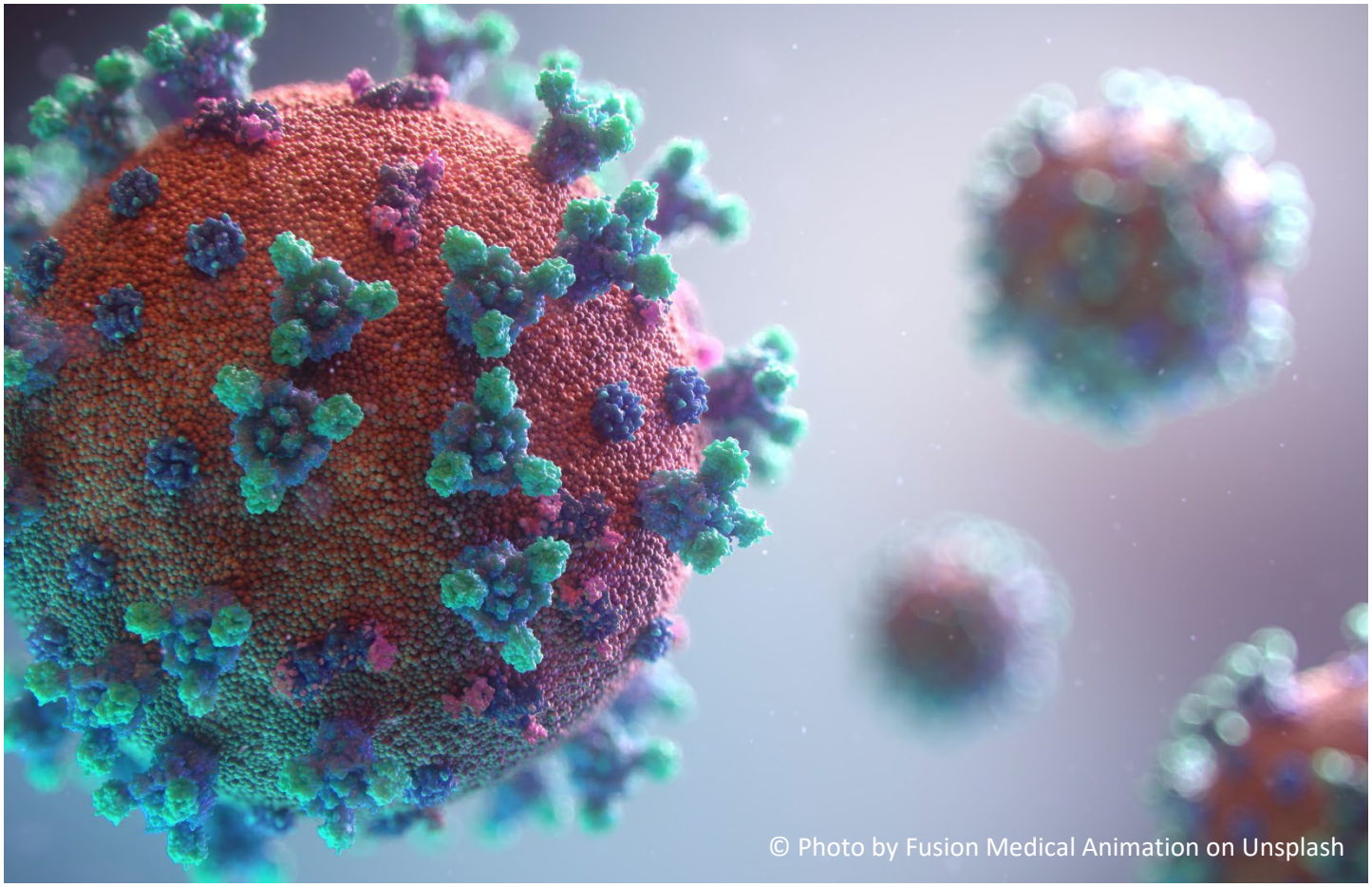

T7 Task Force Global health

POLICY BRIEF

WHY AND HOW THE G7 CAN RESPOND TO THE PUBLIC HEALTH CRISIS OF DRUG-RESISTANT INFECTIONS

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Abstract

The unchecked growth of drug-resistant infections – which are increasingly hard to treat – is a silent pandemic with long-term consequences for global public health and the global economy. According to recently released data published in the Lancet, at least 1.27 million people died of drug resistant infections in 2019. Antimicrobial resistance (AMR) also threatens the viability of surgical and curative medical interventions, such as chemotherapy. It is no longer a threat with future consequences, but a complex existential emergency of infections by multiple microbes. Many countries lack access to existing antibiotics, while in other countries rising rates of resistance require new treatments that have not yet been developed. Drug-resistant infections are a long-term challenge for which governments, including through G7 leadership, as well as the private sector, and civil society, must construct a durable infrastructure to prepare and respond. One pressing concern is for this infrastructure to ensure sustained research and development of novel antibiotics that address priority infections, and responsible access to novel and existing antibiotics to save lives and assure the long-term viability of such critical countermeasures.

Challenges

Just six pathogens, all on the WHO Priority Pathogen List, are responsible for 929,000 of the estimated 1.27 million deaths (73%) due to drug resistance.[i] Yet according to the latest review by the World Health Organization (WHO) of the antibiotic pipeline, and despite some increases in public investment in recent years, current antibiotic research and development (R&D) is inadequate to counter rising rates of drug-resistant infections. Of the 76 anti-bacterials in clinical development, only four have new modes of action not previously exploited by marketed antibacterial drugs, and few address the current problems of drug resistance.[ii] Furthermore, most new antibiotics approved in recent years offer limited clinical benefit over existing treatments, with 82% of recently approved antibiotics derivatives of existing classes with well-established drug resistance.[iii]

