THE PRICE OF A PANDEMIC: Counting the cost of MDR-TB

All-Party Parliamentary Group on
Global tuberculosis

EXECUTIVE SUMMARY

Multi-drug resistant tuberculosis (MDR-TB) represents a clear threat to global health security. The spread of resistant strains coupled with fragile health systems and a lack of new drugs, diagnostics and vaccines to fight the disease are threatening to overturn decades of progress and return us to a pre-antibiotic era.

The estimated economic and social costs of MDR-TB in this report were produced for the independent review of Anti-Microbial Resistance chaired by the economist Jim O'Neill. They estimate that, in a scenario where an additional 40 per cent of all cases of TB are resistant to first-line drugs, leading to a doubling of the infection rate:

- **By 2050 an additional 2.59 million people will die every year from MDR-TB compared to current UN mortality projections.**

- **75 million additional people will lose their lives over the next 35 years as a result of the disease, half of these in just 5 countries.**

- **MDR-TB will cost $16.7 trillion over the next 35 years and will be responsible for reducing global GDP by 0.63 per cent in 2050.**

ABOUT TB:

Tuberculosis (TB) is a disease caused by a bacterial infection. It is transmitted aerially via droplets expelled when a sick person coughs or sneezes. TB is both treatable and curable, yet the disease kills 1.5 million people a year.

More than 4,000 people lose their lives every day as a consequence of TB.

TB bacteria have been infecting humans for tens of thousands of years. The bacteria have adapted to evade the human immune system and can lie dormant in an infected person for decades before becoming active. Increasing numbers of TB bacteria have evolved to be resistant to our best drugs.

Today, drug-resistant TB is increasingly commonplace. An estimated 500,000 people fell ill with multi-drug resistant TB (MDR-TB) in 2013, of which less than one-in-five started treatment. For those who start treatment less than half will successfully complete the course. At current progress, then, of the 500,000 people with MDR-TB today only around ten per cent will be cured.

According to the World Health Organisation, in just the last 25 years, 216 million people have fallen ill with TB and 45 million people have died.

CURRENT TREATMENT REGIMENS

The standard treatment for TB is a six month course of four drugs: isoniazid, rifampicin, ethambutol, and pyrazinamide. These drugs are associated with potentially severe side-effects and many patients in high income countries are prescribed additional painkillers and anti-emetics to help them complete the treatment course.

MDR-TB treatment requires a different combination of drugs over an 18-24 month period including daily intravenous injections for up to eight months. Treating MDR-TB can require patients to take up to 14,000 pills. These drugs are associated with potential side-effects including: permanent deafness, visual impairment, and liver damage. MDR-TB treatment can cost up to 450 times more than standard TB treatment.
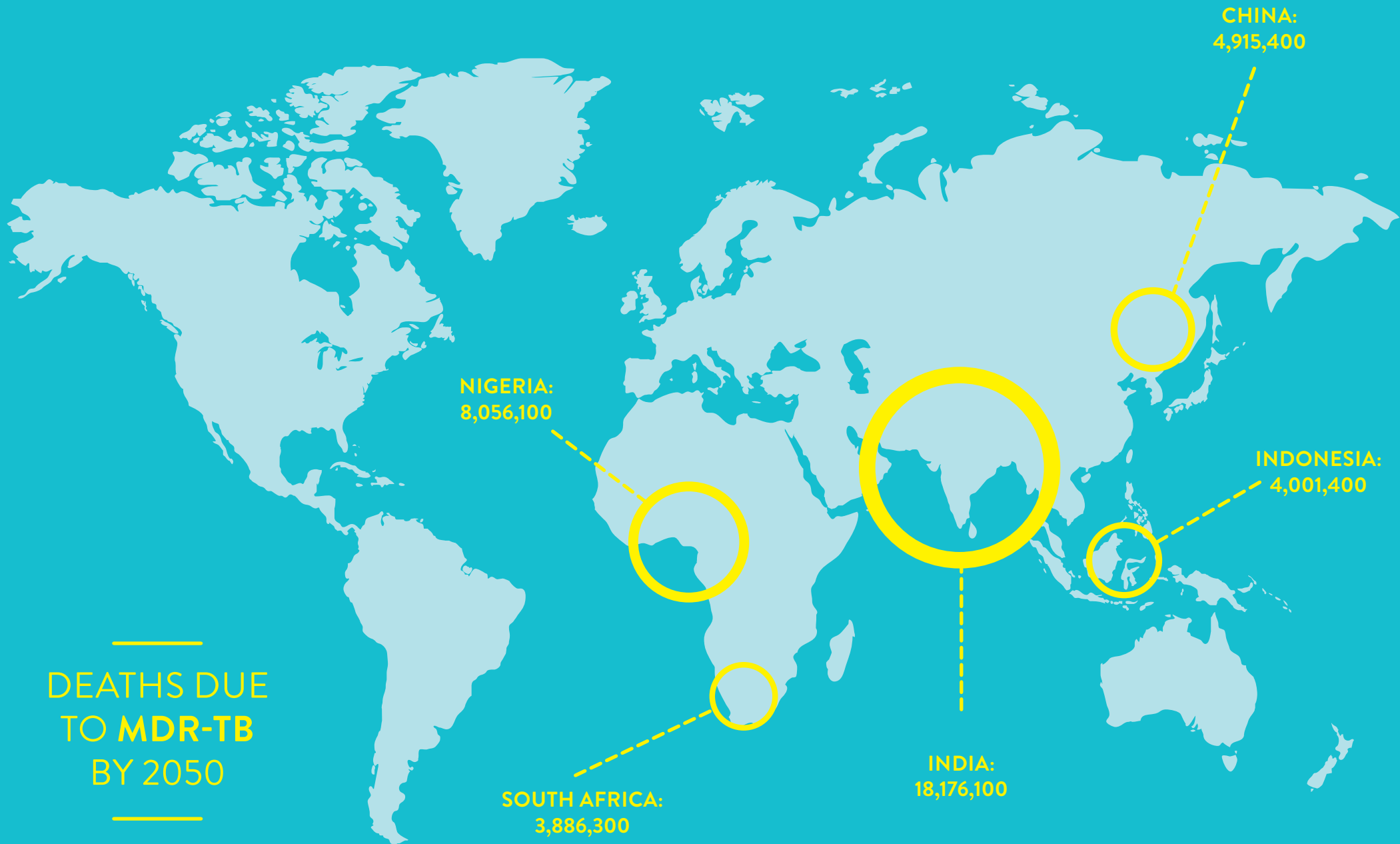
THE BIOLOGY OF DRUG-RESISTANCE

