagnosis in Low Transmission Settings proposed preferred product characteristics for diagnostics for elimination settings and prioritized the development of diagnostic tests with the following characteristics: able to detect parasitaemia of ≤ 2 parasites/microlitre (μl); require a blood sample volume of not more than 50 μl ; an assay that is not instrument-specific and is flexible in power supply; a processing rate of 48 samples/person/platform/day within 16 hours; and allowance of species differentiation on positive samples. These criteria respond to the need for high throughput tests for conducting large-scale surveys and mass

screening in elimination settings. In moving towards further development and evaluation of NAA-based technologies for low transmission areas, WHO has identified the need to develop an international, external quality assurance system to ensure that data obtained from such assays are reliable and comparable.^{8,9} It is understood that WHO is considering the use of an external quality assessment approach for molecular diagnostic testing of malaria.

Investment for sensitive POC tests for screening asymptomatic infections. The PATH DIAMETER (Diagnostics for Malaria Elimination Toward Eradication) project, funded by the Bill and Melinda Gates Foundation (BMGF), has defined target product profiles (TPPs) for various use-case scenarios and is pursuing POC infection detection tests. The DIAMETER project is working on several malaria detection technologies, including enhanced microscopy systems with slide scanning technologies and pattern recognition software, higher performing RDTs, as well as novel disposable NAA tests that do not require infrastructure. These new diagnostic tools will need to be validated and approved by a stringent regulatory authority and/or be prequalified by WHO. It is expected that this will require more than the two years anticipated in the initial timeline of the DIAMETER project.^{10,11}

2.3.2 Point-of-care tests and management of febrile events

The recent expansion of malaria diagnostic testing has shown that the majority of febrile events are not due to malaria, especially where control interventions have decreased its transmission. The WHO has identified the need to focus interventions on supporting health workers to appropriately diagnose the causes of fever at primary health care facilities and at the community level and to promote the integrated management of fever. The WHO took the first step in identifying potential approaches and major research gaps. As a result, WHO has identified the need for new POC tests to detect pathogens or host biomarkers, prioritizing the need for a POC to identify: patients with severe febrile illness; patients with acute respiratory infections who require antimicrobial treatment; and patients with non-specific fever who

require antibiotic treatment. Approaches under consideration include the development of generic tests to identify patients at risk for severe illness (e.g. with host biomarkers), or those with a particular class of infection (e.g. distinguishing bacterial and viral infections). Research groups have identified promising biomarkers for differentiating malaria from bacterial and viral infections, and studies are being planned to cross-validate the biomarkers, as well to assess the cost implications of producing a second test rather than adding multiple reagent lines to an existing test. The WHO has pointed out that POC tests should be affordable, easy-to-use and equipment-free in order to be used at the primary health care and community levels. Diagnostic tests and fever management algorithms should be developed to be introduced and used in the private sector, where much of the management of fever, including malaria cases, occurs.¹² Given considerable variation in the prevalence of fever-inducing diseases, development of new diagnostic products for non-malarial fever also requires an understanding of the epidemiology of fever causes in different geographic areas. It is estimated that POC tests for management of fever will not be developed within a five-year framework.

2.3.3 Point-of-care G6PD diagnostics

The potential for malaria elimination has shifted emphasis from treatment of symptomatic parasitaemia towards comprehensive treatment of all parasites and multiple life stages. There is a renewed interest in diagnostic testing for G6PD deficiency, and the critical examination of the safety of primaquine and the pipeline drug tafenoquine. Pre-existing G6PD deficiency can cause acute haemolytic anaemia on administration of primaquine, hindering its use, despite a WHO recommendation for its use for the radical cure of *P. vivax*. There is currently no well-adapted POC G6PD test for use prior to primaquine treatment. The pipeline medicine tafenoquine (currently in Phase III trial) has the potential to substitute primaquine. However, a major concern and prerequisite for its marketing – and elimination of *P. vivax* – is the development of a G6PD deficiency test able to distinguish different grades of G6PD.

Evaluation of G6PD tests and WHO guidance: Several research groups have evaluated the diagnostic performance of POC G6PD tests compared to other G6PD diagnostic technologies (the fluorescent spot test and spectrophotometric assays). This includes genotyping specific genetic variants of G6PD deficiency in a range of geographical areas. These studies and evaluation were finalized in 2014. Subsequently, WHO convened an Evidence Review Group (Geneva, 8–9 October 2014) to review the G6PD diagnostic options and their comparative performance and utility in the field, with the aim of guiding G6PD status testing prior to administration of primaquine. The WHO published the outcome results in a report to the Malaria Policy Advisory Committee (Geneva, 5–7 March 2015). The WHO Evidence Review Group recommended that the G6PD qualitative POC tests: shall identify G6PD non-deficient patients prior to primaquine administration with more than 95 percent sensitivity compared to spectrophotometry or equivalent quantitative tests; shall be stable at temperatures expected in tropical settings (i.e. 35°–40° Celsius (C)); and shall have a negative predictive value of >95 percent at G6PD enzyme activity levels <30 percent of normal. The WHO Expert Review Group report shows that the same G6PD test devices perform differently based on the geographical area, sex and setting, operator and sample type (venous or capillary blood). The selection of the test to be used should therefore take into account all these parameters.¹³ A description of the POC G6PD tests reviewed by WHO is provided in annex 1.

Current status of new G6PD tools for tafenoquine: Work is ongoing by PATH and GlaxoSmithKline (GSK) to develop a specific POC G6PD test to support the roll-out of tafenoquine in a coordinated manner. GSK is leading the development of a new biosensor, similar to a blood glucose monitor, to detect G6PD deficiency and measure enzyme activity, which will support safe tafenoquine treatment.¹⁴ PATH is working on an evaluation of different technologies for development of a POC G6PD test for tafenoquine, with support from BMGF and the United Kingdom Department for International Development (DFID).

POC G6PD test TPPs: Work conducted by PATH also involves development of TPPs for POC G6PD tests, development of evaluation standards for G6PD test products, setting operational research priorities and evaluating diagnostic tests in the pipeline.¹⁵ The TPP has been constantly revised, with the most recent version established in a workshop in 2013.¹⁶ More than one G6PD test is expected to be launched in the market by 2017 and rolled out in developing countries.

Regulatory issues: Most G6PD tests on the market have obtained only CE mark (formerly EC mark) approval at best. The issue of quality control and performance of G6PD RDTs entering the market is highlighted as a priority to be addressed at the policy level.

2.4 Vaccines

Protozoa such as plasmodia and kinetoplastids are more complex organisms than bacteria and viruses, with more complicated structures and life cycles. This factor presents problems in vaccine development but also increases the number of potential targets for a vaccine. The current vaccination strategy for malaria can be characterized in three main classes of vaccines based on the targeted parasite life cycle stage:

- **Pre-erythrocytic/preventive vaccine:** Aims to protect against sporozoites invading and possibly inhibiting the development of parasites in the liver, thus preventing the parasite from multiplying, re-entering the bloodstream and triggering symptoms of disease.
- **Blood-stage/therapeutic vaccine:** Aims to decrease the number of parasites in the blood in an already infected individual (to prevent merozoite multiplication or the invasion of red blood cells), reducing the severity of malaria in an infected individual.
- **Transmission-blocking vaccine:** Aims to interrupt the cycle of parasite transmission between mosquitoes and humans, such as by preventing the gametocytes from producing multiple sporozoites

in the gut wall of the mosquito and thus making transmission back into a person impossible. This would not give any protective benefits to the individual but would prevent further transmission of the parasite, as part of a policy directed at eliminating the parasite from areas of low prevalence.

The majority of research into malarial vaccines has focused on the *P. falciparum* strain due to the high mortality caused by the parasite and the ease of carrying out *in vitro/in vivo* studies. One vaccine (ChAd63/MVA PvDBV) is in early phase development to target *P. vivax* by the University of Oxford (United Kingdom) with Okairos (Switzerland/Italy) and the International Centre for Genetic Engineering and Biotechnology (ICGEB) (component based in New Delhi, India) (see annex 2). Many vaccine research efforts are directed towards combinations of the many antigens present throughout the parasite life cycle.¹⁷

Current status: Over 20 malaria vaccines are currently being evaluated in clinical trials or are in advanced preclinical development.¹⁸ Those in clinical phase are listed in annex 2. In July 2015, the most advanced candidate vaccine RTS,S/AS01 (GSK in collaboration with PATH) received a positive scientific opinion under the Article 58 procedure at the European Medicines Agency (EMA). The Article 58 procedure allows the EMA, in cooperation with WHO, to evaluate the quality, safety and efficacy of a pharmaceutical product that is intended for use in markets outside of the European Union. This is the first malaria vaccine to be approved for use.¹⁹ WHO will review evidence of its safety and efficacy in order to issue a policy recommendation, which is expected by November 2015.²⁰ Based on currently available data, the vaccine will be evaluated as an additional measure to existing preventive, diagnostic and treatment interventions. A description of RTS,S/AS01 is presented in annex 1. Three vaccines are in Phase IIb trials in endemic countries, undergoing a proof of concept for efficacy. Nevertheless, their development is considered to be delayed by five to ten years in comparison to RTS,S/AS01. Malaria vaccines will need to complete Phase III trials before proceeding for registration. Discussions

are ongoing on whether malaria vaccines could be registered based on data of Phase IIb trials.ⁱ

Malaria Vaccine Technology Roadmap: The current malaria vaccines pipeline is the result of a wide collaborative platform that includes more than 100 organizations. In 2006, the platform defined the Malaria Vaccine Technology Roadmap process with a dual goal: to develop and license a first-generation *P. falciparum* malaria vaccine with a protective efficacy against the severe disease of more than 50 percent by 2015; and to develop and license a malaria vaccine with a protective efficacy against clinical disease of more than 80 percent by 2025.²¹ In 2013, an update of the Roadmap was prepared, with redefined goals: to develop a preventive vaccine for clinical disease with over 75 percent efficacy in malaria-endemic populations; and to develop a vaccine that decreases malaria transmission and, administered through mass vaccinations, will enable malaria elimination.²²

WHO coordinating mechanisms: Several coordinating mechanisms have been implemented by WHO since the development of the Roadmap. Funders are coordinated under the umbrella of the Malaria Vaccine Funders Group, which aims to facilitate information sharing and coordination of vaccine research activities and to reduce overlap and create synergies in order to complement and prioritize efforts. The Malaria Vaccine Funders Group comprises the BMGF, the European and Developing Countries Clinical Trials Partnership (EDCTP), the European Vaccine Initiative (EVI), the European Commission (EC), the PATH Malaria Vaccine Initiative, the United States Agency for International Development (USAID), the United States National Institute of Allergy and Infectious Diseases (NIAID), the Wellcome Trust and WHO.²³ In 2009, WHO also established a Joint Technical Expert Group on malaria vaccines entering pivotal studies in order to provide recommendations on the necessary clinical trial data for evaluation of public health impact, and to provide guidance on the design, conduct, analysis and interpretation of Phase

i Vaccine development for malaria is defined by distinct stage numberings: Phase Ia and IIa trials take place in non-endemic countries, while Phase Ib and IIb trials take place in malaria-endemic countries.

Table 2. Malaria vaccines in Phase III

Vaccine name	Targeted plasmodium	Strategy	Sponsors	Status
RTS, S-AS01 (257049)	P. falciparum	Pre-erythrocytic	GSK/PATH	Phase III completed EMA approval

II, Phase III and Phase IV trials of malaria vaccines.²⁴

As an example, the Group evaluates if a candidate vaccine, based on the results of Phase Ib trials (including 20–50 people), should move to a Phase IIb trial that involves approximately 1,000 people.

SECTION 3

TUBERCULOSIS

SECTION 3

TUBERCULOSIS

3.1 Background/context

There are many developments in the diagnostics and treatment algorithm for drug-resistant TB (DR-TB). A new diagnostic tool (GeneXpert) was recently introduced in the market and is being scaled up in many countries, revolutionizing TB control and care. The global community is aiming for a POC tool for drug-resistant TB that is effective in people living with HIV, in children and among patients with extra-pulmonary TB. On the treatment front, two NCEs have been approved by SRAs, representing the first TB medicines with novel mechanisms of action reaching the market in more than 50 years. Several trials, including other NCEs and several operational research projects are underway to develop shorter, non-toxic regimens. The introduction of NCEs and development of new diagnostics has led WHO to generate policy and treatment recommendations to support the roll-out of new tools in countries. Data and experience gathered during the roll-out of new diagnostic tools is expected to optimize use of these technologies, as well as to pave the way for evaluation of other pipeline products. The policy environment for TB medicines and diagnostics is moving rapidly, and several guidance documents are in preparation to support the introduction of new TB medicines, new regimens and new diagnostics. In May 2014, at its 67th Session, the World Health Assembly approved the 'WHO End TB Strategy', an ambitious post-2015 'Global Strategy and Targets for Tuberculosis Prevention, Care and Control'. Among its main pillars, the plan includes the discovery, development and rapid uptake of new tools, interventions and strategies. It also highlights the urgent need to regulate the production, quality and use of TB diagnostics and medicines. In particular, the plan urges the development of a POC TB diagnostic test, a regimen to treat all forms of TB,

enhancement of research to detect and treat latent TB infection, and the development of an effective TB vaccine.^{25,26,27,28,29,30,31}

3.2 Medicines

The current WHO recommended regimen for multidrug-resistant TB (MDR-TB) consists of a 24-month cocktail of extremely toxic drugs, which includes eight months of daily injections and needs to be tailored to the resistance profile of each individual patient. MDR-TB is extremely difficult to treat, and if resistant profiles are not adequately established (i.e. through drug susceptibility testing (DST)) and individual treatment strategies are not appropriate, additional resistance can be created, leading to extensively drug-resistant TB (XDR-TB). Current treatments for MDR-TB are lengthy, toxic and potentially cause permanent disabilities and/or serious side effects. The cure rate for MDR-TB is approximately 50 percent and around 16 percent for XDR-TB.

Two NCEs with novel mechanisms of action have received conditional approval by SRAs based on Phase IIb clinical data (see table 3). Both bedaquiline and delamanid have been registered with indication for pre-XDR-TB and XDR-TB, to be added to the 24-month regimen currently recommended by WHO for MDR-TB. The potential exists for these new medicines to shorten considerably the regimen for MDR-TB. However, both drugs present potential cardiotoxicity and drug-drug interaction studies are needed to assess if they can be combined in one regimen. Annex 3 provides summary descriptions of these and other NCEs in the pipeline, as well as a brief overview of the clinical trials ongoing and/or planned for shorter regimens, both in DR-TB and drug-sensitive TB (DS-TB).

Table 3: New chemical entities by class and clinical development stage

Class	Drug(s)	Developer	Developmental stage
Diarylquinoline	Bedaquiline	Janssen, Belgium	US FDA conditional approval/Phase III
Nitroimidazole	Delamanid	Otsuka Pharmaceutical Company, Japan	EMA conditional approval/Phase III
	Pretomanid	TB Alliance	Phase III
Oxazolidinone	AZD5847	AstraZeneca, UK	Phase IIa
	Sutezolid	Sequella, US	Phase IIa
Ethylenediamine	SQ109	Sequella, US	Phase IIa

3.3 New tuberculosis regimens under clinical trial

Clinical trials are ongoing using known medicines and/or NCEs to shorten regimens both for DS-TB and DR-TB (see annex 4). The regimens in Phase III trials are reported in table 4. Trials can be grouped based on the type of concept they are investigating for new regimens.

Three clinical trials assessing the use of fluorquinolones and the potential to shorten DS-TB regimens to four months have been concluded. RIFAQUIN and OFLOTUB trial results were released in 2013.^{32,33} Both trials had negative results. The REMOX trial was concluded in March 2014 and the results were disclosed in September 2014.^{34,35} The results of this third trial were also negative, refuting the hypothesis that fluorquinolones could be used to shorten DS-TB regimens.

Another group of trials managed by the United States Centers for Disease Control (CDC) Tuberculosis Trials Consortium (TBTC) is assessing substitution of rifampicin with rifapentine at various dosages for DS-TB (TBTC Study 29). Results were published in May 2013.³⁶ This new regimen will shortly be trialled in a Phase III study (TBTC Study 31).

Another group of trials assesses the use of the NCE pretomanid, in combination with pyrazinamide and moxifloxacin for both DS-TB and DR-TB (NC002). A Phase III trial (Shortening Treatment by Advancing Novel Drugs (STAND)/NC-006) assessing this combination in four-month and six-month periods

started in November 2014, with plans to conclude in 2018.

The STREAM trial assessing shortened MDR-TB regimens will provide results in two phases. The first two arms will be concluded in 2017 and the additional two arms (containing bedaquiline) are planned to run from the second half of 2015 to 2019. If results of shorter nine-month regimens with existing drugs are positive, WHO will proceed to make corresponding recommendations, given the urgency and pressure of moving away from 18–24 month regimens for MDR-TB. This may occur while results of the bedaquiline-containing arms of the trial are still forthcoming.

A number of Phase II and III trials (NC005, NExT, PRACTECAL) combining bedaquiline and pretomanid (among other medicines) are also planned. The TB Alliance has also started enrolling patients in a Phase III trial (NiX-TB) assessing a salvage therapy for XDR-TB patients. While bedaquiline is included in trials for assessing new combinations to shorten MDR-TB and XDT-TB regimens, only one trial including delamanid to explore the same potential is planned (EndTB).

^{37,38,39,40}

Considerations for combining delamanid and bedaquiline in a new regimen. Pharmaceutical companies Otsuka (Japan) and Janssen (Belgium) have agreed that the United States National Institutes of Health (NIH) will perform a drug–drug interaction study of delamanid and bedaquiline. The study (AIDS Clinical Trial Group (ACTG) A5343) will clarify the toxicological feasibility of combining these two new medicines

in an improved shortened regimen. This study has been considered since 2011; it is expected to start in the second half of 2015.

Paediatric-specific studies. Assessment of new treatments for TB should include children, including those living with HIV and the development of child-friendly formulations suitable for high-burden settings. Pharmacokinetic, safety and tolerability profiles of all new tuberculosis medicines should be established in paediatric populations, and should be used to develop optimum dosing in children. Pharmacokinetics and safety of delamanid are being tested in children and adolescents in a Phase

II study (C232), and results are expected in 2016. A dispersible tablet of delamanid is also under development. A Phase II Janssen-sponsored trial assessing bedaquiline in children was planned to start at the end of 2015.

Diagnostic capacity to assist clinical trials. One of the challenges for drug development for TB is the lack of predictive biomarkers. Clinical trials are large scale and lengthy, requiring up to 12–24 months of follow-up after treatment to assess cure or relapse. A predictive biomarker could greatly reduce the duration and number of patients needed for trials.

Table 4. Phase III clinical trials investigating shorter TB regimens

Indication	Study name	Study/Regimen	Stage	Sponsors
DS-TB	TBTC 31	Four-month regimens: two months of isoniazid, rifapentine, ethambutol, and pyrazinamide, followed by two months of isoniazid and rifapentine; two-months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by two-months of isoniazid, rifapentine and moxifloxacin.	Phase III	TBTC-CDC, Sanofi, France
DS-TB, DR-TB	STAND (GABT NC-006)	Four- or six-month regimens: pretomanid, moxifloxacin, pyrazinamide	Phase III	TB Alliance
DR-TB	STREAM	STREAM I: nine-month regimen: ethambutol, pyrazinamide, moxifloxacin and clofazimine throughout supplemented by kanamycin, prothionamide and isoniazid in the four-months intensive phase (4KCMEHZP/5MEZC). STREAM II: two additional arms including bedaquiline: one arm substituting kanamycin with bedaquiline, one arm adding bedaquiline and shortening the regimen to six months.	Phase III	The Union, Medical Research Council, UK, USAID
MDR-TB	NeXT	Six-month regimen: bedaquiline, ethionamide, isoniazid, pyrazinamide, levofloxacin, linezolid.	Phase III	University of Cape Town, South African Medical Research Council (SAMRC)
XDR-TB	NiX-TB	Six-month or nine-month salvage regimen: bedaquiline, pretomanid, linezolid	Phase III	TB Alliance

Source: TAG TB pipeline reports and the DR-TB Clinical Trial Progress Report, accessed on 16 June 2015.

3.3.1 Operational research for shortened tuberculosis regimens

A number of countries are piloting shortened regimens outside the clinical trials framework. WHO has recommended that shortened regimens should only be used in the context of research and under close monitoring for a period of at least 12 months after treatment completion. Patient follow-up allows early identification of patients who may relapse and acquire resistance. WHO recommendations for introduction of shortened MDR-TB treatment regimens include the following criteria:

- Approval of the project by a national ethics review committee, ahead of any patient enrolment.
- Delivery of treatment only under operational research conditions and according to international standards (including good clinical practice and safety monitoring).
- Monitoring of related research by an independent monitoring board set up by, and reporting to, WHO.

WHO offers assistance to countries for the development of the required operational research and programme management capacity. The operational research can also be framed within TB grants from the Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund), following confirmation by WHO that the country meets the above listed criteria. The following countries are implementing shortened regimens under the WHO-supported framework: Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Côte d'Ivoire, Democratic Republic of the Congo, Guinea, Lao People's Democratic Republic, Niger, the Philippines, Rwanda, Senegal, Swaziland and Uzbekistan.⁴¹

3.3.2 Evolving regulatory landscape for new medicines: compassionate use, registration on Phase IIb data

Requirements for regulatory approval for TB medicines are not harmonized across SRAs. For example, the EMA and United States Food and Drug Administration (US FDA) have different requirements for investigation of medicines in children, efficacy

endpoints for late-stage clinical trials, and required follow-up duration. Lack of regulatory harmonization in the approval process for new TB medicines can result in parallel applications with unpredictable outcomes, even within countries that are members of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). Furthermore, regulators in non-ICH countries may not be equipped to introduce NCEs that have been registered in ICH countries based on Phase II clinical data, in a framework called 'conditional approval' or 'accelerated approval'. Many countries do not provide a regulatory framework on compassionate use, which would permit the use of an experimental drug for patients who are excluded from clinical trials and for whom registered medicines no longer constitute effective treatment options. In the field of TB, compassionate use has been requested and advocated for XDR-TB patients, for whom the current cure rate is only 16 percent with existing registered medicines. Few countries have established the legal framework for a compassionate use scheme to use bedaquiline. For NCEs – such as bedaquiline and delamanid, both approved under accelerated mechanisms by SRAs with only phase II data – approval for use in other countries may be difficult and the medicine may instead be authorized for use through waivers for small cohorts of patients.