Alongside the lack of adequate and sustained R&D, many people, especially in low- and middle-income countries (LMICs), lack access to existing antibiotics and new antibiotics emerging from the pipeline. Antibiotics that could improve treatment outcomes are not available, affordable, cannot be used in a timely fashion, or cannot be used appropriately due to a lack of appropriate diagnostics, surveillance data, real-world evidence, and observational studies to guide use. Many deaths from drug-resistant infections should have been averted through access to the antibiotics on the WHO Model List of Essential Medicines. There are several reasons for the current lack of access to existing antibiotics. First, current incentives are insufficient to stimulate the level of R&D that is necessary for a robust pipeline. Even when developed, they are not widely registered: less than half of the eighteen new anti-bacterials approved from 2010 to 2019 are available in even most high-income countries (HICs).[iv] Another reason is that the market for antibiotics is highly fragmented with low volumes and small-scale demand for many products, particularly those antibiotics recommended to be reserved by the WHO. Additionally, the growing problem of shortages, which affects all countries, including G7 Member States, [v] alongside a lack of evidence for optimal use (including across populations) and the lack of diagnostics exacerbates an already complicated issue.

The necessity for novel treatments will continue to grow. Even with appropriate use of antibiotics, resistance can occur, and there are many contributing factors influencing the rate of development of drug resistance. These include overuse and misuse of antibiotics in human and animal medicine, and in food production, poor infection prevention and control (IPC) measures, and the lack of affordable, globally available quality medicines. For data that is available, there is an alarming picture. The Drug Resistance Index (DRI), which provides an aggregate trend measure of the effectiveness of available treatments, confirms these concerns, and specifically illustrates that 'resistance rates for the priority pathogens remain at a level that threatens public health, and the relative effectiveness of antibiotic therapy in low- and middle-income countries (LMICs) is lower than in high-income countries (HICs).'[vi]

The consequences of AMR are not just limited to its impacts on human health. The World Bank has warned that AMR could be as damaging to the global economy as the 2008 financial crisis, with 28.3 million more people falling into poverty between now and 2050, and a global increase in health care costs ranging from US$ 300 billion to US$ 1 trillion per year.[vii] Antibiotics are a critical element of the health-wealth nexus and

need to be recognized as such if global health is truly to be understood as a vehicle to drive economic prosperity.

