THELIFEPRIZE

ANTIMICROBIAL RESISTANCE

SUBMISSION TO THE STANDING COMMITTEE ON HEALTH (HESA)

Submission by Doctors Without Borders/Médecins Sans Frontières (MSF) and The International Union Against TB and Lung Disease

OCTOBER 2017

The Union

International Union Against Tuberculosis and Lung Disease
Health solutions for the poor

MEDECINS SANS FRONTIERES
DOCTORS WITHOUT BORDERS

Introduction

International Union Against Tuberculosis and Lung Disease (The Union) and Doctors without Borders/Médecins Sans Frontières (MSF) provides the following written submission regarding access to medicines and biomedical innovation for consideration by the House of Commons Standing Committee on Health's (the Committee) study on antimicrobial resistance (AMR).

The first descriptions of infectious diseases becoming resistant to the anti-microbial treatments available were in 1948 and were for drugs to treat tuberculosis (TB).[i] Since then, antimicrobial resistance (AMR) has become recognized as a global health threat with glaring economic and social consequences. It is estimated that $100 trillion USD of economic output will be lost due to AMR by 2050.[ii] Moreover, TB - the leading infectious disease killer, causing 1.8 million deaths annually, higher than malaria and HIV combined[iii] - makes up a substantial portion of the AMR problem. Drug-resistant TB (DR-TB) led to over 250,000 deaths globally in 2015[iv]. By 2050, the global annual death toll from DR-TB is expected to rise to 2.5 million representing a quarter of all AMR deaths.[v] It is for this reason that the fight against TB is recognised as "a cornerstone of the global AMR challenge"[vi].

The increasing awareness of AMR's threat to global health has captured the interest of world leaders. In 2014, Canada developed a Federal Framework for action against AMR, with Rona Ambrose, the Minister of Health at the time, acknowledging that the issue holds "profound impacts on [Canada's] healthcare system" as well as being a "global public health concern"[vii]. In the same year, the United Kingdom commissioned the Review on Antimicrobial Resistance, while the United States issued the National Strategy for Combating Antibiotic-Resistant Bacteria. In September 2016, the United Nations held a high-level meeting on AMR, where world leaders committed to making AMR a global priority.

Within Canada, TB affects over 1,600 people, with an 8% mortality rate. These rates have remained stable for the past decade, though TB disproportionately affects Canada's Indigenous communities, particularly Inuit communities, where the incidence reaches 166.2 per 100,000 compared to the national rate of 4.4 per 100,000.

MSF is one of the largest TB treatment providers in the world. In 2016, MSF provided treatment and care to 21,000 patients with TB and 2,700 patients with multi-drug resistant TB (MDR-TB) in 33 countries. Regrettably, current TB treatment is long, painful, and ineffective. Treatment for drug-sensitive TB is six months while DR-TB requires a minimum of 5 different antibiotics, all of which are toxic and include side-effects such as permanent deafness, nausea, vomiting, and pain. Despite the treatment lasting up to 2 years and requiring up to 15,000 pills, the success rate is only about 50%[viii].

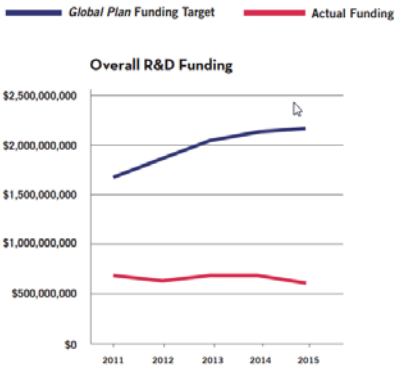

Figure 1 - 2011–2015 Global Plan Funding Targets versus

Unfortunately, even as the global numbers of people affected by drug resistant forms of TB increases year upon year and despite the poor outcomes of the current treatments, investment in TB R&D has decreased. Only $620M USD was invested in TB R&D in 2015, a decrease of $53M USD since 2014 and far below the $2.1B USD required[ix]. Primarily due to low profits from TB treatment (a challenge faced across the

board in AMR), a market failure exists.

