Anti microbial resistance (AMR) has become one of the dominating, and most pressing, global concerns in public health (1). Yet a silent epidemic at the core of AMR often goes largely unnoticed and neglected – tuberculosis (TB), the world’s number one infectious disease killer (2). Multidrug-resistant TB (MDR-TB, defined as resistance to, at least, rifampicin and isoniazid) and rifampicin-resistant TB (RR-TB) are especially devastating. Patients with MDR-TB and RR-TB (MDR/RR-TB) require radical changes in treatment compared to those with drug-susceptible TB. They need prolonged treatment (often up to two years) with costly, highly toxic and much less effective second-line medicines, of which there is only a limited number. Moreover, once fluoroquinolones and injectable agents – leading components in second-line treatment regimens – are compromised by additional drug resistance (extensively drug-resistant TB, XDR-TB, defined as MDR-TB plus additional resistance to at least the two most important groups of second-line medicines: the fluoroquinolones and the injectable agents kanamycin, amikacin and capreomycin), treatment becomes extremely difficult.

Patients with drug-resistant TB face agonising, prolonged suffering and often permanent disability while on second-line treatment, together with devastating economic hardship, stigma and discrimination. On top of the clinical toll taken by M/XDR-TB treatment, patients often face catastrophic economic repercussions, pushing them into extreme poverty. Once treatment options are exhausted, patients and health services are confronted by numerous ethical, legal and human rights challenges, given ongoing airborne transmission of the disease with explosive outbreaks described in congregate settings (3).

A global reduction in TB burden by 2035 to the levels envisaged by the WHO End TB Strategy will require a multifaceted approach to all forms of TB, as well as to latent infection (4, 5). In this article we summarise the global situation of drug-resistant TB using MDR/RR-TB as the main indicator and describe what is needed to mount an appropriate response to "roll back" the progression of this public health, and global health, security threat.

Background
The assessment of country-level, regional and global burden of disease and death attributed to MDR/RR-TB uses standardized...
surveillance and annual data collection from member states by the WHO Global TB Programme, described elsewhere (6). Burden of disease and attributable deaths are derived from empirical data updated annually from country mortality reports and vital registration systems, and from a comprehensive global TB drug resistance surveillance (DRS) programme established in 1994 (7, 8).

Since 1994, data on TB drug resistance have been systematically collected and analysed from 155 countries worldwide (80% of 194 WHO member states), which collectively have more than 95% of the world’s population and TB cases. This includes 83 countries that have continuous surveillance systems based on routine diagnostic drug-susceptibility testing (DST) of Mycobacterium tuberculosis isolates obtained from all TB patients, and 72 countries that rely on epidemiological surveys of bacterial isolates collected from representative samples of patients.

Trends in TB drug resistance have been tracked since 1994, together with targeted programmatic indicators such as diagnostic coverage, treatment enrolment, care delivery systems and treatment outcome. Data are available by country, and aggregated globally and by WHO region. Thirty countries responsible for 80% of the global MDR/RR-TB burden are targeted for specialized technical support to programmatic management of drug-resistant TB and for WHO monitoring and evaluation (9) (Figure 1).

**Current status of the MDR/RR-TB epidemic and reasons why it remains a crisis**

High burden of morbidity and mortality

The 2016 WHO Global TB Report indicated that there were 580,000 (range: 520,000–640,000) new cases of MDR/RR-TB in 2015 (2). An estimated 250,000 (160,000–340,000) MDR/RR-TB patients died in 2015.

Drug resistance surveillance data show that globally, 3.9% (2.7–5.1%) of new and 21% (15–28%) of previously treated TB cases had MDR/RR-TB in 2015. Wide geographical and country variation occur, with China, Russia, India, South Africa, and some Asian and Eastern European countries carrying the heaviest MDR/RR-TB burden (10). Among countries with representative data for at least three years, the burden of MDR-TB is either increasing faster or decreasing more slowly than the overall TB burden, with a slight incremental trend in the number of MDR-TB cases as a proportion of all TB cases (Figure 2).