The US FDA has agreed with the manufacturer of bedaquiline that the medicine should be evaluated in a shorter regimen trial in Phase III rather than proceeding to assess bedaquiline as an additional drug in the current WHO-recommended 24-month regimen, adding an additional regulatory complexity. This approach has attracted some criticism for a perceived lack of involvement of the TB-affected community in the definition of priority research, also raising some doubt about the capacity of the new arms in the STREAM trial to generate the information required on the safety of bedaquiline.⁴² Another regulatory challenge may concern the evaluation of other NCEs, such as pretomanid, that are under investigation as part of totally new regimens. The registration of such NCEs should be made for use in the trialled

regimen not as a standalone medicine, ideally leading to registration of fixed-dose combinations.

3.4 Diagnostics

Only 64 percent of the estimated nine million incident TB cases in 2013 were diagnosed and notified to national TB programmes, with less than five percent of notified TB cases being tested for drug resistance. Improving the performance and availability of diagnosis is key to reducing global morbidity and mortality from TB. In addition to detecting TB infection, patients need to be examined to see if they have resistant forms of the disease.

Since 2007, WHO has endorsed several diagnostic tools and approaches, including light-emitting diode (LED) fluorescence microscopy, culture and DST methods, and two NAA-based tests. There is real potential for an imminent and dramatic shift in TB diagnosis through the introduction of new diagnostic tools. As discussed, TB treatments will undergo significant revision in the next five years, and it is difficult to predict the future needs for detecting MDR-TB and XDR-TB. If new, shorter and standardized treatment regimens prove effective in both MDR-TB and XDR-TB, the need to further invest in diagnostic technologies able to define the resistance profile for other second-line drugs beyond rifampicine and isoniazid will decrease. After establishing a blueprint for the development of TB diagnostics, WHO set TPPs for development of essential TB diagnostic tests (see section 3.4.4).⁴³

In 2015, more than 80 diagnostic companies and test developers work on TB diagnostic technologies. A UNITAID survey published in September 2014 identified over 190 products, of which some 140 were marketed and over 40 were in development. Multi-national pharmaceutical companies are increasingly interested in TB diagnostics. Companies are often secretive about products under development, although in some cases it is possible to source related corporate information. A major constraint on the

impact of new technologies is the uneven capacity to evaluate their performance in field conditions and to generate evidence for allowing WHO to review and make a corresponding policy recommendation (see section 3.4.3). The pipeline is replete with molecular diagnostics but remains lean in relation to biomarker-based POC tests and DST, although more products are now reported to be under development in these two areas. Next generation genome sequencing methods are also under development and appear to represent a new frontier in TB diagnosis and treatment (see section 3.4.5). Research is increasing toward diagnosis of latent TB and its correlation with immunity (see section 3.6).⁴⁴

The TPPs established by WHO should drive diagnostic tool development and the related funding. Major alignment of TB diagnostics development and new TB treatment regimens is also called upon for streamlining the TB diagnostic tool pipeline.⁴⁵

3.4.1 Nucleic acid amplification tests for tuberculosis diagnosis

There has been progress in the development of TB diagnostics, especially in the field of nucleic acid amplification (NAA) tests. Several products are commercially available (see annex 6), but only two have been endorsed by WHO: version 1 of GenoType MTBDRplus (Hain Lifescience, Germany) in 2008; and Xpert® MTB/RIF assay on the GeneXpert system (Cepheid Inc., United States). Endorsed by WHO in 2010, the GeneXpert assay is implemented in over 108 countries and it is considered a major revolution in TB diagnosis, allowing detection of rifampicine resistance in less than two hours at the district and peripheral levels. A new version of the test (Xpert® MTB/RIF Ultra) will be evaluated by WHO in 2015. For more details on GeneXpert, see annex 3. In 2013, WHO evaluated two NAA-based TB tests – the TB-LAMP (Eiken Chemical Co., Japan) and Genotype MTBDRsl (Hain Lifescience, Germany) – but did not endorse them. Both tests are undergoing additional field demonstration studies to generate evidence with a view to WHO endorsement (see annex 3).

Several additional NAA-based assays for TB are commercialized (see annex 5 for a non-exhaustive list) and a number of NAA pipeline products are under development to offer an alternative to Xpert MTB/RIF at the district level (see annex 6 for a non-exhaustive list). During 2014 and 2015, ten other companies were understood to be developing NAA-based products for TB diagnosis. Some of the products under development will provide an alternative to existing commercial products but in fully-integrated systems, with reduced time-to-result than GeneXpert, at a similar or lower cost. Others are being developed for performance in a battery-run system, providing a major advantage for deployment at the peripheral level.^{46,47} A number of these approaches are being developed for diagnosis of other diseases such as HIV, hepatitis C virus, human papilloma virus and other sexually-transmitted infections, dengue and malaria.

As of 2015, three NAA-based diagnostics were undergoing evaluation studies: Genedrive (Epistem, United Kingdom), NATEasy TB Diagnostic Kit (Ustar Biotechnologies, China) and TrueNAT MTB (Molbio Diagnostics, India). Epistem is engaging with several stakeholders for clinical validation studies, Molbio will receive support for clinical validation studies from the Foundation for Innovative New Diagnostics (FIND).

Among new, fully-integrated technologies, the Alere q (Alere, United States), Wave80 Biosciences (United States) and the Northwestern Global Health Foundation (NWGHF) products for TB diagnosis are anticipated for market release in 2016, although timelines could be longer. With few exceptions, such as Alere, many of the newer NAA diagnostic developers are being developed by small companies or academic groups. Among the products under development, Alere q seems to be the most promising following funding by BMGF (US\$21.6 million) to develop a POC diagnostic test requiring minimal inputs and with a test completion time of less than 30 minutes.⁴⁶ The company disclosed entry of Alere q in clinical trials for TB detection in 2015.⁴⁸

The impact of new NAA-based tests on improved TB case detection (or DST screening) before 2020 is expected to be limited despite the wealth of new diagnostic tools in development. Commercialization of new technologies needs to be followed by a generation of evidence for their use in resource-limited settings in order to be endorsed by WHO (see section 3.4.3). A new diagnostic should present advantages over GeneXpert in terms of robustness and options for use at the peripheral level.

Consideration for NAA-based diagnosis of XDR-TB. For medicines other than rifampicine, the correlation between gene mutations and expression of resistance is still being established. As a result, any diagnostic tool aimed at diagnosing XDR-TB cannot currently support clinical decision-making. Basic research is still required to identify gene mutations that lead to XDR-TB, and which can predict correlations with drug sensitivity. Some experts call for the creation of a database of phenotypic and genotypic testing results, to support advancement in identification of resistance to fluoroquinolones and injectable medicines, and subsequently to develop an NAA-based diagnostic tool of utility in programmatic algorithms.⁴⁹

3.4.2 Pipeline of point-of-care and drug susceptibility testing

The need for a POC test: While the TB diagnostic field has yielded considerable progress recently, more innovation is needed and anticipated. The level of infrastructure required for use of existing tests remains significant, which challenges decentralization efforts in many countries. There is a need for less sophisticated and more robust technology and instrumentation. The ideal test would be a biomarker-based, instrument-free RDT requiring minimal instrumentation that is suitable for implementation in the most peripheral settings (e.g. rural health centres or mobile clinics). WHO reiterated and defined the need for an innovative POC test that is able to detect active TB in adults and children, using specimens other than sputum

to facilitate detection of extrapulmonary and TB in a person living with HIV (see section 3.4.4).

POC tests pipeline: A few products are under development as POCTB diagnostics, using antibodies detected in blood, enzymes in sputum samples and volatile organic compounds exhaled during active pulmonary TB. These tests are required to diagnose TB at the peripheral level, with no intent to distinguish the TB resistance profile. A few examples have been listed in annex 7. The research for a POC test based on a biomarker is currently the focus of a number of companies and other research groups. Very little data on performance of newly-identified biomarkers is reaching the public domain, and so any assessment of whether these products hold promise is uncertain at best. One biomarker-based test is in the market, though its applicability is very limited. Alere Determine TB-LAM (Alere, United States) is a lateral flow urine test that detects TB protein among adults living with HIV who have a CD4 count below 50. This niche test is already commercialized, although few studies have been undertaken to validate its performance in field conditions. In May 2015, WHO reviewed current evidence that may lead to a corresponding policy recommendation.

Market estimates for POC TB tests: The TB diagnostic market is evolving with a number of companies

investing significantly. Work is ongoing to estimate potential markets for various diagnostic tests at different levels of the health system and the current TB diagnostic algorithm. For a POC test to substitute microscopy, the conservative estimate based on the current public sector market for smear microscopy is \$109 million per year. For NAA-based at a hypothetical cost of \$5, it is estimated that the market size could be at least 30.8 million tests with a potential market value of at least \$54 million per year. Several of the 22 TB-prevalent countries have a sizeable or even dominant private sector (e.g. Bangladesh, Cambodia, India, Indonesia, Nigeria, Pakistan, the Philippines and Uganda).⁵⁰

New DST assays: There is increased interest in developing better, broader and more rapid DST approaches to guide the rational use of medicines and regimens. Next generation DSTs will be easier to perform and with shorter time to result than the current 'gold standards' of liquid or solid conventional culture. They are essential for determining the complete resistance profile, and hence treatment regimen, for individual TB cases. A few examples are also listed in annex 8. WHO plans to evaluate new DST methods (genotypic and phenotypic) during the first quarter of 2016.

Table 5. WHO endorsement status and pipeline for new tuberculosis diagnostic tools

Test	Developer(s), Country	Type	Intended setting / function	WHO endorsement status
GenoType MTBDRplus	Hain Lifescience, Germany, in development with the Global Consortium for DR-TB Diagnostics	NAA: LPA (PCR)	Reference/MDR-TB detection	Version 1.0: WHO endorsed in 2007. (Version 2.0 not endorsed)
GeneXpert MTB/RIF	Cepheid Inc., US	NAA: Real-time PCR for TB and rifampicin resistance (1.5 h)	Reference/MDR-TB detection	WHO endorsed in 2010 and 2013. The new version MTB/RIF Ultra is planned for review in 2015.
GenoType MTBDRsl LPA, second-line	Hain Lifescience, Germany, in development with FIND	NAA: LPA for genetic mutations associated with resistance to fluoroquinolones and injectables (Am/Km/Cm)	Reference/MDR-TB and XDR-TB detection	WHO reviewed, but not endorsed, in 2013. Second review planned for new version in Q1 2016.
Loopamp TB Detection	Eiken, Japan, in collaboration with FIND	NAA: Loop-mediated isothermal amplification (LAMP) for TB (2h)	District/DS-TB detection	WHO reviewed, but not endorsed, in 2013. Second review in process.

Test	Developer(s), Country	Type	Intended setting / function	WHO endorsement status
Alere Determine TB-LAM	Alere, US and Japan, in collaboration with FIND	POC: Lateral flow urine test	Peripheral/ DS-TB detection in HIV patients with CD4<50	WHO reviewed in May 2015, policy recommendation to be issued by Q4 2015
Alere q	Alere, US, with BMGF funds	NAA: Real-time PCR for TB and XDR-TB resistance (20–40 min)	District/ XDR-TB detection	Planned for WHO review in 2016

3.4.3 Pathway to generate evidence for WHO endorsement

The WHO endorsement process guides countries, particularly those with low regulatory capacity, in the selection and use of reliable diagnostic technologies and tools, in the context of their specific health system needs. WHO endorsement is also a requirement for entry into many donor-funded programmes. Generating the required evidence appears to be a major constraint to reaching endorsement by WHO. The endorsement pathway established for GeneXpert should be regarded as a precedent and a model for endorsement of further diagnostics in the pipeline. The pathway included piloting of the candidate test in several countries and settings (i.e. central to peripheral level) in order to generate evidence about suitability and reliability of its results under field conditions. In the case of GeneXpert, this piloting and validation phase was managed by FIND. A piloting and validation phase led by an independent organization other than the commercial company or academic group developing the diagnostic test is regarded as a necessary step for WHO endorsement.⁵¹ Several new products are either commercialized or under development, but small companies developing such tools cannot afford to invest and perform studies needed to create the evidence base for endorsement by WHO. One of the key steps to progressing the diagnostic pipeline seems to be the identification of promising candidates, and the provision of financial support for the evaluation and field studies needed to generate such evidence.⁵²

3.4.4 Priorities and target product profiles for tuberculosis diagnostics

WHO convened a meeting in April 2014 to determine the priorities for research in the TB diagnostics field. The meeting participants reviewed the TPPs initially elaborated by FIND and McGill University (Montreal, Canada). Four diagnostic tests have been prioritized by WHO for development:

- Rapid biomarker-based instrument-free POC test for non-sputum samples (that can also detect childhood and extrapulmonary TB).
- Rapid, sputum-based, cartridge-based, molecular POC test for use by microscopy centres (with the option of add-on DST option/cartridge).
- Triage/screening test for those seeking cure.
- Centralized, high-throughput DST (incorporating new drugs to support the roll-out of new TB regimens in the post-2014 period).^{53,45}

3.4.5 Whole-genome sequencing for drug resistant tuberculosis surveillance and diagnosis

One area highlighted in several recent reports as a possible next frontier for TB diagnosis, is whole-genome sequencing (WGS). This technology is already used at reference level for surveillance purposes in an increasing number of countries, and in a few industrialized countries it is also used for management of XDR-TB. Current technologies available from the companies Illumina, Oxford Nanopore Technologies, Life Technologies Incorporated and Roche can be used for WGS for TB. If the technology can be developed for use at the peripheral level and made affordable, WGS has the potential to help guide clinicians in the selection of regimens to which a patient's TB organism is susceptible. WHO foresees that gene/

genome sequencing may entirely replace phenotypic DST in surveillance of DR-TB in the coming years. A WHO expert meeting is planned at the end of 2015 to evaluate the role of gene sequencing for surveillance and diagnosis of DR-TB. As highlighted in section 3.4.1, additional basic scientific research is needed to determine the mechanisms of resistance and the spectrum of genes determining resistance to TB drugs.⁵⁴

3.5 Vaccines

The bacille Calmette-Guérin (BCG) vaccine, launched in 1935, remains the only existing vaccine for TB and it is a part of the expanded programme of immunization in countries with high prevalence of the disease. The BCG vaccine has a documented protective effect against TB meningitis and disseminated TB in children, but it does not prevent primary infection and, more importantly, does not prevent reactivation of latent pulmonary infection, the principal source of TB spread in the community. While a number of vaccines are under development to provide better immunity than BCG, research is ongoing to study the BCG conferred immunity in different age groups through the trials for new candidate vaccines.

Types of vaccines

Based on the natural history of TB in humans, TB vaccine research can be framed by the following immunization strategies:

- **Pre-exposure TB preventive vaccines:** Intended for use in newborns or young infants to replace or amplify BCG before exposure to TB. These vaccines are intended to prevent TB in people who have not been infected with *Mycobacterium tuberculosis*. Pre-exposure TB vaccine candidates can be categorized as:
 - ▶ **Prime:** Replace BCG with either recombinant BCG or genetically attenuated *M. tuberculosis* vaccines with higher protective efficacy.
 - ▶ **Boost:** Boost the limited immunity conferred by BCG (or alternative prime vaccines) using either viral-vectored or adjuvanted sub-unit

vaccines, administered as boosters to a BCG prime in infancy or in adolescence when BCG protection begins to dissipate.

- **Post-exposure TB preventive vaccines:** Given post-infancy, typically to schoolchildren, adolescents or adults, who have either been vaccinated or latently infected with the TB bacteria or both; these vaccines reduce progression to active disease.
- **Therapeutic vaccines (immunotherapeutic):** These vaccines are given to individuals with active TB in conjunction with TB drug therapy with the aim of shortening the duration of the drug therapy.

Status of the TB vaccine pipeline: Despite the plethora of registered and planned trials (see annex 8), the current vaccines pipeline will not result in a new vaccine reaching the market by 2020. It is believed that a new vaccine will not be marketed before 2025. The prospects for a better pre-exposure prevention vaccine and/or a therapeutic vaccine are very limited. The two immunotherapeutic vaccines currently in Phase III trials may not be suitable candidates for a policy recommendation by WHO based on proof of concept evidence gathered by a 2010 Cochrane review.⁵⁵ Furthermore, compliance with good clinical practices and review of trials data by international experts should be performed. The *M. vaccae* vaccine, already licensed in China for immunotherapy is undergoing Phase III to assess its effectiveness as a boost vaccine. Results will be available in the second half of 2016. Of the vaccines that have undergone Phase II trial, the MVA85A/AERAS-485 has completed Phase II in children, with negative results.⁵⁶ Similarly, based on Phase IIa results, the Crucell Ad35 vaccine will not progress further in the vaccine pipeline as a stand-alone antigen. The M72+AS01/GSK 692342 has started Phase IIb, which will last around four years and will need to enrol approximately 4,000 patients. VVPM 1002 is planned to start a Phase IIb trial.

Need for basic research: In order to develop a viable TB vaccine pipeline for more efficient prime and boost pre-exposure vaccines – and which might also target post-infection – current TB vaccine research models should be reviewed. More investment is required

for basic research into biomarkers that predict immune responses and for establishing an adapted and harmonized framework for TB vaccine clinical trials. Biomarkers of protective immunity against TB are urgently needed to reduce the cost, time and uncertainty of advancing vaccine candidates through the pipeline. Validated biomarkers are needed to support the determination of efficacy of vaccine candidates at earlier stages and thus improve the selection of candidates for expensive late-phase trials.⁵⁷ The negative results of MVA85A highlighted another need: that of investing in identifying an animal model that can better predict clinical outcomes.⁵⁸

The post-MVA85A AERAS strategy: The disappointing outcome of the MVA85A/AERAS-485 Phase II trial, released in February 2013, has led other vaccine developers to put trial plans on hold and/or to review their research and clinical development strategies. This may also support further collaboration and coordination around TB vaccine research and development approaches. New developments include assessment of vaccine candidates for prevention of infection and prevention of recurrence in patients who were already treated for drug-sensitive TB.⁵⁹ These developments represent two different approaches. Using the prevention of infection approach is expected to reduce the cost, length and size of trials. The trials will also be used to collect data and refine interferon gamma release assays technologies. A Phase II trial using the prevention of infection paradigm has been started by Aeras and partners and will be completed in two years. It will assess the Hybrid 4 candidate vaccine and BCG in TB-naïve adolescents. This trial will also generate data on the usefulness of an existing BCG vaccine as a boost in older recipients. A Phase II trial for prevention of TB recurrence will assess Hybrid 56. The trial started in early 2015 and is expected to take three years. Potential predictive biomarkers of vaccine capacity to prevent infection and recurrence of disease will be researched through extensive screening of blood samples. Similarly, the M72+AS01 Phase II trial will collect blood samples to generate data for biomarker research.

Regulation: Regulatory requirements have not yet been highlighted as a challenge, although no vaccine candidate has reached Phase III for submission to an SRA.

Coordination: On 27 April 2012, Aeras and the Tuberculosis Vaccine Initiative (TBVI) signed a memorandum of understanding to enhance and strengthen collaborative efforts to advance the world's most promising TB vaccines. TBVI, through the NEWTBVAC, a consortium of 35 laboratories and Aeras with EDCTP, are developing a new governance framework, which will provide a matrix process for managing complex portfolios using decision points to advance candidates in a cost-effective manner. The European Commission, European Investment Bank (EIB) and BMGF are supporting strategic coordination on TB vaccine development through a series of meetings involving funders, researchers and developers.⁶⁰ The Global Forum on TB Vaccines, organized by Aeras and TBVI, convened for a fourth time, in Shanghai, China, from 21–24 April 2015. The Forum provides a platform for discussion on research and development of new vaccines and presentation of new approaches, including governance systems.⁶¹

Funding share among vaccine immunization strategies: The majority of TB vaccine resources are currently assigned to the development of boost vaccines. Funds allocated to developing prime and immunotherapeutic vaccines is limited. Research for vaccines that target latent TB infection is almost non-existent.

The WHO Global Vaccine Action Plan: setting targets for vaccine efficacy for HIV, TB and Malaria

In May 2012, the World Health Assembly endorsed the Global Vaccine Action Plan, a framework to achieve the 'Decade of Vaccines' vision by delivering universal access to immunization. Among others, the framework advocates for the introduction of newly available life-saving vaccines and technologies and suggests key targets for further research and development. Key indicators of progress towards this strategic objective include proof of concept for a vaccine that shows greater or equal to 75 percent efficacy for HIV (human immunodeficiency virus), tuberculosis or malaria.⁶²

3.6 Investment on basic science: biomarkers

Investment is urgently needed in basic science to identify and validate biomarkers as surrogate clinical endpoints to help shorten and simplify clinical trials of new drugs, regimens and vaccines.⁶³ Biomarkers are required that distinguish between people who: a) are infected and/or cleared of mycobacteria; b) are infected but will not develop the disease; and c) will develop active TB. Such biomarkers will support programmatic/clinical choices, in terms of chemoprophylaxis, treatment and vaccination approaches. It is estimated that one third of the world population has been infected with TB, a figure that gives the scale of potential interest in the diagnostic field to detect latent TB. Groups working on biomarkers are seeking intellectual property protection. So far, few donors have invested in this area. In 2012, the BMGF invested \$7.7 million and the Canadian Institutes of Health Research invested \$374,493 in a portfolio of 10 grants focused on TB diagnostic biomarkers that may result in a POC test.^{64,65} The NIAID has committed \$10 million for research on the biology of *M. tuberculosis* infection and TB disease.³¹ Biobanks of specimens from TB patients with adequate follow-up to determine long-term treatment outcomes are critical for biomarker research.

SECTION 4

NEGLECTED TROPICAL DISEASES –
HUMAN AFRICAN TRYPANOSOMIASIS,
LEISHMANIASIS AND CHAGAS DISEASE



SECTION 4

NEGLECTED TROPICAL DISEASES – HUMAN AFRICAN TRYPANOSOMIASIS, LEISHMANIASIS AND CHAGAS DISEASE

This report reviews the current product pipelines related to the three NTDs attributable to kinetoplastid parasites: human African trypanosomiasis (HAT), leishmaniasis and Chagas disease. While the focus is primarily on the innovative products in the pipeline, the current challenges of diagnosis and treatment for these diseases are also considered. Access to current WHO-recommended treatments for Chagas disease and leishmaniasis is heavily influenced by the absence of an international governance system to ensure the production and uninterrupted supply of quality-assured single-source medicines. For HAT, a system exists that relies on well-established drug donations from pharmaceutical companies and a supply system managed through WHO. With few exceptions, market volumes are normally not the driver of innovation for this class of diseases, where the ultimate goal is to prevent, diagnose and treat, but also to eliminate these diseases. A number of NCEs are being studied, with one in Phase III for HAT. Optimization of treatment for Chagas disease and visceral leishmaniasis (VL) with known medicines is also sought while NCEs are currently undergoing Phase II trials. There is an urgent need to address cutaneous, mucosal and post-kala-azar dermal leishmaniasis (PKDL) treatment. On the diagnostic front, rapid diagnostic tests have been developed for HAT, Chagas disease and VL. Other challenges exist for development of a biomarker-based test of cure for Chagas disease, PKDL, VL and HAT. While companies and PPPs develop NAA technology for kinetoplastid-caused diseases, the role of NAA methods has yet to be defined. Investments in NAA tests in the absence

of guidance from WHO may result in diversion of already lean resources for interventions and research.

