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EDITORIAL

Antimicrobial resistance and the growing threat of drug-resistant tuberculosis



Antimicrobial resistance (AMR) is a global health emergency, and experts are concerned that the end of the age of antimicrobials is imminent [1–6]. Since the introduction of antimicrobials nearly a century ago, microbes have evolved a variety of methods to resist these drugs. Today, the world is dealing with ‘superbugs’ that are virtually untreatable, including drug-resistant gonorrhoea, carbapenem-resistant enterobacteriaceae, Methicillin-resistant *Staphylococcus aureus*, and extended-spectrum-beta-lactamase producing strains [5]. The antibiotic pipeline is running dry, and AMR is threatening to undo major gains made in the control of infectious diseases. Models suggest that 300 million people are expected to die prematurely because of AMR over the next 35 years and the world’s GDP will be 2–3.5% lower than it otherwise would be in 2050 [6]. This translates into a loss of 60–100 trillion USD worth of economic output by 2050.

AMR is driven by several factors, but major causes include over-use of antibiotics, poor adherence to standard treatment schedules, over-use of antibiotics in livestock, poor infection control in hospitals, lack of hygiene, and challenges with new antibiotic discovery [1,5].

Antibiotic consumption is increasing globally, with 20–50% estimated to be inappropriate [5]. According to the State of the World’s Antibiotics report (2015) [5], the countries consuming the most antibiotics overall in 2010 were India, 13 billion standard units-squared [SU]; China, 10

billion SU; and the United States, 7 billion SU. However, in per capita terms among these countries, the United States led in 2010 with 22 SU per person, compared with 11 SU in India and 7 SU in China [5].

Drug-resistant tuberculosis (DR-TB) is a good example of AMR. The most common form of drug-resistant TB is multi-drug resistant TB (MDR-TB), which refers to TB that is resistant to isoniazid and rifampicin. Globally in 2014, WHO estimated 3.3% of new cases and 20% of previously treated cases to have MDR-TB [7]. Drug resistance surveillance data show that an estimated 480,000 people developed MDR-TB in 2014 and 190,000 people died [7]. Extensively drug-resistant (XDR-TB) strains are resistant to at least four of the core anti-TB drugs, and XDR-TB has been reported by 105 countries in 2014. On average, an estimated 9.7% of people with MDR-TB have XDR-TB [7]. Some studies have also reported totally drug-resistant strains of TB [8].

Why should we care about DR-TB? The answer is straightforward. Drug-resistant TB requires extensive treatment (for 2 years or longer) with multiple, potentially toxic drugs and outcomes are poor. About 50% of patients with drug-resistant TB die because of it [9]. Treatment of DR-TB is also very expensive because of the high cost of second-line TB drugs. Thus, prevention of DR-TB is critical. WHO has proposed 5 priority actions to tackle the global DR-TB crisis: (1) prevent the development of drug-resistance through high quality treatment of drug-susceptible TB; (2) expand rapid testing and detection of DR-TB cases; (3) provide immediate access to effective treatment and proper care; (4) prevent transmission through infection control;

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and (5) increase political commitment with financing [7].

Unfortunately, high TB burden countries are yet to seriously address these priority actions to tackle DR-TB. In many countries, less than 50% of patients with DR-TB are on second-line drug therapy [7]. Quality of TB care for even drug-susceptible TB remains suboptimal in many countries, especially in countries with large numbers of private health care providers [10–12]. In such settings, doctors prescribe irrational drug regimens, and adherence monitoring is poor [10,12]. Empirical antibiotic use is widespread in many countries with weak regulation, and this further increases the risk of AMR [13]. Also, over-the-counter antibiotic abuse is widespread in many high TB burden countries [5]. OTC use of fluoroquinolones, a widely used antibiotic, can delay the diagnosis of TB, and also increase the risk of DR-TB [14]. This is particularly relevant, since some of the emerging new TB drug regimens contain fluoroquinolones.

While molecular tests such as Xpert MTB/RIF (Cepheid Inc, Sunnyvale, CA, USA) are now available to rapidly detect drug-resistance, most high-burden countries are still reliant on sputum smear microscopy [15]. A recent report called 'Out of Step' by Medicins sans Frontiers (MSF) and Stop TB Partnership surveyed 24 high TB burden countries, to see how already existing TB policies and interventions are being implemented [16]. This study found major implementation gaps. For example, only 8 countries included in the survey had revised their national policies to include Xpert MTB/RIF as the initial diagnostic test for all adults and children with presumptive TB, replacing smear microscopy. Six of 24 countries still recommended intermittent treatment for drug-sensitive TB (which is less effective than daily therapy). Even simple interventions such as fixed dose combinations to improve treatment adherence are not routinely used in all countries.

Clearly, TB is a low priority for many developing countries, and current investments are insufficient to make progress in addressing DR-TB. In this context, it may be more impactful for DR-TB control to be seen as one component of a comprehensive strategy to address AMR. Unlike TB, AMR is increasingly seen as a global health emergency and a security threat [1,2,6]. Policy makers and donor agencies have prioritized AMR as a key issue for the global health security agenda [1–6]. The door is wide open for the TB

community to leverage this interest, and advocate for a well-funded AMR initiative that includes DR-TB as a key component. To quote Margaret Chan, "*antimicrobial resistance is a crisis that must be managed with the utmost urgency. As the world enters the ambitious new era of sustainable development, we cannot allow hard-won gains for health to be eroded by the failure of our mainstay medicines.*" [1].

Conflicts of interest

The authors declare no conflicts of interest.

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