When bacteria reproduce, changes can occur by chance that make the second generation bacteria resistant to drugs. When these second generation cells reproduce, the resistance is passed on to the next generation in turn.

Depending on the nature of the change, the bacteria may be resistant to just one drug or to several. If treated with a combination of drugs that work in different ways, bacteria that are resistant to one or some drugs can be killed by the others that are present. However, if treatment with effective drugs is not continued long enough to kill all the bacteria present then the resistant bacteria will continue to survive and reproduce.

These surviving drug-resistant bacteria can continue to make the person sick and can be passed on to someone else infecting them with drug-resistant bacteria.

CHINA:
4,915,400

NIGERIA:
8,056,100

INDONESIA:
4,001,400

DEATHS DUE
TO **MDR-TB**
BY 2050

SOUTH AFRICA:
3,886,300

INDIA:
18,176,100

DRIVERS OF MDR-TB

Two major factors have historically driven the development of drug-resistant strains: patients failing to complete treatment, and inferior treatment quality. As resistant strains have become more commonplace, however, an increasing proportion of patients now develop MDR-TB through a third route: direct transmission from someone who has a drug-resistant form of the disease.

TREATMENT FAILURE

Standard TB treatment is arduous. The drugs are associated with potentially severe side-effects and as symptoms can disappear after a few months of treatment, patients sometimes choose to halt treatment early. Lack of social support due to stigma can also be a factor in patients failing to complete treatment.

An estimated 100,000 women are abandoned every year in India due to TB-related stigma.

INFERIOR TREATMENT

Some patients are unable to secure a six month supply of drugs. If drug supply is patchy or intermittent, as described above, resistance can develop. Similarly, if patients are given drugs of inferior quality which are too weak to kill all the bacteria, resistance can develop.

TB bacteria develop resistance very quickly, when the first anti-TB drug, streptomycin, was developed in the 1940s, researchers identified that some bacteria developed resistance almost immediately. For this reason TB is now treated with a combination of drugs, so even if resistance to one drug develops, the other drugs will continue to be effective. If patients receive only one or two drugs instead of the standard course of four, resistance is more likely to develop.

INFECTION WITH RESISTANT STRAINS

An increasingly common driver of drug-resistant TB is when previously healthy patients are infected with a drug-resistant strain, and develop drug-resistant TB without ever having received any TB drugs previously. In some parts of world over 30 per cent of all new TB cases are now multi-drug resistant and rates are climbing.

THE INCENTIVES DON'T WORK

One of the major drivers of the TB epidemic, and indeed of MDR-TB, is the lengthy standard treatment course. If treatment courses were shorter and less arduous, more patients would complete treatment and fewer cases of resistance would develop.

