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Lessons from COVID-19: the 100 Days Mission and antimicrobial resistance

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The COVID-19 pandemic demonstrated the capacity of the world to rapidly mobilize resources and political will when faced with an immediate, visible global threat. The accelerated development of effective vaccines inspired the Coalition for Epidemic Preparedness Innovations to promote the 100 Days Mission (100DM), an initiative to enable deployment of medical countermeasures within 100 days of identifying a pandemic threat. The success of the 100DM in uniting stakeholders highlights the power of framing challenges to inspire collective action. On the other hand, antimicrobial resistance (AMR) has had insufficient visibility and urgency to galvanize similar levels of political action. Framing AMR in a way that highlights the urgency, aligns incentives and builds multisectoral coalitions can help overcome some of these barriers. Ultimately, pandemic preparedness and AMR are both collective action problems, requiring sustained political will and systemic change. The AMR community must build systems that are agile and resilient and, by creating a unifying vision for AMR analogous to the 100DM, may promote global commitment to combating this slow-moving but devastating health crisis.

This article is part of the Royal Society Science+ meeting issue 'Vaccines and antimicrobial resistance: from science to policy'.

1. Introduction

The COVID-19 pandemic showed us that when faced with a visible, immediate threat, the world can rapidly mobilize resources and political will. Within months of identifying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), we developed safe and effective vaccines—an unprecedented scientific achievement. But this crisis-driven response model cannot be directly applied to all health threats. Solving difficult policy and collective action problems requires understanding and framing those problems in a way that drives action, developing the right tactics and mobilizing political will.

For an organization such as the Coalition for Epidemic Preparedness Innovations (CEPI), the COVID-19 pandemic dramatically raised political attention towards infectious diseases and coalesced will around pandemic preparedness and response. While those of us involved in outbreak response identified the early signs of a health crisis, for the rest of the world, COVID-19 appeared like a sudden wildfire—dramatic and spreading rapidly, commanding immediate resources and attention for firefighting. The visible devastation created public support, and, while political attention and priorities have shifted in the 5 years since, CEPI continues to champion the ambition of the 100DM to reduce the impact of future pandemics by making vaccines and other medical countermeasures available within 100 days of outbreak identification.

Antimicrobial resistance (AMR), by contrast, has not had a single defining health crisis to mobilize similar political action. AMR has characteristics more akin to slow deforestation, progressing almost invisibly until significant damage has occurred, requiring consistent stewardship and prevention. This crucial difference explains why, despite decades of warnings from the scientific community, AMR has struggled to generate the same level of political commitment and resource mobilization as pandemic preparedness.

While CEPI cannot offer those grappling with AMR concrete technical solutions, we can share examples of how to define and understand the problem and the system within which it operates. By examining how the pandemic preparedness and response community frames its challenges, sets questions and addresses them, the AMR community may find new approaches to target the complex challenges at hand and inspire a greater sense of urgency and collective action.

2. The false dichotomy between viral and bacterial threats

Viral pandemic preparedness and bacterial AMR present distinct problems and are driven by different ecological dynamics. Each will require customized solutions, but both represent complex threats to global health security. The community of scientists seeking to address these distinct problems must, among other imperatives, overcome market failures in countermeasure development and address significant issues of inequity in terms of access to these countermeasures.

Despite these many acknowledged differences, the work that CEPI and similar organizations undertake to address the problem of pandemic preparedness can offer oblique lessons for those attempting to address AMR. While CEPI focuses on developing vaccines and biologics against viral outbreak pathogens and preparing for 'Disease X', the AMR community must both develop new countermeasures to replace those we are losing in real time while also solving the complex evolutionary dynamics, driven by the overuse of existing antibiotics, that drive the emergence of AMR.

One lesson that CEPI has learnt in developing and building support for the 100DM is that the solutions to hard problems—and the AMR problem is definitely hard—emerge when one asks the right questions. In our experience, the 'right' questions are almost never the obvious ones. Rather, one discerns the right questions only by understanding the systemic structure of the problem that needs to be solved, and that requires deep study and reflection. We shall return to these questions later in our discourse (§6).

