No antimicrobial resistance research agenda without tuberculosis

The global fight against antimicrobial resistance (AMR) needs a unified, multidisciplinary, and intersectoral approach by a community of stakeholders and implementers working towards common goals. As such, the impetus created by the WHO priority list of antibiotic-resistant bacteria[1] and increasing focus from the international public health community are timely. However, tuberculosis is not sufficiently emphasised in the AMR discussion at the highest decision-making level. Tuberculosis is the top infectious disease killer globally,[2] and is responsible for around a quarter of all deaths caused by AMR bacteria,[3] with nearly half a million estimated multidrug-resistant tuberculosis cases annually.[2] This insufficiency of emphasis is despite the global public health threat[2] that multidrug-resistant tuberculosis poses, and the potential for knowledge sharing given the experience accumulated over decades.

For example, although specific large grants for tuberculosis drug development are available from the European Commission, many UK funders do not include tuberculosis in AMR grants: omissions include a 2018 £32 million call for AMR capital funding.[4] In the USA, for 2018 AMR category projects from the National Institutes of Health, only around 10% of grants and funding for research explicitly mentioned tuberculosis in the title. At the global level, major initiatives driving research and development into new antimicrobials also seem to exclude tuberculosis. Both the 2017–18 and 2018–19 annual reports from the Combating Antibiotic Resistant Bacteria initiative did not mention tuberculosis. The Global Antibiotic Research and Development Partnership's four programmes do not include a focused multidrug-resistant tuberculosis channel. Another new initiative by the Bill & Melinda Gates Medical Research Institute has tuberculosis as one of the three diseases in focus, but the translational research is not specifically targeted at drug resistance. Finally, the lack of research and development investment is reflected in reviews[5] on the progress in antimicrobial resistance that completely ignore tuberculosis. Ultimately, the TB Alliance, which antedates more recent AMR awareness, is the sole global initiative dedicated entirely to tuberculosis drug development.

The reasons for this lack of attention originate from well known difficulties in advocating for tuberculosis action in general,[6] but it could also be because of misconceptions. First, the natural history of tuberculosis suggests that it requires complex interventions through new combination regimens rather than a single new agent. However, tuberculosis has the same needs as many other bacterial diseases: shorter treatment regimens alongside rapid diagnostics. Second, the argument that tuberculosis is already supported by dedicated long-term programmes for research and development is invalid: far less than the 50% of the estimated need is being mobilised.[7]

To address the huge problem of multidrug-resistant tuberculosis, *Mycobacterium tuberculosis* must systematically be included as an integral part of all AMR priority lists for research and development financing. For example, perhaps because tuberculosis is only a footnote on the key WHO priority list table, despite having a chapter in the final report, a 2019 systematic review[8] of AMR modelling has a blank next to the WHO categorisation of priority level for *M tuberculosis*. The inclusion of tuberculosis would be consistent with previous lists of top AMR pathogens, beyond the final WHO list, such as those from the US Centers for Disease Control and Prevention and Longitude Prize Team.

By assuming tuberculosis programmes are inherently separate from research initiatives for other bacteria, both tuberculosis and other pathogens will suffer a lack of shared infrastructure, knowledge, investment, and research overlap.[9] For example, new funding frameworks could be introduced to expand further and jointly develop new antimicrobials and therapies for all bacteria, including and emphasising tuberculosis. The attempt by the Innovative Medicines Initiative to develop an integrated research platform within which tuberculosis is a pillar is an important step forward.[10] The global laboratory initiative, long-established surveillance networks, and WHO reports are all aspects of the tuberculosis world, within which multidrug-resistant tuberculosis focus is increasing, which could provide important lessons for the wider AMR field.[3]

Despite a small increase in new drug financing, in 2017–18,[7] tuberculosis has faced a long-term lack

of focus on investments in drug development when compared with infectious diseases with similar human burden such as HIV and malaria.[7] In the AMR arena, it seems that tuberculosis is also not prioritised, perhaps because it does not cause a problem in high-income settings, where concern about AMR is driven by hospital-associated infections. With the new global focus on AMR, the knowledge of, and lessons learned from, tuberculosis programmes and research, should be embraced within a unified platform across all income groups to move forward more quickly and reduce the burden of all infections caused by AMR pathogens.

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