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Review

Vaccines for Antibiotic-Resistant Bacteria: Possibility or Pipe Dream?

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The increasing incidence of infections caused by antibiotic-resistant bacteria from multiple species, together with the paucity of new antibiotics in the development pipeline, indicates that vaccines could play a role in combating these infections. The development of vaccines for these infections presents unique challenges related to target population selection, vaccine administration, and antigen identification. Advances in genomic, transcriptomic, and proteomic technologies offer great potential for identifying promising antigens that are highly conserved and expressed during human infections. Although important challenges remain, the potential health and economic benefits associated with the clinical implementation of vaccination strategies for the prevention of antibiotic-resistant infections warrant their continued development.

Trends

Vaccines for multiple bacterial species that produce antibiotic-resistant infections are being evaluated in preclinical and clinical studies.

Previous clinical trials have generally been disappointing due to lack of efficacy.

Genomic, transcriptomic, and proteomic technologies are being used to identify high-value antigens.

Do We Need Vaccines for Antibiotic-Resistant Bacteria?

The development of antibiotics represents one of the most notable achievements in biomedicine. Unfortunately, the efficacy of this class of drugs is being compromised by the emergence and dissemination of antibiotic-resistant strains from multiple bacterial species including, but not limited to, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, and *Clostridium difficile*. This worrisome trend has been highlighted recently by reports describing the scale of the antibiotic resistance problem. The Antibiotic Resistance Global Report on Surveillance published in 2014 by the World Health Organization described high rates of antibiotic resistance in infection-producing bacteria in all six regions included in the survey [1]. Similarly, the results of a European Centre for Disease Prevention and Control point-prevalence study assessing antibiotic resistance in health care-associated infections that included over 900 hospitals in 30 countries demonstrated high rates of resistance in multiple bacterial species [2]. The health burden produced by these infections is significant, as indicated by the Centers for Disease Control and Prevention's (CDC's) *Threat Report*, which estimated that in the USA alone more than 2 million people are affected by antibiotic-resistant infections every year (including both bacterial and fungal infections), directly resulting in approximately 23 000 deaths [3]. The economic burden that results from these infections is also substantial in light of estimates that they result in US$20 billion in additional direct health-care costs and US $35 billion in lost productivity annually in the USA alone [3,4].

In this context, novel preventive and therapeutic approaches are needed for infections caused by antibiotic-resistant bacteria. The development of new antibiotics that have activity against multidrug-resistant strains would seem an obvious priority. Unfortunately, however, the introduction of new classes of antibiotics into the clinical setting has stagnated over the past two decades and the number of pharmaceutical companies with active antibiotic-development

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programs has dwindled [5,6]. Although the development of novel antimicrobials will undoubtedly play a role in confronting emerging antibiotic resistance, the scope of the problem warrants that additional approaches are explored. Vaccines have proven to be highly effective in preventing infections caused by multiple viral and bacterial pathogens. The increasing incidence of infections caused by antibiotic-resistant bacteria together with the thinning pipeline of new antibiotics in development have prompted research in both the academic and the biotechnology/pharmaceutical sector aimed at developing vaccines for antibiotic-resistant bacteria. The potential for vaccines to play a role in reducing antibiotic-resistant infections has been recognized by governments and international scientific committees, as evidenced by a recent Executive Order signed by President Obama entitled Combating Antibiotic-Resistant Bacteria that included the development of vaccines as a priority (https://www.whitehouse.gov/the-press office/2014/09/18/executive-order-combating-antibiotic-resistant-bacteria) and the inclusion of vaccine development for antibiotic-resistant hospital-acquired infections as one of 17 recommendations of the Transatlantic Taskforce on Antimicrobial Resistance [7]. In this review we outline the potential benefits and limitations associated with using vaccination as an approach for combating antibiotic-resistant infections, discuss some of the special considerations that must be taken into account during vaccine development, and consider aspects related to vaccine development that have arisen in light of previous clinical trials evaluating vaccines for preventing infections by antibiotic-resistant bacteria.

Can Vaccines Contribute to Reducing Antibiotic Resistance?

Perhaps the most obvious potential benefit of vaccine-based strategies is the possibility of reducing infection rates by difficult-to-treat bacteria and the morbidity and mortality associated with these infections. There is, however, an additional potential positive aspect that could result from the clinical use of vaccines for preventing these infections: a decrease in the emergence and transmission of antibiotic resistance. Immunization-based approaches that decrease infection rates would reduce the need for prescribing antibiotics, which may in turn result in less selective pressure that results in the emergence and subsequent transmission of resistant strains. This idea is supported by studies indicating that a reduction in the clinical use of antibiotics is associated with lower resistance rates [8–10], although not all studies have shown such a correlation [11]. Vaccines are also unlikely to be affected by existing resistance mechanisms and will therefore not produce pressure that favors the survival and transmission of antibiotic-resistant strains. This differs from the use of antibiotics, which strongly selects for the survival of resistant bacteria. Additionally, because the immune response stimulated by vaccination is targeted against only one (or a few) microorganisms, immunization-based approaches are likely to have little effect on nonpathogenic bacteria present in the body. This again is in sharp contrast to the use of antibiotics, which have been shown to affect normal flora in both experimental models and humans [12–14]. This may be of importance in light of recent studies indicating that normal human flora can be a reservoir for genetic resistance determinants [15–17]. Together, these concepts indicate that there is at least a strong theoretical basis suggesting that vaccines targeting antibiotic-resistant bacteria could contribute to reducing the emergence and transmission of antimicrobial resistance.

Vaccines for Antibiotic-Resistant Bacteria Present Unique Challenges

The goal of immunization is to provide protective immunity during the period in which an individual is at risk for infection. For pathogens that produce widespread disease or that could potentially infect large segments of the population, such as influenza virus or hepatitis B virus, a universal vaccination approach is appropriate. However, in many cases antibiotic-resistant bacterial infections occur most frequently in individuals with specific risk factors – for example, *S. aureus* infections in kidney transplant patients and *P. aeruginosa* infections in individuals with cystic fibrosis (CF) – raising the possibility that a targeted vaccination approach may be most appropriate. In addition, given that certain health care-associated infections are often multidrug