THE THREAT OF ANTIMICROBIAL RESISTANCE – HAS IT CHANGED IN TWO YEARS?

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In the run up to the second UN General Assembly (UNGA) High Level Meeting on Antimicrobial Resistance (AMR) on the 26th of September 2024, eight years after the first and unprecedented UNGA meeting on AMR (Quadripartite Joint Secretariat On AMR, 2024), we reflect on the progress made on the issues that we had raised in our 2022 article in *Science in Parliament* entitled *Anti-Microbial Resistance – A Post-Modern Dilemma* (Hanley, 2022).

Antimicrobials have been the mainstay of modern medicine ever since the discovery of Penicillin by Sir Alexander Fleming. Not only are they a cure against infections caused by bacteria, fungi, parasites and viruses, but they are also the facilitators of medical interventions such as general surgery, joint replacements and cancer therapy. The impact of antimicrobials on modern medicine is recognised not only by doctors, scientists and policy makers but also the general public who, in 2017, voted antibiotics as "Britain's Greatest Invention" (BBC Two, 2017).

AMR is, in its simplest form, the development of resistance to antimicrobial agents by bacteria, fungi, viruses and parasites. The arms race between antibiotic development and microbial resistance is one of the most important conflicts whose outcome could threaten human existence on several levels. In addition to the direct effect on humans through the development of resistance by pathogens, the use of antimicrobial agents in agriculture may lead to the creation of a pool of transferable resistance characteristics and an impact on food-producing systems (Woodhouse et al, 2015).

In 2022, we reported on the humanitarian, scientific and commercial challenges of AMR.

1. Firstly, we reflected on the seminal report by Lord O'Neill in 2016 which is still cited by scientific publications, NGOs, media outlets and governments worldwide (O'Neill, 2016).

The report predicted 10 million deaths globally caused by untreatable infections by 2050. This was confirmed by a real-world view of 4.95 million deaths associated with AMR, including 1.27 million deaths directly attributable to AMR, in 2019 (Collaborators, 2022). This was corroborated in 2024 where it was found that 28% of the global burden of disease (all causes) as measured in Disability Adjusted Life Years (DALYs) is due to infections. Half of these, i.e.14% (97 million DALYs) of the global burden of disease, is due to bacterial infections including species such as *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli, Pseudomonas aeruginosa, Acinetobacter baumannii*, and *Helicobacter pylori* (Group, 2024).

Tuberculosis (caused by the bacterium *Mycobacterium tuberculosis*), malaria (caused by the parasite *Plasmodium* spp) and AIDS (caused by the Human Immunodeficiency Virus (HIV)) were recently named as the exerting the largest impact on disease burden as measured by DALYs (Group, 2024). The infections caused by all three of these, can be treated by antimicrobials (Alsayed, 2023) (Abumsimir, 2023) (Landovitz, 2023).

Unfortunately, we have not seen any decreases in deaths directly attributable to AMR in 2024, with the Global Antibiotic Research & Development Partnership (GARDP) estimating that one person dies every 6 seconds from untreatable infections (GARDP, 2024).

2. Secondly, we discussed that the economic model for antimicrobial development is broken.

The development of new antimicrobials is as expensive as developing a new cancer drug, but the drugs themselves do not command a premium price. In addition, because of the development of resistance the prescribing of new antimicrobial drugs is limited to last resort situations, leading to a lower income for manufacturers and a poor return on investment. This has led big pharma to step away from antimicrobial drug development and the development is now left to SMEs.

Prof Kevin Outterson, the CEO of CARB-X (CARB-X, 2024) states that for primary research leading to first in man clinical trials there is a global funding gap of USD370 million needed by the SMEs to deliver six new, high impact treatments per decade. Furthermore, at the NCCR AntiResist event in March 2024 (NCCR AntiResist, 2024) preceding Europe's most significant annual AMR Conference in Basel (AMR Conference, 2024), Prof Outterson presented data from Q3 2023, that showed that of the seven business to have brought a new antibiotic to the market, three went into bankruptcy and the remaining four into distressed sale all due to the lack of an effective market pull. These failures led to private investors losing over USD2.3 billion, not to mention the USD777 million in grants that had been awarded to these companies by the US government.

3. Thirdly, we reported on the then evaluation by NICE of a "Netflix-style" subscription model for access to antimicrobial products which was finalised in 2024. (NHS England, 2024). For Breakthrough antimicrobials that have been evaluated according to the *Antimicrobial Products Subscription Model: Product Award Criteria*, a possible annual payment of £20 million will be made to the company that developed the drug, provided that the total sales made to NHS England in that year were less than that amount (with smaller payments made by the devolved nations). A sliding scale of payments for antimicrobials classified as critical, priority and important by the WHO is also recommended by this evaluation.