4.1 Human African trypanosomiasis: Background

There are two forms of HAT, both transmitted by tsetse flies. *Trypanosoma brucei gambiense* is found in West and Central Africa and accounts for 97 percent of all HAT cases, while *T. brucei rhodesiense* is found in Eastern and Southern Africa, mainly around natural protected areas. HAT is progressing towards elimination. *T. b. gambiense* HAT cases have decreased by over 75 percent in the past decade, reaching the lowest number of cases in 2014 with 3,796 patients reported.^{66,67} Around 100 cases of *T. b. rhodesiense* HAT are reported globally each year. There have been innovations in the field of medicines and diagnostics, which will be key for achieving HAT elimination.^{68,69,70,71}

One new chemical entity (fexinidazole) is progressing through a Phase III trial and is expected to enter the market by 2020. Fexinidazole constitutes a major improvement in the way HAT is treated: It will be administered orally and is potentially effective in both stage 1 and stage 2 of the disease, thus eliminating the need to conduct an invasive lumbar puncture in order to determine the disease stage.

The introduction of rapid serodiagnostic tests represents progress on the diagnostic front. Second generation tests are expected to enter the market by

2017. Among parasitological confirmatory tests, it will be important to secure the production and affordability of the mini Anion Exchange Centrifugation technique (mAECT). The role of NAA-based technologies in NTD diagnosis is yet to be established.

No vaccine is foreseen for HAT, given that the disease is progressing towards elimination and that the parasite's elaborate mechanisms of immune evasion suggest that development of vaccines is unfeasible.⁷¹

4.1.1 New human African trypanosomiasis treatments

Treatment of stage 2 *T. b. gambiense* HAT has improved since the introduction of nifurtimox–eflornithine combination therapy (NECT), a co-administration of nifurtimox, which is given orally, and eflornithine, which is given via intravenous infusion. Treatment with NECT still requires hospitalization and multiple intravenous infusions. The goal of current research and development efforts is to develop an oral treatment that is effective for both stages of the disease. Treatment of stage 2 *T. b. rhodesiense* HAT is performed with melarsoprol, an arsenic-based compound, which remains the only available and WHO-recommended treatment even though it causes five to ten percent mortality due to unpredictable encephalopathy. There are two NCEs under development for HAT. Fexinidazole has reached a Phase III clinical trial; submission for evaluation under the EMA Article 58 procedure is planned for 2017. Fexinidazole is administered orally and potentially can be effective on both stages of HAT disease, greatly simplifying the diagnostic and treatment algorithm as well as the requirements for the supply system. SCYX-7158 is planned for a Phase II/III trial in 2016. Details of NCEs under development for HAT treatment are described in annex 9.

Table 6. Human African trypanosomiasis new chemical entities under Phase II/III

New chemical entity	Sponsors	Status
Fexinidazole	DNDi with Sanofi	Phase II/III

4.1.2 Human African trypanosomiasis diagnostics

The current algorithm for HAT diagnosis is based on the use of a screening test: the card agglutination test for trypanosomiasis (CATT) performed by mobile teams or RDTs. A positive screening test is followed by a confirmatory test to detect the parasites in blood or lymph node aspirates. Lumbar puncture is subsequently used for defining the stage of HAT disease.

Important steps in the diagnosis of *T. b. gambiense* HAT since 2012 include the availability of RDTs that increase the integration of HAT control into the broader health system. By comparison, there is less progress in the screening of *T. b. rhodesiense* HAT. WHO defines the development of RDTs for *T. b. rhodesiense* HAT as a specific need. Despite the 100 cases annually, misdiagnosis is higher for this form of the disease and the consequences of misdiagnosis are rapidly fatal. Other experts are of the view that the currently available diagnostics are sufficient, and that interventions should rather be devoted to creating awareness of the disease in game parks, where *T. b. rhodesiense* HAT foci exist.

This section also reviews the need to define the process for endorsing new diagnostics and the establishment of priorities in the diagnostic field to meet the elimination target.

Table 7. Human African Trypanosomiasis Rapid serodiagnostic tests under introduction in countries

RDT commercial name	Developer(s), country	Type	Intended setting / function	WHO endorsement status
SD Bioline HAT	Standard Diagnostics, Inc., Republic of Korea, with support from FIND and BMGF	RDT native antigens	Peripheral /screening	WHO introduction phase in countries
HAT Sero-K-SeT	Coris BioConcept, Belgium, with support from NIDIAG (European research network supported by the EC) and ITG	RDT native antigens	Peripheral /screening	WHO introduction phase in countries

Rapid serodiagnostic tests

The two rapid serodiagnostic tests (i.e. SD Bioline HAT, Standard Diagnostics, Republic of Korea; HAT Sero-K-SeT, Coris BioConcept, Belgium) that have been developed for *T. b. gambiense* HAT use the same native antigens, both generated using pathogenic trypanosomes and provided by the Institute of Tropical Medicine (ITG) in Antwerp, Belgium. They can be predictive of suspected disease, which then requires confirmatory parasitological tests. The tests are particularly useful where mobile clinics deploying CATT are not able to operate, such as conflict zones, or where low prevalence of the disease makes mobile clinics ineffective. The CATT (EUR 0.5/test) has advantages for active screening by mobile clinics, as up to 50 tests can be performed at once, while RDTs will be used increasingly in passive screening at primary health care centres. In areas where the prevalence is below 0.5 percent, the use of RDTs is recommended for surveillance purposes. Both of the current RDTs can be used outside of a cold chain, and up to 40°C. Details on the RDTs are included in annex 9.

WHO is currently implementing both tests in national control programmes in several countries. In May 2015, WHO convened a meeting to discuss current advances on HAT diagnostics (which included both tests) and RDTs were considered as a useful tool for passive screening. The WHO meeting concluded, among others, that the use of RDTs for mass active screening presents logistical and methodological challenges. WHO does not yet have a recommendation on the use of the two specific RDT products. As of June 2015, 16 of the 24 endemic countries were using RDTs. As with all other HAT diagnostic tests, countries are not purchasing RDTs; donations are used for the roll-out in national control programmes.

Second-generation RDTs

Second-generation tests based on recombinant antigens are under development. The antigens selected for these tests will likely vary, generating RDTs with variable specificity/sensitivity. FIND and ITG are the two main groups working on second-generation RDTs. The tests are expected to enter the market by 2018.⁷² Their cost is expected to be lower than first-generation tests as a result of using recombinant antigens. This should translate into lower market prices for the new RDTs. FIND foresees that its second-generation RDT will be developed, evaluated and marketed by the end of 2015.

RDT for differentiation of malaria and HAT: An additional RDT is under development by FIND and Standard Diagnostics (Republic of Korea) to support the differential diagnosis of malaria and HAT. It is intended for use in countries and areas with low HAT transmission where febrile events can be caused by HAT but may be confused with malaria at the primary health care level. The product will enter clinical trials in the second half of 2015 and is expected to enter the market by 2016.⁷³

Review and endorsement of RDTs: Second-generation RDTs will need to undergo laboratory testing using a WHO specimen blood bank. The aim is to select RDTs that have at least equal sensitivity/specificity to CATT.

Both ITG and FIND, the two main groups working on RDTs, have identified the need to have new diagnostic technologies, including RDTs, reviewed and endorsed by WHO. The system for evaluation of new diagnostic technologies currently in place in WHO consists of the review of evidence from key stakeholders in order to issue a recommendation

on the use of the diagnostic tool. Such a system, however, does not provide guidance on the evidence base required to achieve WHO endorsement. Studies for generating evidence of effectiveness are being designed by the same organizations involved in the development of diagnostic tools, often based on experience acquired with HAT and other diseases. Being based on the same antigens, major differences between the two first-generation RDTs were not expected. The performance of second-generation RDTs based on different antigens is expected to vary, thus the need for an evaluation pathway for their introduction in countries.

Research priorities for human African trypanosomiasis confirmatory diagnostic tests

There is an increased interest by companies and research laboratories to develop and commercialize NAA-based diagnostics for HAT, with several publications available in this field.^{68,71} The investment required for application of NAA-based technologies for HAT is questioned by academic experts, MSF and other key actors involved in HAT diagnosis and treatment, since the technologies would not represent any advancement in comparison to existing parasitological tests, which, regardless of the technique, require a considerable amount of blood (i.e. 1–10 ml). NAA technologies are therefore not expected to present higher performance than existing parasitological confirmatory tests, although some existing PCR techniques used at reference laboratories may have a value for surveillance purposes. Priority should rather be assigned to secure production, affordability and availability of the parasitological confirmatory test mAECT, developed by the Institut National de Recherche Biomédicale (INRB), in the Democratic Republic of the Congo, which is the most sensitive confirmatory method. Experts have also urged consideration be given to improved microscopy. See annex 9 for more information on mAECT and improved microscopy for HAT.

Test of cure for human African trypanosomiasis

Research is ongoing to identify a biomarker in blood, saliva or urine that is predictive of the presence of the parasite after treatment, circumventing the need for lumbar puncture to determine the stage of the disease and/or for follow-up in clinical trials. If a reliable biomarker is identified, FIND plans to develop a test of cure for HAT. If available, such a test could also be used in control programmes, although it is not identified by WHO as a priority. The need to perform lumbar puncture after treatment administration has been revised and is no longer recommended by WHO. A test for HAT cure remains a priority for performing clinical trials and reducing follow-up periods.

4.2 Leishmaniasis: Background

Leishmaniasis is caused by protozoal parasites from over 20 species of *Leishmania*. It is transmitted to humans by the bite of infected female phlebotomine sandflies. There are three main forms of leishmaniasis: visceral leishmaniasis (VL), also known as kala-azar; cutaneous leishmaniasis (CL); and mucosal leishmaniasis (ML). Of special interest is post-kala-azar dermal leishmaniasis (PKDL), which is a dermal sequela of VL that develops in some patients alongside, but more commonly after, apparent cure from VL. Highly endemic on the Indian sub-continent and in East Africa, VL, the fatal form of the disease, has been the focus of most research efforts and funding. An estimated 200,000 to 400,000 new cases of VL occur globally each year. Over 90 percent of new cases occur in six countries: Bangladesh, Brazil, Ethiopia, India, South Sudan and Sudan. Few NCEs have been studied and current research efforts focus on reducing the length and optimization of treatment with known medicines.

Although not fatal, PKDL is thought to be a reservoir for transmission of VL. WHO has set priorities for research on PKDL epidemiology, pathogenesis, diagnosis and treatment. These include: developing new diagnostic tests (antigen detection) and a

test of cure, which must be suitable for use in the field; randomized clinical trials of short-course regimens with existing medicines; and evaluation of immunotherapy (therapeutic vaccines) to be used with chemotherapy to modify the current treatment and to increase the cure rate.^{74,75}

CL and ML are considered the most neglected forms of the disease in terms of diagnosis and treatment, despite the estimated 0.7 million to 1.3 million new cases that occur each year. About 95 percent of CL cases occur in the Americas, the Mediterranean basin, the Middle East and Central Asia, though CL also occurs in West and East Africa. Almost 90 percent of ML cases occur in Bolivia, Brazil and Peru.⁷⁶ CL is classified as “Old World” CL (OWCL) (when occurring in Africa, Europe and the Middle East) and “New World” CL (NWCL) (when occurring in the Americas). A comprehensive mapping of research needs has yet to be undertaken for CL/ML. Section 4.2.2 describes the different types of treatment interventions: topical (pharmacological and non-pharmacological) and systemic that have been studied for CL. Some are advanced in the pipeline, but lack of funds not only freezes the progress of clinical trials but also affects further development and adaptation of new technologies.

Progress has been achieved in VL detection with the introduction of RDTs, but major gaps persist for diagnosis of all other forms.

Few candidate vaccines have been studied for the prevention of VL and CL and as an adjunct to chemotherapy of PKDL. No vaccine candidate will be marketed before 2020. Moreover, the lack of funds also constrains progress in testing vaccines conceived for preventive immunization strategies, which could have utility as immunomodulators and adjuncts to pharmacological interventions.

4.2.1 New treatments for visceral leishmaniasis

Despite progress achieved on VL treatment options in the Indian subcontinent, no ideal drugs are available that fulfil the major requirements for efficient anti-leishmanial therapy, including high efficacy, low toxicity, easy administration, low costs and avoiding occurrence of drug-resistant parasites.⁷⁷ Furthermore, no completely oral treatment for VL exists. Miltefosine, the only available oral medicine, is teratogenic and needs to be used in combination in order to prevent development of resistance. Liposomal amphotericin B is administered intravenously and must be stored below 25°C, making it more difficult to use in health centres. In East Africa, treatment is still based on pentavalent antimony (Sb^V), which is administered intravenously as sodium stibogluconate (SSG) or meglumine antimoniate in combination with paromomycin.^{78,79}

Only one NCE is in clinical development: fexinidazole, currently in Phase II. GSK decided not to progress further clinical development of sitamaquine, based on the results of the Phase IIb study completed in 2007.⁸⁰ Another compound, studied by DNDi and belonging to the oxaborole class, may enter in Phase I by 2016. Summary information on leishmaniasis product innovations, including new chemical entities, is provided in annex 10.

Table 8. Visceral leishmaniasis new chemical entities under Phase II/III

New chemical entity	Sponsors	Status
VL: Fexinidazole	DNDi	Phase II

The strategy highlighted by DNDi consists of developing a treatment based on two oral drugs, one candidate being miltefosine. Research is ongoing to review miltefosine dosage in children, which comprise the majority of VL patients. Pharmacokinetics studies to review the dose of miltefosine in children took place in Nepal and additional studies by DNDi have started in Kenya, Sudan and Uganda to define allometric dosage for children (based on weight, height and other parameters).

Table 9. Cutaneous leishmaniasis pharmacological treatments under Phase II/III trial

New chemical entity	Sponsors	Status
NWCL/OWCL: WR 279,396 (15 percent paromomycin + 0.5 percent gentamicin) topical cream	USAMRMC, in collaboration with WRAIR	Phase II/III
OWCL <i>L.tropica</i> : Liposomal meglumine antimoniate versus liposomal paromomycin (RCT), topical creams	Mashhad University, Teheran University, Islamic Republic of Iran	Phase II
NWCL: Anfoleish (3 percent amphotericin B) topical cream	DNDi PECET at the Universidad de Antioquia Medellín, Colombia; Humax Pharma, Colombia; Farmatech, Colombia	Phase Ib/II

Table 10. Cutaneous Leishmaniasis non-pharmacological treatment

Heat therapy device commercial name	Sponsors	Status
ThermoMed-TM device	Thermosurgery Technologies, Inc., US (WRAIR sponsored a Phase II trial)	Phase II concluded
HECT-CL	Tulane University, New Orleans, US	Phase I/II concluded

4.2.2 New treatments for cutaneous leishmaniasis

Very little progress has been made in the field of CL since 2005, as compared to VL, where treatment options based on combinations of known drugs have been made available. Research for optimization of CL treatment regimens is ongoing.

Cutaneous lesions are generally treated with Sb^V, either by local infiltration (OWCL) or given systemically (NWCL) for 20–28 days. Several different therapeutic interventions, including systemic and topical, pharmacological and non-pharmacological approaches (i.e. cryotherapy or thermotherapy), have been described. The level of evidence to discriminate among interventions is considered weak or very weak based on the very few appropriately designed and reported trials, and no gradient of recommendation was made by WHO for different options. CL treatment is complicated as different *Leishmania* sp. cause the cutaneous and mucosal forms of the disease with diverse severity in different geographical areas.

CL is not a life-threatening condition and the treatment decision is based on the risk–benefit ratio of the intervention for each patient with limited options. Toxic systemic treatments are still administered if the patient suffers from numerous, disfiguring face or complicated lesions, or if topical therapy is impossible or has been tried and failed.^{78,81,82}

Pharmacological and non-pharmacological interventions are under study. Immune modulators could also play a role combined with pharmacological interventions. More robust studies are needed to produce evidence aimed at improving or standardizing treatment options for CL. Furthermore, there is an urgent need to define treatment algorithms for CL with existing and possibly new treatments.

Pharmacological interventions

Among the interventions undergoing clinical trials, one NCE for systemic use (oleylphosphocholine) is planned for a Phase II trial and a few topical treatments are quite advanced in clinical development. WR 279,396 cream (Walter Reed Army Institute of Research (WRAIR), United States) has undergone Phase II and Phase III studies in several geographical areas; Anfoleish (DNDi) is ongoing Phase II for NWCL; and a nanoliposomal amphotericin B cream (University of Mashhad, Islamic Republic of Iran) is in Phase III. It should be noted that advancements in the field of CL are very slow and that study results can take years before being published, even when results are positive. See annex 10 for more information on the developmental status of these medicines.

Non-pharmacological interventions

The two non-pharmacological interventions used in CL are heat therapy and cryotherapy. Cryotherapy

with liquid nitrogen is used in several country protocols, though it has several limitations: multiple applications, lengthy protocols and risk of burns. Some 12 to 15 trials testing thermal therapy have been performed. Applying 30 seconds of heat produces an approximate 50–85 percent cure rate depending on the species and localization extension of skin ulcers.⁸³ Thermal therapy is easier to apply and two devices have been developed: Thermomed-TM (Thermosurgery Technologies, Inc., United States), whose high price halted its application in CL treatment, and HECT-CL (Tulane University, New Orleans, United States), a more recent low-cost tool. See annex 10 for more information on non-pharmacological technologies developed for CL.

Immune modulators

When CL lesions are located on the face, ears or hands or where they are present in large numbers, it may not be possible to treat locally. A pharmacological intervention coupled with an immunomodulator, to enhance the immune host response is, according to several experts, the ideal strategy to pursue (see section 4.2.6.). As an example, the CpG ODN (D35) (US FDA; Osaka University, Japan; DNDi) should be tested as an adjunct to chemotherapy for PKDL and complicated forms of CL. This project has been selected as part of the demonstration projects of the WHO Consultative Expert Working Group on research and development: financing and coordination demonstration projects.⁸⁴ With funding from DNDi, the CpG ODN (D35) project was initiated and in July 2015, the first award of funds were made for the demonstration studies.⁸⁵

Advancing research in cutaneous leishmaniasis treatment

Reviews of CL clinical studies have highlighted the lack of standards for both the conduct and analysis of results.^{86,87} This is a major problem to advance to evidence-based recommendations and to move away from sub-optimal and toxic treatment. Resources for CL research are limited and should not be used to perform clinical trials that do not meet international standards that allow for a comparison of results between interventions. Two articles have

been published to provide guidance for the design, conduct, analysis and reporting of CL clinical trials and therefore to assist WHO in the planning and prioritization of global strategies for related clinical research.^{88,89} As a result, the Special Programme for Training and Research in Tropical Diseases (TDR), in collaboration with DNDi and the Global Health Network at the University of Oxford (United Kingdom), is currently undertaking a consultative process to define an internationally recognized methodology for CL clinical trials that can be adopted by CL researchers worldwide.⁹⁰

For advancing development of topical CL treatments, greater understanding of skin physiology and the use of skin models is important as key steps before proceeding to clinical studies. Expanding screening of new compounds and adaptation to the specificities of CL is also vital, not least because extrapolating results from screening of compounds for VL do not necessarily yield to identification of lead agents against different species of *Leishmania*-causing CL. Screening is currently performed using only two *Leishmania sp.* No appropriate animal model is available for testing compounds for CL; there is need for validated models for CL caused by different species of *Leishmania*.⁹¹ The strategy for treatment and diagnosis should be focused on CL and not be opportunistically arising from VL investigations.

4.2.3 New treatments for post-kala-azar dermal leishmaniasis

Despite its role as a reservoir for VL disease, there are no promising NCEs under development for PKDL. A three-arm trial by DNDi is planned to start in 2016 in Bangladesh, India and Sudan using existing medicines (liposomal amphotericin B and miltefosine). A phase II trial concluded in 2006 using the first-generation vaccine (Alum-ALM + BCG) as an immunomodulator in addition to Sb^V produced encouraging results. A second-generation recombinant protein vaccine (LEISH-F2 + MPL-SE) trialled for PKDL failed to show a similar result as immunomodulator. Other trials are planned but funds are yet to be secured (see section 4.2.6.).

4.2.4 Visceral leishmaniasis diagnostics

Rapid diagnostic tests

RDTs detecting antibodies in serum were recently developed with antigens licensed by the Infectious Disease Research Institute (IDRI), based in Seattle, United States. A WHO evaluation of five commercialized RDTs was published in 2011 (see table A1 in annex 10). The WHO review found that sensitivity of RDTs varied for different regions. In Brazil and in East Africa, rK39-based RDTs perform better than rKE16-based RDTs, yet sensitivity is low (e.g. an estimated 70 percent in Sudan) and a better POC diagnostic is sought. The evaluated RDTs show high sensitivity and specificity in the Indian sub-continent, therefore representing a major improvement in diagnosis of the disease when combined with clinical evaluation. The WHO evaluation of the five available RDTs allows for a better understanding of the limits of performance of each test in different regions; this facilitates their implementation according to pre-defined acceptable limits of performance and within an appropriate diagnostic algorithm. The results of this evaluation are useful to guide procurement decisions. However, one test is not suited for field conditions as it requires cold chain. The WHO evaluation highlighted the need for better RDTs in East Africa and also for additional research into test performance among HIV-VL co-infected patients and in determining the performance of RDTs using whole blood (programmatically more convenient) rather than serum.⁹² The price of the existing RDTs varies between \$0.8– \$1.2 per test. From the outset, competition has allowed for market entry at an affordable price. The RDTs have been introduced in national control programmes since 2012 through WHO and national procurement schemes.

Under development: rK28 antigen-based RDTs are under development and evaluation by IDRI under the coordination of WHO/TDR. If rK28 RDTs are found to be sensitive and specific in East Africa and Latin America, they may enter the market before 2020 and be reviewed by WHO.

Urine-based antigen detection test

Another diagnostic concept is under development that detects antigens present in urine. IDRI and the London School of Hygiene and Tropical Medicine (LSHTM) are working in coordination on two projects to refine and develop this idea for a POC test.⁹³ FIND is also working on a test for detection of *Leishmania* sp. antigens in urine, which is currently undergoing clinical trial that is expected to be completed by 2017.⁹⁴ An antigen detecting test could meet several objectives: it would be used as an RDT for primary detection of VL, could potentially be used to diagnose PKDL, and might also be used as a test of cure, as the absence of antigen in urine might also confirm treatment efficacy.^{74,75}

Research on biomarkers for a test of cure

If patients treated for VL are suspected not to have responded to treatment or that relapse may have occurred, because antibody-based tests remain positive for a long time even after cure, they must undergo lymph node, bone marrow or spleen aspiration. These are invasive procedures that either lack sensitivity or carry significant risks. There is a need to develop a test for a leishmaniasis cure based on biomarkers. Basic research is ongoing in this field and results are expected by 2020, which will subsequently lead to the development of a test of cure.