WHY ARE GOVERNMENTS FAILING TO ACT?

Several G7 governments, including Germany, the US, UK and Japan deserve recognition for their past and present leadership on building multilateral solutions to AMR, including at the G7 and G20. They have facilitated, with other G7 countries, placing AMR on the agenda of both the G7 and G20, spearheaded the creation of the Global AMR R&D Hub, invested in the Global Antibiotic Research and Development Partnership (GARDP), the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and other initiatives, and sought to build collaborations and partnerships with other governments to prioritize and tackle AMR. The German government's G7 Presidency is a renewed opportunity, based on past successes, to build a more durable infrastructure that can tackle drug resistant infections over the long-term.

First, there must be a better understanding of the major challenges that remain overall with the response to AMR, and why they persist. All these challenges ultimately undermine the ability of governments to introduce effective measures to slow the emergence of drug-resistant bacteria, to develop new antibiotics, and to ensure timely diagnosis and access to existing antibiotics. We identify five key problems:

1. ***Despite political commitments and robust Declarations, at the World Health Organization (WHO), amongst Heads of State at the United Nations, and at the G7 and G20, there has not been sufficient translation of high-level commitments into tangible investments and ground-breaking initiatives and partnerships that can facilitate collective action against AMR.*** This may be due in part to a 'free-rider' effect – as some countries look to others to address AMR even as they may recognize a shared responsibility of, and risk to, all countries. While there may be robust collaboration and coordination amongst governments on technical matters, there has not yet been the requisite fiscal and political coordination and alignment. LMICs, which currently bear the most severe consequences of AMR, are often not sufficiently included in international discussions to share their contextual challenges, priorities, experiences, learnings, and needs.

2. ***There continues to be inadequate information and data to understand the scale of the problem, the causes, and consequences.*** Surveillance data of antibiotic resistance remains incomplete in many parts of the world. At present, data is lacking for 40 % of African countries, and data generated through the WHO Global Antimicrobial Resistance and Use Surveillance System (GLASS) is only for a few species and infections and are likely to be underestimated.[viii] Alongside a lack of regional data, evidence and data for specific populations highly affected by AMR, such as children and newborn babies, are lacking. New studies are starting to shed more light on the scale of the crisis facing such populations. The groundbreaking Global Research on Antimicrobial Resistance (GRAM) study, published this year, illustrates the importance of collecting and analyzing such data, both to illuminate the full consequences of AMR worldwide, and inter-regional differences. This year, GARDP and its partners will publish new results from one of the largest ever observational studies on the care of babies with sepsis. The study illustrates the significant detrimental impact that neonatal sepsis has on babies in LMICs, with mortality rates reaching up to 25 % in some settings.[ix]

3. ***Financial resources remain woefully insufficient for all aspects of the response to AMR, despite the current and future economic consequences of a failure to act.*** While most governments have developed comprehensive National Action Plans (NAPs), many of these NAPs remain unfunded or underfunded, thereby limiting the ability of governments to introduce measures to: conduct surveillance, strengthen IPC, and ensure timely diagnosis and access. R&D of new antibiotics also requires significant funding – push funding and new pull incentives – to ensure there is commercial and not-for-profit development of new treatments to address drug resistance. There is currently limited commercial interest and investment for antibiotic R&D due to low returns. Therefore, traditional incentives, and especially the promise of volume-based or high price-per-unit sales backed by patent protection, are insufficient to stimulate investments.[x] Finally, despite the existence of mechanisms, public sector investment to develop new antibiotics remains unbalanced among countries. According to data from the Global AMR R&D Hub, current funding for late-stage clinical development is highly inadequate to ensure the pipeline remains healthy.[xi] Without adequate funding, novel treatments that can reduce morbidity and mortality will remain stuck in the pipeline.