By the end of 2015, XDR-TB cases had been reported by 117...
WHO member states. Over half of patients with MDR/RR-TB had additional resistance to either a fluoroquinolone or a second-line injectable agent or both. Pooled surveillance data show that 9.5% (7.0–12.1%) of MDR/RR-TB cases globally had XDR-TB, i.e. one in 10 patients had little treatment options left (and one in three of them died). Levels of XDR-TB are much higher than the global average in several countries of Eastern Europe and Central Asia (former USSR countries). Cases with resistance to most (if not all) available anti-TB medications have been reported from several settings in recent years (11-13).

Limited diagnostic coverage and treatment enrolment
The well-documented crisis of MDR/RR-TB detection and treatment continues unabated, with slow and limited uptake by countries of technological breakthroughs in diagnostics and treatment over the past 10 years. In 2015, only 24% of new and 53% of previously treated TB patients had drug susceptibility testing (DST) done, despite the 2009 World Health Assembly Resolution 62.15 on universal DST and treatment for all MDR-TB cases. The WHO European Region is the only part of the world where DST coverage has remained comparatively stable at a high level of 60–70%.

Globally, only around 20% of the 580,000 people newly eligible for second-line treatment in 2015 were detected and enrolled on treatment in 2015. This means 450,000 cases with MDR/RR-TB remained undiagnosed and untreated. Multiple reasons exist for the stagnation in detection and treatment of these patients (14); slow uptake of WHO-recommended rapid molecular diagnostics, access to, and cost of, second-line medicines, technical complexities in managing drug-resistant TB patients and health service weaknesses are common themes.

Poor treatment outcomes and significant health service challenges
Only 52% of 87,000 MDR/RR-TB patients who started second-line therapy in 2013 were reported by countries to have been successfully treated, while 17% of patients died, 22% were lost to follow-up or not evaluated and treatment failed in 9% of patients. Among over 4,000 XDR-TB patients started on treatment worldwide in 2013, only 28% completed treatment successfully, 27% died, treatment failed for 21%, and 23% were lost to follow-up or not evaluated. These outcomes have remained static despite improvements in the coverage of treatment and availability of more effective or new medicines, for example, later-generation fluoroquinolones, bedaquiline and delamanid.

Hospitalization of patients with MDR/RR-TB is still the predominant model of care in many countries despite WHO recommendations for a decentralised approach to treatment. Ten high-burden MDR-TB countries reported hospitalization for all MDR-TB patients in 2015, including two of the top three MDR-TB burden countries: China and the Russian Federation. In a further six high MDR-TB burden countries, at least 90%
of MDR/RR-TB patients were hospitalized. In most of these countries the average length of stay was 160 days.

Hospitalization cost is one of the main drivers in the overall cost per patient treated in the high-burden TB countries, ranging from US$ 100–1,000 for drug-susceptible TB and US$ 2,000–20,000 for MDR/RR-TB.

Airborne transmission and inadequate infection prevention and control

MDR/RR-TB is by far the greatest and most serious drug-resistant airborne disease. Transmission occurs almost exclusively via the air to close contacts of such cases, often in congregate settings and in vulnerable groups such as those with HIV co-infection, migrants, healthcare workers, prisoners and miners, or in children. Contrary to earlier assumptions, acquisition of drug resistance does not necessarily lower the transmissibility or virulence of TB strains (15, 16). Explosive outbreaks of M/XDR-TB have been well described in the literature (3, 17). Moreover, modelling studies and recent publications from several countries clearly show that

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transmission is a much more important driver of outbreaks or undetected epidemics than previously thought (18–20).

Lack of appropriate airborne infection control measures, limited tracing of MDR/RR-TB contacts and lack of efficacious treatment for latent MDR/RR-TB infection further compound the problem (21–30). The risk of MDR-TB replacing drug-susceptible TB epidemics has been flagged in modeling studies and is not entirely implausible (31, 32).

Suboptimal investment in MDR/RR-TB management, research and development

The high cost of existing commodities (especially medicines) for MDR/RR-TB severely stretches already limited country resources, and far too little investment goes to much-needed social support systems for patients and building resilient health services able to deliver quality care.