Defining the role of nucleic acid amplification technologies

WHO has identified the need to define the appropriate use of NAA techniques for diagnosis of various leishmaniasis forms. A European multi-centre study is investigating molecular species differentiation in leishmaniasis diagnosis, and among other objectives, it aims at establishing and validating standards for NAA technologies.⁹⁵ NAA techniques could detect asymptomatic carriers, though its utility is not clear with the current treatment options, as their toxicity does not allow a "test and treat" approach.

4.2.5 Post-kala-azar dermal leishmaniasis and cutaneous leishmaniasis diagnostics

There has yet to be a comprehensive prioritization exercise to define diagnostics needs to guide researchers and manufacturers in the development of diagnostics for different forms of leishmaniasis. The need for a simple test for diagnosis of PKDL using detection of antigens has been highlighted. Paucity of parasites in some form of PKDL necessitates a sensitive test based on parasite antigens, since antibody tests post-VL cannot be used for diagnosis. There is no user-friendly and consistently reliable diagnostic test for PKDL, which is problematic because current treatments are long and toxic. In PKDL, quantitative PCR (qPCR) is under study as a diagnostic tool to confirm PKDL and as a potential test of cure.

Experts underline the need for a reliable diagnostic test for CL. Diagnosis is not complicated if laboratory capacity is available. In countries such as South Sudan or in refugee camps in the Middle East, where an increasing number of CL cases are found, parasitological confirmation using microscopy is difficult. A POC test would be important to support diagnosis in such resource-limited or emergency settings. The RDTs for CL should be specific for the species endemic in the area where the test will be used. Few RDTs for CL have been commercialized, but their performance in field conditions and in different geographical regions has not been evaluated.^{96,97}

4.2.6 Leishmaniasis vaccines and immunomodulators

A number of vaccines – including second- and third-generation vaccines based on recombinant proteins and deoxyribonucleic acid (DNA) constructs – have reached the clinical experimental stage. Table A2 in annex 10 summarizes the vaccines and their clinical phase of development. The majority of these studies were completed, but in only very few cases have results been published. For several vaccine candidates, clinical development appears to have stopped or been put on hold. No candidate vaccine appears to be ready for the market by 2020. The global

scientific community advocates for the development of a vaccine for different forms of leishmaniasis based on recent advances in vaccine technologies. Vaccine candidates developed for prophylaxis have been trialled for therapeutic use to reduce length of treatment, increase the cure rate or reduce drug dosage, especially for CL, ML and PDKL forms of the disease.^{98,99} Prophylactic vaccine development, particularly for VL, is expensive and requires long and complex studies enrolling large numbers of healthy volunteers and patients. Immunotherapeutic trials are far less complicated and require fewer subjects than prophylactic vaccines.

Reviewing the pipeline of leishmaniasis vaccines and immunomodulators: Only first-generation vaccines (killed parasites plus BCG as adjuvant (ALM+BCG)) have reached phase III trials with disappointing results for prevention of VL and CL. The killed parasites plus BCG and alum (Alum-ALM + BCG), showed encouraging results in phase II trials for prophylaxis of VL and as adjunct to chemotherapy of PKDL.^{99,100,101} Despite recommendations to expand trials examining the prophylactic and therapeutic effects for PKDL and VL, investments have yet to be made to pursue this possibility.¹⁰² Further studies were abandoned with the advent of second-generation vaccine candidates based on recombinant proteins, which unfortunately have proven not to be efficacious. Further development and investigation of killed parasite vaccines with new adjuvants may be justified, given the possibility of vaccine production at low cost and proven safety in some resource-limited countries. More recently, DNA-based vaccines have been developed using a new approach of selecting T-cell epitopes recognized by human cells.¹⁰³

A few promising new candidates, which are exploiting advances in the field of vaccine technology, are entering clinical development, including ChAd63-KH (Phase I, York Teaching Hospital, United Kingdom), MGN1331 (LEISHDNAVAX consortium), CpG ODN (D35) (US FDA, Osaka University (Osaka, Japan), DnDi) and KSAC and KSAC GLA-SE (IDRI).¹⁰⁴

Main players: The major donors for vaccine development have been the EU-7 Framework for preclinical development and BMGF for clinical development. The IDRI has been the main player in development of leishmaniasis vaccines. In July 2013, IDRI signed an agreement with Zydus Cadila (India) for a third-generation vaccine (KSAC GLA-SE), moving to a PPP for this product.¹⁰⁵

Coordination for leishmaniasis vaccine development: An in-depth review of approaches for development of prophylactic and therapeutic vaccines for different forms of leishmaniasis would be an important step for identifying goals and prioritizing candidate vaccines.

4.3 Chagas disease: Background

Eight million people worldwide are estimated to be infected with the Chagas disease causative agent *Trypanosoma cruzi*. Once confined to Latin America, Chagas disease has also spread to North America, Europe and a number of Western Pacific countries as a result of population movements. The global rate of Chagas disease infection detection is below 10 per cent, highlighting the critical need to improve diagnostic capacity. New or improved treatments are needed. The current treatment with benznidazole or nifurtimox takes 60 days and presents several adverse events.^{106,107} Research is ongoing for three NCEs, with two (posaconazole and E1224) likely to be further investigated as companion drugs to benznidazole and nifurtimox. One Phase II trial to assess efficacy of fexinidazole in Chagas disease began in June 2014. Research is also starting with the aim of optimizing benznidazole and nifurtimox treatment posologies.

On the diagnostic front, a review of several commercialized Chagas infection RDTs is aimed at the introduction and increased use of POC diagnosis, facilitating a major increase in detection capacity both in developing and developed countries. The ultimate goal is to define a diagnostic algorithm based on two RDTs, as adopted in other infections

such as HIV. There is an urgent need for a test of cure to determine if and when a patient treated for Chagas disease has been cured. Such a test is fundamental to progress in the research of improved Chagas disease treatments.

No vaccine candidate has reached the clinical stage, while preclinical research is ongoing.

4.3.1 Chagas disease NCEs

Two NCEs have been investigated for Chagas disease treatment: E1224 and posaconazole. Recently concluded Phase II clinical trials have not provided results to support further development of these NCEs as single agents for Chagas disease treatment. However, both drugs are likely to be further investigated as companion drugs for benznidazole. As a result of trials comparing these NCEs and benznidazole, increasing evidence has been generated on the use of benznidazole, a drug that at current dosages causes several adverse events. One additional drug, fexinidazole, will be tested for efficacy in Chagas disease. Much of the research on Chagas disease treatments appears to be undisclosed and additional NCEs that have not been reported in the public domain could be under clinical investigation.

The recent results of the RCT assessing posaconazole and benznidazole lend themselves to open up new strategies for advancing treatment for Chagas disease.^{108,109} Investigations should be made to assess different benznidazole posologies in the acute and chronic phases of the disease, alone and in combination with NCEs. Ideally, this should be trialled and validated in multi-centre trials covering various geographical regions, given the differences among those regions.¹⁰⁹ Among others, DNDi is planning trials looking at shortening benznidazole treatment and benznidazole combinations. Summary information on Chagas disease NCEs and the optimization of benznidazole is presented in annex 11.

Table 11. NCEs in Phase II/III for treatment of Chagas disease reported in the public domain.

New chemical entity	Sponsors	Status
E1224 (ravuconazole pro-drug)	DNDi with Eisai Co., Ltd., Japan	Phase II
Posaconazole	Merck & Co., Inc., US	Phase II
Fexinidazole	DNDi	Phase II

Companies are seeking orphan drug designation by the US FDA for benznidazole and nifurtimox. One designation for benznidazole was granted in February 2014 to Chemo Research SI (Spain). Two designations have been granted for nifurtimox, one to Bayer (Germany) in 2010 and one to MetronomX Therapeutics, LLC (United States) in 2013.¹¹⁰ Neither drug is US FDA-approved.

4.3.2 Chagas diagnostics

As noted, the global rate of Chagas disease detection is below 10 percent. There are good serological tests based on indirect haemagglutination, enzyme-linked immunosorbent assay (ELISA), indirect immunofluorescence and chemiluminescence techniques that, when used as part of specific algorithms, support diagnosis at the laboratory level. However, they are frequently not suitable for use in the typical poor, rural communities where Chagas disease is most commonly acquired in Latin America. They are also diagnostically inefficient in industrialized countries where Chagas disease mostly affects immigrants. As an example, the detection rate is below one percent in the United States. Infections are usually discovered in the chronic phase, when treatment is most challenging. Several RDTs based on serology have been commercialized and there is potential to achieve a complete paradigm shift in the detection of Chagas disease by 2018.

Rapid diagnostic tests

The WHO, MSF, United States Centres for Disease Control, and national reference laboratories in endemic and non-endemic countries, have jointly undertaken a two-phase project to evaluate RDTs for detecting Chagas disease. The first phase reviewed commercialized RDTs in a multi-centre study, and

compared performance at reference laboratory level. Results were published in May 2014.¹¹¹ The multicentre project used the WHO international biological standards for the control of the analytical sensitivity of in-house and commercially available tests.¹¹² The second phase is further evaluating six RDTs in countries selected to support extrapolation of results to various regions. More details of the project and the list of evaluated RDTs are presented in annex 11.

Policy recommendations and implementation: Given the involvement of national control laboratories of endemic and non-endemic countries under the supervision of WHO, the implementation and use of RDTs may occur even before formal policy recommendations are issued by WHO. Cost effectiveness studies of new diagnostic algorithms involving RDTs will also be performed by 2019 to support uptake of new diagnostics at the country level.

Antigen detection/test of cure

Research is ongoing to develop a test detecting the Chagas disease parasite antigens, with the aim of offering a diagnostic tool as well as a test of cure. As of 2015, treatment success is evaluated based on a 'lack of failure' principle (absence of parasites in the blood). This is less than optimal because Chagas disease has a complicated and not fully understood pathogenesis that can vary for given species in different settings. The parasite can target, reside and move in different organs, and therefore may not be detectable in blood. Seroconversion can also vary, from as short as six months to as long as five to twenty years. The effective assessment of NCEs, as well as that of new combinations/regimens of existing medicines and benznidazole, requires a test of cure that is able

to detect whether the parasite has been completely cleared in the body before seroconversion occurs.

Biomarker research for therapeutic response: Identifying a non-DNA based biomarker that can be used to develop a test of cure is considered of utmost importance. This is likely to require a constant resource and research investment of eight to ten years. The identification of a good biomarker will require multi-centric validation studies, establishment of additional blood banks that guarantee the quality of blood samples, and standardized sample collection schedules. Research on biomarkers is ongoing by different research groups and institutions including DNDi, McGill University (Montreal, Canada), Geneva University Hospital (Switzerland), US FDA, Hospital São Rafael (Bahia, Brazil), the Oswaldo Cruz Foundation (Brazil), and the Barcelona Centre for International Health Research (CRESIB) (Spain). As of mid-2015, there is no consensus among the various research groups on the best therapeutic response markers to evaluate efficacy treatment protocols. The CRESIB has attempted to define TPPs for biomarker criteria to support research investments and coordination.¹¹³

Biomarker research for evolution of disease: In addition to the research on therapeutic response markers, interest is growing to identify biomarkers to predict the evolution of disease from an asymptomatic stage to symptomatic forms, to discriminate between different grades of disease severity, and to decide whether or not to treat a Chagas disease patient.¹¹⁴

In the absence of prioritization and coordination of research efforts, other important aspects of Chagas disease diagnosis have not been scrutinized, including: diagnosis in pregnant women, congenital Chagas disease, acute cases and outbreaks through contaminated foods. Thus, the related prioritization and TPPs have not been established, resulting in projects that are developed by single institutions. As an example, FIND is working on a LAMP assay (Eiken, Japan/FIND) for the accurate diagnosis of congenital Chagas disease, for which evaluation of a prototype was initiated in Argentina. Beyond the

LAMP development for congenital Chagas disease, the role of real-time qPCR in improving detection of parasitaemia in the blood and tissues during acute and chronic phases should be investigated and defined as conventional parasitological techniques are not very sensitive.

In June 2015, TPPs, assembled by a group of experts convened by the Pan-American Health Organization,¹¹⁵ have been released for POC tests for the acute and chronic phases of Chagas disease. The review, refinement and adoption of TPPs by WHO could have a major leverage effect on the channelling of funds and research efforts.

4.3.3 Chagas disease vaccines

There are no Chagas vaccine candidates under clinical development. One therapeutic vaccine (Tc24 TSA-1), developed by the Sabin Vaccine Institute (United States), is in a preclinical phase.¹¹⁶ The candidate (TcPA45), developed by the Institut Pasteur (France) more than a decade ago, did not progress to a clinical phase.¹¹⁷ The feasibility of developing preventive vaccines for Chagas is also debated within the scientific community, indicating venues to explore therapeutic immunization approaches.^{118, 119}

4.3.4 Coordination of research

Basic and applied Chagas disease research is characterized by fragmentation and competition for funds. A comprehensive exercise to review strategies and needs for basic and applied research for prevention (including vaccination), treatment and diagnosis of Chagas disease is required. WHO could play an important role in the review of the status of research, defining priorities and strategies to advance innovation in this area.

SECTION 5

CONCLUSIONS

SECTION 5

CONCLUSIONS

This section presents a number of the observations arising from the pipeline analysis, which addresses key factors related to the introduction, access and use of the pipeline products described in this report.

5.1 Prevention, treatment and diagnostic needs based on epidemiology

Major diagnostic and treatment gaps exist for the diseases covered in this report.

Malaria: While the global community works towards malaria elimination, there were an estimated 198 million malaria cases (uncertainty range: 124–283 million) and over half a million deaths worldwide in 2013. An estimated 3.3 billion people in 97 countries and territories remain at risk of malaria, and 1.2 billion are at high risk (>1 case of malaria per 1,000 population each year). Approximately 82 per cent of malaria cases and 90 per cent of malaria deaths occurred in Africa, with children aged under five years and pregnant women most severely affected.¹²⁰

Tuberculosis: One-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*. Nine million people developed TB and 1.5 million died from the disease in 2013. About three million people who developed TB were missed by national notification systems, highlighting a major gap in the diagnosis of TB using current tools and public sector systems. In 2013, an estimated 480,000 people developed MDR-TB, causing an estimated 210,000 deaths. The number of people diagnosed with DR-TB reached 136,000 worldwide in 2013, but only 97,000 received treatment. XDR-TB has now been reported in 100 countries. The number of

MDR- and XDR-TB cases reported worldwide tripled between 2009 and 2013, largely due to the recent roll-out of the GeneXpert diagnostic test.¹²¹

Human African trypanosomiasis: HAT cases have been decreasing since 2009. In 2014, there were 3,796 cases recorded, 98 per cent of which were due to the gambiense form. Global T.b rhodesiense HAT incidence is around 100 cases annually, and WHO is moving towards HAT elimination. Despite the steady decrease of reported cases, better diagnostic and treatment tools are needed to reach the elimination goal.^{67,122,123}

Leishmaniasis: Each year, there are an estimated 200,000 to 400,000 cases of VL and an estimated 0.7 million to 1.3 million new cases of CL and ML worldwide. An estimated 20,000 to 40,000 people die from VL annually.^{124,76}

Chagas disease: Over eight million people are estimated to be infected with *Trypanosoma cruzi*, mostly in Latin America, and many cases occur in industrialized countries due to migration from Latin America. Originally confined to Latin America, Chagas disease has now spread to Europe and North America, where congenital or blood transfusion transmission can also occur. The global detection rate is estimated at only 10 percent.¹²⁵

5.2 Trends in vaccines, diagnostics and medicines markets

Preventive and therapeutic vaccines: For malaria and TB – where 3.3 billion are people at risk for malaria and two million people are infected with TB – prevention

through vaccination is actively pursued, with several candidate vaccines undergoing clinical trials. Given the current epidemiology, the potential to sustain a vaccination strategy for prevention of diseases is considerable. However, this potential market is not sufficiently attractive for pharmaceutical companies, hence much of the research is led by public institutions, academic groups and PDPs. The value of immunotherapeutic vaccines for CL, ML (and possibly, VL in certain foci not responding to pharmacological interventions), and their potential to address over two million people affected by these neglected diseases, warrants a funding and development strategy that takes full advantage of research undertaken to date. Recent reviews have hinted at the potential for developing immunotherapeutic vaccines for Chagas disease, which could benefit over eight million people currently infected with the disease, considering that detection of the disease will greatly improve by 2020 and that drug development for an optimal regime faces several challenges.

Diagnostics: The development and commercialization of RDTs is appealing to small- and medium-sized companies, even when markets are relatively small, such as for HAT. Where a larger market exists, such as for VL or Chagas disease, several RDTs are commercialized and the market is characterized by competition and relatively low prices.

For other diagnostics, the landscape is very different. The production and supply of the best confirmatory test for HAT, the mAECT, also known as the “Minicolumn” test, is yet to be secured at affordable prices. Investment on NAA-based technologies is increasing for several diseases. For malaria and TB, WHO has defined TPPs for NAA diagnostics and indicated their applicability within the health system. For Chagas disease, HAT and leishmaniasis, a clear definition of NAA technology’s role in disease diagnosis would help avoid diversion of already lean public resources into development of diagnostic tools that do not address the most important public health needs. Major investments for NAA technologies by small and large companies, are seen in the TB field, which presents a major pipeline of products under

development and several commercialized products. The main challenge for such a market is to ensure that funds can be available for the evaluation and field studies required by WHO for building evidence of applicability within the health systems and for issuing a policy recommendation. Despite the global health community’s expressed urgency for more innovative diagnostics for TB and Chagas disease, such as POC/test-of-cure, investments have been relatively small and slow in coming, as this would imply major investment in basic research to identify reliable non-DNA biomarkers. The BMGF is a major investor in TB diagnostics, funding selected NAA products/companies and investing with several grants on basic research for biomarkers and POC tests. For HAT, leishmaniasis and Chagas disease, there is no major funding source available for diagnostics development.

Medicines: Conditions for a ‘healthy market’ – characterized by competition and affordable prices – appear to exist when the number of reported cases of a disease reach eight million, as is the case for malaria medicines and first-line TB drugs. When detection rates remain extremely low and the potential market is consequently small, problems may be encountered with securing production and supply of sufficient medicines, as has been the case for medicines for Chagas disease, leishmaniasis and drug-resistant TB. Several medicines currently used for Chagas disease and leishmaniasis are single source. In the past decade, there have been instances of global shortages of active pharmaceutical ingredients (API) and finished products for MDR-TB, Chagas disease and leishmaniasis, as a result of production problems or discontinuation of production. The NCEs pipeline for these diseases has been developed mainly through PPPs; only in a few instances are NCEs developed solely by the pharmaceutical industry. Academic groups and public health institutions are often deeply involved in clinical drug development. Nevertheless, the first TB NCEs to reach the market in over 50 years have been developed solely by the pharmaceutical industry, but their roll-out in countries for pre-XDR-TB and XDR-TB according to the WHO recommendation is

progressing very slowly. For HAT, where the ultimate goal is to achieve disease elimination, a production-for-donation system is in place for existing medicines, and this system will also be used for new medicines under development.

5.3 Research priorities and target product profiles

WHO has defined research priorities and promoted coordination in relation to medicines, vaccines and diagnostics for malaria.

Within the TB field, WHO developed a roadmap in 2009 for TB diagnostics and the corresponding TPPs in 2014 that will channel investments towards the desired diagnostics. WHO monitors the pipeline for NCEs and new regimens and develops the policy guidance for the introduction of NCEs. At present, there is no formal WHO mechanism for coordinating the research agenda on new TB regimens, which should necessarily take account of resistance surveillance data. In the TB vaccines arena, the coordination is led by a global partnership of TB vaccines PPPs (Aeras, TBVI) with support of main donors in the field (BMGF, EC, EIB).

The situation is less defined for NTDs. While research priorities were set in 2012 for PKDL, no comprehensive exercise has been undertaken to define research priorities, TPPs or milestones for improved CL/ML treatments and diagnostics. For Chagas disease, there are a number of key stakeholders, but the need for a priority-setting exercise and definition of TPP for vaccines, diagnostics and treatments is acute. For HAT, a WHO task force has been created to define the elimination strategy as well as the essential innovation needs. Agreed priorities for HAT diagnosis are of utmost importance given some contrasting views and limited resources in this area.

As has been done in the case of malaria, priorities for research, innovation and product development should ideally be defined and coordinated within a disease field. This approach can support targeted use of limited resources to respond to public health

needs, and to channel global community and industry efforts towards the appropriate products for optimal public health impact. In addition, the basic research needs could also be identified and defined.

It should be noted that WHO is in the process of establishing a Product Development for Vaccines Advisory Committee to provide advice on the strategic prioritization of a long list of pathogens at early stages of vaccine research and development,¹²⁶ which could potentially facilitate the prioritization exercise for research and development of vaccines for various diseases.

Epidemiological research needed to support innovation: Resistance profiles of malaria and TB have an important impact on the development of new medicines, and are also drivers for the development of diagnostic tests that detect resistance. Moreover, epidemiological studies also address more targeted needs (e.g. G6PD RDTs, RDTs for discrimination of febrile events). Similar needs also exist in relation to RDTs for CL. More complex studies looking at DNA sequencing, genotypic and phenotypic resistance profiles – such as those developed for TB and malaria – could be fundamental in predicting and supporting strategies for optimizing and designing treatment regimens. For example, multi-country research is ongoing to review genotypic and phenotypic resistance of TB to pyrazinamide and fluorquinolones.¹²⁷

Clinical trials design and animal models for preclinical studies: For malaria vaccines, a Joint Technical Expert Group has been established by WHO to provide recommendations on the necessary clinical trial data for evaluation of public health impact, and to provide guidance on the design, conduct, analysis and interpretation of Phase II, III and IV trials. A similar approach is being developed by the main PPPs and donors supporting TB vaccine development through the Global TB Vaccine Partnership, with WHO as an observer. This type of approach will support the optimization of resources, as well the advancement of the TB vaccines pipeline. The failure of TB vaccine candidates in Phase II has also shown that animal models were not predictive of immunity in humans and that more work is required to determine the role

of animal models in leishmaniasis immunization. The need for appropriately designed and reported trials to compare interventions for CL have been described. WHO is in the process of developing guidance for the design, conduct, analysis and reporting of CL clinical trials and planning and prioritization of global strategies for related clinical research. Furthermore, no good animal model is available for testing NCEs for CL. Building a base of appropriate evidence is necessary for issuing recommendations on CL treatments, which are currently inadequate. The priorities for research have also been described for PKDL, including treatment, vaccines and diagnostics, as well as the identification of animal models for PKDL.