3. From the 100DM to antimicrobial resistance action

What can the AMR community learn from the 100DM approach? The answer lies not simply in the technical solutions but in how we frame challenges to inspire urgency and collective action. The 100DM—aiming to make vaccines, diagnostics and therapeutics available within 100 days of identifying a pandemic threat—has succeeded in coalescing stakeholders across the medical countermeasures value chain around a unifying goal. This approach to establishing multisectoral coalitions and governance mechanisms offers a blueprint for creating analogous coalitions within the AMR community.

To the extent that vaccines, as a class of countermeasure, are part of the solution for AMR, there will be some directly transferable lessons from CEPI's work, for example, in relation to vaccine design and parallel conduct of the various phases of clinical trials. The technical tools for developing vaccines against viruses and bacteria overlap to a certain extent. While the platforms that will allow us to deliver against the 100DM have accumulated vastly more data against viral targets than bacterial ones, we are hopeful that messenger ribonucleic acid (mRNA) technology will find applications against tuberculosis (TB), malaria and bacterial pathogens. Modified Vaccinia Ankara (MVA) and Chimp adenovirus viral-vector vaccines have shown promise against TB and *Plasmodium falciparum*, and other novel technologies will no doubt find their advocates.

But the data remain relatively thin, and other technologies may prove more immediately promising for bacterial threats. CEPI is investing in artificial intelligence (AI) technology for protein design and platform technologies that could also accelerate bacterial countermeasure development. CEPI's investments in broadly protective vaccines (e.g. for coronaviruses) and adopting a viral family approach to prepare for 'Disease X' by developing prototype vaccines could plausibly benefit AMR innovation. The concept of developing generalizable countermeasure designs against prototype pathogens within families might be adapted to address bacterial threats as well.

This is more challenging for bacteria because they are vastly more complex pathogens than viruses, and targets of protective immunity are often bacterial sugars rather than proteins. Nevertheless, there are common approaches and technology platforms that can readily be applied to design vaccines against a range of bacterial pathogens, from glycoconjugation to reverse vaccinology and outer membrane vesicle production. Some of these platforms (e.g. glycoconjugation) lend themselves to having suitable facilities for process development, upscaling and manufacture in place. This requires investment in such facilities, such as for pilot- and large-scale good manufacturing practice (GMP) fermentation capacity, in advance. Others, though lengthier in nature (e.g. reverse vaccinology), can benefit from the ready availability of pathogen whole-genome sequences, dedicated dry-lab capacity and use of AI for *in silico* prediction of likely target immunogens for vaccine design.

Although not in scope for this article, similar approaches to the development of monoclonal antibodies as therapeutics against pandemic viruses can be applied to the problem of AMR, particularly because such antibodies can now be manufactured at vastly lower cost than in the past. Monoclonal antibodies against AMR bacteria have the potential to be a valuable alternative treatment to antibiotics, with the dual benefits of not contributing to the development of AMR themselves, while having the potential to be still effective when a bacterial species becomes resistant to all available antibiotics.

4. Beyond science: addressing collective action problems

But these lessons are narrowly defined and still rather speculative. What CEPI can offer those grappling with the challenge of AMR will rather be more by way of demonstration and analogy; by how CEPI defines and understands the problem it has been assigned and the system within which CEPI operates; by the questions CEPI sets for itself, by how CEPI sets out to address these, and by how CEPI achieves and contributes to systems change. At their core, both pandemic preparedness and AMR represent not just scientific challenges but problems of collective action. They require the world to mobilize resources, align incentives and sustain commitment over time.

In relation to pandemic and public health preparedness, we are pretty sure we are on the right track. We have come to recognize that the problem COVID-19 set for the world, where vaccines were concerned, was achieving speed, scale and access. The world succeeded at the first two and systematically failed at the third. The roots of that failure were manifold and structural. Against these structural barriers, efforts through COVAX, the vaccine sharing facility established during the pandemic by CEPI, GAVI, WHO and UNICEF, while heroic, admittedly fell short.

