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Vaccines take a shot at antimicrobial resistance

Economic and policy issues rein in industry enthusiasm for vaccines as an answer to drug-resistant bugs.

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As health authorities, clinicians and drug developers grapple with the emerging antimicrobial resistance (AMR) crisis, vaccines are gaining attention as a possible solution. Industry and policymakers are now working to figure out a business model that will sustain this new way of thinking about the value of vaccines.

Already, a number of candidates against some of the worst bacterial culprits are in mid-stage clinical development (TABLE 1). But until industry can be assured of a return on its investment into expensive studies aimed at showing that vaccines can provide explicit AMR benefits, companies are treading cautiously. Likewise, until payers can be sure that vaccination can address drug resistance, they remain wary of agreeing to pay more for a vaccine than a standard cost-effectiveness assessment would dictate. It's a catch-22 that is holding up the emerging field.

"My major problem right now is not technology," says Rino Rappuoli, chief scientist at GlaxoSmithKline Vaccines. "My major problem is how to make this attractive to companies. We have to build a plan which makes business sense."

And success here will depend on coming up with ways to model the economic benefits of vaccines in terms of their impact on AMR, an area of research that is still in its infancy.

Stakeholders started to hash out the issues during two meetings last year — at the UK's Chatham House in March, and at the GSK campus in Belgium in July — leading to optimism that the community may yet resolve the situation.

"Ultimately if there's assurance from a public health perspective that there is a market, I think you'll see greater interest from industry," predicts James Wassil, business unit lead for Vaccines at Pfizer.

Vaccine attractions

To date, industry's efforts to address AMR have primarily centred on attempts to use antibiotics more sparingly, and to develop novel antibiotics. But as drug development failures have accumulated, pharma has exited the area and the clinical pipeline has dried up. Initiatives such as CARB-X, a public–private partnership established to fund preclinical antibiotic development, give some hope that the antibiotic pipeline may yet be revitalized. But vaccines — which are in some ways easier to develop than antibiotics (BOX 1) — promise another way forward.

The case for vaccines against AMR threats depends on an interplay of related mechanisms. Most obviously, they prime an individual's immune system to eliminate an invading pathogen, preventing potentially resistant infections and providing herd immunity to non-vaccinated individuals in the community. In addition, by preventing infection they reduce the use of antibiotics, minimizing the opportunities to select for resistant strains of a target pathogen and bystander species in the host microbiome.

But vaccines also bring other unique advantages to the table. Many microbes do not develop resistance to vaccines, as exemplified by the long-standing success of immunization programmes against diphtheria, smallpox and others. And whereas antibiotics are generally given to symptomatic patients, at a point when the invading bacterial population is sufficiently large and diverse to include resistant organisms, the prophylactic nature of vaccines means that infections are usually cleared by the host's immune system before resistant strains can emerge. "Basically it's a numbers game," says Rappuoli.

Another advantage is that vaccines can drive immunity against multiple pathogenic targets — from several epitopes on a single antigen to numerous targets on a live-attenuated whole organism — further reducing the risk of resistance. By contrast, "one antibiotic targets one molecule in the bacterium. And bacteria can get around that pretty quickly," says Rappuoli.

The evidence base to show that vaccines can help to control AMR comes, however, mainly from large retrospective studies of approved vaccines. For example, researchers found that childhood immunization against *Streptococcus pneumoniae* in the USA caused a 59% reduction in multidrug-resistant strains between 1999 and 2004. Latest estimates suggest universal coverage with Pfizer's Prevnar-13 *S. pneumoniae* vaccine could avoid 11.4 million days of antibiotic use per year in children under 5 years. And, a randomized trial in Finland showed that vaccination of infants against *Haemophilus influenzae* significantly reduced outpatient antibiotic purchases.

Prospective AMR-related data collection for experimental vaccines would give industry a faster route to prove a vaccine's worth, but is not yet well established.

For Marc Lipsitch, professor of epidemiology at the Harvard School of Public Health, this creates an opportunity to embed AMR-related end points directly into vaccine clinical trials. "It's pretty rare still that resistant infections are an outcome, or antibiotic prescribing is an outcome of clinical trials for vaccines. But they very often could be, and it would build an evidence base to let us know what is the potential benefit," he notes.