This lack of investment in TB R&D has resulted in only 2 new compounds registered for the treatment of DR-TB in the last 50 years and only 7 compounds in clinical development, far short of the Stop TB Partnerships Global Plan (2011 -2015) which set a target for 21 compounds to be in phase 1 trials by 2015. (Fig 2)

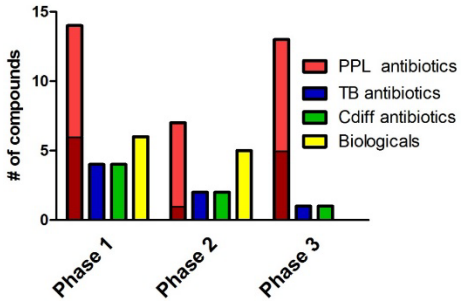

Figure 2: Number of compounds in clinical development for Priority AMR pathogens.

TB requires a combination of drugs to be used together. Because the new drugs have been developed independently, they have not resulted in a shorter or less toxic treatment because they were not initially studied in combination with one another. It is only now that the new drugs are registered and on the market that they are being trialled as part of shorter treatment combinations.

It is clear that not only is investment in TB antibiotic development insufficient but that the current model of R&D is not meeting the public health needs for TB. To address this, MSF, The Union, and others have launched a new project - the Life Prize – to develop new TB treatments and address the multiple challenges that exist for TB antibiotic development.

The Life Prize is a new way of incentivising and rewarding investment in developing antibiotics for TB by piloting a new and innovative mechanism that could have far reaching impacts for the development of new antibiotics for other priority pathogens.

About the Life Prize

The Life Prize is a new and innovative funding mechanism for the development of drugs and treatments for TB. It aims to deliver a short regimen for all forms of TB that works for everyone, everywhere within the next ten years.

The Life Prize will award prizes to researchers with drugs entering clinical development, rewarding them for investing in and developing new drugs for the treatment of TB. Receiving a prize will come with an obligation that all the data and intellectual property generated from these new products will be pooled to allow others to access and use new knowledge and data, leading to easier and faster combination product development for treatments that improve the current TB treatment. Incremental improvements will be seen in the treatment of TB, particularly improvements in DR-TB treatment in the short term, with the ultimate aim of a short cure for all forms of TB, i.e. a pan-TB regimen. By rewarding and funding the research into new drugs and treatments, all the treatments that are developed through the Life Prize framework will be affordable and accessible to all in need of them.

How it relates to AMR

The numerous reports and statements from world leaders and experts recognize the need to change the R&D approach to AMR. The UN Declaration on AMR, the UK AMR review and the UN High Level Panel (HLP) on Access to Medicines all suggest "delinking the costs of research and development from the end product" as a path forward.[x] These de-linkage models promote the development of affordable medicines based on the needs of patients rather than on potential profits for pharmaceutical companies.

The successful implementation of the Life Prize will act as a springboard for future AMR drug development. It will show that a new model of financing R&D, which de-links the cost of R&D from the end product, can work and result in a treatment that answers the public health need and is available for all. Antibiotics that are effective for TB often have other infectious disease indications and by stimulating R&D into TB antibiotics, additional new antibiotics may be discovered and developed for other antimicrobial indications.

The Life Prize is a solution to a significant proportion of the AMR problem, is ready to launch now, and can be a pathfinder for some of the new models suggested for AMR.

How the Life Prize aligns with Canada's goals

The Government of Canada has committed itself to be an international leader in innovation and stewardship against AMR[xi]. The Federal Action Plan on AMR lays out actions to be undertaken in the fight against AMR including: "Promote innovation through funding collaborative research and development efforts on antimicrobial resistance both domestically and internationally."

The Government of Canada acknowledges the need for more AMR-related innovation in the life sciences sector, and hopes to model how barriers to innovation can be overcome. The Life Prize will promote such innovation in the fight against TB, and against AMR more broadly, by increasing R&D activity in the drug sector. This aligns with Canada's aims and will place Canada in a global leadership position for future discussions.