5.4 Intellectual property

The role and impact of intellectual property rights (IPRs) vary across the product/disease categories, depending on the actors involved in the research and development. It can be expected that pharmaceutical companies will seek IPR protection, while PPPs/PDPs may be guided by considerations of ensuring availability and affordability of their products. Research is also carried by academic groups and smaller companies, especially in the area of biomarkers and diagnostics, which may seek IPR protection.

Medicines: Two NCEs for TB treatment that have been developed solely by multinational companies (delamanid by Otsuka Pharmaceutical (Japan), and bedaquiline by Janssen Pharmaceutica (Belgium)) are now on the market following conditional market approval. Two other TB NCEs are owned by a smaller company (Sequella Inc. (United States)), which has sought wide patent protection. The UNITAID Market Dynamics Group has commissioned a patent landscape report for all TB NCEs developed by the industry and by PPPs (e.g. TB Alliance). The malaria NCEs portfolio is dominated by multinational companies such as GSK, Novartis (Switzerland) and Sanofi S.A. (France), with MMV involvement in some product development phases. The most advanced candidate (tafenoquine) should not be subject to IP barriers for generic competition.

The IPR landscape for malaria NCEs has not been investigated. The NTDs treatment pipeline comprises NCEs under development solely by the industry (e.g. posaconazole/Merck) or by PPPs via DNDi.

Diagnostics: The diagnostic pipeline for all diseases is characterized by research and development by both large and small companies. Several small companies are investing in RDTs and also in more complex technologies, such as, NAA for TB. IPRs do not seem to have been a barrier for new RDTs that have reached the market for several diseases (e.g. HAT, leishmaniasis and Chagas disease). The impact of IPRs should be investigated for NAA-based technologies and POC tests/tests for cure, which are sought for a number of diseases including TB, leishmaniasis and Chagas disease.

Vaccines: Work on almost all vaccines/immunomodulators under development for malaria, TB and leishmaniasis is being undertaken within PPPs (e.g. IDRI, Aeras, TBVI, PATH, Oxford University (United Kingdom)).

5.5 Regulatory aspects

The regulatory framework is a key aspect of the development and delivery of health products. Even in the absence of complex technologies, the requirement to support quality production and maintain quality standards for medicines is an ongoing challenge in several middle-income countries. Paradoxically, weaknesses in the diagnostics regulatory field are found also in countries that have stringent regulations for medicines. Moreover, in developing countries, regulatory mechanisms for diagnostic tests are often absent or weak. It should be noted that the variability in malaria RDT quality has created a general wariness of the product, which can affect the speedy uptake of RDT technology.

Medicines: In the TB field, accelerated marketing approval based on Phase IIb data and compassionate use has been adopted to expedite the introduction of two NCEs for MDR-TB. The approach adopted by the regulatory agencies in the United States and Europe with regard to bedaquiline and delamanid is

noteworthy, with Janssen Pharmaceutica (Belgium) now required to perform a Phase III trial for bedaquiline as part of a shorter DR-TB regimen than that currently recommended by WHO. Regulatory frameworks in developing countries typically do not cover approval on grounds of compassionate use or introduction of medicines approved on Phase IIb data. Recognition of WHO prequalification status and marketing approval from SRAs is also limited in low- and middle-income countries. Regulatory harmonization for review and approval of NCEs and novel regimens is thus needed among ICH members.¹²⁸ For single source medicines, such as benznidazole or other leishmaniasis medicines produced outside the scope of SRAs, there does not appear to be a system to ensure compliance with WHO standards for production. Another regulatory aspect that may pose a challenge for developing improved treatments for children is the lack of guidance on bioequivalence studies required by WHO for the prequalification of paediatric FDCs. This has been a factor affecting the development of new FDCs for first-line TB treatment.¹²⁹ In addition, it may be useful to assess various incentive programmes, such as those related to orphan drug development, priority review vouchers and breakthrough therapy, to better understand their impact on development timelines and costs.

RDT diagnostics. A multi-centre laboratory assessment of Chagas infection RDTs has shown that commercialized tests have not performed as well as claimed by the manufacturers, highlighting the critical role for independent multi-centre evaluations. A WHO review of leishmaniasis RDTs provided valuable information on their performance in different geographical areas. A similar approach could be sought for second-generation HAT RDTs. Currently the same groups involved in HAT RDT development are also carrying out evaluation studies. There is concern about the roll-out of future G6PD tests, which should be introduced alongside of 8-aminiquinolone malaria medicines. A review and also a quality assurance system is anticipated.¹³⁰ Review exercises undertaken by WHO typically comprise a first phase where RDTs are evaluated at laboratory level and a second phase where their performance is evaluated under

field conditions. It should be noted that these evaluation studies are distinct and not to be confused with the WHO prequalification scheme for diagnostics, which has been extensively used for malaria and HIV RDTs.¹³¹

More complex diagnostics: NAA-based technologies (and other more complex diagnostics) are commercialized in a largely unregulated market. The number of commercialized NAA-based technologies for TB detection is relatively large, yet only two have been endorsed by WHO. As noted, a requirement for WHO to endorse a TB diagnostic is that it has been evaluated by a third party under field conditions. While WHO has set a pathway for endorsing new TB diagnostics, the main barriers are funding and identification of a suitable third party to undertake evaluations. A similar approach has also been suggested for malaria elimination-related diagnostics. WHO has indeed highlighted the need for an international quality assurance scheme while defining TPPs for NAA-based diagnostics for malaria elimination.

5.6 Pharmacovigilance

In 2007, pharmacovigilance (Phase IV) was promoted by WHO for artemisinin-based combination therapies (ACTs) because safety in the context of large-scale use had not been fully assessed, especially in children and pregnant women.¹³²

For NCEs entering the market for TB, the need for pharmacovigilance may be more acute given that some TB medicines have reached the market based on Phase IIb clinical data. In 2012, WHO produced a handbook on pharmacovigilance for TB¹³³ and recommended establishing active pharmacovigilance in countries using bedaquiline and delamanid. WHO recommended adopting cohort event monitoring (CEM), the most comprehensive method of active pharmacovigilance, similar in design and management to an epidemiological cohort study and particularly well suited to the post-marketing surveillance of new drugs. WHO offers technical assistance to national programmes for the

introduction and strengthening of pharmacovigilance for bedaquiline and delamanid. Regulatory agencies and pharmaceutical companies may request additional pharmacovigilance measures. Specifically in relation to bedaquiline pharmacovigilance, the US FDA requested the manufacturers (Janssen, Belgium) to establish a patient registry for bedaquiline in the United States. A global patient registry is under consideration by the company. The manufacturer of delamanid (Otsuka, Japan) also aims to establish a patient registry for that treatment. If tafenoquine is registered and subsequently recommended by WHO, it is likely that its introduction will require increased pharmacovigilance efforts due to complications from G6PD deficiencies. For fexinidazole, the NCE in advanced stage for HAT, pharmacovigilance is foreseen but its implementation will be less challenging given the small scale of treatment and administration through national control programmes.

5.7 Procurement and supply systems for new medicines, vaccines and diagnostics

The majority of products under development offer some potential dispensing and supply advantages. New drug development for TB and NTDs are aimed at fully oral administration of medicines, eliminating injectables and shortening treatment duration. Dosages are also being reviewed in order to reduce side effects while ensuring efficacy. Treatment will therefore be simpler to administer by health workers and easier to adhere to by patients. New diagnostic tools under development also present potential advantages. For example, RDTs under development for several diseases do not require cold chains, and more complex diagnostic tests are designed to be as simple as possible for decentralized use. When recommending the use of specific interventions, WHO considers several factors, in addition to the efficacy/safety profiles of medicines and sensitivity/specificity of diagnostic tests. One crucial factor is quality assurance. For example, only supply of quality-assured generic medicines and diagnostics

is supported by donors, such as Global Fund and United States-funded initiatives for TB and malaria. A similar driver for the production and supply of quality-assured medicines does not exist for NTDs. For diagnostics, the WHO-supported evaluations of new diagnostic tools and donors' requirements for quality also has a similar effect in promoting procurement and supply of quality assured/endorsed diagnostics for national programmes for tuberculosis and malaria.

Malaria: Medicines and RDTs are procured and supplied through both the public and private sectors. New treatments and diagnostics under development within PDPs are intended to be as affordable as current products to enable their deployment in both sectors as well. Going towards elimination, NAA-based high throughput diagnostics for conducting large-scale surveys and mass screening will be introduced and used at the peripheral laboratory level.

Tuberculosis: Low-income countries often rely on a mix of external and national funds to finance TB national control programmes, including the procurement and supply of medicines and diagnostics. A number of donors, including the Global Fund and UNITAID, have had a major role in financing TB medicines and GeneXpert diagnostics. Depending on the volume to be procured, these countries have either procured TB medicines through national tenders or relied on procurement agents. The Global Drug Facility (GDF) serves as a procurement agent for both first- and second-line TB drugs that are purchased or donated to low-income countries, and has expanded its portfolio to include new diagnostics since 2007. The market share of GDF covers 35.4 percent of reported cases of drug-sensitive TB and 31.7 percent of reported MDR-TB.¹³⁴ Middle-income countries – such as Brazil, the People's Republic of China, India, the Russian Federation and South Africa (BRICS) – rely on their national procurement and supply systems using primarily national funds. The BRICS countries are highly affected by drug-sensitive and drug-resistant TB. In a number of other countries, the private sector plays a major role in diagnosis and treatment of TB. A review of the TB market in ten countries demonstrated that 67 percent of new

TB cases were detected and treated in the private sector.¹³⁵ In certain countries (e.g. China and India), the private sector is not regulated, often resulting in suboptimal diagnosis and incomplete provision of treatment of uncertain quality.

Quality of medicines for TB: Given their high and increasing burden of TB, the BRICS countries could consider a pooled demand mechanism for quality-assured TB drugs. The TB NCEs and new treatment regimens may offer an opportunity to slow down or reverse the trend of increasing TB resistance and support infection control, but only if strict regulations on the production and supply of quality medicines are enacted and adhered to in all countries. Without effective regulatory processes and structures, supply of NCEs and/or new regimens may not result in the anticipated public health outcome for TB control.¹³⁶

Leishmaniasis: The procurement and supply systems for VL medicines and RDTs are partly channelled via WHO. Nearly all VL medicines are from a single source and WHO has negotiated prices with manufacturers.¹³⁷ Middle-income countries (e.g. Brazil and India) use national tender systems for procurement of medicines. For CL, treatment often takes place with home-made remedies. Confirmatory laboratory diagnosis is scarce in developing countries (and in refugee camps, in particular) and medicines are often not available in health centres. Several potential innovations are under study, but the major challenge remains securing commercialization and supply at affordable prices for new or improved CL treatments.

Chagas disease: Single source production and supply of benznidazole relies on a fragile system. Production was halted in 2010 and resumed with another company in 2012. Governments from developing and developed countries depend on production by a partnership between a single nation (Argentina) and two private companies for the API and finished formulation. A review of commercialized RDTs performed in collaboration with national reference laboratories in Chagas disease-endemic countries

should support the introduction of RDTs as screening tools. Considering the substantial cost of Chagas disease treatment, especially for the chronic form of the disease, countries may be compelled to support the introduction of innovative diagnostics and new medicines. Global costs of Chagas disease are estimated to be \$7.19 billion per year and \$188.80 billion per lifetime.¹³⁸

HAT: HAT drugs are donated by pharmaceutical companies (Bayer (Germany), Sanofi (France)) and channelled through a centralized WHO procurement system to countries. Fexinidazole, if registered by the EMA and subsequently recommended by WHO, should be produced by Sanofi and channelled through WHO to countries, with the system already established for NECT. The financing for storage and supply to countries will continue to be assured by Sanofi. The introduction of fexinidazole should reduce the volume and transport costs now borne by national HAT control programmes. First-generation RDTs are now supplied free of charge by WHO following donations by the two companies that commercialized the tests. No system has been put in place for financing of RDTs, although one first-generation test is subsidized. If needed, a subsidy system for second-generation tests should ideally be implemented for any test introduced or recommended by WHO.

GLOSSARY

Article 58 of Regulation (EC) No 726/2004 allows the Agency's Committee for Medicinal Products for Human Use to give opinions, in co-operation with WHO, on medicinal products for human use that are intended exclusively for markets outside of the European Union (EU).

A **biomarker**, or **biological marker**: A characteristic (often a molecule/substance) that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.

Compassionate use: The terms "compassionate use," "expanded access" or "special access" refer to programmes that provide potentially life-saving experimental treatments to patients suffering from a disease for which no satisfactory authorized therapy exists and/or who are not in a position to enter a current clinical trial.

Drug susceptibility testing (DST): Testing to establish the sensitivity of a patient's TB bacteria and whether the person has DR-TB.

Phenotypic drug susceptibility tests: a test that takes a culture of m. tuberculosis in the presence of anti-TB drugs in order to detect growth (indicating drug resistance) or inhibition of growth (indicating drug susceptibility).

Genotypic drug susceptibility tests: a test that detects the specific genetic mutations associated with resistance.

Drug-susceptible/drug-sensitive TB (DS-TB): Strains of TB that are sensitive to first-line drugs.

Extensively drug-resistant TB (XDR-TB): TB that is resistant to second-line drugs, including at least one from the class known as fluoroquinolones and one of the injectable drugs.

Immunotherapy: A medical term defined as the treatment of disease by inducing, enhancing or suppressing an immune response. The active agents of immunotherapy are collectively called **immunomodulators**.

Multidrug-resistant TB (MDR-TB): Strains of TB that are resistant to (at least) the two most powerful first-line antibiotics used to treat TB, rifampicin and isoniazid.

Nucleic acid amplification (NAA) test: Molecular technique used to detect small amounts of DNA or RNA of viruses, bacteria or other organisms in test samples. Developed to shorten the period between infection and positive results using typical antibody tests.

Polymerase chain reaction (PCR): Technique in molecular biology used to amplify a single copy or a few copies of a piece of DNA, generating thousands to millions of copies that can then be readily detected.

Seroconversion: Development of detectable specific antibodies to microorganisms in the blood as a result of infection or immunization.

Serological tests: Diagnostic tests that detect serum antibodies specifically associated with certain diseases.

Stringent drug regulatory authority (SRA): A regulatory authority that is: (a) a member of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH); (b) an ICH Observer (i.e. European Free Trade Association as represented by SwissMedic, Health Canada or WHO; or (c) a regulatory authority associated with an ICH member through a legally binding mutual recognition agreement (i.e. Australia, Iceland, Liechtenstein, or Norway).

ANNEXES

SUMMARY OF PRODUCTION INFORMATION



ANNEX 1

INFORMATION ON MALARIA PRODUCTS

Medicines

Tafenoquine (Phase III)

Description of product: Tafenoquine belongs to the class of 8-aminoquinolines. It is the lead investigational medicine for treatment and radical cure of *Plasmodium vivax*. It has a long half-life, which should reduce treatment from 14 days, as required with primaquine (currently recommended for *P. vivax* liver-stage cure), to a single-dose cure.

Ownership/development partners: Tafenoquine is developed by GSK in collaboration with the United States Army Medical Research and Material Command (USAMRMC) and MMV.

Current phase: Results of the Phase IIb study investigating tafenoquine for the treatment and prevention of *P. vivax* (relapsing) malaria were pre-published in December 2012.¹³⁹ Two Phase III trials were started in April 2014: the DETECTIVE study (TAF112582), which aims to evaluate the efficacy, safety and tolerability of tafenoquine co-administered with chloroquine; and the GATHER study (TAF116564), which aims to assess the incidence of haemolysis and safety and efficacy of tafenoquine compared to primaquine.¹⁴⁰

Other issues:

Safety and POC for G6PD deficiency: Medicines from the 8-aminoquinoline class are associated with haemolytic anaemia in individuals with inherited glucose-6-phosphate dehydrogenase (G6PD) deficiency. There are therefore safety concerns for patients who carry the G6PD deficiency, and G6PD screening is a necessary step before drug administration. The feasibility of

introducing and using such a G6PD deficiency POC diagnostic is a precondition for the roll-out of a single-dose formulation of tafenoquine. Work is ongoing to review existing G6PD tests and to develop new diagnostic tools (see section 2.3.3).

Regulatory: In December 2013, the US FDA granted "breakthrough therapy" designation for tafenoquine. This designation is one of the newest US FDA programmes aimed at accelerating the development and review times of drugs for serious or life-threatening conditions. If the drug progresses through Phase III trials successfully and is shown to be safe and effective, it may be registered by the US FDA by 2017. WHO will then proceed to review evidence for its use and, based on its safety profile, define its public health use.

Intellectual property: The patent on the compound (US4617394) expired in 2005,¹⁴¹ and there should not be intellectual property barriers for tafenoquine. However, a patent landscape on tafenoquine and the malaria pipeline drugs has not been performed and disseminated in the public domain.

OZ439 (INN: artefenomel) (Phase IIa)

Description of product: OZ439 is a fully synthetic peroxide that could provide an alternative to artemisinin derivatives, avoiding dependence on agricultural production. The active site of the molecule (endoperoxide bond) is consistent with that of artemisinin derivatives. However, the molecule itself is believed to be structurally distinct enough not to be jeopardized by emerging artemisinin-resistant strains of *P. falciparum*. Preliminary results of a Phase II trial of a

single dose of OZ439 have confirmed that the plasma exposure is similar to that observed in healthy volunteers with similar efficacy as artemisinin against both *P. falciparum* and *P. vivax*. These results confirm the potential of OZ439 to be developed as a single-dose combination therapy for acute malaria.

Ownership/development partners: OZ439 was discovered in partnership by three academic institutes, with the support of MMV: University of Nebraska Medical Center (Omaha, United States), Monash University (Melbourne, Australia) and the Swiss Tropical and Public Health Institute (Basel, Switzerland). MMV is responsible for clinical development of the single agent. Sanofi S. A. (France) is the developer of combinations of OZ439 with ferroquine and piperazine.¹⁴²

Current phase: OZ439 has concluded a Phase IIa study. Preclinical drug–drug interaction studies led to the identification of two candidates compatible with OZ439. A randomized controlled Phase IIb trial is planned that combines OZ439 with various doses of piperazine in adults and children with uncomplicated *P. falciparum* malaria. One Phase IIb trial is planned for the combination OZ439/ferroquine. MMV is conducting a proof-of-concept study (Ib) to assess the effect of a range of doses of combined therapy with OZ439 and DSM265 against early *P. falciparum* blood stage infection.

Other issues: In terms of pricing, an FDC containing OZ439 should be cost-competitive with ACTs.

Arterolane/piperazine (Commercial name: Synriam®)

Description of product: Arterolane is one of the first fully synthetic trioxolane peroxide, non-artemisinin antimalarial compounds. It has schizontocidal activity against all erythrocytic stages of *P. falciparum* without any effect on hepatic stages.¹⁴³

Ownership/development partners: Ranbaxy Laboratories (India) is the developer of arterolane/piperazine. MMV was initially involved in development of this medicine, which was discovered through a collaborative drug discovery project.¹⁴⁴ MMV withdrew its

support in 2007 and development was then carried on by Ranbaxy on its own.¹⁴⁵ The fixed-dose combination is marketed in India.

Current phase: A randomized controlled trial (RCT) sponsored by Ranbaxy was concluded in 2008 in India.¹⁴⁶ The University of Oxford (United Kingdom) is now planning an RCT in areas of emerging resistance to artemisinin-combination therapies. The trial will compare parasite clearance parameters and efficacy of arterolane-piperazine with standard treatment with dihydroartemisinin (DHA)-piperazine in adult patients with uncomplicated falciparum malaria.

Other issues: The arterolane/piperazine (Synriam®) has been registered in India.

KAE609 (INN: cipargamin) (Phase IIa)

Description of product: KAE609 (formerly NITD609) is a novel, synthetic antimalarial molecule with a novel mechanism of action with the potential to inhibit *P. falciparum*. KAE609 belongs to the spiroindolone class. Its mode of action differs from those of artemisinin derivatives, and could present potential for treatment and elimination of artemisinin-resistant strains of malaria. It shows pharmacological properties compatible with single-dose combination therapy. Based on *in vitro* assays, it inhibits the early and late development of *P. falciparum* gametocytes and is effective in reducing transmission to *Anopheles* sp.¹⁴⁷

Ownership/development partners: The discovery partners for KAE609 are: the Novartis Institute for Tropical Diseases (Singapore); the Wellcome Trust (United Kingdom); Swiss Tropical and Public Health Institute (Switzerland); Biomedical Primate Research Institute (the Netherlands); and the Genomics Institute of the Novartis Research Foundation (United States).¹⁴⁸ It is under development by Novartis. MMV provided support to pre-Phase II studies.

Current phase: KAE609 completed a Phase IIa trial. Given the likely coupling with companion drug(s), it is still in an early phase of development. Plans for a Phase II b trial have not yet been disclosed by Novartis.

KAF156 (Phase IIa)

Description of product: KAF156 belongs to the new class of imidazolopiperazines antimalarial drugs exhibiting in vitro potency against blood, liver and gametocyte stages of *Plasmodium sp.*

Ownership/development partners: Novartis is the developer of KAF156.¹⁴⁹

Current phase: KAF156 has concluded a Phase IIa clinical trial for safety, efficacy and tolerability in *P. falciparum* and *P. vivax* infections.¹⁵⁰

DSM265 (Phase IIa)

Description of product: DSM265 belongs to a class of triazolopyrimidine-based, highly-selective inhibitors that target *Plasmodium sp.* dihydroorotate dehydrogenase (DHODH), a key enzyme for malaria parasite survival and reproductive cycle. If successful, DSM265 would be the first antimalarial to target DHODH.

Ownership/development partners: DSM265 is under development for malaria treatment through a collaboration between the Global Health Innovative Technology Fund, Takeda Pharmaceutical Company (Japan) and MMV.¹⁵¹

Current phase: It is undergoing a Phase IIa trial to examine the efficacy in uncomplicated *P. vivax* and *P. falciparum* blood-stage malaria in adult patients. A Phase Ib study is also ongoing to explore if it can be combined with OZ439 (see above).

AQ13 (Phase IIa)

Description of product/background: AQ-13 has a structural analogue of chloroquine that is active against chloroquine-resistant *Plasmodium sp.* in animal models.¹⁵²

Ownership/developmental partners: The molecule was discovered by Tulane University (New Orleans, United States) and then licensed to Immtech Pharmaceuticals, Inc. (United States) for further development, manufacture and commercialization.¹⁵³

Current status: A Phase II proof of concept study is ongoing to assess efficacy of AQ13 in comparison to artemeter/lumefantrine in uncomplicated *P. falciparum* malaria.

