Vaccines for Healthcare-associated Infections: Promise and Challenge

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As antibiotic resistance increases and the rate of antibiotic development slows, it is becoming more urgent to develop novel approaches to prevent and mitigate serious bacterial and fungal infections. Healthcare-associated infections (HAIs), including those caused by Clostridium difficile, Staphylococcus aureus, Pseudomonas aeruginosa, Acinetobacter baumannii, carbapenem-resistant Enterobacteriaceae, and Candida species, are a major cause of morbidity, mortality, and healthcare costs. HAIs are also a key driver of antibiotic use. Vaccines directed toward these pathogens could help prevent a large number of HAIs and associated antibiotic use if administered to targeted populations. Despite numerous scientific and operational challenges, there are vaccine candidates in late-stage clinical development for C. difficile, S. aureus, and P. aeruginosa. Basic, preclinical, and early clinical research to develop vaccines for other types of HAIs is also under way. In addition, other prophylactic immune interventions, such as monoclonal antibodies, for several of these pathogens are in advanced development. Here we describe the promise, challenges, and current pipeline of vaccines to prevent HAIs.

Keywords. vaccines; healthcare-associated infections; Clostridium difficile; Staphylococcus aureus; antibiotic resistance.

Antimicrobial resistance (AR) is a complex, multifaceted problem, and many of the key factors contributing to the development and spread of resistance are concentrated in healthcare settings. For example, healthcare facilities have a high population density of bacterial and fungal pathogens, an increasing number of high-risk patient populations, a large number of indwelling devices such as catheters, and high usage of broad-spectrum antibiotics [1]. Exacerbated by inadequate infection control measures and the lack of rapid diagnostics for many pathogens, healthcare-associated infections (HAIs) are a serious cause of morbidity and mortality in the United States. In 2013, the Centers for Disease Control and Prevention issued a report [2], which estimated that >2 million infections and 23 000 deaths per year in the United States were attributable to resistant bacterial and fungal infections. In addition, Clostridium difficile, which takes advantage of the gut dysbiosis associated with broad-spectrum antibiotics to establish infection, causes 453 000 illnesses and was associated with approximately 29 000 deaths in 2011 [3]. The report outlined 3 categories of resistant pathogens of concern: urgent, serious, and concerning [2]. Of the 15 urgent and serious threats, 8 are significant nosocomial pathogens: C. difficile, carbapenem-resistant Enterobacteriaceae (CRE), multidrug-resistant Acinetobacter, fluconazole-resistant Candida, extended-spectrum β-lactamase-producing Enterobacteriaceae, vancomycin-resistant Enterococcus, multidrug-resistant Pseudomonas aeruginosa, and methicillin-resistant Staphylococcus aureus (MRSA).

As AR has grown, new antibiotic and antifungal development has declined. There are few drugs in clinical development to treat resistant infections, and those that do receive regulatory approval will likely encounter resistance shortly after their introduction. For this reason, there is now widespread support for the development of “nontraditional” approaches to combat AR, including vaccine and passive immunization approaches [4–6]. Such immune-based prophylaxis approaches are particularly attractive in their promise to decrease the overall burden of bacterial disease and the associated need for antibiotics.

Pneumococcal vaccines are an excellent example of how vaccines can prevent community-associated bacterial infections that have been associated with high antimicrobial use and resistance development. Within 4 years of its licensure, the 7-valent pneumococcal conjugate vaccine (PCV7) contributed to an overall 57% drop in incidence of multidrug-nonsusceptible strains. This included an 84% decrease in the rate of multidrug-nonsusceptible invasive pneumococcal disease (IPD) in children <2 years of age and a 49% decrease in penicillin-nonsusceptible IPD in individuals >65 years of age due to reduced transmission from children [7]. Nonsusceptible IPD has further decreased since the introduction of the broader-spectrum 13-valent pneumococcal conjugate vaccine (PCV13) [8].

