GEARING UP TO END TUBERCULOSIS: A MODEL FOR TACKLING ANTIMICROBIAL RESISTANCE?

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Antimicrobial resistance (AMR) is occurring everywhere in the world, compromising our ability to treat infectious diseases, including HIV, tuberculosis (TB) and malaria, as well as undermining many other advances in health and medicine.

Although the World Health Assembly issued a resolution on antimicrobial resistance in 2001, no country has seriously addressed it or taken any concrete action. It is only in the past five years that antimicrobial resistance has received increased attention, not only by the medical, public health and scientific community, but also among businesses and political leaders.

The world has finally woken up to the fact that antibiotic resistance – when bacteria mutate so that antibiotics no longer work in people who need them to treat infections – is now a major threat to global public health.

The emergence of multidrug-resistant TB (MDR-TB) has been undermining TB control progress over the past two decades and fueling the antimicrobial resistance crisis. Detection and treatment gaps are especially serious among people with MDR-TB.

In 2014, only about a quarter of the 480,000 MDR-TB cases were detected and reported to national authorities. The three countries with the largest numbers of cases are China, India and the Russian Federation.

Unless MDR-TB is confronted head on as part of the global efforts to contain antimicrobial resistance, we risk having an uncontrollable spread of MDR-TB in several countries in the near future and not reaching the Sustainable Development Goal of ending TB by 2030.

The road to ending TB

The fight against TB is a glass half full and a glass half empty story. If we look at the glass half full, we see that the tuberculosis (TB) response to date is paying off.

Since 1990, 70 million people have been cured from TB, 43 million lives were saved thanks to effective diagnosis and treatment and deaths decreased by nearly half. Most of the improvement has come since 2000, the year the United Nations' Millennium Development Goals (MDGs) were set out by world leaders.

But the glass is also half empty, which means huge challenges still remain. TB has now become the top infectious disease killer worldwide alongside HIV/AIDS. In 2014, over 1.5 million people died from it, which means an astounding 4,100 each day. And more than 9 million people developed TB.

To reduce TB's overall burden, detection and treatment gaps need to be closed, funding shortfalls filled and new diagnostics, drugs and vaccines developed.

A new and accelerated response is necessary and urgent. For this reason, in 2014 the World Health Assembly adopted the new "End TB Strategy", which is being implemented by countries this year. It has an ambitious target of ending the TB epidemic by 2030, calling for zero deaths, zero disease and zero suffering due to TB.

The End TB Strategy is aligned with the new 2030 Sustainable Development Goals (SDGs) set by the United Nations in 2015. The SDGs inject renewed momentum into improving the state of our planet and the well-being of people, building on the achievements of the Millennium Development Goals.

Ending TB will require a dramatic decline in TB cases and deaths, and the elimination of the economic and social burden of TB. The World Health Organization's End TB Strategy is essentially meant to guide countries in reaching this ambitious goal.

The strategy calls for better patient-centred care and prevention, bolder policies and systems – including universal health coverage and social protection – and bigger investments in research and innovation.

The growing threat of antimicrobial resistance

Although the World Health Assembly issued a resolution on antimicrobial resistance in 2001, no country seriously addressed it or took any concrete action at the time. It is only in the past five years that antimicrobial resistance has received increased attention, not only by the medical and scientific community, but also among businesses and political leaders.

In 2010, in view of our experience with antibiotic resistance as part of World Health Organization's (WHO) Global TB Programme, the WHO Director-General asked us to organise World Health Day 2011[1] and devote it to antimicrobial resistance in an attempt to raise global awareness.

We developed a policy package on antimicrobial resistance that was promoted by WHO. It contained six essential interventions, which we derived straight from our programmatic experience in responding to TB:

- A well-financed national response plan;
- Surveillance of drug resistance among the most important pathogens through strengthening of laboratories;
- Availability of quality-proven antimicrobials;
- Use of antimicrobials in the human and the animal husbandry sectors;
- Infection control measures in all facilities where people at-risk aggregate; and
- Research and development of new antimicrobials.

After World Health Day 2011, a few countries – led by Sweden, the United Kingdom and the United States – showed interest in tackling antimicrobial resistance because they started seeing it in the context of the global security agenda. But it took a few years before other countries made antimicrobial resistance a political priority.

