TUBERCULOSIS – THE CORNERSTONE OF THE AMR THREAT

What is AMR?

Antimicrobial resistance (AMR) is a process in which microbes, including bacteria, evolve to be able to resist the action of drugs, making drugs ineffective. When drugs act on a population of microbes, naturally genetic variations allow certain bugs to survive and reproduce. These next generations are then resistant to the drugs designed to target them, lowering the effectiveness of antimicrobials, such as antibiotics. Currently, 700,000 people die from drug resistant infections every year. This number is expected to rise to ten million annually by 2050 if action is not taken. It is estimated that by 2050 AMR could result in a reduction of 2-3.5% in global GDP.[1]

Despite antimicrobials under-pinning much of developed and developing countries medical procedures, investment into research of new drugs is limited. Any new product brought to market is likely to have its use restricted and limited to cases of last resort, due to the rapidness of the development of resistance to new antibiotics. This offers a limited return on investment to drug developers and, coupled with the high risk of drug development, results in low investment into antimicrobial research and development (R&D).

What is TB?

Tuberculosis (TB) is a disease caused by a bacterial infection and is transmitted through the air when someone with the disease coughs or sneezes. TB is both preventable and treatable with antibiotics, yet kills more people every year than any other infectious disease. 2015 saw 1.8 million people die from the disease, more than HIV and malaria combined.

TB bacteria have certain attributes which make them more likely to develop resistance to antibiotics. TB is caused by a hardy organism which possesses an unusually thick, waxy cell wall and has the ability to survive in multiple locations in the body. This means that successful treatment of standard TB needs a combination of four different drugs for at least six months.

In the five decades since the current standard treatment was introduced, resistance has developed; partly due to the length and difficulty of standard TB treatment.

1. Tackling Drug-Resistant Infections Globally: Final report and recommendations. The Review on Antimicrobial Resistance, May 2016

Drug-resistant tuberculosis; the world's AMR threat right now

Tuberculosis (TB) is the world's only major airborne drug-resistant epidemic. Nearly 200,000 people died from multi-drug resistant TB (MDR-TB) in 2015; almost one-third of all AMR deaths.[1]

The threat posed by MDR-TB is significant and, the economic impacts catastrophic. It is one of the biggest drivers of the AMR threat.

• Human life – By 2050, it is estimated that AMR will be responsible for 10 million deaths every year, with a quarter of those from MDR-TB. This means an estimated 75 million people dying from MDR-TB over the next 35 years, or one person every 12 seconds.[2]

• Economic Impact – MDR-TB cost to the global economy is estimated at US$16.7 trillion by 2050, equating to 0.63% of global GDP. The lowest income countries are predicted to lose 2.45% of their GDP by 2050 due to the disease[3].

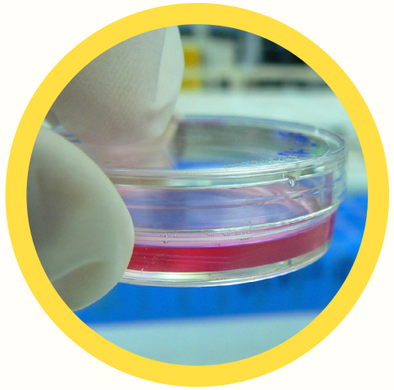
• Universality – TB and MDR-TB is particularly a burden for low- and middle-income countries. The majority of the burden is found in the BRICS countries and Indonesia. However, these countries are not unique in being affected by TB. MDR-TB is estimated to result in an additional 2.1 million deaths in Europe by 2050, at an economic cost of US$1.1 trillion[4].

TB in Europe

While the number of people with TB has been decreasing in the Europe Region, the region has the highest rates of MDR-TB and the lowest treatment success rates in the world[5]. It is estimated that the European region accounted for one in five multidrug-resistant TB cases globally in 2015. Drug resistant TB in Europe is a key threat to both the current and future AMR response and without addressing the epidemic in Europe, the Sustainable Development Goal 3.3 and others will not be achieved.

