Written evidence from TB Alliance

Antimicrobial Resistance Inquiry
TB Alliance
October 9, 2018

About TB Alliance
TB Alliance is a not-for-profit organization dedicated to the discovery and development of better, faster acting and affordable drugs for tuberculosis (TB). Before TB Alliance was established in 2000, there were no new TB drugs in clinical development. TB Alliance successfully launched childhood TB products—already reaching patients in over 80 countries—and coordinates the largest ever portfolio of novel TB drugs and regimens ranging from early drug candidates to regimens ready to introduce in the coming years—more than 30 active projects in all. The goal of these programs is to introduce new treatments that will significantly impact the TB pandemic.

Background
TB is the single largest infectious disease killer globally. In 2017, about 10 million people developed TB, and it killed about 1.3 million people. TB is also the leading cause of death globally from AMR, with almost one third of deaths associated with TB drug resistance.

Multi-drug resistant (MDR)-TB is resistant to two of the common first line drugs. The WHO 2018 report estimated 457,560 people developed MDR-TB in 2017 and almost 600,000 people if you add people with resistance to at least one of the key drugs from the current treatment regimen. Treatment for DR-TB is long, very expensive, more complex (requires injections), and toxic. The success rate for MDR-TB treatment is only about 50 percent globally and for XDR-TB this declines to 30%. The worrying fact in TB is that the majority of new DR-TB cases are caused by primary infection—patients infecting other patients. Currently, countries devise regimens to treat drug-resistant TB from nearly 20 drugs, many which are sub-optimal, produce harsh side effects, and require daily injections.

Among cases of MDR-TB in 2017, 8.5 percent (38,892) were estimated to have extensively drug-resistant (XDR-) TB, which requires up to three years of treatment and even then, treatment is only effective in about 28 percent of cases. XDR-TB is a growing global concern; there have been cases reported in over 100 countries. Today, there is no approved regimen for XDR-TB. Instead, health care providers try to individualize treatment, often using antibiotics not approved for TB, as well as highly toxic medicines not intended to be used for the length of time that TB treatment requires.

Two reports, from 2013 and 2015, published by the UK Parliament and the London Assembly, quoted the overall cost to treat drug-resistant TB in the UK to be about £50,000-£70,000 per patient (data was going as far back as 1998) and estimated now at about £100,000 per patient, compared to average cost of treating drug sensitive TB is £5,000 per patient. It also calculates that TB treatment in London alone costs £30 million per year. These estimates calculate direct health care expenses only and do not include expenses for surveying, contact tracing, or the economic or social impact of TB on patients and their families. Even more alarming are the costs associated with treating XDR-TB in the UK. A single case of XDR-TB can cost more than half a million pounds to manage.¹,² These costs will no doubt stress the UK
health system and the financial impact of an unchecked drug-resistant TB pandemic, will certainly weigh heavy on taxpayers in the UK as the country endeavors to pay for increasingly complicated treatment and care.

**MDR-TB and Children**

One model to estimate TB incidence globally suggests that, in 2010, almost 32,000 children developed MDR-TB, accounting for about 3 percent of all estimated TB cases among children.\(^3\) Children who are treated for MDR-TB have success rates better than those seen in adult populations; however, fewer than 1,000 children with MDR-TB are started on treatment each year leaving the vast majority of children vulnerable to this deadly disease. Given the similar symptoms of TB compared to other big childhood killers like pneumonia, it is reasonable to assume that MDR-TB kills significantly more children than currently registered.

Adolescents, particularly girls, with MDR-TB have higher rates of mortality and worse treatment outcomes when compared with adults and younger children. There are no child-friendly formulations of current second-line drugs used for the treatment of MDR TB.

Newer drugs and shorter regimens for drug-resistant TB are in development, but children do not benefit from these scientific advances, as there are no studies assessing the safety and dosing of treatments in children and limited plans to develop child-friendly formulations of these medicines.

**Economic impact**

In addition to the devastating impact on people in their most productive years, TB jeopardises economic and social development. The O’Neil Committee analysis shows that of the 10 million total deaths that might be associated with AMR each year by 2050, between one-third and a quarter will be caused by drug-resistant strains of TB.

Analysis done by KPMG in the UK, and published by the Global TB Caucus in November 2017, estimates that during the period of 2000-2015, TB related mortality caused the loss of US$ 616 billion. If action is not taken, future TB related mortality may lead to a further loss of US$ 984 billion globally between 2015 and 2030—a figure equivalent to the size of the Netherlands’ economy in 2016. No country is exempt.