The Pan American Health Organization (PAHO) began to address the need to confront antimicrobial resistance while the European Centres for Disease Control (ECDC) initiated surveillance programmes. Antimicrobial resistance, however, was not being addressed in most low- and middle-income countries. As a result, WHO Member States began pushing for action. A steering committee (the Strategic AMR and Technical Advisory Group on antimicrobial resistance) was constituted in 2013 and WHO's Global Action Plan on AMR was approved by the World Health Assembly in 2015. Overall, it took 15 years for antimicrobial resistance to get the recognition it needed and be placed on the world's political agenda.

TB resistance stable overall, but some worrying developments

When we look at the latest global figures on TB, we see that in some countries the issue is very serious, although we cannot say that drug-resistant TB has increased globally over the past few years.

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The good news is that resistance to TB drugs is probably low in Africa. There are a number of possible reasons for this. Some countries have had good management programmes or there has been no drug overuse or even availability of some medicines. These have probably contributed to keeping antimicrobial resistance under some control, although information is missing in some settings due to lack of capacity and resources to assess it.

In the *Global TB Report 2015*, we published the latest data on drug-resistant TB and its trends where it could be assessed. Although MDR-TB exists in most countries, the largest problem is in the Russian Federation and the former Soviet republics: Belarus, Ukraine, and those in Central Asia. While the Baltic States (Estonia, Latvia and Lithuania) have mounted a big effort to tackle MDR-TB, achieving major reductions. In Belarus, for instance, 35% of new TB cases are drug-resistant and similar levels have been detected in some oblasts of the Russian Federation.

If we look at global trends, however, one cannot conclude that drug resistance is on the rise. Compared to the past, there is just more information and more awareness. Overall, the global figures remain stable, ranging between 450,000 and 480,000 new MDR-TB cases each year. New information from large countries like India will be crucial in allowing a better understanding of global trends,

In addition to MDR-TB, over the past 10 years there has been the progressive resistance to second-line TB drugs, which has led to the emergence of extensively drug-resistant TB (XDR-TB, defined as a form of MDR-TB where resistance to the two most important classes of second-line medicines is also present). In fact, TB germs causing XDR-TB are resistant to any of the fluoroquinolones and at least one of three injectable drugs.

TB kills as many as HIV/AIDS, but is relatively neglected

Investments in TB, both domestic and international, have

1. WHO/CDS/CSR/DRS/2001.2 WHO Global Strategy for Containment of Antimicrobial Resistance
http://www.who.int/csr/resources/publications/drugresist/en/EGlobal_Strat.pdf

increased considerably compared to 15 – 20 years ago, which is quite extraordinary. In 2015, US$ 6.6 billion was available for TB prevention, diagnosis and treatment.

Despite the increased funding, both domestic financing and global financing are lower than for other infectious diseases. This results in an annual gap in the range of US$ 1.4 billion, which is quite surprising given that TB kills the same number of people every year as HIV/AIDS – 1.5 million.

In preparation for the Sustainable Development Goals, the Copenhagen Consensus Center published a report in 2015, featuring a table that *The Economist* later called "no-brainers", illustrating the most cost-effective health and development interventions worldwide. TB ranked as the first health-related "no brainer" given that for each dollar spent on TB control, a country or investor can expect up to US$ 43 in return.

Nonetheless, TB is still not "visible" enough on the political agenda. For example, at last year's G7 Summit in Germany, the health issues on the agenda were Ebola and antimicrobial resistance. However, no mention of MDR-TB appeared in the communiqué, showing how little consideration is being paid to MDR-TB in the response to antimicrobial resistance.

In my view, TB remains less visible because it affects the poorest of the poor. If we look at the patient population and people at risk, in Europe and elsewhere, we see that they are very poor, live in overcrowded conditions, and suffer from poor-quality housing. They include people living with HIV, drug abusers, the homeless, tobacco smokers and the jobless. These are all marginalized people, often migrant populations, without any voice or power to sensitize politicians about the tragedy of being affected by TB.

If we are to end TB, we must tackle the "fuelers" of the disease – poverty and inequity. TB should not be treated as only a health issue.

MDR-TB in India, China and Russia

The three countries with the largest numbers of MDR-TB cases are China, India and the Russian Federation.

The level of drug resistance found among TB cases in India is estimated to be relatively low, ranging from 2% to 3%. However, there is a very high case-load with over two million new TB cases per year, including 60,000 to 65,000 new MDR-TB cases.