Furthermore, the Government of Canada requires innovation go hand in hand with stewardship, which is at the heart of the Life Prize. The Life Prize will ensure good stewardship of new TB drugs, ensuring fair access through wide distribution and affordable prices, as well as stringent manufacturer requirements.

The Life Prize aligns not only with Canada's objectives for boosting innovation and ensuring stewardship for AMR, but also those of the international community, including the World Health Organization (WHO). The WHO Global Action Plan on AMR states that "new concepts are needed for providing incentives for innovation and promoting cooperation among policy-makers, academia and the pharmaceutical industry". The importance of "equitable access to quality-assured products" is further stressed, as the fight against AMR must be global and collaborative[xii].

The WHO further recommends national governments work on the "piloting of innovative ideas for financing research and development and for the adoption of new market models to encourage investment and ensure access to new antimicrobial products"[xiii]. This reiterates the need for new incentive structures to ensure pharmaceutical companies invest in the necessary R&D to fight AMR.

This is at the core of what The Life Prize will achieve, and again provides an opportunity for Canada to be the global leader in the field of innovative R&D models.

This sentiment is mirrored by G7 and G20 health ministers. The former are "committed to explore innovative economic incentives to enhance the research and development of new antibiotics". The Life Prize aligns closely to the G7's declaration, which emphasises "a market entry reward mechanism". Furthermore, the G20 recognises not only that DR-TB is an important threat within AMR but also that the R&D pipeline for new antimicrobials is drying up. This can be reactivated through "incentive mechanisms that avoid the reliance on high price/volume combinations", which is a specific characteristic of the Life Prize. Canada should seize its opportunity to be a global leader in the fight against AMR by placing innovative ventures such as the Life Prize high on the global agenda during its presidency of the G7 in 2018.

The Life Prize lays the path for Canada to tackle the threat of AMR within its borders, helping the 1,600 Canadians affected by TB yearly and reversing the high rates of TB within key populations and creates an opportunity for Canada to cement its position as an innovative global health leader.

Mechanisms of the Life Prize

The phase one entry prize will be awarded to drugs with specific characteristics decided upon by an independent Scientific Advisory Committee (SAC). To be eligible for the prize the drug developer will also need to commit to sharing the intellectual property and pre-clinical data with the Life Prize. The prize is open to all entities involved in drug development, including: academic institutions, small and medium sized biotech companies, and larger pharmaceutical companies.

Once the compound has won the prize, it enters the Life Prize framework and is available for further development. All further clinical development will be grant funded by the Life Prize network[1]. After the initial phase one trial for the individual compound, i.e. from phase 2 onwards, only clinical trials looking at new combinations working towards a target regimen profile, as specified by the WHO[xiv], will be funded. (Figure 3). The sharing of the data and intellectual property will facilitate researchers and developers who wish to test new combinations to do so, rather than being hamstrung by long negotiations or unaffordable licensing fees. This allows for earlier, easier and faster development of new antibiotic combinations for the treatment of TB.

[1] The framework includes new grant funding given by the Life Prize but also existing entities funding TB clinical trials such as NIH, NIAID, EDCTP.