Rectal artesunate

Description of product/background: Rectal artesunate (or artesunate suppositories) was recommended by WHO for treatment of severe malaria at the community level before referral to primary/secondary health care in 2006.¹⁵⁴ This formulation will not substitute injectable artesunate (moving therefore from intravenous administration to a route that does not require specific training), but it will be used as a complementary tool at the community level before referral. The lack of WHO prequalified and/or stringently approved products has not yet allowed implementation of this recommendation.

Ownership/developmental partners: Intrarectal artesunate was first developed and trialled with the support of the Special Programme for Research and Training in Tropical Diseases (TDR)/WHO in several countries. MMV, with funds from UNITAID, is responsible for the coordination of development of this formulation through support to pharmaceutical companies to develop bioequivalent formulations, and is also facilitating an information exchange with the WHO prequalification programme for the development and assessment of a bioequivalent intrarectal artesunate.¹⁵⁵

Current status: Two companies are engaging in the development of rectal artesunate formulations (Cipla (India) and Strides, Inc. (United States)). Related bioequivalence studies are expected to be completed in 2015, with the dossiers then submitted to WHO for prequalification. A product is expected to come to market and be prequalified in 2016.¹⁵⁶

Other issues:

Temperature: The product requires storage below 40°C, which can still be a challenge at the community level in tropical countries, where it should be stored and used for patient referral.

Expedited quality review: Artesunate suppositories are listed in the *Expression of Interest* for product evaluation by the Global Fund Expert Review Panel, which provides advice on the use of Global Fund grants for procurement of products, pending WHO prequalification. A dossier has not yet been submitted to WHO for prequalification.

Diagnostic tests

G6PD screening tests

Description of WHO reviewed products: Among commercialized qualitative G6PD tests, the following have been reviewed by WHO (see section 2.3.3):¹⁵⁷

BinaxNOW6PD assay (Binax, Inc., United States): A qualitative assay that uses a lateral flow test platform. It requires a temperature range of 18°–25°C, and therefore is unsuited to many field settings where *P. vivax* is prevalent. The reported cost (\$16.00 per test) is prohibitively high for mass screening or routine clinical use where malaria is endemic.

CareStart G6PD RDT (AccessBio, Inc., United States): Qualitative POC test using a visual dye colourization method, with results provided in 10 minutes. The assay temperature is reported to be a range of 18°–32°C.¹⁵⁸ It is reported to have a cost of \$1.50 per test.¹⁵⁹

G6PD qualitative kit (Ultraviolet (UV) lamp method) (R&D Diagnostics Ltd., Greece): Visual estimation of G6PD activity under special UV lamps.¹⁶⁰

G6PD screening quantitative kit (R&D Diagnostics Ltd., Greece): A quantitative kinetic colorimetric assay expressing G6PD activity in units per gram of haemoglobin. It can be used on all automated analyzers (or manually). It is used with a two-step protocol to give results in less than 15 minutes. The test kit needs to be stored at 2°–8°C and the test to be performed at 37°C.¹⁶¹

G6PDH – Spot Test (Trinity Biotech PLC, Ireland): Qualitative assay in which fluorescence of nicotinamide adenine dinucleotide phosphate (NADPH) is directly

observed. Requires storage temperature at 2°–8°C. G6PD substrate solution is stable for at least two weeks if stored frozen (–22°C), one week stored refrigerated (2°–8°C) or up to four hours at room temperature (18°–26°C).¹⁶²

Vaccines

RTS,S/AS01 vaccine (Commercial name: Mosquirix®)

Description of product: RTS,S/AS01 is the first vaccine ever registered against *P. falciparum*, with no protection expected against *P. vivax*. The antigen RTS,S consists of sequences of the circumsporozoite protein and the hepatitis B surface antigen, coupled with AS01 adjuvant.¹⁶³

Ownership/development partners: The vaccine has been developed by GSK Vaccines (United States), which in 2001 entered into a PPP with the PATH Malaria Vaccine Initiative (MVI), with support from BMGF, to develop the vaccine with a utility for infants and young children living in malaria-endemic countries in sub-Saharan Africa.

Current phase: A large-scale Phase III trial began in May 2009 and has completed enrolment in January 2014 with 15,459 children in seven countries in sub-Saharan Africa (Burkina Faso, Gabon, Ghana, Kenya, Malawi, Mozambique and the United Republic of Tanzania). Three doses of vaccine were administered at one month intervals, followed by a booster dose administered 18 months after the primary schedule. The vaccine was trialled in two age groups of 6–12 weeks and 5–17 months of age. The latest results of the trial were released in April 2015. In the younger age group, efficacy against clinical malaria was 26 percent to the end of the study (over an average follow up of 38 months across trial sites). In the 5–17 month age group efficacy was 36 percent. In the absence of a booster dose, the efficacy of a three-dose primary schedule was 18 percent in infants and 28 percent in children. The efficacy of RTS,S was evaluated in the context of other malaria control measures such as the use of insecticide-treated bednets.¹⁶⁴

Other issues

Regulatory and WHO guidance: The EMA granted registration to the vaccine in July 2015 through article 58. A WHO recommendation on the use of RTS,S is expected by November 2015.¹⁹ Following the scientific opinion provided by EMA, WHO will convene the Strategic Advisory Group of Experts on Immunization and the Malaria Policy Advisory Committee to review all evidence regarding efficacy and safety. The WHO decision regarding a potential policy recommendation will be based on this comprehensive evidence review.

Pharmacovigilance: The EMA approval foresees a follow-up programme with GSK to ensure that the safety and effectiveness of the vaccine is continuously monitored.

Supply/Financing: This vaccine could be considered for the support of the GAVI Alliance for introduction in developing countries, depending on the outcome of regulatory and WHO guidance processes.¹⁶⁵

ANNEX 2

LIST OF VACCINES IN CLINICAL DEVELOPMENT FOR MALARIA

Vaccine name	Targeted plasmodium	Strategy	Sponsors	Status
RTS, S-AS01 (257049)	Pf	Pre-erythrocytic	GSK with PATH	Phase IV
ChAd63/MVA ME-TRAP	Pf	Pre-erythrocytic	University of Oxford, UK, with European Vaccine Initiative (EVI)	Phase IIb
MSP3 [181–276]	Pf	Blood-stage	African Malaria Network Trust with LSHTM and Institut Pasteur	Phase IIb
GMZ2	Pf	Blood-stage	African Malaria Network Trust with EVI and Statens Serum Institut, Denmark	Phase IIb
Ad35.CS.01	Pf	Pre-erythrocytic	Crucell, The Netherlands, with PATH	Phase Ib
PFSPZ	Pf	Pre-erythrocytic	National Institute of Allergy and Infectious Diseases (NIAID), with Sanaria (US), PATH, University of Maryland ,US, and US Naval Medical Research Center	Phase Ib
EBA 175.R2	Pf	Blood-stage	NIAID, US	Phase Ib
SE36	Pf	Blood-stage	Osaka University, Japan	Phase Ib
P27A	Pf	Blood-stage	University of Lausanne, Switzerland, EVI	Phase Ib
PFAMA1-DiCo	Pf	Blood-stage	Institut National de la Santé et de la Recherche Médicale (INSERM), France	Phase Ib
Pfs25-EPA	Pf	Transmission-blocking	NIAID, US, with PATH, Johns Hopkins University (Baltimore, United States), and University of Bamako, Mali	Phase Ib
RTS,S/AS01B + ChAd63 and MVA encoding ME-TRAP	Pf	Pre-erythrocytic	University of Oxford, UK, with GSK and PATH	Phase IIa
ChAd63 MSP1/MVA MSP1	Pf	Pre-erythrocytic	University of Oxford, UK, with European Commission	Phase IIa
rCSP adjuvanted with GLA-SE	Pf	Pre-erythrocytic	NIAID, US	Phase IIa
Ad35.CS/RTS,S-AS01	Pf	Pre-erythrocytic	GSK with PATH and Crucell, Netherlands	Phase IIa
ChAd63/MVA AMA1	Pf	Blood-stage	University of Oxford with Okairos, Switzerland and EVI	Phase IIa
FMP2.1-AS01B (AMA1 3D7)	Pf	Blood-stage	U.S. Army Medical Research and Materiel Command (USAMRMC) with GSK, PATH, and WRAIR	Phase IIa
NMRC.M3V.D/Ad.PfCA	Pf	Blood-stage	USAMRMC with USAID, and US agencies	Phase IIa
ChAd63/MVA ME-TRAP + Matrix M	Pf	Pre-erythrocytic	University of Oxford (UK)	Phase Ia
Polyepitope DNA EP 1300	Pf	Pre-erythrocytic	NIAID with Emory University (Atlanta, US) Ichor Medical Systems, US, and VaxOnco Inc., Republic of Korea	Phase Ia

Vaccine name	Targeted plasmodium	Strategy	Sponsors	Status
PfCelTOS FMP012	Pf	Pre-erythrocytic	USAMRMC with USAID, WRAIR and IDRI	Phase Ia
CSVAC	Pf	Pre-erythrocytic	University of Oxford (UK) with EVI	Phase Ia
PfPEBS	Pf	Pre-erythrocytic/ Blood-stage	Vac4All with Institut Pasteur (France), Sentinext Therapeutics, Malaysia, EVI, and the University of Lausanne (Switzerland)	Phase Ia
ChAd63/MVA PvDBV	Pv	Blood-stage	University of Oxford (UK) with Okairos, Switzerland, and ICGB (India)	Phase Ia
Pfs25 VLP	Pf	Transmission- blocking	Fraunhofer USA, Center for Molecular Biotechnology, (US) with MVI and BMGF	Phase Ia
ChAd63 RH5 +/- MVA RH5	Pf	Pre-erythrocytic	University of Oxford (UK) with European Commission	Phase Ia

Source: WHO malaria vaccine projects “Rainbow table” accessed on 17 June 2015 http://www.who.int/entity/immunization/research/development/Rainbow_tables/en/

Note: Vaccine development for malaria defined with different stage numberings: Phase Ia and IIa trials take place in non-endemic countries, followed by Phase Ib and IIb trials in endemic countries.

Pf: *Plasmodium falciparum*, Pv: *plasmodium vivax*.

ANNEX 3

INFORMATION ON TUBERCULOSIS PRODUCTS

Medicines/New chemical entities

Bedaquiline (Commercial name: Sirturo®)

Description of product: Bedaquiline is a first-in-class diarylquinoline compound with a novel mechanism of action, the inhibition of mycobacterial adenosine 5'-triphosphate (ATP) synthase, and potent activity against drug-sensitive and drug-resistant TB.

Ownership/development partners: Bedaquiline has been solely developed by Janssen Pharmaceuticals (Belgium).

Current phase: It received conditional registration by the US FDA in December 2012.¹⁶⁶ The US FDA approval was based on data from two Phase IIb studies of 440 people with MDR-TB. Most drugs used to treat MDR-TB have serious side effects and those associated with bedaquiline include moderate QT prolongation (a disturbance in the heart's electrical activity that could potentially lead to serious and even fatal events). One Phase IIb trial (C208) found excess mortality in the bedaquiline arm: 13 percent (10/79) of patients who took bedaquiline died, versus only two percent (2/81) in the placebo arm. Given the small number of study participants, more data is required to evaluate the safety of bedaquiline. Because of safety and drug interaction issues, the US FDA urged caution when using bedaquiline with medicines that also cause QT prolongation.

To address safety questions, the US FDA requested Janssen to establish a patient registry of all those who receive the drug in the United States, and reviewed the original Phase III trial design to collect data on bedaquiline efficacy and compliance with the conditions of US FDA approval. The initially planned Phase III trial, which was modelled on the Phase II trial (based on the 24-month WHO-recommended regimen), has been withdrawn. The US FDA requested Janssen to look at the efficacy and safety of bedaquiline in a shortened improved MDR-TB regimen.

Two bedaquiline-containing arms were added to the STREAM trial: one substituting the injectable kanamycin with bedaquiline in the nine-month regimen; and one arm including both the injectable kanamycin and bedaquiline in a shortened six-month regimen. Enrolment for these two arms was expected to start in quarter 2 2015. Information from the STREAM bedaquiline arms will be used as evidence to complete US FDA registration. This approach garnered criticism from civil society owing to the bedaquiline arms' STREAM trial design and the lack of community engagement.¹⁶⁷

A Phase II trial is investigating the potential of bedaquiline to shorten drug-sensitive TB regimens (GABT NC-005). There are also two Phase III trials combining bedaquiline with other NCEs: NiX-TB has started enrolling pre-XDR-TB and XDR-TB patients to trial a salvage treatment regimen; and the NExT trial is awaiting South African Medicines Control Council approval to trial a DR-TB injection-free shortened regimen (see section 3.3, table 4 and annex 4).

Other issues

WHO guidance: In June 2013, WHO issued interim guidelines on the use of bedaquiline to treat MDR-TB. WHO recommends its use in pre-XDR-TB and XDR-TB patients when an effective treatment regimen containing four second-line drugs in addition to pyrazinamide, according to WHO recommendations, cannot be designed; and there is documented evidence of resistance to any fluoroquinolone in addition to multidrug resistance. MDR-TB patients with strains resistant to fluoroquinolones or the second-line injectable drugs (i.e. kanamycin, amikacin, capreomycin) represent a particular concern given that these are the two most effective classes of second-line drugs. WHO recognizes that in such cases, bedaquiline may have a crucial role to play to strengthen a regimen, bringing the number of drugs likely to be effective to a minimum of four, and averting the acquisition of additional resistance. The WHO interim guidelines set a number of conditions for the use of bedaquiline, such as the need to work under closely monitored conditions, adhering to best practices in treatment delivery, obtaining informed consent from patients, and implementing active pharmacovigilance for safety and drug–drug interactions.¹⁶⁸ WHO is involved in piloting the introduction of bedaquiline in four countries (Indonesia, Kazakhstan, the Philippines and Viet Nam); the implementation will inform the subsequent revision of WHO guidelines on bedaquiline.

WHO Essential medicines listing: Bedaquiline was included in the 19th *WHO Model list of essential medicines* in April 2015.¹⁶⁹

Compassionate use/Donation: Janssen established a compassionate use programme in 2011. As of 5 June 2015, 660 patients worldwide had received bedaquiline through the compassionate use framework.²⁹ In March 2015, USAID and Janssen signed an agreement to provide 30,000 treatment courses of bedaquiline over a period of four years to eligible MDR-TB patients. This donation programme is open to 100 low- and middle-income countries and will be channelled through the GDF.¹⁷⁰ The list of countries has not been disclosed in the public domain.

Registration status: The US FDA approved bedaquiline under the accelerated approval programme in December 2012. Furthermore, the US FDA also granted bedaquiline ‘fast track’ and ‘orphan product’ designations and priority review. Janssen obtained conditional registration of bedaquiline by the EMA in March 2014.¹⁷¹ Bedaquiline obtained regulatory approval in 2013 in the Russian Federation; in 2014, in Europe, Peru, the Philippines, Republic of Korea and South Africa; and in 2015, in India. Regulatory approval is currently being sought in Armenia, Azerbaijan, Bangladesh, People’s Republic of China, Colombia, Georgia, Indonesia, Kazakhstan, Kyrgyzstan, Thailand, Turkmenistan, Uzbekistan and Viet Nam.^{29,172}

Prices: A pricing scheme was disclosed by Janssen to MSF in November 2013.¹³⁶ Janssen will be implementing a three-tiered pricing framework. For a six-month treatment course, a country in the high-income bracket would pay \$30,000, a country in the upper middle-income bracket would pay \$3,000, and a country in the least-developed/resource-limited bracket would pay \$900. The company has not yet divulged placement of individual countries in the three respective groups.

Supply: Bedaquiline became available for supply via the GDF in 2014.¹⁷³ The GDF will also manage the bedaquiline donation programme. Janssen signed an agreement with the Russian company Pharmstandard JSC, for the production and commercialization of bedaquiline in the Russian Federation and the Commonwealth of Independent States.¹⁷⁴

Intellectual property: UNITAID published a related patent landscape description in January 2014. All of the patents were filed and remain in the name of the Johnson & Johnson subsidiary, Janssen Pharmaceuticals (Belgium),¹⁷⁵ which is solely responsible for the marketing and access programme of bedaquiline for MDR-TB. Janssen has signed an agreement with the TB Alliance that grants the Alliance a royalty-free license for the worldwide development and access to bedaquiline in the field of drug-sensitive TB.¹⁷⁶

Delamanid (Commercial name: Deltyba®)

Description of product: Delamanid is a nitroimidazole with a new mechanism of action. It inhibits the synthesis of mycolic acid, a component of the TB bacterium cell wall.

Ownership/development partners: Delamanid has been solely developed by Otsuka Pharmaceuticals (Japan). It was discovered via a screening programme carried out by Otsuka.

Current phase: It received conditional registration by the EMA in November 2013 based on Phase IIb trial data. Following a Phase III trial, EMA will grant full registration. The drug is registered for six months use as part of the 24-month WHO-recommended MDR-TB regimen.¹⁷⁷ A Phase III trial was started in mid-2012 (C213). A safety, efficacy and pharmacokinetic trial of delamanid in children from birth to less than 18 years of age (C232) is taking place with results expected in 2016. A dispersible tablet for pediatric use is in development.

Other issues

WHO guidance: WHO issued interim guidelines on the use of delamanid in October 2014.¹⁷⁸ Experts noted a number of problems in the design and conduct of the delamanid trials performed by Otsuka and made an analysis of the flaws of the trials. The expert group had a very low level of confidence in the short- or long-term efficacy of delamanid given that the available evidence was very limited and of low or very low quality (for efficacy and safety, respectively). WHO has nevertheless defined interim guidance for the use of delamanid while awaiting a Phase III clinical trial to be concluded in 2015. In the interim guidance, WHO recommended that delamanid (100 mg BD for six months) may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB under specific conditions. It also foresees use in pre-XDR-Tb and XDR-TB patients. As for bedaquiline, the interim guidance on delamanid also recommended following a duly-informed decision-making process by patients including the provision of information on

uncertainty about the impact and side effects. It also requires use of active pharmacovigilance techniques, such as cohort event monitoring (CEM), to improve the early detection of adverse drug reactions. Following the interim guidance on bedaquiline and delamanid, WHO issued a companion book to support programmatic management of TB including the use of these NCEs.¹⁷⁹

WHO Essential medicines listing: Delamanid was included in the 19th WHO Model list of essential medicines in April 2015.¹⁶⁹

Compassionate use: As of 4 June 2015, 23 patients were enrolled in the compassionate use scheme for delamanid, enacted in January 2015.^{29,180}

Registration status: There was conditional registration by the EMA in November 2013 based on Phase IIb trial data. Eastern European countries, members of the European Union and the EMA may still require separate submission of registration dossiers with a delayed entry of the product in the market. The regulatory agencies of Japan and the Republic of Korea granted registration in 2014.^{29,181}

Safety/Pharmacovigilance: Delamanid presents mild to moderate QT prolongation. Otsuka (Japan) aims to establish a non-mandatory patient registry.

Prices: No tiered pricing scheme has yet been announced. As of September 2014, Otsuka had launched Deltyba only in Germany and the United Kingdom at the cost of \$28,499 and \$33,244, respectively for a six-month course of 100 mg twice daily.¹⁸² As of April 2015, only 50 patients were reported to have received delamanid outside of a clinical trial scheme.¹⁸³

Intellectual property: UNITAID released a patent landscape in January 2014. All of the patents were filed and remain in the name of Otsuka Pharmaceutical Co. Ltd.¹⁸⁴

Pretomanid (Phase IIb)

Description of product: Pretomanid, formerly indicated as PA-824, is a nitroimidazole under development both for drug-sensitive and drug-resistant TB in novel regimens.

Ownership/development partners: Pretomanid was discovered by the PathoGenesis Corporation (United States), which was acquired by the Chiron Corporation (United States) in 2000. Novartis AG (Switzerland) acquired the Chiron Corporation in 2006. The TB Alliance is leading the clinical development of pretomanid, having gained global exclusive rights to this compound and to related ones for the treatment of TB following an agreement with Chiron in 2002.¹⁸⁵

Current phase: Pretomanid is under trial in two new shortened regimens for both drug-sensitive and drug-resistant TB; one additional trial is planned for XDR-TB. A Phase IIb trial NC002 is concluded. A Phase III trial (STAND/NC006) combining pretomanid, moxifloxacin and pyrazinamide (also referred to as PaMZ) is planned to start in the second half of 2015 and expected to end in 2019. An ongoing Phase IIb trial NC005 combining pretomanid, bedaquiline, clofazimine and pyrazinamide is expected to be concluded in 2016.

A Phase III trial NiX-TB combining bedaquiline, pretomanid and linezolid in a six-month salvage therapy regimen for XDR-TB patients started in May 2015 in South Africa, and could be extended to other countries. Results are likely to be made public throughout the progress of the trial because of the urgency for finding a salvage therapy for XDR-TB patients. If the regimen tested in NiX-TB is successful and safe in XDR-TB, it could expand testing to people with MDR-TB and then eventually those with drug-sensitive TB.

Other issues

Regulatory: Pretomanid will not undergo registration as a single medicine, but only as part of a new regimen upon positive results of Phase III trials. In 2007, the US FDA approved a request for 'orphan drug' designation for pretomanid. The TB Alliance

aims for registration of pretomanid by the US FDA as part of a regimen. The development of FDCs is the ultimate goal.

Compassionate use: No compassionate use programme is available. The NiX-TB trial may answer needs for compassionate use in the countries where it will be undertaken. The TB Alliance plans to establish a philanthropically funded pre-approval access programme.²⁹

Intellectual property: The agreement with the Chiron Corporation ensured that PA-824 would be made available royalty-free in endemic countries. The TB Alliance can seek different companies for industrial development. An agreement has been signed with Janssen (Belgium) and Sequella (United States), the owners of bedaquiline and sutezolid, which also relates to availability and affordability of a future combination therapy. UNITAID released a patent landscape of pretomanid in January 2014.¹⁸⁶

Price: The PaMZ regimen as whole should be priced at 90 percent less than the current MDR-TB treatment, at around \$100 per course. The desired price of other regimens that include pretomanid have not yet been disclosed in the public domain.

SQ109 (Phase IIb)

Description of product: SQ109 is an ethylenediamine with a novel mechanism of action. Although SQ109 was originally identified by creating analogues of etambutol, it is not activated by the same mechanism.

Ownership/development partners: SQ109 was developed by Sequella (United States), discovered in partnership with the United States National Institutes of Health (NIH).

Current phase: A Phase IIa early bactericidal activity study has been completed. A Phase IIb trial (MAMS-TB-01) combining SQ109 with other TB medicines (including moxifloxacin) is ongoing. This trial aims to investigate new DS-TB regimens.

