COMMENT

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Vaccines can have an effect on antimicrobial resistance by reducing the number of ill people and avoiding unnecessary antibiotic prescriptions.

Deploy vaccines to fight superbugs

Immunizations combined with antibiotics could be our best shot at combating drug-resistant microbes, argue **Rino Rappuoli**, **David E. Bloom** and **Steve Black**.

Bacteria, viruses, parasites and fungi that are resistant to drugs cause 700,000 deaths each year. By 2050, such 'superbugs', inured to treatments, could cause up to 10 million deaths annually and cost the global economy US$100 trillion[1–2]. If this happens, antimicrobial resistance (AMR) will be a bigger killer than cancer is now.

Antimicrobials alone won't be able to mitigate the threat. The supply of naturally occurring antibiotics seems thin. And efforts to engineer new ones have floundered.

We think that vaccines could be a key way to stem the crisis. To launch a global strategic effort to prioritize their development, scientists, policymakers and key stakeholders need to see antibiotics and vaccines as complementary tools. Here we focus on antibiotic-resistant bacteria, for which the need for solutions is most urgent.

INFECTION RISK

Unchecked, AMR could substantially limit our ability to conduct routine surgery, ▶

chemotherapy and transplantation and return us to a world in which infectious diseases drastically shorten lives. Strains of many pathogenic bacteria, such as *Neisseria gonorrhoeae* and *Staphylococcus aureus*, are already resistant to most antibiotics.

The genes conferring AMR are often carried in plasmids: small, circular pieces of DNA that bacteria exchange easily[3] through a process called horizontal gene transfer. Genes from many plasmids can even combine into one unit that renders bacteria resistant to most antibiotics in a single step.

Between 1950 and 1980, new antibiotics reached the clinic with regularity. But the pipeline has run dry. No truly new ones active against a wide range of pathogenic bacteria have been deployed in the clinic in three decades. Antibiotics need to reach targets that are usually behind the bacterial cell wall — a formidable barrier — and avoid being ejected by potent efflux pumps. These challenges continue to hamper clinical development despite numerous technological advances, from new ways to construct and modify molecules to genomics.

The story is much more encouraging for vaccines. They almost never prompt bacteria to develop resistance[4]. Antibiotics are generally prescribed after a person has become infected and has hundreds of millions or billions of bacteria in their body. One bacterium in a billion can acquire the ability to thrive in the presence of antibiotics through a spontaneous mutation or by obtaining a plasmid encoding resistance genes. With vaccines, by contrast, the host builds immunity before encountering the pathogen, and bacteria are neutralized at the beginning of the infection, when they number only a few hundred or thousand. Thus one-in-a-billion genetic events are much less likely.

Furthermore, most antibiotics consist of a single compound. Vaccines — which can contain entire bacteria or viruses, or several antigens — usually induce immunity against multiple targets. This makes the development of resistance even harder.

In other words, vaccines seem to be almost evolution-proof[4]. Diphtheria and tetanus vaccines, for example, have been used for 70 years or more without generating resistance. Likewise, by 1980 the smallpox vaccine had eradicated the naturally circulating virus worldwide without generating resistance.

Vaccines have also proved more 'discoverable' than antibiotics[5]. Since the 1980s, 22 vaccines have been developed thanks to various advances in molecular biology (see 'Vaccines in the lead'). Researchers produced vaccines against hepatitis B and human papillomavirus (which cause liver cancer and cervical cancer, respectively) using recombinant DNA technology. They fused genetic elements to create new synthetic sequences that would not otherwise occur. Conjugate vaccines have drastically reduced the incidence of meningitis caused by *Haemophilus influenzae*, pneumococcus (*Streptococcus pneumoniae*) and meningococcus (*Neisseria meningitidis*). These are produced by making covalent links between bacterial polysaccharides and proteins.