4. ***Governments are not yet pursuing innovative approaches to develop novel antibiotics, including not-for-profit models and alternative pricing and reimbursement mechanisms.*** The current drug development model is not fit-for-purpose for antibiotics. Half of all antibiotics in use today were discovered between the 1950s and 1970s.[xii] Since then, drug discovery and development has become more time consuming, expensive, and complex. Thus, in the last twenty years, no new antibiotic class for hard-to-treat Gram-negative bacteria has been approved. Developing new classes and targets to address drug-resistant infections is scientifically challenging and risky and yet governments have not taken decisive steps to ensure that such complex discovery and research is unaffected by financial shortfalls or inadequate incentives. There is also a lack of political cooperation to identify and support alternative models, including not-for-profit models, to pay for R&D sustainably and efficiently, and that ensure novel antibiotics are developed with public health as the primary objective. Furthermore, there are few alternative pricing mechanisms that could form a sufficient pull incentive to maintain a healthy private sector ecosystem. The insufficiency of the current R&D model to develop needed medical tools is even more serious for vulnerable populations, such as neonates, and more generally for LMICs. The lack of innovative models also affect access to new antibiotics, since there are no incentives or funding to ensure that such treatments are evaluated for use in LMICs and in vulnerable populations, as well as to ensure that there is timely registration, adequate supply, and affordable prices.

5. ***Many health systems are not prepared to address drug-resistant infections or lack key commodities to address AMR.*** Laboratory facilities remain insufficient to assist with appropriate diagnosis of samples, and diagnostic technologies are either unavailable in many countries or not suited to assist health care workers to make a timely diagnosis. Even when diagnosis is made, many countries are increasingly facing shortages of essential antibiotics, including many old drugs that can be easily manufactured.[xiii] Novel antibiotics are often unavailable in most countries.

LEARNING THE LESSONS OF COVID-19

The COVID-19 pandemic, like the 1918 flu pandemic, is an all-encompassing, global economic, political, and social crisis. COVID-19 has reinforced the importance of development, testing, and deployment of treatments, vaccines, and diagnostics to prevent and treat pandemic diseases, the importance of preparedness (and the consequences of inaction), and the inequities between and within countries in response to COVID-19. As noted in the T7 policy paper by Gitahi et al, underlying trends of urbanization, climate change and deforestation will result in increased frequency and severity of pandemics in the future.

Drug-resistant infections are a silent pandemic. They spread rapidly through international travel and migration, though impacts are felt more slowly in well-resourced settings. The unchecked growth of drug-resistant infections has long-term implications for global health security. Therefore, identifying and acting upon the lessons of the COVID-19 pandemic are critical for the G7, and all countries, to strengthen the long-term response required to address AMR.

This includes the use of antibiotics during pandemics. It is now clearer that antibiotics will play a critical role in future viral pandemics, but that use of antibiotics must also be carefully monitored to avoid spikes of inappropriate use that fuel resistance. The widespread and often empiric use of antibiotics during the early stages of the COVID-19 pandemic is understood as having accelerated the development of drug-resistant infections, although this may have been somewhat counter-balanced by lower use of antibiotics for other health needs.

Broader lessons of the COVID-19 pandemic are also relevant to addressing antimicrobial resistance. We present five lessons especially relevant to ensure timely development and responsible access to treatments:

1. Investments in preparedness are necessary, and cost effective for a pandemic, including research and development of new treatments and vaccines.

2. COVID-19 has clearly shown that a single country cannot solve the challenges of a fast-moving pandemic on its own.

3. Medical countermeasures need to be developed in a timely manner that requires significant and long-term financing (requiring both preparedness and an emergency response).

4. Equitable and affordable access to medical countermeasures is an essential element of a comprehensive and effective pandemic response.

5. Inadequate access to medical countermeasures can undermine the trust many countries have in the international system.

Proposals

A CALL FOR R&D AND ACCESS INFRASTRUCTURE TO SUSTAIN THE GLOBAL RESPONSE TO AMR

AMR requires investment, sound policy, and engagement by the G7 in coordination with the G20, to safeguard and recouple the world's long-term health and economic security. This year's G7 is a key opportunity to announce new investments that, within a relatively short timeframe, can reverse a worrying trend of rising resistance and deaths from drug-resistant infections, including by reflecting upon some of the lessons of COVID-19.

