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What tuberculosis can teach us about combating multidrug-resistant Gram negative bacilli

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ABSTRACT

There are striking similarities between the dual pandemics of multidrug-resistant tuberculosis (MDR TB) and multidrug-resistant Gram negative bacilli (MDR GNB) despite fundamental differences in the pathogenesis and epidemiology of these pathogens. In this perspective, we highlight several strategies that have been used by the global TB community to address the MDR TB problem, including approaches to: encourage appropriate use of anti-TB medications, enhance appropriate utilization of molecular diagnostic testing, facilitate development of new antimicrobial agents, and strengthen surveillance systems and infection control practices. Understanding the successes and challenges of these strategies for MDR TB control will be instructive for efforts to curb emergence and spread of MDR GNB.

MDR TB and MDR GNB: disease burden

MDR TB was first recognized as a problem in the late 1990s and now affects roughly 500,000 people annually, accounting for 3% of new TB cases and 20% of previously treated TB cases worldwide [1]. Although 50% of the global burden of MDR TB occurs in India, China, and the Russian Federation [1] (Fig. 1), MDR TB and extensively drug-resistant TB (XDR TB) have emerged and spread worldwide, with transmission often facilitated through international travel. Foreign-born individuals account for 90% of US MDR TB cases [2] and stories of XDR TB patients traveling by commercial airlines make headlines [3]. As there are few new, effective drugs to treat these resistant strains, MDR/XDR TB patients receive second line agents that are more toxic and costly, and less effective than first line therapies. Globally, among patients with MDR TB who are initiated on therapy, only about half are successfully treated. In 2014 there were an estimated 190,000 deaths due to MDR TB [1]

While attention has been focused on MDR TB for decades, the global emergence of other drug resistant bacteria has only recently been recognized as a public health emergency [4]. The press increasingly report stories about extensively drug-resistant bacteria that are resistant to most existing antibiotics and are thought to be "untreatable" [5, 6]. In 2014, President Obama's Council of Advisors on Science and Technology published a report calling antimicrobial resistance a *national security threat* that causes over 2 million illnesses, $20–35 billion in excess direct healthcare costs, $35 billion in loss of productivity, and 8 million additional hospital days each year in the US [7]. Worldwide, it is estimated that by 2050, 10 million people will die annually from antibiotic-resistant infections [8].

GNB are among the most alarming antibiotic-resistant pathogens as they are often resistant to multiple antibiotic classes and capable of rapidly spreading resistance genes through mobile genetic elements. For example, the pandemic emergence of the highly drug-resistant clone of *Escherichia coli*, sequence type 131 (ST131), occurred in less than 10 years [9]. Limited surveillance data suggest that in some regions of the world nearly 70% of GNB clinical isolates produce extended-spectrum β-lactamases (ESBLs), which make them resistant to most β-lactam antibiotics [10, 11]. Even more alarming is that in some studies, resistance to carbapenems, known as last-resort antibiotics, has been reported in up to 68% of *Klebsiella pneumoniae* isolates [12–15]. India, which has one quarter of the global burden of MDR TB, is also the epicenter of carbapenem-resistant, New Delhi-metalloprotease (NDM)-producing strains of *Enterobacteriaceae* [16], which have been found contaminating environmental sources [17]. As with MDR TB, international travel has facilitated spread of MDR GNB, with travel to regions of the world with high ESBL and carbapenem-resistant *Enterobacteriaceae* (CRE) rates identified as a

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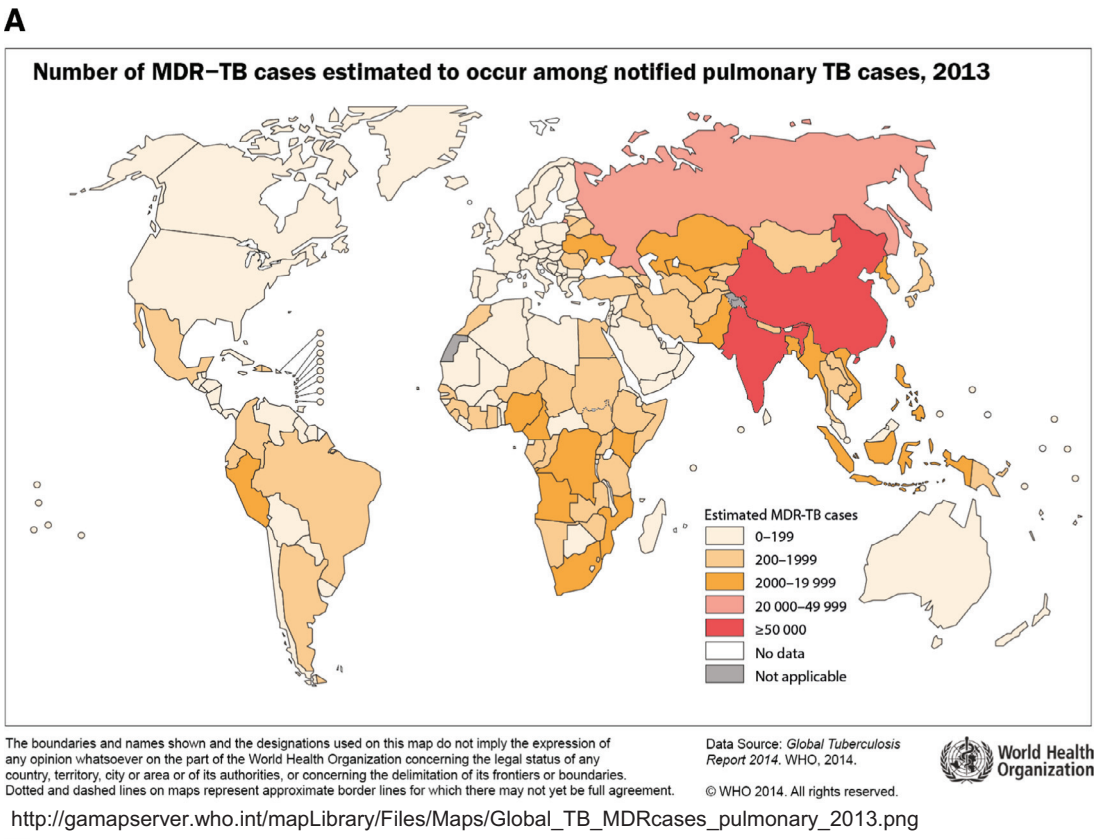

Fig. 1. MDR TB (A) and extended-spectrum β-lactamase (ESBL)-producing *E. coli* (B) are prevalent in similar regions of the world.

risk factor for acquisition of MDR GNB in several studies [18–22]. Similar to patients with MDR TB who must rely on second-line anti-TB drugs, those with MDR GNB often receive second-line agents that are more toxic and expensive but less effective than first-line therapies, contributing to poor outcomes. Mortality rates for carbapenem-resistant *Enterobacteriaceae* infections range from 18-48% [23, 24] compared to 10% for carbapenem-susceptible infections [25]. In India alone, drug-resistant pathogens, many of which are GNB, are estimated to cause 58,000 neonatal deaths [26].

MDR TB and MDR GNB are human-made problems

Both MDR TB and MDR GNB have arisen through missteps at the level of patients, providers, and health systems and are human-made problems. They have flourished in regions of the world with