China has a comparable number of MDR-TB cases, with a rate of 5.7% to 6%. Since China has roughly one million cases a year, this translates into 60,000 MDR-TB cases.

In the Russian Federation, there are about 40,000 cases of MDR-TB per year. The percentages are among the highest in the world.

Former Soviet republics: Dug resistance parallels increases in poverty

In the Russian Federation and other former Soviet republics, the problem of drug resistance emerged in part from the economic difficulties during the perestroika era of the late 1980s when drug availability started to become erratic. The first time I went to the Russian Federation, Kyrgyzstan and Kazakhstan in 1994–1995, I remember distinctly that essential drugs were lacking at the Central TB Research Institutes of these countries.

In Kyrgyzstan, the central TB treatment unit was lacking rifampicin and pyrazinamide, and doctors were treating people with what they had, basically isoniazid and streptomycin. This is when resistance started emerging and it was exacerbated by the poor socioeconomic conditions at the time.

The fact that clinicians did not apply the international standards for TB treatment, and the increase in poverty, alcohol abuse and other social factors, combined with the overcrowding in small apartments in cities like Moscow, fuelled the spread of drug-resistant TB among the population. Likewise, in prisons, transmission of MDR-TB bacilli became rampant.

Only recently have we seen promising signs in the region with a reduction of MDR-TB cases in certain former Soviet republics.

Access to diagnostics, drugs and health services needed

To effectively tackle TB, especially in the era of antibiotic resistance, a three-pronged approach is needed: universal access to diagnostic tools to identify the bacteria and its specific susceptibility to drugs, universal access to the necessary medicines, and well-staffed healthcare delivery systems.

With the support of UNITAID, WHO and its partners have delivered diagnostic tools, including GeneXpert machines, initially to 27 countries. In the four years since WHO's recommendation to introduce GeneXpert diagnostics, we have seen substantial progress with over 100 countries now using GeneXpert.

One needs to consider that out of 9 million TB cases estimated per year, the actual number of officially notified cases is 6 million. It is impossible to speculate about the level of drug resistance among the 3 million cases that are not notified. The use of rapid diagnostics like Xpert and line-probe assays will help us diagnose the "missing" TB and MDR-TB cases.

While universal access to diagnosis of TB and drug resistance is still an issue today, an ongoing effort exists to deploy rapid molecular tests where they are needed. This successful response could also be replicated to tackle other drug-resistant infections. Our system could be seen as a model for antimicrobial resistance in general and funding agencies interested in combating antimicrobial resistance could explore similar mechanisms.

The World Health Assembly in 2014 adopted our proposed strategy of universal access to diagnosis for susceptibility[2], which means that everyone should have access to susceptibility testing[3] – as is the case in rich countries. However, once

2. WHO guidelines on drug susceptibility testing http://whqlibdoc.who.int/publications/2009/9789241598675_eng.pdf
3. WHO guidelines on drug susceptibility testing

diagnosis is established, access to proper drugs is still an issue.

Of the 125,000 identified MDR-TB cases last year, we discovered that only approximately 110,000 were started on proper treatment. This means there are countries where detected MDR-TB cases were not treated because they did not have access to drugs.

Second-line drugs are quite expensive and sometimes quite hard to procure. Access to drugs is a big issue and there is still a gap between patients tested and diagnoses, and patients treated. This is a major ethical issue because one cannot get people diagnosed and then be unable to provide treatment.

Well-organized healthcare delivery systems are also key if we are to end TB. Even in countries with access to diagnosis and proper treatment, only 50% of the treated people with MDR-TB actually get cured. This points to inadequate health delivery services. There is a large percentage of patients who default because of side effects, high costs, and also because healthcare services do not have the capacity to follow up personally with each patient. Significant progress could be made if healthcare services were staffed with more qualified doctors and nurses. However, the lack of adequate human resources is a chronic challenge among poor countries.

Finally, infection control in congregate settings is also essential. The outbreak of MDR-TB in South Africa's KwaZulu-Natal resulted from poor transmission control of airborne infections. MDR-TB patients shared the same ward with HIV-positive people, spreading airborne infections and drug-resistant tuberculosis to other patients who were highly vulnerable to TB infection and disease development. The need for strong infection control is therefore crucial if we are to truly combat antimicrobial resistance.