Modern drug discovery is hugely challenging. There are high rates of failure during the process and development takes many years of costly research. Accordingly, pharmaceutical companies are rarely prepared to commit the resources needed to bring a product to market unless there is the prospect of a financial return for that product.

In high income countries, that market incentive is present even when the burden of a particular condition is relatively small. Well-resourced healthcare systems effectively pool demand and offer guaranteed markets for any company that develops a new drug. Those same incentives are rarely present in low-income countries regardless of the size of the disease burden.

TB offers a unique example of the importance of incentives. At the time that the first anti-TB drug, streptomycin, was manufactured in 1943, rates of mortality due to TB in the USA were higher than are currently found in 13 of the WHO high burden TB countries, and rates in England and Wales were higher still (FIGURE 1). High income governments were prioritising anti-microbial drug development and by 1961, all four drugs which make up the modern standard TB regimen had been discovered.
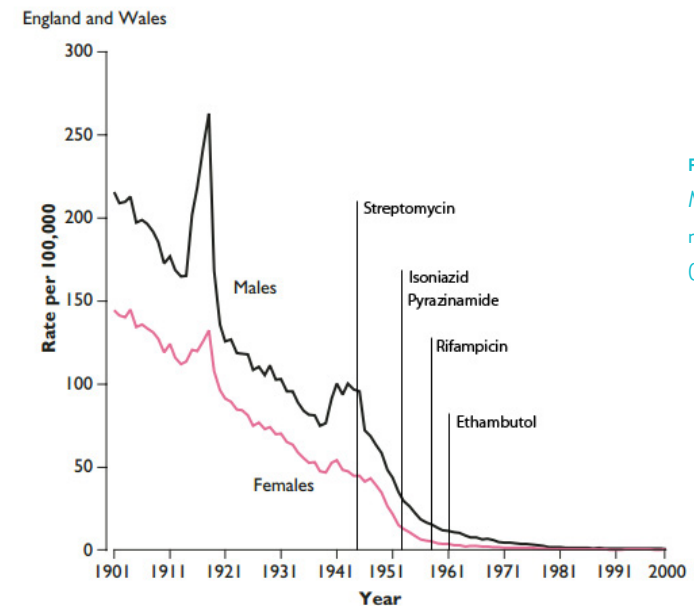

FIGURE 1:
Male and female mortality for TB (1900-1999)

Wider improvements in living standards and health provision, along with the introduction of anti-TB drugs, saw rapid declines in rates of TB in the developed world. By the discovery of ethambutol in 1961, the demand for TB drugs in developed markets was plummeting, and so, therefore, were the market incentives that could have driven private sector investment in R&D.

With TB no longer a health threat in the major high income markets, R&D all but halted due to a lack of commercial incentives. Public funders did not step into the gap and were prioritising other conditions, such as through the US National Cancer Act in 1971.

As a consequence, since 1967 no new classes of anti-TB drugs have entered the first-line regimen and only two new anti-TB drugs have received approval by the EMA.

Between 1975 and 2004 just 1.3 per cent of approved new drugs were specifically developed for neglected tropical diseases and TB. One of the tragic, and often unrecognised, consequences of poverty is that it simultaneously provides the perfect breeding ground for infectious diseases whilst providing a seemingly insurmountable barrier to the development of drugs to treat them.

Across that period, however, the R&D landscape slowly but steadily changed and there is cause for optimism. New approaches like Product Development Partnerships (PDPs) have leveraged significant additional resources for R&D and helped create the most robust pipeline of drug, diagnostic and vaccine candidates in decades. Some governments have increased funding of TB R&D as the epidemic has reappeared on the political agenda, particularly in Europe, whilst a number of pharmaceutical companies, notably Janssen, Otsuka, and Lilly have invested heavily in developing new anti-TB drugs or in technology transfer programmes.

However, unless further approaches that do not require a market incentive to drive R&D can be developed, and unless successful existing approaches are further supported and sustained, we will still be struggling to control the disease for another 150 years.

TACKLING MDR-TB

DIAGNOSTICS

Identifying whether a patient's TB is resistant to certain drugs is critical to ensuring that they receive the right treatment. If they are put on treatment to which the TB bacteria are already resistant, the treatment will be less effective, they will remain infectious, and the bacteria are more likely to develop resistance to the other drugs in the regimen.

VACCINES

The most effective way to counteract drug-resistance is to ensure that people do not become sick in the first place. However, BCG, the existing TB vaccine, only protects some children from severe forms of TB and is unreliable in preventing pulmonary (lung) TB, the most common form of the disease. New vaccines that will protect all people against all forms of TB are essential to controlling and ultimately eliminating the disease. It has been estimated that even a partially efficacious preventive TB vaccine for adolescents and adults could avert 40-50 million new cases over the course of 25 years.