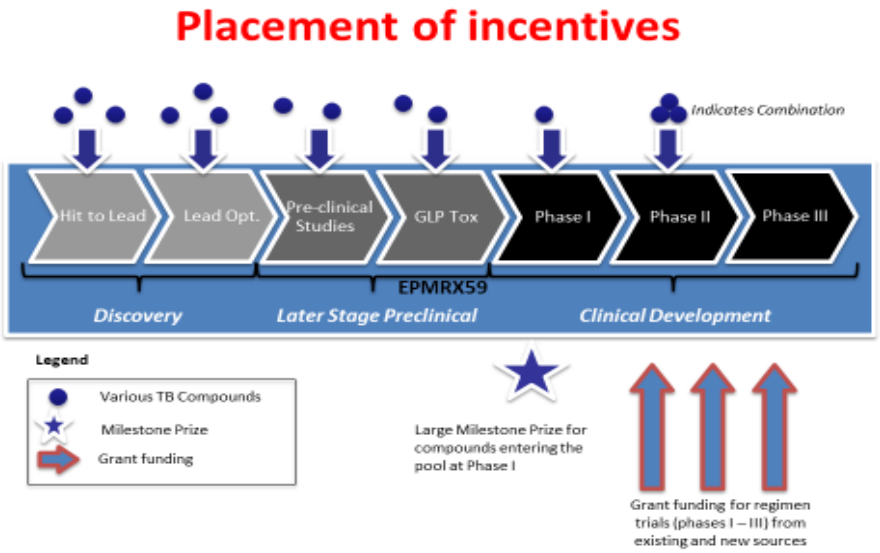

Figure 3: The incentives for the Life Prize.

Once a successful new treatment combination has been developed it will be made available for large scale production. Where appropriate, competition will be encouraged to decrease prices and ensure the medicines are affordable. Secondly, manufacturers will be held to certain quality and stewardship standards and any behaviour violating such standards or otherwise seen as promoting "inappropriate use" will lead to the manufacturer's licence being retracted.

Who is the Life Prize

The Life Prize is a collaboration of major TB organisations. The Steering committee of the project is chaired by the South African Director General of the National Department of Health and has representatives from the major TB organisations. SC members in Appendix A.
The Medicines Patent Pool (MPP)[2] will in-license and manage IP (e.g. as obtained through the prize and grants), and out-license the IP fairly to encourage collaboration, regimen development, and affordable or competitive production of the final regimens. All scientific data produced through Life Prize-funded research will be shared, via the Critical Path Institute (C-Path)[3]. The data are standardized using the CDISC TB Clinical Data standard which allows for the aggregation of data across multiple sources to maximize scientific insights and can speed up registration of final regimens by meeting the expectations of regulatory agencies. The International Union Against Tuberculosis

[2] The Medicines Patent Pool (MPP), is a United Nations-backed organisation founded in July 2010. The MPP aims to improve access to appropriate, affordable HIV medicines and technologies for people living with HIV in developing countries. Working in partnership with a range of stakeholders, the MPP opens the door to generic low-cost production of key HIV therapies as well as fixed-dose combinations and paediatric formulations by creating a pool of relevant patents for sub-licensing and product development. It has recently had its mandate extended to include TB

[3] C-Path has over 10-years of experience managing large data collaboration programs and leads multiple TB–focused data collaboration efforts

and Lung Disease (The Union) will be the acting secretariat of the Life Prize and will accept and manage grants and prizes. It will also coordinate the fundraising and advocacy of the Life Prize with the other key partners.

Current TB Costs

With half a million people affected by DR-TB yearly, the human cost of the disease is high, and this translates to a significant economic cost. Furthermore, this cost is steadily increasing, with an extra 2.5M people estimated to be dying yearly from DR-TB by 2050. This disease is expected to cost US$ 16.7T over the next 35 years, reducing global GDP by 0.63%.

15,993 cases of TB were reported in Canada between 1997 and 2008[xv]. 1,231 of these were DR-TB and 176 were multi-drug-resistant TB, treatment for which amount to around CA$ 250,000 per patient[xvi]. These resistant forms of TB represent the minority of TB cases but require significant funds to cure. Developing new TB regimens that are shorter and more affordable would decrease the economic burden of TB and MDR-TB on Canada.

Cost of The Life Prize

The large majority of funding needed for the Life Prize will be for prize and grant pools. It is estimated that in order to achieve an entirely new pan-TB regimen, the project will need to support at least 18 prizes for drugs obtaining investigational new drug (IND) approval. With a value of US$ 30-40M each, the total prize funding will be $900M.

Grant funding for trials will be provided leading up to each drug development phase. The Life Prize will look to secure funding for at least 18 grants of US$ 2-3M for drugs entering Phase I, 13 grants of US$ 10-15M for those entering phase II, and 6 grants of US$ 70-80M for Phase III. This amounts to a total grant pool of $580-725M.