Other issues

Regulatory: SQ109 received US FDA ‘fast track’ and ‘orphan drug’ designation in 2007.

Intellectual property: Sequella (United States) highlighted that the SQ109 patent family contains both issued and pending patents in the European Union, Eurasia, China, Japan, South Africa and the United States and in other key international markets.¹⁸⁷ UNITAID released a patent landscape in January 2014. The identified patents were filed in the names of Sequella and the NIH.¹⁸⁸

Sutezolid (Phase IIa)

Description of product: Sutezolid (previously known as PNU-100480) is an oxazolidinone that was identified at the same time as linezolid, which is US FDA-approved for severe infections caused by gram-positive bacteria that are resistant to other antibiotics, and which is also used in treatment of pre-XDR-TB and XDR-TB. Despite early evidence of activity against TB, sutezolid was left without significant development for over a decade.

Ownership/development partners: Sutezolid was developed by Pfizer (United States) prior to 2005 for use in resistant gram-positive bacterial infections. Pfizer granted worldwide exclusive rights to Sequella (United States) in July 2013 to continue the development of sutezolid.

Current phase: A Phase IIa EBA trial (B1171003) assessing potential efficacy in drug-susceptible and drug-resistant TB has been concluded. The NiX-TB trial was initially planned to include sutezolid, but moved ahead using linezolid.

Other issues

Sutezolid received ‘orphan drug’ designation in both the United States and European Union.

Intellectual property: There are more than 20 issued patents and additional patent filings, including patents from the European Union, China, Japan and the United States, on composition, methods and use claims for treatment of TB and other infectious

pathogens.¹⁸⁹ UNITAID released a patent landscape in January 2014. The identified patents were filed in the name of The Upjohn Company (United States), Pfizer Inc. (United States) and Johns Hopkins University (Baltimore, United States).

AZD5847 (Phase IIa):

Description of product: AZD5847 belongs to the class of oxazolidinones (see sutezolid and linezolid).

Ownership/development partners: AZD5847 is developed by AstraZeneca (United Kingdom and Sweden).

Current phase: AZD5847 moved into a Phase IIa clinical trial in late 2012. This two-year EBA study compared four different dosing schedules of AZD5847 with a control arm of the standard four-drug, first-line therapy. Results were expected in 2014, but it is reported that data analysis is still ongoing.

Other issues

Intellectual property: A patent landscape was released by UNITAID in January 2014.¹⁹⁰

Diagnostic tests**Xpert® MTB/RIF assay (Cepheid Inc., United States)**

Description of product: Xpert MTB/RIF, also called GeneXpert, is an automated, cartridge-based NAA assay for the simultaneous detection of TB and rifampicin resistance directly from sputum in less than two hours.

Ownership/development partners: The technology is based on the GeneXpert platform and was developed as a partnership between FIND, Cepheid Inc. (United States) and the University of Medicine and Dentistry of New Jersey (United States), with support from the NIH.

Current phase: GeneXpert was endorsed by WHO in 2010. The revised WHO recommendations, issued in 2013, reinforced the use of Xpert MTB/RIF as a first-line diagnostic test for individuals suspected

to have MDR-TB or HIV-associated pulmonary TB. The revised recommendations also extended the use of Xpert MTB/RIF to diagnose paediatric TB and extrapulmonary TB using cerebrospinal fluid specimens and non-respiratory specimens (lymph nodes and other tissues).¹⁹¹ By the end of 2005, WHO will review evidence of the new version Xpert MTB/RIF Ultra. The new version, which should be marketed in the first half of 2016, consists of a new sample processing cartridge with increased sensitivity to aid in detection of patients with smear-negative TB.¹⁹²

Building evidence for implementation: The introduction of GeneXpert provided a number of lessons and defined a pathway for endorsement of new technologies by WHO. GeneXpert is being optimized through operational research aimed at improving its laboratory performance and programmatic use. In addition to piloting studies, which led to endorsement by WHO in 2010, several other studies, by groups and organizations in various settings, generated data on suitability and reliability of use at district and more peripheral levels, as well as expansion of its application in varied populations and using specimens other than sputum. Operational research data provides an essential component in the refinement of this platform, generating evidence to improve the Xpert® MTB/RIF cartridge specificity and sensitivity. Evidence from various studies has been collected and reviewed, supporting new recommendations for use.¹⁹³

Other issues:

Cartridges for other diseases: Cepheid (United States) is developing new cartridges to be used on the GeneXpert platform to allow detection of XDR-TB and also determination of HIV viral load (in collaboration with FIND and with support from BMGF). Additional cartridges that have already been developed and commercialized for GeneXpert include cartridges to detect nosocomial bacterial infections, chlamydia and gonorrhoea, influenza viruses (including the 2009 H1N1 strain), and enterovirus meningitis.¹⁹⁴

Status of roll-out: WHO is monitoring the global introduction of the technology to help promote coordination. As of December 2014, over 3763 GeneXpert instruments and over 10 million Xpert MTB/RIF cartridges were procured at eligible concessional pricing.¹⁹⁵

Prices: In June 2012, the cartridge concessional price was decreased from \$16.86 to \$9.98 per cartridge through a joint agreement with UNITAID, BMGF and the United States President's Emergency Plan for AIDS Relief (PEPFAR). This concessional price is not applicable, however, to the private sector, which is a key player in TB diagnosis in many countries. The price is still considered high due to the monopolistic situation. Major philanthropic and public funds are invested in the development of the Cepheid Xpert diagnostic platform. The United States Department of Defense invested \$120 million in the platform's development, and NIAID and BMGF invested \$21 million and \$9.73 million, respectively, in TB cartridge development. Nevertheless, a clear pricing policy has not yet been established and implemented for the introduction of the technology for public health needs, one that balances public investments with those of Cepheid (United States). The pricing policy should also incorporate the potential return on investment from the application of the platform for diagnosis of diseases other than TB.¹⁹⁶

TB-LAMP (Eiken Chemical Co., Japan)

Description of product: TB-LAMP is a new manual TB detection method based on the novel loop-mediated isothermal amplification (LAMP) platform from Eiken Chemical Co. (Japan) developed in collaboration with FIND. TB-LAMP has several features that make it attractive as a diagnostics platform for resource-poor settings: It is fast (15–40 minutes), isothermal (requiring only a heat block), robust to inhibitors and reaction conditions that usually adversely affect PCR-based methods, and it generates a result that can be detected with the naked eye.

WHO endorsement status: A WHO Expert Group evaluated the tool in May 2013 and identified a number of deficiencies and concerns, which precluded its endorsement.

Evidence generation: The TB-LAMP is currently undergoing additional demonstration studies.¹⁹⁷

Genotype MTBDRsl (Hain Lifescience, Germany)

Description of product: Genotype MTBDRsl is aLPA, developed by Hain Lifescience (Germany) in collaboration with FIND, for detecting genetic mutations associated with resistance to fluoroquinolones and injectables.

WHO endorsement status: Genotype MTBDRsl was evaluated by WHO in 2013 but not endorsed. The WHO expert group concluded that the Genotype MTBDRsl assay showed moderate test sensitivity for the detection of fluoroquinolone and second-line injectable resistance, with high test specificity, but it could not be used as a replacement test for conventional phenotypic DST. The results of the Genotype MTBDRsl assay could not be reliably used to adjust and optimize XDR-TB treatment regimens.

Evidence generation: Genotype MTBDRsl is undergoing additional demonstration studies.¹⁹⁸

ANNEX 4

CLINICAL TRIALS WITH NEW AND EXISTING COMPOUNDS TO SHORTEN TUBERCULOSIS TREATMENT

Indication	Study name	Study/Regimen	Stage	Sponsors
DR-TB	STREAM	STREAM I: Nine-month regimen: ethambutol, pyrazinamide, moxifloxacin and clofazimine throughout, supplemented by kanamycin, prothionamide and isoniazid in the four-months intensive phase (4KCMEHZP/5MEZC). STREAM II: Two additional arms including bedaquiline : one arm substituting kanamycin with bedaquiline, one arm adding bedaquiline and shortening the regimen to six months	Phase III (STREAM I completed, STREAM II Q3–4/2015)	International Union against Tuberculosis and Lung Disease (The Union), MRC, USAID
DS-TB	TBTC 31	Four-month regimens: two months of isoniazid, rifapentine, ethambutol, and pyrazinamide, followed by two months of isoniazid and rifapentine; two months of isoniazid, rifapentine, moxifloxacin, and pyrazinamide, followed by two months of isoniazid, rifapentine, and moxifloxacin	Phase III	TBTC-CDC, Sanofi
DS-TB, DR-TB	STAND (GABT NC-006)	Four- or six-month regimens pretomanid , moxifloxacin, pyrazinamide	Phase III	TB Alliance
DS-TB	TRUNCATE-TB	Two months: novel combination regimens, including NCEs and re-treating relapses with a six-month course of standard treatment	Phase III (planned)	University College London with UK MRC; Wellcome Trust/UK DfID; and Singapore National Medical Research Council
DR-TB	NExT	Six-month regimen: bedaquiline , ethionamide, isoniazid, pyrazinamide, levofloxacin, linezolid	Phase III (planned)	University of Cape Town (South Africa); South African Medical Research Council
Pre-XDR/ XDR-TB	NiX-TB	Six-month salvage study: bedaquiline , pretomanid , linezolid	Phase III (ongoing)	TB Alliance
DR-TB	EndTB	Evaluation of 6 nine-month regimens, each containing one NCE: bedaquiline , delamanid, linezolid, moxifloxacin, levofloxacin, clofazimine	Phase III (planned)	PIH, MSF, Interactive Research and Development, with UNITAID
DR-TB / XDR-TB	PRACTECAL	Evaluation of 3 six-month regimens comprising bedaquiline , pretomanid , linezolid, plus moxifloxacin or clofazimine	Phase II/III (planned)	MSF, University College of London (UK), LSHTM, DNDi, TB Alliance
DR-TB	TBTC Study 32 (OptiQ)	High-dose levofloxacin versus standard-dose levofloxacin or standard-dose moxifloxacin, all in combination with optimized background MDR-TB regimen	Phase IIb (planned)	TBTC-CDC, Sanofi

Indication	Study name	Study/Regimen	Stage	Sponsors
DS-TB	MAMS-TB-01	Three-month regimen: different combinations of ethambutol, isoniazid, moxifloxacin, pyrazinamide, rifampicin (10, 20, or 35 mg/kg) and SQ109	Phase IIb (ongoing)	University of Munich (Germany), Sequella, US, Pan African Consortium for the Evaluation of Antituberculosis Antibiotics (PanACEA)-EDCTP
DS/DR-TB	NC-005	Two-month regimen: bedaquiline , pretomanid , pyrazinamide	Phase IIb (ongoing)	TB Alliance
DS/DR-TB	B1171003	Sutezolid 600 mg twice daily vs. sutezolid 1,200 mg daily vs. isoniazid, rifampicin, ethambutol, pyrazinamide	Phase IIa (two-week Early Bactericide Activity (EBA) study) (completed)	Sequella
DS/DR-TB	AZD5847	AZD5847 500 mg once or twice daily, 1,200 mg once daily, or 800 mg twice daily	Phase II (2-week EBA study) (completed)	AstraZeneca (UK/Sweden)
DS/DR-TB	ACTG A5343	(Safety, tolerability and pharmacokinetics) Drug–drug interaction study of bedaquiline and delamanid	Phase II (planned)	ACTG, NIH
DS/DR-TB	TBA-354	Safety, tolerability and pharmacokinetics of TBA354	Phase I (ongoing)	TB Alliance

Source: Adapted from the TAG Pipeline report 2013, 2014, TB Alliance pipeline, Resist TB Clinical Trial Progress report, MSF.

ANNEX 5

COMMERCIALLY AVAILABLE NAA ASSAYS FOR DIAGNOSIS OF PULMONARY TUBERCULOSIS FROM SPUTUM SAMPLES (INTENDED FOR PERIPHERAL AND/OR MDR-TB DIAGNOSIS)

Test	Developer(s), Country	Type/Sample	MDR TB detection	Intended setting	Regulatory approval	WHO-endorsed
Anyplex II	Seegene, Republic of Korea	qPCR (6h)	Yes, XDR	Reference	CE-IVD	No
Drug Resistance Detection Kit	CapitalBio, China, in collaboration with FIND	PCR, Microarray for detection of DR-TB and non-TB mycobacteria (8h)	Yes	Reference	CE-IVD	No
Genedrive MTB/RIF ID	Epistem, United Kingdom, in collaboration with FIND	Real-time PCR for TB and rifampicin resistance (1.5 h)	Yes	District	CE-IVD	No
GeneXpert MTB/RIF	Cepheid Inc., US, in collaboration with FIND	Real-time PCR for TB and rifampicin resistance (1.5 h)	Yes	District	CE-IVD, Health Canada	Yes
GenoType MTBDRsl line probe assay (LPA), second-line	Hain Lifescience, Germany, in development with FIND	LPA for genetic mutations associated with resistance to fluoroquinolones and injectables (Am/Km/Cm)	Yes, XDR	Reference	CE-IDV	Reviewed, but not endorsed.
GenoType MTBDRplus	Hain Lifescience, Germany, in development with Global Consortium for DR TB Diagnostics	LPA (PCR)	Yes	Reference	CE-IVD	Yes (version 1.0)-2008 No (version 2.0)
MeltPro TB/RIF and MeltPro TB/INH	Zeesan Biotech, China	Closed-tube real-time PCR for detection of rifampicin and isoniazid resistance respectively	No	Reference	China FDA (CFDA)	No
Loopamp TB Detection	Eiken, Japan, in collaboration with FIND	Loop-mediated isothermal amplification (LAMP) for TB (2h)	No	District	CE-IVD, Japan	Reviewed, but not endorsed.
NATeasy TB Diagnostic Kit	Ustar Biotechnologies, China	Isothermal NAA and lateral flow detection cartridge	No	District	CE-IVD	No
REBA MTB-MDR, REBA MTB-Km and REBA MTB-FQ	YD Diagnostics, Republic of Korea	Line probe assay for detecting resistance rifampicine, Km, fluoroquinolones	Yes, XDR	Reference	Unknown	No

Test	Developer(s), Country	Type/Sample	MDR TB detection	Intended setting	Regulatory approval	WHO-endorsed
TBMDx m2000	Abbott Laboratories, US	Automated real-time PCR for TB detection	No	Reference	CE-IVD	No
TRC Rapid MTB	Tosoh Corporation, Japan	Automated rapid RNA amplification method for TB detection (1 h)	No	Reference	Japan	No
Truelab/Truenat MTB	Molbio Diagnostics/ BigtecLabs, India, in collaboration with FIND	Chip-based NAAT for MTB; runs on a portable battery-operated device (8h)	No	District	CE-In vitro diagnostics	No
VereMTB	Veredus Laboratories, Singapore, in collaboration with FIND	Chip-based NAAT for MTB and 9 other mycobacteria, able to detect DR-TB	Yes	Reference (Research)	Unknown	No

Source: Adapted from UNITAID TB diagnostics landscapes. CE-IVD: CE marking for in vitro diagnostics. Am: amikacin, Km: kanamycin, Cm: capreomycin, INH: isoniazid.

ANNEX 6

NAA-BASED DIAGNOSTIC TESTS REPORTEDLY UNDER DEVELOPMENT FOR TUBERCULOSIS

Test	Developer(s), Country	Type/Sample	MDR-TB detection	Intended setting	Status
Alere Q	Alere, US / BMGF (funding)	Molecular diagnostic platform to screen MTB and drug resistance (less than 30 min)	Yes, XDR	District/ Microscopy centre	In development (expected marketing by 2016)
BD MAX	Becton Dickinson, US	qPCR in automated BD MAX for TB detection	No	Reference	In development
B-SMART	Laboratory Corporation of America Holdings (LabCorp), US, technology licensed by Sequella, US	Combines NAA and detection with phenotypic DST to detect MDR TB	Yes	District/ Microscopy centre	In development
EOSCAPE-TB-DST	Wave 80 Biosciences, US	Qualitative assay for identifying resistance to R and fluoroquinolones from sputum	Yes, Fluoroquinolones	District/ Microscopy centre	In development (expected marketing by 2016)
LATE-PCR with Lights-On/ Lights-Off Probes and PrimeSafe technology	Stellenbosch University, South Africa; developed by Brandeis University, US	PCR for simultaneous detection of MTB and resistance to I, R, E and injectables	Yes, XDR	District/ Microscopy centre	In development
UltraFast LabChip Real-time PCR	Nanobiosys, Republic of Korea	Real-time PCR (15 min), with separate sample preparation device	Unspecified	District/ Microscopy centre	In development
RT-PCR Testing Platform NWGHF or NWGHF Integrated TB device	Northwestern Global Health Foundation (NWGHF), US	Real-time PCR, fully integrated	Yes	District/ Microscopy centre	In development (expected marketing by 2016)
TruArray MDR-TB	Akonni Biosystems, US	Simplified Microarray-based NAAT	Yes	District/ Microscopy centre	In development
Q-POC MDR-TB	QuantuMDx, UK, in collaboration with FIND	Smartphone-like device, integrated sample preparation, drug resistance biomarker panel	Yes	District/ Microscopy centre	In development
Helicase Dependent Amplification technology (HDA)	BioHelix Technologies, US	Isothermal DNA amplification system using a helicase enzyme	Unspecified	District/ Microscopy centre	In development

Test	Developer(s), Country	Type/Sample	MDR-TB detection	Intended setting	Status
HYDRA	InSilixa Inc., US, with Stanford University	Microarray, fully integrated, hand-held and highly multiplexed genotyping tool	Yes, XDR	District/ Microscopy centre	In development (expected marketing by 2016)
TBDx System	Keck Graduate Institute, US	LAMP/CPA, lateral flow strip	No	District/ Microscopy centre	In development (expected marketing by 2018)

Source: Adapted from TAG pipeline report 2013, 2014, UNITAID TB diagnostics Landscapes Reports 2013, 2014 and MSF Access Campaign data.

ANNEX 7

PIPELINE OF POINT-OF-CARE TESTS AND NEXT-GENERATION CULTURE-BASED DRUG SUSCEPTIBILITY TESTS

Test	Developer(s), Country	Type/Sample	MDR-TB detection	Intended setting	Status
POC biomarker based tests					
POC blood test	MBio Diagnostics, US/ FIND	Antibody detection through POC blood test for active TB using the MBio multiplexed immunoassay platform	N/A	Peripheral	In development
GBD TB REaD™	Global BioDiagnostics (GBDbio), US: University of Texas, (US);Stanford University (Palo Alto, US); and BMGF, with support from FIND.	Reporter enzyme fluorescence (REF) to detect β -lactamase produced by live bacteria in sputum samples	N/A	Peripheral	In development
ImmiPrint	ProteinLogic, UK	Detection of antibodies as TB biomarkers in blood and other specimens using Immiprint platform	N/A	Peripheral	In development
SOMAmer-based detection of tuberculosis biomarkers	SomaLogic, US with support of BMGF	Proteomic assay performed on Somascan platform – measurement of TB bacterial and host proteins from blood sample	N/A	Peripheral	In development
Volatile organic compounds					
TB Breathalyser	Rapid Biosensor Systems, UK	Portable biosensor device for volatile organic compound in breath distinguishing active TB	N/A	Peripheral	In development
Breathalyzer device	Next Dimension Technologies, Inc. US, with support from BMGF	Device for volatile organic compounds to identify active TB	N/A	Peripheral	In development
Aeonose	The eNose Company, The Netherlands	Portable device for volatile organic compounds to identify active TB	N/A	Peripheral	In development
Breath analysis instrument	Metabolomx, US	Device for volatile organic compounds to identify active TB	N/A	Peripheral	In development
Breathalyzer test	Colorado State University (US), with Menssana Research Inc., US, with support from BMGF	Diagnostic breath test to identify TB	N/A	Peripheral	In development

Culture-based drug susceptibility testing					
BNP Middlebrook	NanoLogix, US	Culture based on BNP technology	Yes, XDR	District	In development
TREK Sensititre MYCOTB MIC plate	TREK Diagnostic Systems/Thermo Fisher Scientific, US	Dry microdilution plate containing lyophilized antibiotics for determination of minimum inhibitory concentrations of 12 TB drugs	Yes, XDR	District	In development.
MDR-XDR TB Colour Test	FIND and Imperial College, UK	Rapid colorimetric drug susceptibility test	Yes, XDR	District	In development.

Source: Adapted from TAG pipeline report, UNITAID TB Diagnostics Landscapes Report, with information from MSF Access Campaign and company websites.

ANNEX 8

TUBERCULOSIS VACCINES PIPELINE

Agent	Strategy	Type	Sponsors	Status
M. indicus pranii	Immunotherapeutic	Whole-cell M. indicus pranii	Ministry of Science and Technology, India, with Cadila Pharmaceuticals Ltd., India	Phase III
M. vaccae	Immunotherapeutic/Boost	Whole-cell M. vaccae	AnHui Longcom, China	Phase III
M72 + AS01 /GSK 692342	Boost /Post-infection	Adjuvanted subunit	GSK with Aeras	Phase IIb
VPM1002	Prime/Boost	Live recombinant rBCG	Vakzine Projekt Management GmbH, Germany; Max Planck Institute for Infection Biology, Germany; Tuberculosis Vaccine Initiative (TBVI); and Serum Institute of India	Phase IIb (planned)
ESAT6-CFP10	Prime/Boost	Adjuvanted subunit	AnHui Longcom, China	Phase IIb
RUTI	Boost/Post-infection/ Immunotherapy	Fragmented MTB	Archivel Farma S.L., Spain	Phase IIa
Hybrid 1 + IC31	Prime/ Boost / Post-infection	Adjuvanted subunit	Statens Serum Institut, Denmark; TBVI; Intercell AG, Austria and EDCTP	Phase IIa
Hybrid 56 + IC31 / AERAS-456	Prime/Boost/Post-infection	Adjuvanted subunit	Aeras; Statens Serum Institut, Denmark; Intercell	Phase IIa
Hybrid 4 + IC31/ AERAS-404	Prime/Boost	Adjuvanted subunit	Aeras; Statens Serum Institut, Denmark; Sanofi Pasteur, France; Intercell	Phase IIa
MTBVAC	Prime	Live genetically attenuated MTB	Biofabri, Spain; University of Zaragoza; TBVI	Phase IIa
ID93 + GLA-SE	Boost	Adjuvanted subunit	IDRI, US, with Aeras (US)	Phase IIa (planned)
Ad5Ag85A	Prime/Boost/Post-infection	Viral vector	McMaster University, Canada, with CanSino Biotechnology, Inc., China	Phase I
Crucell Ad35/MVA85A	Prime/Boost	Viral vector	Crucell, The Netherlands; Oxford University, United Kingdom; Aeras	Phase I
Dar-901	Prime/Boost	Whole-cell M. vaccae	Dartmouth-Hitchcock Medical Center (US) , with Aeras, US	Phase I
TB/FLU-04L (ESAT-6)	Prime	Viral vector	Research Institute for Biological Safety Problems, Kazakhstan	Phase I
ChAdOx1.85A/MVA85A	Prime	Viral vector	Oxford University, University of Birmingham, UK	Phase I
MVA85A aerosol	Prime	Viral vector	Oxford University, UK	Phase I
MVA85A/IMX313	Prime	Viral vector	Oxford University, UK, Imaxio, France	Phase I

Source: AERAS pipeline table, STOP TB pipeline table, TAG pipeline reports.