The 2016 WHO Global Report showed that international donor funding for TB falls far short of donor contributions for HIV and malaria, despite the fact that TB is the top infectious cause of death worldwide. The latest data from the Organisation for Economic Co-operation and Development (OECD) credit reporting system show the overall investment in MDR/RR-TB fell to a minimum of US$ 5.4 billion for HIV/AIDS, US$ 1.7 billion for malaria and US$ 0.7 billion for TB in 2014 (2). Despite being by far the largest external donor in TB (more than 80% of international resources come from this mechanism), the Global Fund to Fight AIDS, TB and Malaria – which is the major international donor for the three diseases – invests less than 20% of its funding in TB control (33).

Research investment in developing transformational interventions for TB is also vastly insufficient. Funding for TB research and development is at its lowest level since 2008, at only US$ 620 million per year against the global estimated minimum annual need of at least US$ 2 billion (34). Funding during the decade 2005–2014 never exceeded US$ 0.7 billion per year, partly explaining the rather modest pipeline for new TB vaccines, medicines and, to a lesser extent, diagnostics (2) (Figure 3). In comparison, investment in anti-retroviral development has been many times more than in anti-TB agents, allowing more treatment options to be delivered to HIV patients in recent years.

Complacency and insufficient political commitment

Progress in response to the global MDR/RR-TB crisis is dismal. M/XDR-TB constitutes both a public health and international health security crisis which requires urgent, innovative and sustained interventions involving multiple state and non-state sectors. Unfortunately, the essential political will – which should translate into adequate financial and human resources to address the MDR/RR-TB crisis – is lacking in many countries, often those hardest hit by the epidemic. Complacency about TB as an “ancient” disease and reluctance by policy-makers to embrace innovations (notably rapid diagnostics and new drugs) threaten the strides made in TB control over the last ten years and poses a major barrier to containing and reversing the MDR/RR-TB crisis.

Discussion

The WHO End TB strategy is firmly positioned within the context of the post-2015 era of the Sustainable Development Goals (SDGs). Both the SDGs and the End TB Strategy share a common aim: to end the global TB epidemic and leave no one behind. However, doing so will require an unprecedented acceleration in the rate at which TB incidence falls globally, together with an effective crisis response to contain the MDR/RR-TB epidemic while it is still possible.

The lethality of XDR-TB comes close to that observed among Ebola patients in the recent outbreaks in western Africa (2, 35). However, few realize that MDR-TB kills more than 10 times as many people every year as the entire last tragic Ebola epidemic. Poignantly, much of the MDR/RR-TB burden is man-made and largely preventable by curing patients without drug-resistant strains the first time around. Currently, only a few countries will achieve universal access to MDR/RR-TB care by 2025 should they sustain their current pace of progress. In most other countries a radical scale-up is needed to positively impact the MDR/RR-TB crisis and its devastating effects on patients and health services. Five priority actions have been identified by WHO to do so:

- Prevent the development of drug resistance through high-quality treatment of drug-susceptible TB;
- Expand rapid testing and detection of drug-resistant TB cases;
- Provide immediate access to effective treatment and proper care;
- Prevent transmission through proper infection control; and
- Increase political commitment and provide adequate financing.

Changing the course of the TB epidemic will require technological breakthroughs – for example, a post-exposure vaccine, short and efficacious treatment for latent TB infection, novel diagnostics to identify those at greatest risk of developing active disease once infected, and completely new, universal short treatment regimens that would be effective despite the presence of drug resistance. Accelerated uptake of emerging innovations such as digital health technologies (36, 37), combined with efforts to improve quality-of-life of people while on treatment, are equally important.

Some technological breakthroughs are already available and
ready for immediate scale-up (Figure 4). WHO recommended four new diagnostic tests in 2016 alone – one of these being a rapid DNA-based line probe assay that identifies genetic mutations in MDR/RR-TB strains, providing results in 24-48 hours and helping to guide appropriate treatment regimens (38). Furthermore, bedaquiline and delamanid, the first completely new MDR/RR-TB drugs ever, were recommended by WHO in 2013 and 2014 respectively (39, 40). In 2016, WHO recommended a shorter, standardized treatment regimen for the majority of MDR/RR-TB patients, which could overcome several of the barriers faced by patients and health services in MDR/RR-TB care delivery (41, 42). Policy guidance on the shorter MDR-TB regimen also benefited from strategically targeted operational research, as shown recently (43).