More recently, reverse vaccinology led to a vaccine against meningococcus B (ref. 6). In this approach, researchers mine the thousands of proteins encoded by bacterial genes in search of possible vaccine candidates, such as proteins that are exposed on the cell surface. Reverse vaccinology could also identify sequences that are unique to pathogenic microorganisms. This could prevent investigators from producing vaccines that accidentally harm beneficial commensal microbes, such as those in the gut[7].

Finally, work on potent and safe new adjuvants — compounds that make vaccines more effective — has achieved some impressive feats. These include a malaria vaccine, and a herpes zoster vaccine licensed by the US Food and Drug Administration just two months ago. This vaccine induces a potent immune response against the virus that causes shingles, even in people aged 80 or older[5,8].

Vaccine technologies continue to evolve. For example, scientists are analysing the atomic structure of antigens with a view to modifying them to make them more effective as vaccines. Progress in immunology and synthetic biology, too, are likely to make it possible for researchers to tackle diseases that have so far remained out of reach, such as respiratory syncytial virus and cytomegalovirus[6].

VACCINES FOR AMR

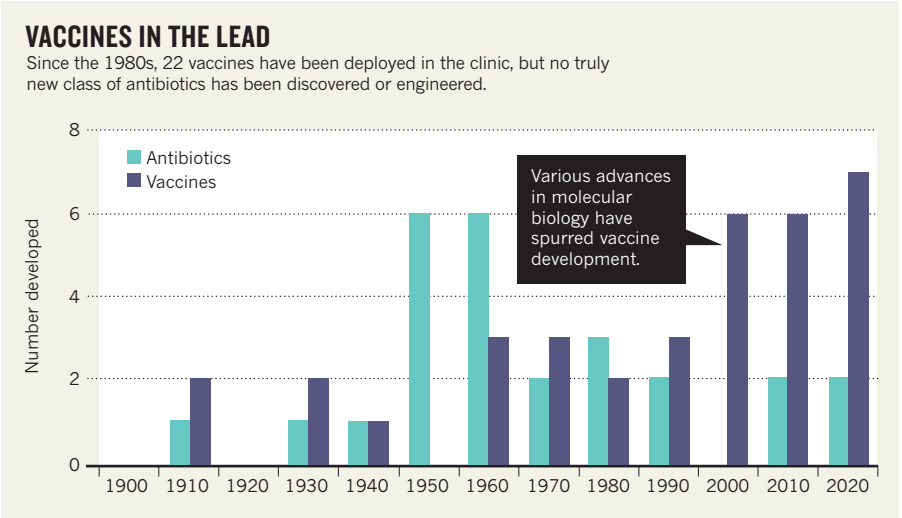
Antibiotics remain the only life-saving treatment for an acute bacterial infection. Yet several vaccines already help to stem AMR. Some, such as the pneumococcal vaccine, do so directly by reducing the carriage and transmission of antibiotic-resistant bacteria[9]. Others do so indirectly. The influenza vaccine, for instance, cuts the incidence of fevers, and so minimizes the number of antibiotic doses that are needlessly prescribed and taken[10].

We call for a global strategic effort to develop a portfolio of vaccines that target AMR. Launching this will require policymakers and stakeholders to make advances on three fronts.

Economics. If current methods were used to calculate the economic value of vaccines, many of those targeting resistant bacteria would not be deemed cost-effective because the effects on AMR are not factored in. To persuade governments and drug companies to invest in vaccines, health economists must model the incremental cost of AMR and count the avoidance of that cost as a benefit of vaccine development and use.

Awareness. Recent discussions with the UK Wellcome Trust, the Bill & Melinda Gates Foundation and the US National Institutes of Health suggest that all these organizations recognize vaccines as important tools in the fight against AMR. Yet the reports and mission statements of manufacturers and of policymakers, such as the World Health Organization (WHO) and the United Nations General Assembly (UNGA), indicate that most key players see AMR as a problem that needs to be addressed primarily through stewardship and the development of new antibiotics.