Rappuoli and colleagues also highlighted the need for novel trial end points as a top priority for the field, in a comment article in *Nature* last year. "Manufacturers of vaccines must begin discussions with regulators to

Table 1 | **Selected vaccines in development for antimicrobial-resistant bacteria**

Name	Developer	Pathogen	Status
PF-06425090	Pfizer	*Clostridium difficile*	Phase III
GSK-692342	GlaxoSmithKline/ Aeras	*Mycobacterium tuberculosis*	Phase II
Group B *Streptococcus* vaccine, maternal immunization	GlaxoSmithKline	Group B *Streptococcus*	Phase II
PF-06290510	Pfizer	*Staphylococcus aureus*	Phase II
JNJ-63871860	Johnson & Johnson	Extra-intestinal pathogenic *Escherichia coli*	Phase II

Box 1 | **R&D challenges**

As R&D prospects, vaccines offer some unique attractions and challenges versus novel classes of antibiotics.

For one thing, developing a vaccine involves fewer steps than developing a drug: after identifying a pathogen target that is potentially protective, all that remains is to administer that target to the patient and let their immune system do the rest. "You essentially don't have to make the drug," explains Keith Klugman, director for Pneumonia at the Bill & Melinda Gates Foundation. By contrast, a drug developer who has a target lined up still has to find a drug that can inhibit the target without being too toxic to the host. "It turns out that drugs are much harder to find than targets for drugs," says Klugman.

Indeed, industry has deployed more new vaccines than novel antibiotics into the clinic since the 1980s.

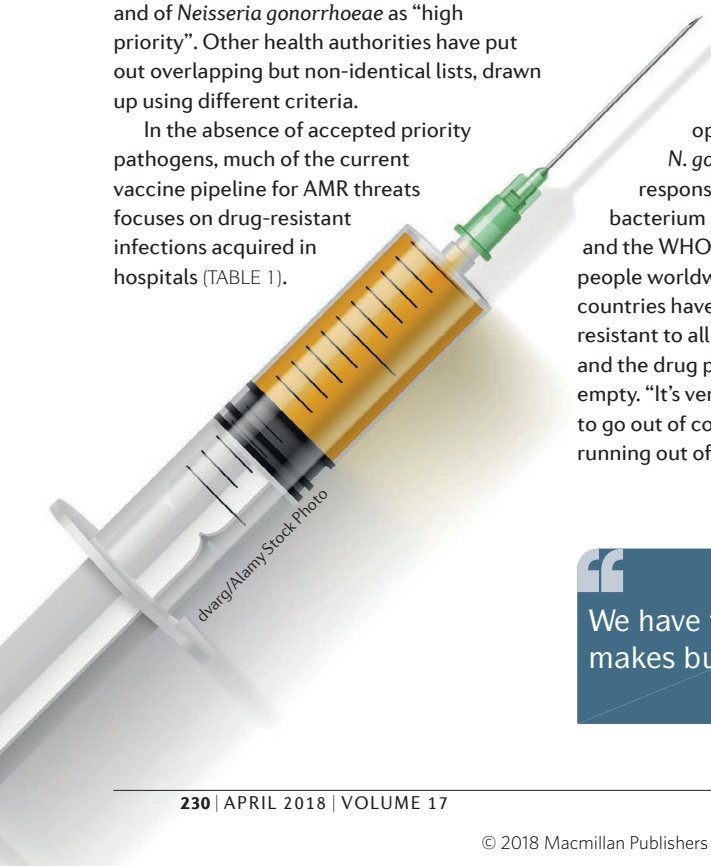
That said, vaccine development still poses significant challenges. Deciding on which bacterial components to target and figuring out which antigens will cover the most strains of a pathogen can be a complex and costly process. Adjuvant selection is as much an art as a science. And, the prophylactic nature of vaccines calls for particularly large and lengthy clinical trials, making any failures all the more onerous. Recent notable failures attest to the challenges: in September 2016 Valneva pulled the plug on its *Pseudomonas aeruginosa* vaccine candidate VLA43 following weak phase II/III data, and Sanofi recently terminated phase III testing of its *Clostridium difficile* vaccine after an interim analysis flagged low probability of success.

establish which clinical trial designs would demonstrate the effectiveness of vaccines targeting AMR," they wrote.

Priority pathogens

Another focus for the community is the need for more clarity around which drug-resistant pathogens to prioritize for vaccine development efforts. In February 2017, the WHO published a global priority list of antibiotic-resistant bacteria, which flagged several carbapanem-resistant Gram-negative bacteria as "critical" and included multidrug-resistant strains of *Staphylococcus aureus* and of *Neisseria gonorrhoeae* as "high priority". Other health authorities have put out overlapping but non-identical lists, drawn up using different criteria.

