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Antimicrobial resistance and the role of vaccines

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Stanley Falkow (Fig. 1) dedicated his life's work to the study of bacteria and infectious disease. He was a leader in the discovery of the mechanisms of antibiotic resistance and among the first to recognize and raise the alarm about the problem of multidrug resistance. The articles of this Special Feature on Antimicrobial Resistance and the Role of Vaccines are dedicated to his memory (Box 1).

Rising antimicrobial resistance (AMR) is one of the greatest health challenges the world currently faces. Resistant pathogens, including viruses, parasites, fungi, and especially bacteria cause significant morbidity and mortality. For example, antibiotic resistance is estimated to cause 33,000 deaths annually in the European Union and European Economic Area (1), at least 23,000 deaths annually in the United States (2), and at least 38,000 deaths annually in Thailand (3). Furthermore, resistant bacteria reportedly caused the deaths of more than 58,000 babies in India in 1 y (4). One estimate places current global annual deaths from AMR at a minimum of 700,000 (5).

While the current global death toll from AMR is relatively modest compared with other major causes of mortality, the problem is expected to worsen. Any use of antimicrobials, including common antibiotics that treat every day respiratory, gastrointestinal, and skin infections, drives the evolution of resistance, regardless of the appropriateness of use. Importantly, antimicrobial use is increasing, which will likely continue in the foreseeable future, as access to antimicrobials improves in the developing world.

The progression of AMR has daunting ramifications, including increased spread of infectious disease, increased likelihood of dying from what are now considered routine illnesses, and inability to perform certain medical procedures, such as elective surgery, due to fear of untreatable hospital-acquired infections. Cases of *Neisseria gonorrhoeae* are now becoming almost untreatable with currently available antibiotics, with resistance to azithromycin and ceftriaxone

being reported (6). These health consequences will have damaging social and economic sequelae, such as lost productivity due to increased morbidity and mortality, and even social distancing, as fear of interpersonal contact grows.

Although projections of AMR's future burden depend on several assumptions and are therefore uncertain, the idea that the health and economic consequences of AMR will become significant is reasonable. In 2014, the *Review on Antimicrobial Resistance* (5), commissioned by David Cameron and chaired by Lord Jim O'Neill, suggested that if left unchecked, AMR could cause as many as 10 million annual deaths—more than the 8.2 million deaths caused by cancer today—and cost USD100 trillion in cumulative economic damage by 2050. A World Bank simulation projects that the global economy could lose as much as 3.8% of its annual gross domestic product by 2050 in a worst-case scenario (7).

AMR is not a new problem. Resistance emerged with the advent of antimicrobial therapy, beginning with the discovery of penicillin. Multidrug resistance was identified as early as the 1950s. Antibiotic resistance occurs when bacteria become immune to previously effective drugs through some mutation in their genetic code. These mutations often exact some fitness cost (in the absence of antibiotics), but provide the resistant bacteria a survival advantage when antibiotics are present (8). However, sustained use of antibiotic therapy—at the individual or population level—exerts pressure on bacterial populations to become increasingly resistant.

Emergence of resistant clades within several bacterial species—including *Escherichia coli*, *Salmonella typhi*, *Staphylococcus aureus*, and *Clostridium difficile*—that resist antibiotics without imposing any fitness cost have been recently detected (8). In some cases, these clades are also more transmissible or aggressive in causing disease than other members of the same species. Many of these clades have spread to different