Whilst £20-£25 million per annum may be insufficient to keep an antimicrobial developer from bankruptcy, if more countries globally follow a similar model, then antimicrobial development becomes a viable business opportunity again. Boston University (BU) published an AMR Financial Model (Boston University, 2021) which calculates the fair share that countries should pay per annum per new drug. The BU model agrees with the decisions by NHS England on the value to be paid and suggests that the G7+EU27 countries should pay an extra USD290 million annually as an appropriate payment for the development of new antimicrobials.

The UK was the first country to establish and implement such a model and the model is now being copied globally with developments to launch such programmes in Canada and Japan.

4. The science of developing new antimicrobials has not become any easier. In the press release for the WHO's antimicrobial pipeline review (WHO, 2024), it was reported that

> *"Overall, antibacterial agents in the clinical pipeline combined with those approved in the last six years are still insufficient to tackle the ever-growing threat of the emergence and spread of drug-resistant infections."*

The current clinical antibacterial pipeline (not including antifungal, antiviral or anti-parasite agents) contains 97 agents. 57 of these are antibiotics (small- or large molecule drugs which kill bacteria) and 40 are non-traditional agents which include bacteriophages (viruses that kill bacteria) and products that enhance the activity of antibiotics. However, only 20% of the antibacterials in clinical development are innovative, meaning that the remainder are modifications of, or combinations of, existing antibacterials.

A further concerning issue regarding antimicrobial development is the report by the AMR Industry Alliance Professionals (AMR Industry Alliance, 2024) that the AMR R&D workforce is limited and declining. The Alliance which includes numerous UK-based SMEs estimates that there are only 3,000 AMR researchers currently active in the world (estimated range of 1,218-4,726), compared to as many as 46,000 for cancer and 5,000 for HIV/AIDS.

This decline is reflected in the total number of authors on AMR related peer-reviewed publications which has declined from a high of 3,599 in 1995 to only 1,827 in 2020. This decline is also reflected in the number of peer-reviewed scientific outputs where in 2022, there were 35 times more papers published on cancer than WHO priority bacteria. It is furthermore reflected in the development of new antimicrobial specific IP where in 2022 there were 20 times more patents awarded for cancer than antibiotics.

Finally, since the launch of WHO's Global Action Plan on Antimicrobial Resistance in 2015 (WHO, 2016), the threat of AMR has gained recognition as one of the world's most pressing global health challenges. The action plan echoed recommendations which were presented in Lord O'Neill's report (O'Neill, 2016) focussing on increased awareness of the threat of AMR, improving the understanding of AMR through research, reducing infections through effective hygiene and sanitation, optimising the use of antimicrobials and finally, developing an economic case for sustainable investment for the development of new drugs, diagnostics and vaccines.

At a practical level, this WHO action plan and subsequent first UNGA High Level meeting on AMR led to the country-specific development of National Action Plans (NAPs) on AMR. The UK's second action plan, the UK 5 Year action plan for antimicrobial resistance 2024 to 2029, was published in May 2024 (UK Government, 2024). To date, 178 countries have developed NAPs. However, only 27% of these have implemented their NAPs and only 11% of countries have allocated national budgets to do so.

Efforts to address AMR are however, often hindered by low levels of implementation together with a lack of coordination and financial priority in most countries and at a global scale. The COVID-19 pandemic showed that global collaboration is possible to fight infectious disease and that joint working

can produce concrete public health benefits.

The approach of the second UN General Assembly (UNGA) High Level Meeting approaches serves as a reminder that the UK has historically played a leading role in driving the global agenda to fight AMR as a public health crisis in the making. It is imperative that the UK continues its leadership in AMR, both scientifically and politically, to ensure that the AMR agenda maintains its momentum, gains made to date are not lost and that the threat of AMR remains a global priority for policymakers and population alike.

Notes:

1. The theme of the 26 September 2024, UNGA High Level Meeting is *"Investing in the present and securing our future together: Accelerating multi-sectoral global, regional and national actions to address Antimicrobial Resistance."*

2. CARB-X is the most significant funder of AMR research globally and is part funded by the UK Government's Department of Health and Social Care (DHSC), through its Global Antimicrobial Resistance Innovation Fund (GAMRIF) (CARB-X, 2024).

3. The AMR Conference (https://amr-conference.com/) is part funded by UKRI and is annually attended by a delegation of UK companies supported through the UKRI's Global Business Innovation Programme (GBIP) (https://iuk.ktn-uk.org/opportunities/global-business-innovation-programme-in-switzerland-antimicrobial-resistance-amr/).

4. GARDP is part funded by the UK Government's Department of Health and Social Care (DHSC), through its Global Antimicrobial Resistance Innovation Fund (GAMRIF) with the latest investment being £2.5million in February 2024 (GARDP, 2024).

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