To change mindsets, epidemiologists need to mine the data and demonstrate the impact existing vaccines already have on AMR (see 'Resistance curbed'). They also need work with economists to model the health and economic benefits of greater investment in vaccines. This evidence must be communicated to policymakers and the



SOURCES: VACCINES DATA COMPILED FROM S. A. PLOTKIN & S. L. PLOTKIN *NATURE REV. MICROBIOL.* **9**, 889–893 (2011); ANTIBIOTICS DATA COMPILED FROM L. L. SILVER *CLIN. MICROBIOL. REV.* **24**, 71–109 (2011).

public. (The growth of the anti-vaccine community in recent years is a signal that those of us who recognize the health benefits of vaccines need to do better at communicating them.) Meetings between scientists and stakeholders from both the vaccine and the antimicrobial communities should be promoted and funded to enable discussion of an integrated strategy to target AMR.

Prioritization and trial design. Policymakers, funders and manufacturers must agree on what resistant strains to prioritize for vaccine development, depending on the threat they pose and the feasibility of vaccine development. The WHO and other key stakeholders, such as the US Centers for Disease Control and Prevention, that already make recommendations about which strains to prioritize in the hunt for antibiotics, could take the lead.

Likewise, manufacturers of vaccines must begin discussions with regulators to establish which clinical-trial designs would demonstrate the effectiveness of vaccines targeting AMR. Also, the effects of vaccines on AMR should be included in the information leaflets that accompany them, to facilitate recommendations by agencies such as the UK Joint Committee on Vaccination and Immunisation and the US Advisory Committee on Immunization Practices.

No single strategy will suffice when it comes to overcoming the challenges posed by drug-resistant pathogens. The use of antibiotics and vaccines must be accompanied by improved diagnostics to allow caregivers to make better use of the drugs we already have. Enhanced stewardship programmes need to be developed, such as those involving improvements to sanitation, to prevent the spread of infections. And better global surveillance of drug resistance is also required to preserve the effectiveness of our current antibiotic armament[2]. Lawmakers need to bring in more effective regulation to lessen the inappropriate use of drugs (for instance as growth promoters for livestock, or as a result of people buying cheap drugs on the black market in emerging economies). Also, shortcomings in health systems worldwide (primarily, a lack of care givers who are sufficiently informed about when vaccinations or antibiotics are the best course of treatment) could hamper vaccination strategies, even when effective vaccines are available.

These weaknesses must be shored up, for instance by overseas training programmes. One example is the master's in vaccinology at the University of Siena in Italy, which trains visiting physicians from low-income countries in vaccine development and implementation, enabling them to apply this knowledge when they return to their home countries.

Over the past few years, key institutional stakeholders — notably the WHO, the UNGA, the World Bank, the G20 group of countries, the European Union and the UK and US governments — have called for researchers to develop new antibiotics to expand our arsenal in the war against superbugs. We appeal to these organizations to call now for a multi-layered strategy that prioritizes the development of vaccines to target resistant strains. ■

PER-ANDERS PETTERSSON/GETTY

Vaccines rarely prompt bacteria to develop resistance.

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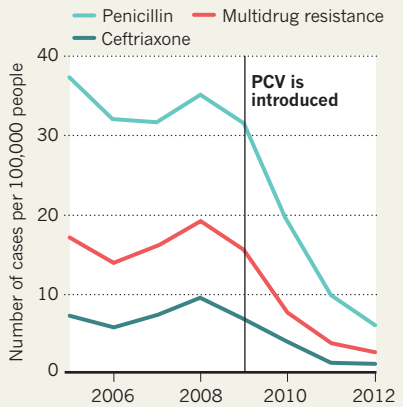
RESISTANCE CURBED

The number of two-year-olds in South Africa with resistant strains of pneumococcus fell after pneumococcal conjugate vaccine (PCV) was introduced.



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