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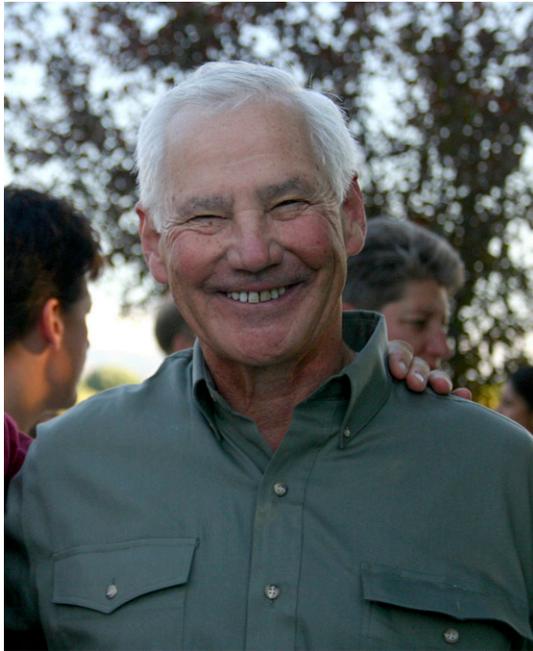


Fig. 1. Stanley Falkow, January 24, 1934–May 5, 2018, a pioneer in the fight to understand and address AMR. Image courtesy of Manuel R. Amieva (photographer).

parts of the globe. Their continued proliferation could make combating the burden of resistance through strategies like antibiotic stewardship (ABS) or antibiotic cycling more difficult.

While AMR poses a daunting threat, options are available for mounting a response. Developing new antibiotics and other antimicrobials, as well as new forms of treatment, such as monoclonal antibodies, provide options to ensure that otherwise pan-resistant infections remain responsive to some form of treatment. Better ABS in inpatient and outpatient settings can help preserve existing

Box 1. Dedication

This Special Feature on Antimicrobial Resistance and the Role of Vaccines is dedicated to the memory of microbiologist Stanley Falkow. Professor Falkow was a pioneer in understanding how bacteria cause disease and discovered how antibiotic resistance spreads among bacteria. In 1964, Falkow was the first to physically isolate a distinct band of DNA comprising the episome (plasmid) with the genetic material coding for antibiotic resistance in a cesium chloride gradient. As early as 1975, he wrote a book entitled *Infectious Multiple Drug Resistance* (17) and noted that while “we owe to chemotherapy [antibiotics] the debt of reducing the high mortality rate of many bacterial infections [and to hygiene and vaccines the debt of preventing them], in helping to solve some of the problems of infectious diseases, chemotherapy created some problems of its own.” The “problems” Falkow refers to were, of course, the multidrug-resistant bacterial strains generated as a natural consequence of the drugs’ use.

Falkow received numerous honors in recognition of his work, including election to the National Academy of Sciences in 1984, the Royal Society in Britain in 2007, and presentation of the National Medal of Science in 2014. Stanley Falkow died at his home in Portola Valley, California, on May 5, 2018, at the age of 84.

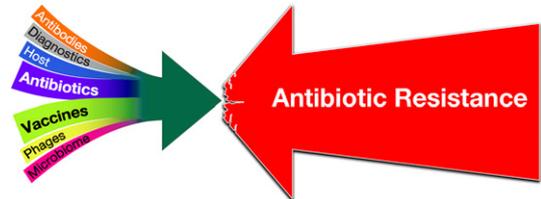


Fig. 2. A globally integrated strategy that includes antibiotics, vaccines, diagnostics, antibodies, and new tools targeting the host, the microbiome, or delivered by phages is required to fight AMR effectively. This figure was inspired by a figure in an early draft of Klemm et al. (8).

therapies’ effectiveness. Similarly, improving regulation of access to antimicrobials in human and animal populations, while ensuring that access is not denied to anyone who needs them, can help limit the inappropriate use of drugs and the corresponding evolutionary pressure toward resistance. Widespread dissemination of rapid and accurate diagnostics could help clinicians treat infections more precisely, further alleviating evolutionary pressure. Improving sanitation and hygiene, especially in low- and middle-income countries, could also make an appreciable difference.