The successes in achieving the required speed and scale of response demonstrated the value of a strategy focused on fostering preparedness by investing in generalizable vaccine designs and advancing rapid response platforms, such as mRNA, as a means of delivering plug-and-play vaccines against novel pathogens. When CEPI released funds to support Moderna's COVID vaccine development on 23 January 2020—just 12 days after the SARS-CoV-2 viral sequences were released—it was to support the production of clinical trial material for a vaccine that had been designed in 36 h by adapting insights on immunogen design gained from the development of Moderna's prototype MERS vaccine. Even with this gigantic head start, it still took 11 months to receive Emergency Use Authorization. Every stage of development was compressed, with phases performed in parallel rather than sequentially, yet this unprecedented speed was still insufficient.

The failure to achieve adequate global access is a challenge that must be addressed going forward. This is also crucial for vaccines against AMR bacteria, where equitable access will be vital to help contribute to stemming the tide of AMR. To an extent, Gavi, the Vaccine Alliance (www.gavi.org), is well placed to address the issue of access to such vaccines that are already available in low- and middle-income countries (LMICs) where the burden of AMR infections is highest [1] (see article by Jadeja N *et al.* [2] in this issue). However, funding support for Gavi has been insufficient to allow it to meet its goals for vaccine access in recent years.

Had vaccines been developed and deployed more quickly, much of the suffering caused by the COVID-19 pandemic could have been alleviated. Many of the millions who perished might have been saved. The economic damage that the global economy sustained could have been dramatically reduced. This realization catalysed CEPI's articulation of the 100DM.

5. The prototype pathogen approach

Core to the 100DM is the concept of developing generalizable vaccine designs and reagents against what Barney Graham & Nancy Sullivan, in a seminal 2018 review article in *Nature Immunology*, first designated 'prototype viruses' [3].

Graham & Sullivan argued that there are a limited number of virus families known to cause disease in humans. Within each family, they proposed developing a database of information with accompanying reagents and assays for prototypic viruses based on properties of tropism, transmission routes and other distinguishing features of pathogenesis and structure. They proposed that 'Candidate vaccine approaches could be designed on the basis of features of the overall viral structure, transmission dynamics, entry requirements, tropism and replication strategy, and they could be evaluated in small animals for immunogenicity and protection against challenge where feasible' [3, p. 26].

For a large and phylogenetically diverse family, such as the paramyxoviruses, one might anticipate needing to develop such repositories against numerous prototype viruses—against measles and mumps and parainfluenza, for example, as well as against Nipah and Hendra. Collectively, such immunogen designs, vaccine candidates and other materials would form the contents of a virtual global vaccine library. CEPI has prioritized the paramyxo-, arena-, pox-, corona-, filo- and phenuiviruses as the families we will focus on first. CEPI has established an immunogen design consortium, partnering with world-class structural virologists and immunogen designers to develop and optimize techniques of antigen stabilization and expression on different platforms. Pre-clinical and clinical testing of initial 'exemplar vaccines' against Lassa, Junin, Nipah and mpox ramped up in 2024.

CEPI's efforts in this regard are aligned with those of the World Health Organization (WHO). Beginning in late 2022, the WHO convened expert working groups, comprising over 200 scientists from 54 countries, to (i) evaluate the evidence related to 28 viral families and one core group of bacteria, encompassing 1652 pathogens, (ii) identify priority and prototype pathogens, and (iii) outline priority research to accelerate the development of medical countermeasures against these. Ultimately, the WHO and the newly established Collaborative Open Research Consortia dedicated to each Priority Pathogen Family will roll out research and development roadmaps for each viral family. We have come a long way in translating the concept of prototype pathogens into practical research agendas [4].