Cases of extremely drug resistant TB (XDR-TB), to which even the treatment for MDR-TB is not effective, are also becoming more prevalent. On the current trajectory, we face a world in which totally drug resistant strains of TB to which we have no effective treatment is a very realistic prospect.

The current MDR-TB treatment is arduous. People with TB can take up to 14,000 pills over two years, requiring eight months of daily intravenous injections. In most places, completing such a treatment is challenging. A new, safer, shorter treatment would decrease the global burden of both MDR-TB and drug sensitive TB and provide solutions to solve part of the AMR problem.



Why is TB research and development not working?

In order to combat MDR-TB, and AMR more generally, it is essential to keep ahead of evolving microbes by replacing drugs that are no longer effective. However, there are a number of blockages to the drug development process which are stifling research and development. Since 1967 there have been no new categories of anti-TB drugs entering the first-line regimen.

Inadequate financial incentives for companies to invest - Funding into research and development for TB has decreased in recent years, falling to its lowest levels in 7 years in 2015 at just 33.7% of the USD$2 billion annual funding target outlined by the WHO[6]. The contrast between increasing rates of TB infections and deaths, and reducing investment in the research in new tools to end TB suggests a lack of viable incentives in the current R&D model. It also points to a lack of political emphasis on overcoming the disease.

Market size – A large and profitable market for drugs is most often found in conditions which have a large presence in high-income countries. TB, whose burden falls hardest on poorer populations, has not provided enough of an incentive to invest in R&D as procurement is likely to occur mostly by donor and philanthropic organisations who are less likely to pay high prices.

The need for a TB regimen – The incentive to develop TB drugs is further weakened by the need for a combination of drugs (a regimen) to treat the disease successfully. Developing a regimen requires several drugs to be tested together which is more complicated.

1. Tackling Drug-Resistant Infections Globally: Final report and recommendations. The Review on Antimicrobial Resistance, May 2016
2. Review on AMR, Antimicrobial Resistance: Tackling a crisis for the health and wealth of nations, 2014.
3. The Price of a Pandemic: Counting the cost of MDR-TB. UK All Party Parliamentary Group on Global Tuberculosis. 2015
4. Tackling Drug-Resistant Infections Globally: Final report and recommendations. The Review on Antimicrobial Resistance, May 2016
5. Global TB Report 2016, Regional Profiles
6. 2016 Report on Tuberculosis Research Funding Trends, 2005-2015: No Time To Lose, Treatment Action Group, 2016.

What does a solution to TB need?

A totally new drug combination - Adding a new drug to an existing regimen risks accelerating resistance to any new drug added. A completely new combination of drugs, to which the TB bacteria has not been exposed to, is required to slow down the development of resistance and could be used to treat both TB and DR-TB.

New drugs tested early in combination - Traditionally, drugs are developed individually and only tested together once brought to market. This adds years to the development of a new TB regimen. Testing in combination early and throughout the development pipeline would prove more effective in determining the combined utility and potential side-effects, as well as saving years in fast-tracking an effective treatment to market.

A mechanism that addresses both the need for a new TB regimen and the lack of incentive for commercial investment into R&D for TB would accelerate progress against the world's deadliest infectious killer and bring major immediate benefits across the globe.

TB R&D – a solution for AMR

Any solution that unlocks R&D for TB could have a number of benefits for tackling wider AMR. Such solutions for TB would provide innovative ways of incentivising research and development which may have applicability for wider AMR challenges.

Demonstrating a solution for market failure – a new way of doing TB R&D could demonstrate the efficacy of a new market failure model. Therefore, research into TB drugs could be beneficial to the discovery of new antimicrobials for different forms of AMR as well as TB. However, investment into incentivising only the development of single antibiotics will have limited impact for TB due to the need for a combination of drugs which work together.

Immediate impact for AMR - Any new TB regimen would be able to be immediately deployed and be used to treat both drug resistant and standard TB. Therefore, investments into TB R&D would provide instant global health impact, in reducing deaths from both resistant and standard forms of TB, as well as preventing further drug resistance developing.