However, the reality is that no single response is sufficient for stemming the rising tide of AMR. Antibiotic research and development (R&D) faces substantial challenges, and novel and effective antibiotics are sorely needed to ensure the ability to treat infections that may otherwise be resistant to all existing options. Given how fast resistance has evolved to each new class of antibiotics introduced historically and the challenges in producing new antibiotics, focusing on antibiotic R&D alone is clearly insufficient. A globally integrated and multipronged strategy is required. In this Special Feature, we argue that developing new vaccines, along with new antibiotics and new diagnostics, should be a significant part of that strategy (Fig. 2). Increasing coverage of existing vaccines and developing new vaccines that target antibiotic-resistant organisms can play important roles.

Vaccination is also a solution that has been largely undervalued (9). Vaccines can counteract AMR through multiple pathways (10). Vaccination directly reduces the incidence of sensitive and resistant infections. It also reduces both appropriate and inappropriate use of antimicrobials by reducing overall disease incidence, including infections caused by susceptible pathogens and by viruses (such as influenza) that are often inappropriately treated with antibiotics. This reduced antimicrobial use further diminishes pressure toward resistance among bystander members of the normal human flora.

Overall, the articles in this Special Feature highlight why vaccines should be seriously considered as an important tool against AMR. The first reason, as Kennedy and Read (11) point out and Fig. 3 shows schematically, is that resistance is inevitable when antibiotics

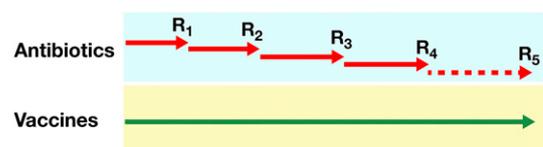


Fig. 3. Schematic representation showing that the use of antibiotics selects for resistance (R), making the antibiotic obsolete. Therefore, a continual pipeline of new antibiotics is needed for effective treatment. In contrast, vaccines can be used for a very long time without generating significant resistance [see Kennedy and Read (11)].

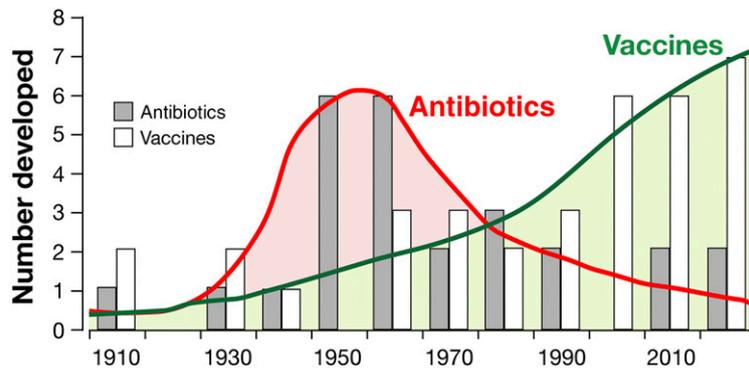


Fig. 4. Vaccines and antibiotics licensed during the last century, showing the golden era of antibiotics in 1950s, the present golden era of vaccines, and the limited pipeline of new antibiotics during the last decades.

are used, and every antibiotic that is introduced becomes rapidly obsolete, so that a continual pipeline of new antibiotics is needed. In marked contrast, vaccination has the benefit of sustainability and can be used for decades without generating significant resistance. Thus far, vaccines have been able to overcome the evolution of resistant strains. Several reasons exist for this phenomenon. First, vaccines are used prophylactically, when pathogen populations are relatively small, lessening the likelihood that resistance-conferring mutations will appear and proliferate. Second, many vaccines target pathogens in multiple ways, requiring multiple mutations to confer resistance. Finally, in the rare instances in which resistance to vaccines has been detected, disease reduction has still been attained. Furthermore, research on these rare cases may allow better vaccine targeting to avoid potential future problems.

Baker et al. (12) address the second reason to consider vaccines in combating AMR, showing that the antibiotics pipeline is quite limited: Only a few new antibiotics have been licensed during the last 40 y (Fig. 4), and no antibiotic employing a novel mechanism against Gram-negative bacteria has been introduced in that time frame. In contrast, vaccines—thanks to many revolutionary technologies—are in a golden era. Not only have numerous vaccines been licensed during the last 40 y, vaccines are also well poised for further development against many AMR bacteria.