Although forecasts indicate that the greatest burden of the disease will fall on less developed countries in South East Asia and Africa, the G20 countries will be the most severely affected economically, absorbing over two-thirds of all costs ($675b). It is estimated that by 2050 drug resistant TB may cause a lost economic output of 10.5 trillion US dollars in G20 countries, and an additional 6.2 trillion US dollars outside of G20 countries.

**TB Alliance: Progress towards new TB drugs**

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2. Drug resistant Tuberculosis, Old disease – new threat, UK All Party Parliamentary Group on Tuberculosis, April 2013
TB Alliance is currently testing two regimens for TB that show potential in curing all forms of TB. With sufficient investments, over the next five years, we aim to introduce an effective 6 month or shorter treatment for every person with TB, even those with the most resistant forms of the disease—including XDR-TB patients.

The two multi-drug regimens tested in the trials (SimpliciTb and Nix/ZeNix-TB) are comprised of a common “backbone” of novel drugs—bedaquiline (B) and pretomanid (Pa). When B and Pa are paired with linezolid (L), the regimen shows a much more effective, shorter, simpler, and safer treatment for XDR-TB. When bedaquiline (B) and pretomanid (Pa) are paired with moxifloxacin (M), and pyrazinamide (Z), the regimen shows promise to offer a single, relatively short, all oral treatment that could be effective in virtually all patients (perhaps 99 percent of all TB patients) including those with MDR-TB. If successful, these regimens could dramatically improve treatment of drug-resistant TB. These results also point to the potential for countries to procure just two regimens and treat all types of TB with all orally-taken drugs in no more than six months.

We have also made significant progress in highlighting the path that over ten years will allow us to treat all patients with TB in three months or less with the same, once-a-day, all oral, highly effective, safe and affordable TB therapy.

This means we can eradicate drug-resistant TB. Science is not holding us back: funding and political will to invest in new tools and ensure their uptake is the key factor! The current glacial pace of funding TB research is costing both lives and livelihoods.

Recommendations

TB is the largest single source of antimicrobial resistance globally both in terms of health, social and economic burden with almost one third of the global burden of AMR attributed to TB. The TB world has faced antimicrobial resistance for a long time and can be an example how to win this fight.

We cannot address AMR without addressing TB. The challenges of dealing with drug resistance are deeply intertwined with the challenges of tackling TB and the global response to AMR is fundamentally incomplete if it does not directly address TB.

1. **We need globally coordinated and pooled investments.** Product development is expensive and can best be done globally and in a coordinated manner to share risk and broaden transparency. Product development requires a global action plan and investment; however, many R&D plans are strictly linked to national capacity and (economic) interests.
   - DFID took a bold step to allocate 3 percent of its total budget for R&D (for each relevant sector it engages in). This approach would work well in health with a potentially significant impact on product development as it links and integrates R&D with delivery programs.

2. **A valley of death exists in all cases of AMR. Incentives, especially push or grant mechanisms are needed to maintain progress.** Academic research is very important but not the same as product development. Many governments believe that their significant investment in academic research and early discovery will lead to innovative products and they rely on the private market for product development. This market does not exist for TB, however. TB is a disease of poverty and does not incentivize private market investment because the end users cannot afford to buy the product. Other antibiotic markets face challenges due to the need to incentivize stewardship and minimize use, something obviously contrary to the interest of industry. Therefore, other potential
mechanisms like prizes are needed. The “Life Prize” program has developed a well-researched approach that is worth evaluating.

3. Another important lesson to learn from Industry and TB Product Development is that **long-term investments are needed**. Drug development is complex and takes 10-15 years to come to fruition. This has been experienced in the pharmaceutical industry and is proven to be true for non-profit PDPs based on a series of new products and regimens currently coming to registration (including the two novel TB regimens for all forms of TB developed by TB Alliance).

4. The revised UK AMR strategy should include a **concrete commitment to close the global TB R&D funding gap along fair-share principles, with a commitment to invest at least 0.1% of the UK’s Gross Expenditure on R&D on TB research**.

5. The government should **leverage its existing leadership on the AMR agenda to drive global collaboration and coordination of increased investments in TB research**, including through the G20 AMR R&D Collaboration Hub.

6. **The revised UK AMR Strategy should retain its commitment to ensuring rapid and equitable access to the products of innovation**, including through delinking the cost of treatment from the price of innovation, the harmonization of regulatory pathways and the rapid implementation of new tools.

The major limiting factor to a world without TB is a stronger commitment from the global community, including all of you. Without sufficient investment, we will fall short in our combined efforts to once and for all eradicate TB.

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