We have seen outbreaks of tuberculosis and MDR-TB in hospitals and nursing homes whenever there is poor infection control, even in wealthy countries. Infection control is one of our top priorities and it requires isolation capacity and universal access to rapid diagnosis and treatment.

Partners are key, but more are needed

Coalitions of various stakeholders and public-private partnerships (PPPs) are necessary to accelerate the TB response through proper investments. Of the funding available for TB annually, about 87% comes from domestic sources, particularly in the BRICS countries (Brazil, the Russian Federation, India, China and South Africa). Of the remaining 13% coming from international sources (about US$ 800 million per year), the majority comes from The Global Fund to Fight AIDS, Tuberculosis and Malaria. However, that is only 18% of its total investments, with the rest being spent on AIDS and malaria. The Global Fund has helped particularly the lowest income countries, but the proportion of 18% is currently blocked at that level in their funding system. While the Global Fund is crucial in supporting the TB response, much more funding needs to be identified if all gaps are to be closed.

> ***Bigger investments are urgently needed in research and innovation, especially in basic science, if we are to transform our response to TB and end it by 2030***

Domestic funding accounts for more than 90% of total funding for TB in three country groups: BRICS countries; upper middle-income countries; and regions outside Asia and Africa. However, gaps exist also in those countries and the need to identify who could help fill such gaps cannot be emphasized enough. In fact, some of the countries have not been able to effectively tackle MDR-TB largely due to lack of resources.

UNITAID has also done remarkable work in developing a pre-payment mechanism to make GeneXpert accessible to developing countries. It has supplied millions of pre-paid cartridges at low cost, with support from the US Government and The Bill & Melinda Gates Foundation. It has also funded the Global Alliance for TB Drug Development (TB Alliance) to develop the first-ever fixed-dose combinations for children with TB, launched in Cape Town in December 2015.

Other PPPs in existence are devoted to TB research. For example, the Geneva-based Foundation for Innovative New Diagnostics (FIND), has co-developed with Cepheid Xpert MTB/RIF® and other diagnostic tools. These include the Line Probe Assay (LPA), produced by the German company HEIN, which WHO also recommends for use as it allows fairly rapid identification of both isoniazid and rifampicin resistance. It is a bit more laborious than Xpert, but is also considered a very good test.

The TB Alliance is another important PPP based in New York that collaborates with WHO and is involved in the development of new anti-TB medicines and drug regimens. It is currently conducting trials of its new drug, pretomanid, combined with pyrazinamide and moxifloxacin or combined with linezolid and bedaquiline. Results are expected in the next two to three years. There is more in the development pipeline, but it will take a few more years to see results.

Over the past ten years there has been an injection of new funding for TB research from the The Bill & Melinda Gates Foundation, the US National Institutes of Health and a few other agencies, which has resulted in the development of new tools against TB. But bigger investments are urgently needed in

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research and innovation, especially in basic science, if we are to transform our response to TB and end it by 2030.

The pharmaceutical industry is potentially a key partner in the TB fight, but at the moment only a handful of companies are active in the discovery and development of new agents. This is a general concern that goes beyond TB. At the World Economic Forum in Davos this year, over 80 leading international pharmaceutical, biotechnology and diagnostics companies issued a declaration, calling on governments to work closely with industry to tackle the rising threat of antimicrobial resistance.

The companies have committed to reducing the development of drug resistance, encouraging better and more appropriate use of new and existing antibiotics, increasing investment in R&D to develop new diagnostics, antibiotics and vaccines, and improve access to high-quality antibiotics for all who need them around the world.

This is definitely a step in the right direction. We hope that the collective action recently taken by the pharmaceutical industry will provide a much-needed boost for ramping up the fight against MDR-TB and other drug-resistant infections.

Conclusion

The TB response has taught us that some critical elements are absolutely necessary for the control of infectious diseases in countries. These include good quality surveillance, rapid diagnosis of drug resistance, appropriate treatments, infection control in places where at-risk people come together, and good delivery systems with trained health personnel.

The antimicrobial resistance response could greatly benefit by adopting some of TB's "lessons learned". There is no need to reinvent the wheel when it comes to tackling drug-resistant infections.

Time is of the essence. All stakeholders in the antimicrobial resistance fight – political leaders, the international community, health officials, scientists and the pharmaceutical industry – must work together to thwart the growing threat of antimicrobial resistance. ■

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4. (http://www.tballiance.org/newscenter/view-brief.php?id=1116).

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