Yet more innovations are at the door. Novel genome sequencing technologies could expand and refine surveillance of drug-resistant TB and, in the longer term, guide individual patient care (44, 45). Nine anti-TB drugs are currently in an advanced stage of development and 13 vaccine candidates are in clinical trials (2). Novel regimens are under development and could potentially reach the market by 2020, the first milestone for measuring progress in the WHO End TB Strategy (46, 47).

Conclusions
The MDR/RR-TB crisis demonstrates many of the challenges that will be faced by broader AMR control efforts. The response to this challenge has shown that several critical elements are essential for the control of drug-resistant infectious diseases in countries. These include good quality surveillance, rapid diagnosis of drug resistance, appropriate treatment, improved infection prevention and control, and good care delivery systems with trained health personnel. Moreover, problems in treating MDR/RR-TB can point to a country or institution’s readiness to tackle AMR.

The AMR response at global and country level could greatly benefit from the challenges faced by TB care and control and by adopting some of TB’s “lessons learned”. Moreover, diagnostic platforms, logistics and digital technologies for sharing data can be used to link TB and AMR programmes at the country level. Existing regulatory frameworks, surveillance systems, infrastructure for laboratory services and infection control, and human resources already in place to manage drug resistance in tuberculosis, HIV and malaria could be additional resources to governments implementing AMR plans (48).

At the global level, at least two high-level initiatives present ample opportunity to address MDR/RR-TB within broader health agendas: the WHO Global Action Plan on Antimicrobial Resistance calls for inclusive, multi-sectoral and innovative partnerships to foster the development of antibiotics, responsible use of medicines, coordinated research and development of new drugs, diagnostics and vaccines (in close collaboration with industry), with strategies to ensure affordability and access for all. The Global Health Security Agenda (GHSA) is an effort between nations, international organizations and civil society to accelerate progress towards a world safe and secure from infectious disease threats and to promote global health security as a national and international priority (49).

Prominent space for the MDR/RR-TB crisis, enhanced...
linkages and increased collaboration within these global agendas is urgently needed. The upcoming WHO Ministerial Conference co-hosted by the Russia Federation in November 2017 and the planned 2018 United Nations General Assembly high-level meeting on TB (50, 51), will be key opportunities to firmly position MDR/RR-TB within the AMR and global health security agendas; secure political commitment and dedicated funding to tackle the MDR/RR-TB crisis; form strategic partnerships exerting enough pressure to reduce the cost of commodities; agree on a prioritized research agenda; and consider existing global measures such as the International Health Regulations to contain the M/XDR-TB crisis. Time and renewed political will are, however, of the essence.

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Dr Fuad Mirzayev leads the team on Policy Transfer and Uptake of the WHO Global TB Programme Unit for Laboratories, Diagnostics and Drug Resistance (LDR). He holds a degree in medicine from the State Medical University of Azerbaijan and MPH from the School of Public Health and Tropical Medicine at Tulane University, USA. He joined the World Health Organization in 2004 and his main areas of work included management of drug-resistant tuberculosis and access to second line anti-TB medicines via Green Light Committee Initiative; coordination of multi-country projects to expand access to innovative TB diagnostics. Prior to joining WHO he has worked for the International Committee of the Red Cross with its pioneer TB Control programme in penitentiary systems of countries in transition.

Professor Mario C. Raviglione, MD, has been Director of the Global TB Programme at WHO since 2003. He was part of the team that developed the DOTS strategy in 1994, and set up the global drug-resistance surveillance project (1994) and the global TB surveillance and monitoring system (1995). He directed the teams who developed the latest global strategies: Stop TB in 2006 and End TB in 2014. As a leading expert in TB, he has worked in over 50 countries worldwide. He has served as a visiting professor at Johns Hopkins University, Université de Genève, Università di Modena; Reggio Emilia, Università di Pavia and University of Brescia where he is professor. He has published over 350 articles and book chapters, and he is among the top 10 most cited authors in the TB field. He is editor of the 3rd and 4th (2006, 2009) editions of Tuberculosis - A Comprehensive International Approach. He graduated from the University of Turin in Italy in 1980, and trained in internal medicine and infectious diseases in New York (where he was Chief Medical Resident at Cabrini’s Medical Centre) and Boston, where he was an AIDS Clinical Research Fellow at Beth Israel Hospital, Harvard Medical School. In 2005, he received the Princess Chichibu TB Global Award for his achievements in TB control.