AMR bacteria are amenable to a similar approach, and this has been alluded to earlier in §2. Indeed, in 2017 the WHO identified AMR bacterial pathogens of concern for further research and development prioritization, including vaccine development, with the list updated in 2024 [5]. Bacteria can be grouped similarly, e.g. into the Enterobacteriaceae family, which includes several key AMR bacterial genera and species including *Escherichia coli*, *Salmonella*, *Shigella* and *Klebsiella*. Certain groups of bacteria are amenable to similar vaccine technologies, such as the encapsulated bacteria (pneumococcus, meningococcus, *Haemophilus influenzae* b, *Salmonella* Typhi) to glycoconjugation of capsular polysaccharide to a suitable carrier protein such as tetanus toxoid.

Currently, licensed vaccines for Enterobacteriaceae are limited to those developed for *Salmonella* Typhi, which is also an encapsulated bacterium. Nevertheless, good progress is being made in the development of vaccines against other members of the Enterobacteriaceae family of AMR concern. Much of such work takes advantage of all of these being Gram-negative bacteria with an outer membrane consisting of lipopolysaccharide and outer membrane proteins. Candidate vaccines in clinical development against *Salmonella* and *Shigella* species include glycoconjugates where the O-antigen of lipopolysaccharide is conjugated to a carrier protein [6,7], and native outer membrane vesicles (alternatively termed 'generalized modules for membrane antigens' (GMMA)), which exploit the natural shedding of blebs of outer membrane from Gram-negative bacteria [8].

The amassed whole-genome sequences of many thousands of isolates for each bacterial species of interest are similarly valuable for AI-guided protein immunogen design, as mentioned before. However, for certain key AMR bacteria, such as *Staphylococcus aureus* and *Neisseria gonorrhoeae*, the target antigens and mechanism of immune protection are uncertain, thereby hampering rational vaccine design. While mRNA technology holds considerable promise for vaccine development against pandemic viruses, this technology, and indeed all other currently available technologies, fail to hold similar levels of promise for bacterial vaccine development.

6. Overcoming scepticism

When the 100DM was first proposed, we encountered significant scepticism. The idea was frequently—and sometimes brutally—dismissed as a mere fundraising slogan or pipe dream. Those who closely followed the 2020 vaccine development efforts understood what worked and what had not, but conviction alone was not sufficient to win over doubters. We had a credibility problem on our hands.

CEPI staff were directed to develop the report entitled *Delivering Pandemic Vaccine in 100 Days: What Will It Take?*—a 60-page monograph on the topic that was published in November 2022 [9]. In developing the report, CEPI talked to representatives of every vaccine manufacturer, including those in Russia and China, whose vaccines were authorized in the first 18 months of the pandemic, and we catalogued and assessed the vaccines' impact against the criteria of speed, scale and access of some 50 innovations they had considered or implemented to accelerate vaccine development timelines across pre-clinical and clinical development, filing and approval and manufacturing.

Through systematic analysis and engagement with stakeholders, it became clear that the main approach adopted in 2020—trying to compress and complete all phases of clinical development, including Phase 3, before filing with regulators—simply would not work within the 100 day timeframe. It was like trying to put a large square peg in a small round hole. Even with maximum compression, the timeline might be reduced to around 250 days at best.

A paradigm shift in thinking was required. If the goal was to deliver vaccines in 100 days, what could be done now to prepare regulators? What research could be undertaken to enable them to make decisions about emergency authorization on the basis of Phase 1/2 data rather than waiting for complete Phase 3 results? How would clinical trials be conducted? Could protocols be developed in advance? Could cohorts of subjects be pre-enrolled? What data could be collected after emergency authorization to continue building the safety and efficacy profile?

We are now, we believe, asking the right questions. By asking these questions and designing programmes to answer them, either now or when the time comes, CEPI has become better at explaining how investments in preparedness will yield dividends and why we must prepare so assiduously for a sprint.