In total, the incentive mechanism will require $1.5-2.1B in funding over ten years. Funding for the incentive mechanism is likely to come from a consortium of governments and other research funders.

Conclusion

With the risks of AMR increasing rapidly, clear and immediately implementable solutions for ensuring the treatments of the future are developed need to be found, and ensure affordability and access of final antibiotics developed. It is important that the products developed are used sparingly to preserve the efficacy, and this generally means that the current model of re-couping R&D costs through high prices while marketing the product widely is not suitable for AMR. Simply put, new antibiotics are used sparingly, for a short amount of time, and thus their potential to generate significant revenue relative to their development costs is limited. This lack of profitability has resulted in a withdrawal of some major pharmaceutical companies from R&D into antibiotic development, particularly in the area of TB antibiotic development, leaving the pipeline of new treatments dry and unable to respond to the rising numbers of drug resistant infections, particularly DR-TB. By investigating new models that try to overcome the challenges of incentivising the much needed research into R&D into AMR whilst ensuring affordability and stewardship will be key to developing the treatments of the future. The Life Prize is one of these solutions, enhancing R&D for

DR-TB, and creating a path for future AMR research with the potential to transform the drug development landscape towards a more equitable model.

As well as funding to support these new models, political and policy support is needed to create an environment that allows these new models to reach their potential and ensure that public investment results in affordable and appropriate products that address the obvious public health need. The prominent position of the Canadian government as not only a leader in global health but as the upcoming chair of the G7 will allow for new ideas and solutions and the policies required for them to be discussed at the highest level.

Recommendations

1. **Support new incentives and models of R&D for AMR.**

The Canadian government is at the forefront of discussions on AMR at both the G7 and G20. With the recent focus on practical market incentive options, the Standing Committee on Health can recommend that the government promote and support (politically and financially) new models of R&D and incentives that consider the market challenges that exist for AMR and TB. This should include ensuring appropriate access and affordability provisions are considered from the beginning of clinical development of an antibiotic, particularly when the R&D receives direct or indirect public funding. **We ask the Health Committee to recommend that the government use Canada's G7 Presidency to leverage investments in global initiatives that address the market failures that exist in AMR and continue to build on the work of the G20 examining practical market incentive options to stimulate R&D that results in new, affordable, and accessible antimicrobials.**

2. **Investigate how public funding with public health oriented terms and conditions can promote and support good stewardship practices**

Antimicrobial stewardship can be defined as the promotion of appropriate use of antimicrobials while reducing their inappropriate use; improving patient outcomes; reducing microbial resistance; and decreasing the spread of infections caused by multidrug-resistant organisms. The ultimate aim of such stewardship is to conserve the effectiveness of antimicrobial medicines by delaying the formation of resistance as long as possible through appropriate use. In the case of TB, an important component of stewardship is ensuring that new drugs are developed as part of new regimens rather than being added to existing treatments or made available as single agents. For new TB regimens developed through the Life Prize, key stewardship considerations will be in-built from the start through contractual mechanisms. Although many of the most important mechanisms for promoting the appropriate use of antimicrobials, such as clear treatment guidelines, proper training for healthcare professionals and the availability of appropriate diagnostic tools, are beyond the scope of the terms and conditions included in a manufacturing licence for an antibiotic, there are important stewardship-related considerations that can be included. These include, for example, the requirement for manufacturers to meet international quality standards (WHO prequalification, Stringent Regulatory Agency approval), guidelines on proper waste disposal to reduce the release of antibacterial active pharmaceutical ingredients into the environment, and guidelines relating to appropriate marketing and promotion. The Medicines Patent Pool (MPP) will ensure that the licences for manufacture of any outputs of the Life Prize will include requirements for promoting good stewardship practises in line with their stewardship report[xvii]. **We ask the Health Committee to**

examine how Canadian Government funding for R&D can reinforce and promote the stewardship of new antibiotics, including new TB regimens, while ensuring access and availability of these new drugs, particularly for developing country markets.