Drug resistant infections are a long-term challenge for which governments, the private sector, and civil society must build a durable infrastructure to prepare and respond. Even as health systems build their own national infrastructure, through health system investments, surveillance capacity, and personnel, there must also be a complementary international infrastructure to support, connect and build upon these efforts. Other proposed forms of infrastructure, such as a reusable, interoperable, open data infrastructure, as proposed in the T7 policy paper by Fung et al, could strengthen data collection, surveillance, and other pillars of the AMR response.

One critical area that governments, led by the G7, should support, is infrastructure to ensure sustained R&D of novel antibiotics that address priority infections, and optimal access to novel and existing antibiotics to save lives and assure long-term viability of such countermeasures. Such infrastructure will respond to several of the challenges noted above, although other investments are required to comprehensively respond to AMR.

First, there must be an end-to-end R&D infrastructure that can ensure that unmet needs are prioritized, that there are adequate resources dedicated to developing and advancing medical technologies through the pipeline, to ensure that appropriate evidence and data to guide its use is collected, and that such products are adapted to the different contexts and populations that require access. Some components of this infrastructure include entities established by or now supported by the G7 Members. Yet more is needed to construct a fully functioning end-to-end R&D infrastructure, including clinical trial networks, pull incentives that benefit a broad geography of countries.[xiv]

Second, there must be infrastructure sponsored by the international community to complement national level efforts to ensure optimal access to novel and existing antibiotics. The G7 should establish an AMR Working Group (hereinafter the G7 AMR Working Group) – including representatives from all relevant players established public-private partnerships, the Global AMR R&D Hub, the AMR Action Fund., the pharmaceutical industry, civil society, and representatives of G7 (and G2O) Ministries of Health, to identify and design the critical infrastructure to ensure optimal access. Specific investments could include regulatory capacity to ensure there is timely assessment, approval, and registration of novel antibiotics, coordinated procurement to ensure that supply matches demand, and that such medical technologies are available in countries in need and manufacturing capacity that can ensure such products are produced in a timely fashion while meeting standards of quality.

Third, there must be adequate governance – especially inter-governmental coordination, that can facilitate priority setting, decision-making, and coordination. The One Health Global Leaders Group on AMR is a critical starting point to encourage collaboration and cooperation. This must evolve into a sustained political dialogue amongst governments to ensure that aspirations are transformed into commitments and mutual accountability. The G7 AMR Working Group should work alongside the One Health Global Leaders Group on AMR, and other key stakeholders, to accelerate a political dialogue, cooperation, and concrete action amongst governments.

Finally, there must be sustained, predictable, long-term funding and financing to support needs-based R&D as well as access to novel and existing antibiotics that satisfies priorities enumerated on the WHO Priority Pathogen List. Such resources may emerge from government health, development, and research budgets, and include private sector collaborations, and via novel pull incentives that can both stimulate private sector research and development and ensure equitable access through appropriate obligations. While top-line figures for financing and funding are well understood, urgent action is required to ensure that such resources are mobilized. The G7 AMR Working Group could work with appropriate governments and the Secretariats of the Tripartite agencies to convene an AMR Financing Summit during this year's UN General Assembly, or during another appropriate high-level meeting, such as the High-Level Meeting on AMR (October 2022).

We know now that AMR is not just a future threat, but a crisis for many people today that requires a forceful, urgent, and comprehensive response that can be sustained for decades to come. The moment has come for the G7 to use its resources and experience to ensure the world can keep pace with resistance, save lives, and protect the global economy.