In the absence of accepted priority pathogens, much of the current vaccine pipeline for AMR threats focuses on drug-resistant infections acquired in hospitals (TABLE 1).



In November, for example, an independent FDA advisory panel concluded that Pfizer's investigational *S. aureus* vaccine PF-06290510 could be considered for use in patients undergoing elective hip and knee surgery on the basis of the company's data in patients undergoing elective spine surgery.

Hospital-acquired infections offer a controlled setting to test the vaccine approach against AMR bacteria, providing a clear benefit for these types of indication. But, at the same time, the potential market for these vaccines is small compared with community-based drug-resistant infections. As such, AMR in the hospital can be considered "a kind of orphan disease," says Rappuoli.

Another area of clear opportunity is around *N. gonorrhoeae*, the bacterium responsible for gonorrhoea. The bacterium is high on all the priority lists, and the WHO estimates it affects 78 million people worldwide. In recent years several countries have reported cases that are resistant to all available treatment options, and the drug pipeline for this disease stands empty. "It's very high prevalence and about to go out of control," says Rappuoli. "We are running out of options."

> "We have to build a plan which makes business sense"

Researchers recently serendipitously found, however, that immunization with a group B meningococcal vaccine reduced the risk of gonorrhoea by about 30% in New Zealand. Similarities between the two offending pathogens, both of which belong to the *Neisseria* genus, probably account for the crossover.

Respiratory syncytial virus (RSV) and influenza viruses are high on Chatham House's priority list. Although these viral pathogens do not directly drive the AMR crisis, they contribute indirectly by increasing antibiotic use — both appropriately for secondary bacterial infections and inappropriately due to incorrect diagnosis. A study in Canada showed that free influenza immunization to everyone aged over 6 months cut influenza-associated antibiotic prescriptions from 17.9 to 6.4 per 1,000 people.

Candidates such as Novavax's RSV vaccine, currently in phase III testing in pregnant women, and a putative universal influenza vaccine from researchers at Oxford University, which recently entered a phase II trial, provide hope in this regard.

There is also plenty of room for vaccines against other AMR pathogens, as described in a recent *Nature Medicine* review by researchers at Pfizer's Vaccine R&D unit.

Traditional regulatory incentives such as priority review and fast-track designation could help incentivize companies, says Wassil, but health authorities need to take a more leading stance as well. "If public health is willing to say 'we need vaccines to reduce AMR for the following diseases,' and that they're prepared to ensure there's some sort of market or market-based incentive, I think industry would be willing to venture out and try and develop something."

Path forwards

Public health charities and public–private partnerships could have a key role in this future. Organizations including Gavi, the Vaccine Alliance, and the Bill & Melinda Gates Foundation have previously worked in partnership with drug companies to fund vaccine R&D, provided the recipients make their vaccines affordable for developing countries. "We play an essential part because we can fund a significant portion of vaccine development, so we can de-risk a vaccine programme," says Keith Klugman, director for Pneumonia at the Gates Foundation. "That way it can be a win for everyone." The foundation is now encouraging vaccine researchers to consider AMR in grant applications, adds Klugman.

Gavi, for its part, created the Advance Market Commitment (AMC) funding model to incentivize Pfizer and GSK to manufacture a Group B *Streptococcus* vaccine for use in developing countries. Donor pledges, brokered through the AMC, enabled Gavi to guarantee a set price for a portion of the vaccine doses, assuring a market for the companies and enabling them to develop the vaccine for the first-world market (in pregnant women, to reduce the need for prophylactic antibiotics).

The Coalition for Epidemic Preparedness Innovations (CEPI) — a global non-profit public–private partnership founded in January 2017 by organizations including the World Economic Forum, the Gates Foundation and the Wellcome Trust — funds R&D from post-discovery up to and including phase II for vaccines to address outbreaks such as Ebola.

Wassil thinks these funding models could also be applied to AMR vaccine R&D.

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But charitable organizations cannot provide all the financial backing, and if the public health value of vaccinations includes AMR benefits, then stakeholders expect that appropriate public financing should follow.

Klugman is cautiously optimistic. "Over the next 5 years, I envisage a number of vaccines coming to market which could impact resistance," he says. "AMR is unfortunately here to stay, and we're going to need a number of interventions to reduce AMR in the long-term."