3. **Require that public investment in R&D results in open knowledge sharing with data and IP generated through publicly funded research is made available for all.**

Sharing data in public repositories offers field-wide advantages in terms of accountability, data longevity, efficiency and quality. Prominent funding agencies such as Research Councils UK in the United Kingdom and the National Institutes of Health (NIH) and National Science Foundation (NSF) in the United States have increased pressure on researchers to share data. We urge the Committee to request that all R&D efforts in AMR, including TB, funded by the Canadian government ensure that their data are available in a timely, open and transparent way. The Life Prize has data and IP sharing principles that could be applied. **We ask the Committee to review the data access provisions for products developed with Canadian public funding (e.g. CIHR) to ensure that they promote and require open access to data and intellectual property that results from this public R&D funding.**

Appendix A – Steering Committee Members

South African Director General of the National Department of Health – Chair of the SC

Critical Path Institute (C-Path) – C-Path will manage data collection and sharing of IP.

The International Union Against Tuberculosis and Lung Disease (The Union) – Public face of 3P coordinating fundraising and advocacy.

Medicines Patent Pool – Manage IP licencing for compounds and combinations developed through 3P.

Médecins Sans Frontières (MSF) – Support advocacy and ensure uptake of 3P regimens.

Stop TB Partnership – Support The Union with advocacy, communication and long-term fundraising.

World Health Organization (WHO) – Non-participating observer.

Medical Research Council of South Africa (SAMRC)

Medical Research Council of India

TB Community Advisory Board

The Global TB Alliance

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[i] "Tuberculosis", M. Pai et al, October 2016, p7. Available from http://go.nature.com/2eMEsVb

[ii] TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS THE REVIEW ON ANTIMICROBIAL RESISTANCE. May 2016, p4. Available from http://bit.ly/2cYSQa4

[iii] "Tuberculosis, Global Tuberculosis Report 2016", World Health Organization. Available from http://who.int/tb/publications/factsheet_global.pdf

[iv] "Multidrug-Resistant Tuberculosis (MDR-TB) 2016 Update", World Health Organization, October 2016. Available from http://www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf
[v] TACKLING DRUG-RESISTANT INFECTIONS GLOBALLY: FINAL REPORT AND RECOMMENDATIONS THE REVIEW ON ANTIMICROBIAL RESISTANCE. May 2016, p60. http://bit.ly/2cYSQa4
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[vii] "Antimicrobial Resistance And Use In Canada, A Federal Framework For Action", p1, Government of Canada, October 2014.
[viii] "Global Tuberculosis Report 2016", p1, World Health Organization. Available from http://apps.who.int/iris/bitstream/10665/250441/1/9789241565394-eng.pdf
[ix] "Global Action Plan on Antimicrobial Resistance", p19 World Health Organization, 2015. Available from http://www.wpro.who.int/entity/drug_resistance/resources/global_action_plan_eng.pdf
[x] "Report of the United Nations Secretary-General's High Level Panel on Access to Medicines", p29, The United Nations Secretary-General's High-Level Panel on Access to Medicines, 2016. Available from http://www.unsgaccessmeds.org/final-report/; see also The Review on AMR, p54
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[xii] Global Action Plan on Antimicrobial Resistance, p19
[xiii] Global Action Plan on Antimicrobial Resistance, p19
[xiv] "Target regimen profiles for TB treatment", WHO. Available at http://apps.who.int/iris/bitstream/10665/250044/1/9789241511339-eng.pdf
[xv] "Multidrug and Extensively Drug-resistant Tuberculosis in Canada 1997–2008: Demographic and Disease Characteristics", Minion J, Gallant V, Wolfe J, Jamieson F, Long R, 2013
[xvi] "WHO reports high rates of drug-resistant TB", Angela Mulholland, CTV News, 2008
[xvii] http://www.medicinespatentpool.org/wp-content/uploads/STEWARDSHIP-REPORT_FINAL.pdf