Implementation

AMR is a global problem that requires a global solution, with leadership from the G7. At the 2022 Summit, as well as the meetings of the Health and Finance Ministers, G7 countries should consider the following recommendations:

1. Commit to a contribution of up to 500 million USD over 5 years to fund the key activities of three critical entities, the Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), the Global Antibiotic Research and Development Partnership (GARDP) and SECURE[xv], that will improve research, development, stewardship, and access to life-saving treatments. Such funding can ensure the G7 can be immediately start addressing drug-resistant infections with the urgency required. The G7 should also work together to identify and introduce new funding mechanisms to support AMR either through national level budgets or through a collaborative entity – for example, a Global Financing Facility for AMR - that can pool resources of G7 Member States and other interested countries to finance both R&D and access to antibiotics.

2. Identify at least one pull incentive for which there can be collaboration or cooperation amongst G7 countries, and which can both provide a market for new and existing antibiotics while also improving access. Several G7 Member States have already introduced novel reimbursement mechanisms

(including subscription mechanisms) and they should be adopted by each G7 Member State. however, such mechanisms are insufficient as they don't solve the small volume problem with "Reserve" antibiotics Collaboration with the G20 may also be an effective way to ensure broader participation of governments. Furthermore, G7 Member States should also support the WHO, GARDP, and new initiatives, such as SECURE, which is both intended to operate as a reimbursement mechanism through the participation of diverse countries while assuring stewardship and timely access.

3. Use the link established under the UK G7 Presidency to bring together Ministries of Finance and Health to identify one or more long term and sustainable financing vehicles to generate and disseminate resources to pay for R&D and facilitate access, either at this year's UN General Assembly or during the planned High-Level Meeting on AMR scheduled for October 2022. The G7 should also build a credible business case to the private sector, including entities that have significant pools of capital such as insurance companies, socially-minded funds, and those involved in the broader Environment, Social and Governance (ESG) movement to make investments that both benefit public health as well as their bottom line, whether for example, reducing the long-term drivers of resistance or introducing new technologies that improve stewardship and access. The G7 should also explore novel incentives or other measures that will accelerate private sector investment.

4. Invest in studies, partnerships, and collaborations that seek to improve access to existing antibiotics and assure development of and access to new antibiotics to meet the needs of all populations, including people living in LMICs, newborn and children, and people with co-infections and co-morbidities. Observational studies, such as the recently completed NeoObs study that was referred to previously, are required, with coordination amongst governments, the private sector, and academia, to address unmet needs.

5. Identify barriers to equitable and optimal access to novel and existing antibiotics and provide resources to appropriate entities that can overcome such barriers.

6. In collaboration with the Tripartite agencies and the One Health Global Leaders Group, identify an appropriate framework to strengthen priority setting, coordination, and oversight of R&D and access of new and existing antibiotics. To avoid the shortcomings of the COVID-19 response, G7 countries will need to ensure that inter-governmental coordination is truly inclusive of LMICs to ensure that the specific priorities and needs of such countries are included– particularly from both a decision-making and investment perspective.

Disclaimer:

All authors are responsible for the content and recommendations contained within this policy brief. The policy brief has been written as part of a consultation process for the T7 Taskforce for Global Health, led by Taskforce's Co-Chairs Ilona Kickbusch, Anna-Katharina Hornidge and Githinji Gitahi, but it does not represent the official position of the Taskforce or the authors' employers.

Endnote

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[xv] SECURE is being developed by World Health Organization (WHO) and the Global Antibiotic Research and Development Partnership (GARDP) in collaboration with the United Nations Children's Fund (UNICEF) and the Clinton Health Access Initiative (CHAI). SECURE will increase access to essential antibiotics, while investing in stewardship, and producing needed data on the local AMR situation and clinical use of new antibiotics. SECURE countries will primarily be LMICs but will be open to all countries.

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Matt is currently Head of External Relations with GARDP having joined the public-private partnership in January 2020. Prior to that, he worked at the World Health Organization (WHO) in the Office of the Director, Essential Medicines and Health Products and the Science Division. From 2016, during his time as Senior Advisor to a public affairs consultancy firm, he set up and managed the G20 Health and Development Partnership and has since engaged in both the Think7 and Think20 processes under several Presidencies. He has also held staff and consultancy roles with several public-private partnerships in global health.

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