7. Reframing the challenge: the Formula One analogy

The most powerful explanatory model that CEPI has discovered for the 100DM is the Formula One pit stop. Everyone knows that today a pit stop can be completed in 2 or 3 seconds. That is not how it used to be. Back in the 1950s, a pit crew comprised three or four people, and a pit stop would take a minute or more. Now, the cars and the pit crew's tools have been engineered to enable ultrarapid pit stops: the pit crews have grown and everyone has a highly specialized role; the processes have been perfected; and the pit crews practice, practice, practice until their performance is flawless. By doing this, all in pursuit of a performance edge in what is ultimately just a pastime (albeit one where money flows freely), they have reduced the pit stop cycle time by 97%. Safety is paramount; the driver needs to know that his wheels will not fall off.

This is not a superficial analogy but what we would describe as a 'deep analogy'. The more we examine how Formula One teams accomplish what they do, the more we learn what we can use to address the problems we have set for ourselves. The Formula One teams show how it is possible through specialization, practice, investment, continuous cycles of improvement and focus to solve a speed problem without compromising safety. And still win races. Two-second pit stops do not happen by accident. The pit crews do not depend on luck. They have engineered the system to produce the desired results, because in Formula One every second counts. We have a lot to learn from them.

Although we are already aware of the key bacterial species of AMR concern [1], the pit stop analogy of the 100DM has relevance. While not quantified in seconds, or even days, time is not on our side in addressing AMR, as the O'Neill Report [10] and World Bank Report on AMR [11] indicated in 2016/2017, and we are in danger of losing the race against the silent pandemic of AMR. As with Formula One, resources and practice need to be applied to the development of vaccines against AMR bacteria. This is where a CEPI-equivalent for AMR vaccines could be transformative.

8. A way forward for antimicrobial resistance

The AMR community must develop its own version of the 100DM—a framing that captures the imagination, creates urgency and drives collective action. This does not mean adopting the same technical approaches, but rather learning from how the pandemic preparedness community defines its challenges, organizes its response and contributes to systems change.

AMR presents unique challenges distinct from pandemic preparedness. Where pandemic preparedness benefits from the memory of COVID-19, AMR lacks a singular catastrophic event to galvanize action. Although not a global crisis, the outbreak of extensively drug-resistant typhoid in Pakistan in 2019 and the deployment of the recently licensed typhoid conjugate vaccine to counter this comes close and give an excellent example of how vaccines can be successfully deployed against AMR (see article by Qamar FN and colleagues in this issue [12]). Nevertheless, the effects of AMR accumulate gradually, making it harder to communicate urgency.

AMR infections are also a major problem among animals, partly driven by the extensive use of antibiotics as growth promoters among livestock (see article by Yugueros-Marcos J & Etienne F, in this issue [13]). Thus, the development of vaccines against AMR must encompass the veterinary space as well as human health. As mentioned before, AMR affects LMICs more extensively than high-income countries [1] and, echoing the lack of access to COVID-19 vaccines in such countries, research and development of AMR vaccines are severely underfunded. This is especially problematic in relation to the absence of facilities for vaccine manufacture in LMICs, particularly in Africa.

Despite these differences, there are commonalities and transferable lessons. Once we properly understand the structure of the AMR challenges and frame the questions that need answering, the path to solutions will become clearer. Some of these have been discussed above and include understanding which technologies are required for different families of AMR bacteria and making provision and allowing access to these, as well as AI-based immunogen design utilizing whole-genome sequencing, reverse vaccinology and the analysis of monoclonal antibodies from patients infected with AMR pathogens (see article by Cardinali G and colleagues in this issue [14]). Acceleration of clinical trial execution can equally be applied to AMR vaccine development as epidemic viral vaccines. Similarly, trust in vaccines among the general public, politicians and health care workers is vital at a time of vaccine hesitancy and misinformation.

Just as Formula One teams have engineered systems to achieve seemingly impossible speed without compromising safety, we must engineer health systems and incentive structures that can respond rapidly to emerging bacterial threats while sustaining the long-term investments needed to preserve antimicrobial effectiveness. This will require creativity, persistence and an unwavering commitment to global health equity.

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