Stewardship, Accessibility and Affordability - Any framework that includes strong licensing agreements with manufacturers can prohibit inappropriate use or high prices and therefore provide an extra layer of protection to patients and for the prevention of further drug resistance developing.

Case Study: The Life Prize as a solution for TB R&D

The Life Prize (formally known as the 3P Project) aims to overcome the barriers to TB drug development to deliver short, effective and affordable TB treatments. Within a decade, the ambition is to radically reduce the burden for people with TB and their healthcare providers. It aims to ensure a healthy TB drug pipeline and guarantee that promising candidates are developed as combination regimens, are affordable, and are accessible to all.

The Life Prize is a framework for TB regimen development based on adequate and timely incentives for those working in TB R&D. It ensures the sharing of data and pooling of intellectual property (IP) to facilitate regimen development.

The Life Prize will help achieve TB regimens with shorter treatment times by:

Prize funding for drugs having reached certain milestones in the drug development pipeline.

Additional grant funding to finance the testing of drugs in combination to develop regimens.

All funding to require sharing of IP and data to ensure open collaborative research and fair licensing for the competitive production of the final product.

The Life Prize aims to show how a new market incentive can transform the future development and access to much needed antibiotics needed to treat TB, and ensure that the treatments developed are suitable and available for all those who need them.

"Tackling TB and DR-TB must be at the heart of any global action against Antimicrobial Resistance. The burden of TB is too great and the need for new treatment too urgent."[8]

Global action

Recent declarations on AMR, including the G20 and the United Nations (UN) declaration following the high level meeting on AMR in 2016, not only recognise the importance of TB within AMR but the challenges that exist for developing new treatments and the need to consider new incentives and models of R&D. The benefits of addressing the shortfalls in TB drug development will provide an immediate worldwide impact, preventing millions of deaths and trillions of dollars in economic impact. Addressing the market failure of TB also comes with a relatively modest price tag, and could help develop antibiotics suitable for other AMR issues.

Tackling the complexities of AMR and TB R&D will require high level political backing. The 2017 German G20 prioritised AMR and with it set an unprecedented level of global political commitment to end TB. The G20 Hamburg declaration[7] singled out TB as a priority for research and development, called for a Collaboration Hub to maximise the impact of existing and new anti-microbial research initiatives and product development, and tasked the OECD, WHO and others to research and report on practical market incentive options. It is crucial that these initiatives facilitate regimen development if they are tackle MDR-TB. As Argentina take on the Presidency in 2018, G20 commitment to TB R&D could be the step-change the world needs.

2018 sees the world faced with unparalleled opportunities to tackle TB. The Global Ministerial Conference on ending TB in the sustainable development era in Moscow in 2017 and the UN High-Level Meeting on Tuberculosis in 2018 both represent opportunities for world leaders, community & civil society representatives and other stakeholders to ensure that TB drug development is given the global attention it deserves.

RECOMMENDATIONS FOR GOVERNMENTS:

- All country governments should support a new mechanism for incentivising research and development into drugs, diagnostics and vaccines for antimicrobials through the G20 and the UN High Level Meeting on TB in 2018.
- TB is prioritised at the heart of any global, regional or national action on AMR, including within AMR National Action Plans.
- Any supported mechanism is realised with adequate funding to overcome the barriers for incentivising R&D into AMR

RECOMMENDATIONS FOR CIVIL SOCIETY:

- Advocate to your national government officials to call for action on TB R&D to be prioritised the High Level Meeting on TB
- Keep stressing TB as a key component of the AMR response

TBEC is an informal advocacy network of civil society organisations and individuals that share a commitment to raising awareness of TB and to increasing the political will to control the disease throughout the WHO Europe Region and worldwide. For more information on TBEC please get in touch with us at **coordinator@tbcoalition.eu**, or visit our website **http://www.tbcoalition.eu**

7. G20 Leaders Declaration; Shaping an Interconnected World. Hamburg July 2017.
8. Tackling Drug-Resistant Infections Globally: Final report and recommendations. The Review on Antimicrobial Resistance, May 2016

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