DRUGS

TB bacteria develop resistance to drugs to which they have been exposed. New drugs, with new mechanisms of action, could overcome the current resistant TB bacteria. Similarly, a shorter, less arduous, standard regimen could help prevent the treatment interruptions that drive resistance.

OPERATIONAL RESEARCH

Every year, an estimated 3 million people – one-third of everyone who falls ill with TB – are not officially diagnosed or treated. Many of these receive sub-standard drugs or poor quality treatment, making them particularly susceptible to developing resistance. New and innovative methods of identifying infections, delivering TB care and prevention, and a focus on increasing outreach and screening of vulnerable populations, are required to close the gap and ensure everyone who falls ill with TB receives high quality, affordable treatment.

THE BURDEN OF MDR-TB

The independent Review on Antimicrobial Resistance was launched by the Prime Minister in July with the remit of producing a package of actions for tackling the development of AMR. The Review looked at several common drug-resistant conditions, including TB. In their first report in December 2014, the Review estimated the potential cost, both in economic and human terms, of increases in anti-microbial resistance.

The Review looked at several scenarios for these conditions, one of which projected the potential human and economic costs of an additional 40 per cent of all cases being resistant to first-line treatments, and a doubling of the infection rate as a result of these greater levels of resistance.

The Review estimated that in this scenario a steadily increasing number of people would die each year as a result of MDR-TB, reaching an additional 2.59 million lives lost by 2050. In total, an additional 75 million people would lose their lives to MDR-TB over the next 35 years.

In economic terms, the additional morbidity, mortality and other costs associated with the pandemic would cost a cumulative 16.7 trillion (2013) dollars over the next 35 years, equivalent to the current economic output of the European Union. By 2050, MDR-TB alone will reduce entire global GDP by 0.63 per cent.

OUR SOLUTIONS:

The figures in this report are forecasts: they are not inevitable. Those lives can be saved and those costs avoided if decisive action is taken to combat the TB epidemic. The next few years will be critical. If we scale-up of existing interventions and invest in developing new ones we can turn the tide against TB, but if we fail to act, if we let MDR-TB strengthen its hold, we will pay a heavy price, both in human and economic terms, for our inaction.

1 – **R&D CHALLENGE FUND** – The UK should support the establishment of the pooled fund agreed at the WHA and promote the fund to countries that currently do not support product development R&D. The fund managers should ensure that those contributing provide new money and that the fund not only supports existing approaches but also supports the development of new innovative approaches such as MSF's 3P Proposal or other mechanisms that may incentivise commercial sector R&D.

2 – **BASIC RESEARCH** – Key gaps remain in our fundamental understanding of the biology of the TB bacterium, for example, how it remains latent in the body and the immune response it provokes. These gaps should be clearly identified, potentially through an update of the Stop TB Partnership/WHO "TB Research Roadmap" or through the work of the WHO Global Health R&D Observatory, and funders of basic research should work together to ensure that these research gaps are addressed as effectively and efficiently as possible.

3 – **SUPPORT EXISTING PIPELINES** – The pipelines of candidates for new drugs, diagnostics and vaccines are stronger than they been for decades but, nonetheless, remain fragile and underfunded. Leading donors such as the UK should work with other nations to secure additional R&D financing and ensure that the progress of promising candidates is not delayed due to a lack of funding.

4 – **OPERATIONAL RESEARCH** – TB and MDR-TB cannot be beaten whilst one-third of infections are not officially diagnosed or treated. Funders should invest in operational research programmes that can build the evidence base for innovative ways to expand TB diagnosis, care and prevention.

5 – **BILATERAL PROGRAMMES** – Aid agencies across the world should invest more in strengthening health systems and infrastructure, including national TB programmes, to improve care and prevention of the disease before increasing rates of MDR-TB make tackling TB even more complex and costly. TB control, with its heavy reliance on health workers and drug supply chains, should also be considered part of the list of key indicators for the success of universal health coverage.

6 – **RECOGNISE TB AS A PILLAR OF THE AMR CRISIS** – TB is the only major airborne drug-resistant infection and a threat to global health security. The UK government has played a critical role in ensuring that the world recognises the importance of AMR and has contributed to the resolution being presented to the World Health Assembly in May. Now the UK, and other nations, must ensure that key resistant infections that affect the poorest such as HIV, TB and malaria are incorporated as central pillars of the effort to tackle AMR, including in the WHA Resolution.