

## The overlooked pandemic of antimicrobial resistance



As COVID-19 rages on, the pandemic of antimicrobial resistance (AMR) continues in the shadows. The toll taken by AMR on patients and their families is largely invisible but is reflected in prolonged bacterial infections that extend hospital stays and cause needless deaths.<sup>1</sup> Moreover, AMR disproportionately affects poor individuals who have little access to second-line, more expensive antibiotics that could work when first-line drugs fail.

Previous attempts have been made to accurately estimate the global burden of AMR, both to focus policy makers on the extent of the problem and to identify geographical areas with the greatest burden.<sup>2-4</sup> These estimates have been challenged by unreliable data on resistance and infections and the difficulty of attributing burden to AMR specifically.<sup>5</sup> Patients with longer hospital stays are more likely to have resistant pathogens than those with shorter stays. Is it AMR that causes these longer hospital stays or is it just that patients who stay longer happen to pick up drug-resistant infections? How can we distinguish between patients who died with resistant pathogens from those who died of resistant pathogens?

In *The Lancet*, Christopher Murray and colleagues present their ambitious effort to address the question of the global burden of AMR.<sup>6</sup> The authors estimated disease burden for 23 pathogens and 88 pathogen-drug combinations in 204 countries and territories in 2019 on the basis of two counterfactual scenarios: one in which all drug-resistant infections were replaced by drug-susceptible infections, and one in which all drug-resistant infections were replaced by no infection. Using this method, the study directly addresses the difference between burden associated with resistance, and burden attributable to resistance. Murray and colleagues estimated a median of 1.27 million (95% uncertainty interval 0.911–1.71) deaths in 2019 directly attributable to resistance, a value that is nearly the same as global HIV deaths (680 000)<sup>7</sup> and malaria deaths (627 000)<sup>8</sup> combined, and ranks behind only COVID-19 and tuberculosis in terms of global deaths from an infection.

The study's estimate of 4.95 million (3.62–6.57) deaths associated with bacterial AMR globally in 2019 indicates that there are substantial gains to be made from preventing infections in the first place. Of the

major bacterial pathogens covered in this study, only pneumococcal pneumonia is preventable through vaccination. Preventive vaccines against viral pathogens including influenza, respiratory syncytial virus, and rotavirus could be effective in reducing the need for treatment, thereby reducing inappropriate antibiotic consumption.<sup>9-12</sup> In high-income countries, improved water and sanitation, public health, and hospital hygiene have been the primary ways in which infections have been controlled, but these methods have been difficult to implement in resource-poor settings despite economic progress.

Ironically, the burden of resistance partly reflects the insufficient access to antibiotics.<sup>13</sup> The problem of excessive and inappropriate use of antibiotics co-exists with the problem of insufficient access even in the same geographical areas. Pneumococcal pneumonia is easily treatable with antibiotics, but the burden estimated by Murray and colleagues reflects the lack of access to even inexpensive drugs such as penicillin. Some of the AMR burden in sub-Saharan Africa is probably due to inadequate access to antibiotics and high infection levels, albeit at low levels of resistance, whereas in south Asia and Latin America, it is because of high resistance even with good access to antibiotics. Over two-thirds of attributable deaths were due to resistance to first-line antibiotics including fluoroquinolones and  $\beta$ -lactam antibiotics (carbapenems, cephalosporins, and penicillins).

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The true burden of resistance could be greater than that estimated in this study. Modern medicine, including surgeries, chemotherapy, organ transplantations, and other invasive procedures require effective antibiotics. Untreatable infections reduce the value of these procedures and thereby lower their value to patients,<sup>14</sup> but this additional burden is difficult to measure and is not addressed. By the same token, it is possible that tertiary care institutions that have laboratory capacity also have patients who are sicker and higher levels of resistance than other care facilities, which could lead to an overestimate of the resistance problem.

The wide uncertainty intervals in Murray and colleagues' study reflect the general scarcity of data on numbers of bacterial infections—and AMR—particularly in low-income and middle-income countries (LMICs). Most of the raw data in the study come from high-income countries. Although much progress has been made in the past decade on data collection from LMICs on AMR and consumption of antibiotics,<sup>15</sup> much remains to be done. Progress ahead will depend on projects such as those supported by the Fleming Fund, which aim to improve laboratory capacity in LMICs while also uncovering resistance data that lie on dusty shelves and in long-forgotten hard drives.

From being an unrecognised and hidden problem, a clearer picture of the burden of AMR is finally emerging. Even the lower end of 911 000 deaths estimated by Murray and colleagues is higher than the number of deaths from HIV, which attracts close to US\$50 billion each year.<sup>16</sup> However, global spending on addressing AMR is probably much lower than that. This needs to change. Spending needs to be directed to preventing infections in the first place, making sure existing antibiotics are used appropriately and judiciously, and to bringing new antibiotics to market. Health and political leaders at local, national, and international levels need to take seriously the importance of addressing AMR and the challenge of poor access to affordable, effective antibiotics.

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