The third reason to consider vaccines for AMR is that the potential for vaccinations to affect resistant infections is more than speculative. As Klugman and Black (13) point out, studies of the effects of pneumococcal conjugate vaccine from Africa, the United States, and Europe demonstrate reductions either in instances of resistant invasive pneumococcal disease or in antibiotic use or both. Reduced circulation of resistant strains has also been demonstrated in several locations following introduction of pneumococcal conjugate vaccine. Reductions of up to 64% in antibiotic consumption in individuals vaccinated against influenza compared with unvaccinated controls have been reported. For influenza vaccine, indirect effects on antibiotic use have also been documented. Thus, existing empirical evidence indicates that vaccination has considerable direct and indirect impacts on resistance.

Relman and Lipsitch (14) describe the fourth reason to consider vaccines, which is to preserve the microbiome. Antibiotics disrupt the human microbiome, which has harmful effects on general health, especially in children. This disruption can alter the immune system's development and negatively affect nutritional status. Tedijanto et al. (15) show how, in addition to

selecting for resistance in target pathogens, antibiotics can modify the microbiome composition by selecting for resistance in bystander bacterial species within the microbial flora. In fact, repeated use of antibiotics can create a reservoir of host-specific resistant genes and organisms (14). Broad-spectrum treatments are especially likely to contribute to bystander selection.

In conclusion, although new antibiotics are desperately needed to overcome existing resistance, the failure to develop new antibiotic classes in recent years is discouraging. The availability of other new technologies for use in antibiotic innovation is relatively limited. Pharmaceutical companies and others are currently exploring the feasibility of potentiating nonessential parts of bacteria to sensitize them to attack and of hijacking bacterial nutrient-uptake mechanisms to introduce antibacterial agents. Significant scientific challenges to antibiotic R&D must be overcome to improve the situation. On top of these scientific challenges, the economic model for antibiotic R&D is complicated, as social interest in limiting the use of novel antibiotics to preserve their effectiveness is sometimes at odds with manufacturers' profit-seeking behavior.

In contrast, the number of vaccine technologies developed over the past half century is promising for the future of vaccine R&D (12). New technologies or approaches to vaccine development introduced since the 1990s include reverse vaccinology, vaccine adjuvants, structural vaccinology, bio-conjugates, and genetically modified outer membrane vesicles. Moreover, the economic model for vaccines is much more straightforward, as social interest in promoting vaccine uptake aligns well with manufacturers' interests.

While an integrated strategy is clearly necessary, what is less clear is how investments in fighting AMR should be apportioned among the competing options. To rationally determine the optimal allocation of resources to combat AMR, economic evaluations of vaccination and other health technologies should be conducted in an AMR-sensitive manner. Initial qualitative analysis suggests that investing in vaccination may use resources more efficiently than investing in alternative strategies for addressing resistance in at least some pathogens over the long term (16). Ultimately though, answering this question more completely and with a greater degree of certainty will require new data and further refinement of available epidemiological and economic methods to conduct rigorous quantitative analysis.

How best to implement an integrated AMR strategy is another open question. In the short run, vaccine funders (such as Gavi, the Vaccine Alliance, and national governments) should begin to consider the AMR benefits of vaccination in

their investment decisions. In the longer run, establishing an international coalition akin to the Coalition for Epidemic Preparedness Innovations but with a focus on vaccines for AMR may be warranted. National investment in such a collaborative organization would be justified on the grounds that having effective antimicrobials and fewer infections represents a global public good. Finally, greater investment in basic and applied sciences and in economics research to determine the optimal

allocation of resources to addressing AMR is urgently needed. While open questions remain about how best to tackle AMR, clearly the time to act is now.

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