ANNEX 9

INFORMATION ON HUMAN AFRICAN TRYPANOSOMIASIS PRODUCTS

Medicines/New chemical entities

Fexinidazole (Phase II/III)

Description of product: Fexinidazole, part of the class of nitroimidazole, was discovered by the German pharmaceutical company Hoechst AG, but its development as a pharmaceutical was halted in the 1980s.

Ownership/development partners: DNDi, which signed an agreement with Sanofi (France) in 2009, has been managing the preclinical and clinical development, while Sanofi will manufacture, register and finance the distribution of the product to endemic countries through WHO.¹⁹⁹

Current phase: Fexinidazole is currently undergoing Phase II/III clinical trials for use in all stages of the *T. b. gambiense* disease. The pivotal trial directed to advanced second stage adult patients with direct comparison with NECT and completed patient enrolment (394) in April 2015. The protocol foresees enrolment of a total of 510 patients, including children. Follow-up is planned for 24 months with an endpoint at 18 months. Two additional trials (cohort studies with fexinidazole only) were started in 2014, with complementary populations of adults and children above six years of age. Both trials should end inclusions by the end of 2015, with an endpoint at 12 months and follow-up at 18 months. DNDi plans to trial Fexinidazole for *T. b. rhodesiense*. A trial size of 111 patients is planned for a single arm Phase II (proof of concept) study. The Swiss Tropical and

Public Health Institute is expected to perform the study with DNDi funds beginning in late 2015.

Regulatory: Sanofi and DNDi are planning registration through EMA Article 58. Following registration, fexinidazole shall be supplied and used under control conditions (Phase III trial) in health centres in place of hospital settings.

Potential market for other indications: Fexinidazole is undergoing investigation for leishmaniasis (Phase II) and Chagas disease (Phase II). The potential market could therefore be extended, especially in light of the investigation for canine leishmaniasis by Merial, the veterinary branch of Sanofi. No information is available in the public domain apart from a patent application by Merial for fexinadole use to treat canine leishmaniasis dated July 2014.²⁰⁰

Administration: Fexinidazole treatment is administered orally and lasts 10 days. In order to be absorbed, it requires administration following food intake.

Prices: Fexinidazole is expected to be priced around \$50 per course of treatment, but the price could be lowered with increased use of the medicine for other diseases and veterinary use. It will be much cheaper than NECT, the current treatment option for stage 2 (advanced stage) HAT gambiense, which costs EUR 220 per course.

Simplification of storage and supply: A NECT kit of four treatments is bulky, weighing 36 kg.²⁰¹ If proven effective and safe in Phase II/III, the introduction of

oral fexinidazole will also have a positive impact on the cost of storage and distribution of HAT medicines.

Financing of production and supply: The financing system and the system for production, procurement, storage and supply of fexinidazole are expected to be the same as that used for NECT. Sanofi will fund production, storage and distribution of fexinidazole to countries through a centralized system managed by WHO.

SCYX-7158 (Phase I)

Description of product: SCYX-7158 belongs to the class of oxaboroles. It has a long half-life and could potentially be administered as a single dose.

Ownership/development partners: SCYX-7158 was originally provided by Anacor Pharmaceuticals (United States) and screened for activity against *T. brucei* at the University of California, San Francisco (United States).²⁰² It has been licensed to DNDi, which undertook clinical development. Discussions are ongoing with Sanofi for industrial development.

Current phase: Phase II/III is expected to start in 2016 using/expanding the pool of clinical trials sites used for the fexinidazole trial.

Rapid diagnostic tests

SD Bioline HAT

Description of product: Developed by Standard Diagnostics, Inc., Republic of Korea/Alere, United States, with the support of FIND and funding from BMGF. It was brought to the market in September 2013.^{203, 204}

Prices: Its full cost is USD 0.75/test, but the price has been subsidized by BMGF to reach USD 0.5/test. The subsidy is for 1 million tests.

Field validation: FIND has evaluated the test both in the laboratory and in the field and is introducing the test, as well as mobilizing funds for procurement

by national programmes. WHO has received 20,000 tests for review of its use in the field.²⁰⁵

Additional information: FIND is piloting different strategies for *T. b. gambiense* HAT diagnosis, for the roll-out of this RDT coupled with LAMP, and improved microscopy in eight countries.

HAT Sero-K-SeT

Description of product: HAT Sero-K-SeT was developed by Coris BioConcept (Belgium) and the European research network, NIDIAG, with the support of ITM, which included laboratory evaluation and field validation of the test.²⁰⁶

Prices: The cost of this test, which is not subsidized, is EUR 1.20/test.

Field validation: The results of laboratory and field evaluations have been published in scientific journals, the last being released in May 2014.^{207,208} WHO will review 2,000 tests for use in the field.

Confirmatory diagnostic tests

mini Anion Exchange Centrifugation technique (mAECT)

Description of product: This confirmatory parasitological test, known also as 'mini-column', allows filtering and concentration of parasites, to be subsequently detected through microscopy. The parasites are separated from venous blood in a gel column by anion exchange chromatography and collected in a sealed glass tube.

Ownership: Developed and produced by INRB (Kinshasa, Democratic Republic of Congo), with support from ITG and FIND.²⁰⁹

Price: The test is expensive, costing between \$3.00 and \$5.00 per test based on volumes produced. Production depends on the availability of a gel produced solely by General Electric (United States).

Securing material and production: Discussions are ongoing between WHO and the General Electric Foundation to secure production, reduce cost and possibly fund the supply of mAECT to national control programmes.

WHO aims to find a partner to support production, availability and supply.⁶⁸

Improved microscopy to support HAT confirmation

Description of product: Light-emitting diode (LED)-based fluorescence microscopy is being trialled for HAT diagnosis. Visualization of the trypanosoma parasites is much easier with LED microscopy. Work is ongoing on parasite-concentration techniques and improved performance of microscopy for HAT. The platform was first developed for TB diagnosis and in 2011, WHO recommended substitution of conventional fluorescence microscopy with LED microscopy.²¹⁰

Developers: FIND partnered with Carl Zeiss Micro-imaging GmbH (Germany) for development of a durable, affordable and easy-to-operate LED-based fluorescence microscope. Other producers of microscopes are also including LED lamps in commercialized models.

Price: The LED microscope lamp is inexpensive when compared to the mercury vapour or halogen lamp used in regular fluorescent microscopy and has a life span of more than 10,000–50,000 hours.

Additional information: FIND is using LED microscopy in its country piloting studies for defining a HAT diagnostic algorithm.

ANNEX 10

INFORMATION ON LEISHMANIASIS PRODUCTS

Medicines/New chemical entities for visceral leishmaniasis

Fexinidazole (Phase II)

Description of product: Fexinidazole belongs to the class of nitroimidazole. It was discovered by the German pharmaceutical company Hoechst AG, but its development was halted in the 1980s.

Developers: DNDi for preclinical and clinical development with Sanofi for industrial development for HAT.

Current phase: The Phase II trial in Sudan was stopped to review the drug dosage and duration. Drug–drug interaction studies of fexinidazole with miltefosine will take place in first quarter of 2016 in order to assess feasibility to combine the two drugs in an FDC.

Other issues: See section 4.1.1 as fexinidazole is trialled for HAT in Phase II/III.

Regulatory: If successful in Phase III, fexinidazole is likely to be developed and registered by the EMA through Article 58 as a single entity for VL.

Pharmacological topical interventions for cutaneous leishmaniasis

WR 279,396 (Phase II/III)

Description of product: A topical cream (15 percent paromomycin + 0.5 percent gentamicin).

Ownership/Developers: The United States Walter Reed Army Institute of Research (WRAIR) is the developer of the WR 279,396 cream.

Current phase: It is undergoing several Phase II and III studies. The results of a Phase III trial in Tunisia conducted in collaboration with the Institut Pasteur of Paris and Tunis University (Tunisia) were published in 2013.²¹¹ WR 279,396 is currently under Phase III trial in Panama to explore the use of the topical cream for NWCL.

Other issues: No commercial partner has been yet identified for this topical cream. The US FDA has designated WR 279,396 as eligible for fast-track review and granted 'orphan drug' designation. The Office of the Surgeon General of the United States Army sponsored the submission of an investigational new drug application (IND 50098).

Anfoleish (Phase II)

Description of product/Developers: A topical cream (three percent Amphotericin B) developed by the Programa de Estudio y Control de Enfermedades Tropicales (PECET), Universidad de Antioquia, Medellín, Colombia, and Humax Pharma, Colombia, in collaboration with DNDi for NWCL.

Current phase: Enrolment in a Phase II trial is expected to be concluded by the end of 2015. If successful, it will move to Phase III in 2016.

Nano-liposomal paromomycin cream (Phase III)

Description of product/Developers: A topical formulation (liposomal formulation containing 10 percent of paromomycin) developed by the Tehran University (Islamic Republic of Iran).

Current phase: Currently under Phase III trial in OWCL. One trial was supported with domestic funds. Another trial combining the topic formulation with meglumine antimoniate and comparing it to heat therapy is expected to be undertaken with funding from the WHO Regional Office for the Eastern Mediterranean.²¹²

Another paromomycin ointment formulation (Phase I) is under development by the Oswaldo Cruz Foundation (Fiocruz) (Brazil).

Pharmacological systemic interventions for cutaneous leishmaniasis

Oleylphosphocholine (OIPC) (Phase I)

Description of product: l-α-oleylphospholipid oleylphosphocholine (OIPC) is a structural analogue of miltefosine. In preclinical studies it shows promise in VL and CL/ML.

Ownership/development partners: OIPC was discovered at the Max Planck Institute for Biophysical Chemistry

(Germany) and licensed to Dafra (Belgium).²¹³ Dafra is seeking public and/or private partners for developing this NCE for leishmaniasis.

Current status: The drug is undergoing a Phase I (safety and pharmacokinetics) study in Kenya.²¹⁴ Results are expected to be published in the second half of 2015. Phase II trials are planned for CL/ML in

New World and Old World. The company is aiming for market entry by 2020.

Regulatory: Dafra obtained 'orphan drug' designation from the US FDA and EMA.²¹⁵ If there is success in the clinical phase, registration will probably be undertaken with US FDA, where incentives such as the tropical disease voucher are available upon registration of tropical disease drug products.

Non-pharmacological interventions for cutaneous leishmaniasis

Thermomed

Description of product: Thermomed, developed for skin cancer treatment, is a non-invasive medical device that utilizes radio frequency to generate heat within the skin tissue. The abnormal and diseased cells cannot tolerate the heat and die, while the surrounding healthy cells are not compromised as the temperature is within a tolerable range. The death of the diseased cells activates the immune system, improving the healing of the treated area.

Ownership/development partners: Thermosurgery Technologies, Inc., United States, developed Thermomed.

Current phase: Randomized controlled trials comparing a single application of heat with Thermomed with systemic treatment have been performed on CL for NWCL and OWCL.^{216,217}

Other issues

Regulatory: Thermomed received US FDA market approval for CL, among other diseases.²¹⁸

Intellectual property: Thermomed is covered by patents.

Price: High price (around \$25,000) and some issues related to power supply, have hindered its use as a non-pharmacological treatment for CL. In 2013, following a change in the management of the

company, the price of the machine was reduced to USD \$6,500 for CL and improvements were made to the device.

HECT-CL (Phase I/II)

Description of product: Hand-held exothermic crystallisation therapy for CL (HECT-CL) is a customised heating pack that delivers controlled conduction heat starting at 52°C and decreasing to 48°C over a three-minute period when applied over a CL lesion. It is a vinyl pouch containing a super-saturated sodium acetate salt solution; it can be activated to achieve 52°C in 10 seconds.

Status: HECT-CL was tested in two small cohorts of patients in Pakistan and Peru.^{219,220}

Price: HECT-CL is designed to be a low-cost tool to expand thermotherapy at the community level. The price is expected to be less than \$3.00.²²⁰

Applicability: HECT-CL is administered in a safe and easy manner by health workers upon training, with the aim of allowing use at the community level.

Nitric oxide-releasing patch (Phase III concluded)

Description of product: A Phase III trial focused on a nitric oxide-releasing patch. The topical administration via a transdermal patch producing a continuous release of nitric oxide ($\approx 3.5 \mu\text{mol NO}/\text{cm}^2/\text{day}$ for 20 days) was compared with intramuscular meglumine antimoniate for the treatment of NWCL.

Status: The Phase III results, low frequency of adverse events and the facility of topical administration promote the development of new generations of nitric oxide releasing patch (NOP) systems for the treatment of CL.²²¹

Diagnostic tests for visceral leishmaniasis

Table A1. List of VL RDTs evaluated by WHO.

Test	Developer(s), Country	Type	WHO reviewed
Kalazar Detect™	Inbios, US, with IDRI	RDT rK39	Yes
DiaMed-IT LEISH	Bio-Rad Laboratories, Inc., Brazil	RDT rK39	Yes
Crystal®KA	Span Diagnostics Ltd., India	RDT rKE16	Yes
Signal®-KA*	Span Diagnostics Ltd., India	RDT rKE16	Yes
Onsite Leishmania Ab Rapid Test (2.0)	CTK Biotech, Inc., US	RDT rK39	Yes

* Require storage between 2°–8°C.

Leishmaniasis vaccines and immunomodulators

Table A2. List of leishmaniasis vaccines listed for clinical trials.

Vaccine	Strategy	Sponsors/Developers	Status
VL/CL: ALM + BCG	Preventive	CL: Tehran, Isfahan and Kerman Universities with the Razi Vaccine and Serum Institute and the Ministry of Health, Islamic Republic of Iran VL: The Institute of Endemic Diseases (IED), University of Khartoum (Sudan)	Phase III completed
VL: Alum ALM+BCG	Preventive & Therapeutic	Razi Vaccine & Serum Institute, Islamic Republic of Iran, and IED, Sudan	Phase IIb completed
CL: LEISH-F1+MPL-SE (Leish-111f + MPL-SE)	Preventive	IDRI with BMGF	Phase II completed
CL: LEISH-F2 + MPL-SE with SSG	Therapeutic	IDRI	Phase II completed
PKDL: LEISH-F2 + MPL-SE with SSG	Therapeutic	IDRI and IED, Sudan	Phase IIb completed
ML: LEISH-F1+MPL-SE (Leish-111f + MPL-SE)	Preventive	IDRI with BMGF	Phase I completed
CL: LEISH-F1+MPL-SE with meglumine antimoniate	Therapeutic	IDRI	Phase I completed
CL: autoclaved L.major antigen +rhIL-12+ aluminium hydroxide gel	Preventive	NIAID with National Institutes of Health Clinical Center, US	Phase I completed
VL/PKDL: ChAd63-KH	Therapeutic	York University (UK), Wellcome Trust (UK), Okairos, Switzerland, and Robert Koch Institute, Germany	Phase I completed
VL: LEISH-F3 + SLA-SE compared to LEISH-F3 + GLA-SE	Preventive	IDRI with BMGF and Zydus Cadila, India	Phase I ongoing
MGN1331	Preventive	LEISHDNAVAX consortium and Mologen AG, Germany	Phase I (planned)
PKDL/CL: CpG ODN (D35)	Therapeutic	US FDA, Osaka University, Japan, and DNDi	Phase I (planned)

ANNEX 11

INFORMATION ON CHAGAS DISEASE PRODUCTS

Medicines/New chemical entities for Chagas disease

Posaconazole (Phase II)

Description of product: Posaconazole is an antifungal triazole drug approved by the US FDA in November 2013 with the commercial name, Noxafil®, for prophylaxis of invasive *Aspergillus sp.* and *Candida sp.* infections in severely immunocompromised patients above 13 years of age and for the treatment of oropharyngeal candidiasis, including when refractory to itraconazole and/or fluconazole. It is also registered in Europe, the Middle East and Africa and in countries in other regions.²²²

Ownership/development partners: Posaconazole was discovered and developed by the Schering-Plough Corporation, which has merged with Merck & Co. (United States).

Current phase: Two Phase II trials have tested the its efficacy in Chagas disease. The results of one Phase II trial (CHAGASAZOL), undertaken by the Hospital Universitari Vall d'Hebron Institut de Recerca in collaboration with the Tropical Medicine and International Health Unit of Drassanes, and the International Health Unit Metropolitana Nord of Santa Coloma, in Barcelona, Spain, assessed the efficacy and safety of posaconazole as compared to benznidazole in adults, were published in May 2014. Posaconazole showed anti-trypanosomal activity in patients with chronic Chagas disease. However, significantly more patients in the posaconazole groups than in the benznidazole group had treatment failure during follow-up.¹⁰⁸ The other trial

(STOP CHAGAS), sponsored by Merck (US), has three arms, which compare posaconazole, the combination posaconazole with benznidazole, and benznidazole. Results are expected by the end of 2015.

E1224 (Phase II)

Description of product: E1224 is a water-soluble monolysine salt pro-drug of ravuconazole with improved absorption and bioavailability compared to ravuconazole.

Ownership/development partners: E1224 was discovered by the Eisai Co. (Japan). In 2009, DNDi signed an agreement with Eisai to develop this NCE for Chagas disease.

Current phase: A Phase II clinical trial, performed by DNDi and Eisai, compares different doses of E1224 and benznidazole. The study concluded recruitment of 231 adult patients with chronic indeterminate stage of Chagas disease in June 2012 and its results were presented in November 2013 at the Annual Meeting of the American Society of Tropical Medicine and Hygiene. E1224 was found to be ineffective as monotherapy if compared to benznidazole. DNDi has thus revised its strategy around this NCE and a drug–drug interaction study to assess the feasibility to combine E1224 with benznidazole was concluded in December 2014. A Phase II proof-of-concept trial will start by the end of 2015 to assess combinations at different dosages and lengths of treatment. The DNDi goal is to proceed to Phase III in 2017.

Fexinidazole (Phase II)

Reference is made to description given under section 4.1.1.

Current phase: A Phase II trial to assess efficacy in Chagas disease began in June 2014; the follow-up period is expected to be completed in 2015. Based on the outcome of Phase II trials on fexinidazole monotherapy, E1224-benznidazole combinations and lower dose/reduced course of benznidazole (see below), DNDi will proceed to design a Phase III trial with several arms to compare different interventions.

Benznidazole low dose/reduced length

Current phase: Several groups are investigating shorter treatment durations, intermittent treatment and different dosages of benznidazole to achieve better efficacy, safety and tolerability profiles. Among those, DNDi is going to assess shorter benznidazole treatment at a lower dosage in a Phase II trial. The trial is expected to start by the end of 2015 in several countries.

Ownership and governance: Benznidazole is now produced by Laboratorio ELEA (Argentina). Benznidazole was developed and marketed by Roche (Switzerland), which decided to stop production and transferred technology to the Government of Brazil in 2003. LAFEPE Medicamentos, a Brazilian state company, took over drug production and supply in 2006. However, there was no sustainable plan for securing the API and for meeting ANVISA (Brazilian Health Surveillance Agency) and WHO quality standards in the production of the finished formulation. The ANVISA Good Manufacturing Practice (GMP) certificate of LAFEPE expired in 2010 and it was not renewed for over three years, leading WHO to stop the supply of the drug.²²³ Benznidazole production resumed in March 2012 through a PPP that brought together the Ministry of Health of Argentina, Fundación Mundo Sano (Spain), Maprimed S.A. (Argentina) (in charge of the synthesis of the active ingredient), and Laboratorio ELEA (Argentina) (responsible for development, registration and distribution of the finished formulation).²²⁴ The global shortage of benznidazole in 2011–2012 is one

of the striking examples of the lack of governance systems for single source medicines for neglected tropical diseases.

Rapid diagnostics tests for Chagas disease

WHO/MSF multi-centre Chagas infection RDTs evaluation project

Phase I concluded: The multi-centre study at the national reference laboratory level determined that eight out of 11 assessed RDTs were valuable for use. The retained RDTs for second phase evaluation are listed in table A3. Of the eight tests, two (ImmunoComb II Chagas Ab kit and the Serodia-Chagas test) require laboratory resources, longer reading time or a more lengthy procedure to meet the conventional definition of RDTs. They could be defined as 'semi-RDTs'. The retained RDTs can be recommended for screening and surveillance in endemic and non-endemic areas, but the results need to be confirmed in a reference laboratory. To confirm the present data, especially the reproducibility in resource-limited settings, further studies should be conducted in various laboratory and field settings.¹¹¹

Phase II ongoing: The evaluation will be performed at POC to generate evidence for use of RDTs in detection of Chagas disease by selecting the best-performing RDT for the endemic species and context of the country. Two approaches are pursued based on the outcomes of this validation process. The first approach is to recommend a screening RDT with high sensitivity to be executed at primary health care and that, if positive, will lead to a confirmatory test at the laboratory level. The second and most desired approach is to define an algorithm for the use of one or two RDTs, enabling Chagas disease diagnosis at primary health care with no need for laboratory confirmation. It is foreseen that the definition of such RDT-based diagnostic algorithms targeted to different geographical areas should be feasible within a four-year period.

Table A3. Chagas infection rapid diagnostic tests retained during the first phase of the WHO/MSF evaluation

Test Name	Manufacturer (Country)	Type of test	Storage temp (°C)	Reading time (min)	WHO multicentre review outcome	
					Use	Setting
OnSite Chagas Ab Rapid test	CTK Biotech Co., US	RDT	2–30	15	screening*	primary health care
WL Check Chagas	Wiener Laboratories, Argentina	RDT	2–30	25–35	screening*	primary health care
Trypanosoma Detect Rapid Test	InBios, Inc., US	RDT	2–28	10–15	screening*	primary health care
Chagas Quick Test	Cypress Diagnostics, Belgium	RDT	2–28	10–15	screening*	primary health care
Chagas Stat-Pak assay	Chembio, US	RDT	8–30	15	screening*	primary health care
SD Chagas Ab Rapid	Standard Diagnostics, Inc., Republic of Korea	RDT	1–30	15	screening*	primary health care
Serodia Chagas	Fujirebio Diagnostics Inc., Japan	Semi- RDT (ELISA)	2–8	120	screening*	laboratory infrastructure required
ImmunoComb II Chagas Ab	Orgenics Ltd., Israel	Semi- RDT (agglutination test)	2–8	60	screening*	laboratory infrastructure required

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