Using vaccines to prevent HAIs could have a significant impact on the burden of HAIs and could decrease antimicrobial usage in healthcare settings. However, there are no currently licensed vaccines for bacterial or fungal HAIs, and an
examination of the field reveals significant scientific and implementation challenges that have thwarted successful development of such vaccines. Vaccine development for HAIs, as with other pathogens, has been hampered by a poor understanding of correlates of protection and the lack of predictive animal models. Unlike many other disease areas, universal vaccination against HAIs would not be appropriate, so a careful analysis of high-risk target populations must be undertaken. An additional challenge is that major risk groups for HAIs include elderly and immunocompromised patients, who may have trouble mounting a protective immune response. In light of these considerations, the current paradigm for vaccine development may need to be reexamined in the case of these infections, where even short-term protection can be a valuable tool to prevent HAIs. For the same reason, passive immunization should also be considered a viable and cost-effective prophylactic option. Herein we describe the development pipeline of prophylactic immune interventions for the most common HAIs.

CLOSTRIDIUM DIFFICILE

Clostridium difficile is a gram-negative, spore-forming bacterium that is now the most common HAI in the United States [9]. It is the leading cause of antibiotic-associated diarrhea and is associated with broad-spectrum antibiotic use, advanced age (>65 years), hospitalization, and underlying comorbidities. Clostridium difficile can cause asymptomatic colonization, diarrhea, pseudomembranous colitis, toxic megacolon, and death. The past decade has seen a dramatic rise in the incidence of C. difficile infection (CDI), with a corresponding increase in disease severity and mortality [10]. These trends have been associated with epidemic strains of C. difficile (BI/NAP1/027), which appear to have enhanced fitness and heightened virulence [11, 12].

Defense against CDI is primarily mediated by the gut microbiota (ie, colonization resistance), and perturbation of this ecosystem through the use of antibiotics induces significant changes in the metabolic environment (particularly the ratio of primary and secondary bile acids and carbon sources) that favor C. difficile germination and growth [13]. Once vegetative, C. difficile produces 2 exotoxins, toxin A and toxin B, which are its primary virulence factors. A third toxin, CDT or binary toxin, is expressed by BI/NAP1/027 strains of C. difficile, and the activity of this toxin also appears to contribute to pathogenesis [14, 15].

Treatment for CDI involves discontinuation of the inciting antibiotics and initiation of different antibiotics (vancomycin, metronidazole, or fidaxomicin) that effectively control CDI symptoms. However, approximately 20% of patients experience at least 1 recurrence, and the rate of recurrence increases with each subsequent episode [16]. There are approximately 83,000 recurrences each year, with many utilizing fecal microbiota transplant to reset the gut microbiome and stop the cycle of recurrence [9]. The economic burden of CDI, including the costs of complications and recurrence, has been estimated at $4.8 billion annually in the United States [17]. Although targeted infection control procedures, alone or in combination with antibiotic stewardship, have the potential to reduce CDI incidence, a vaccine against C. difficile is likely the most effective way to decrease CDI incidence.

The host immune response to CDI has been analyzed in human cohort studies, and the presence of antitoxin antibodies appears to be an important predictor of disease outcome [18]. Antibodies against C. difficile are present in most adults, having been exposed during infancy or from different environmental sources. In general, high serum antitoxin antibody titers, particularly immunoglobulin G against toxin A, have been associated with asymptomatic colonization and protection from CDI recurrence [18]. Indeed, early preclinical efforts to develop a vaccine against CDI focused on toxoid preparations of toxin A and toxin B formulated with alum, and were designed to elicit systemic antibody responses against both toxins. A number of C. difficile toxin–based vaccines are currently in human clinical trials [19, 20].

The most advanced C. difficile vaccine is currently being developed by Sanofi Pasteur under the trade name Cdiffense [21]. Cdiffense consists of purified full-length toxin A and toxin B that have been formalin inactivated and absorbed to alum. Numerous phase 1 and several phase 2 studies have been successfully completed with this vaccine [22–26]. The vaccine appears safe and immunogenic in the target population, and a phase 3 study is currently recruiting adults aged 50–85 years who are at risk for CDI. This trial has an estimated completion date of December 2017 [27].

Pfizer is also developing a toxoid-based vaccine but has simplified the manufacturing process by producing recombinant full-length versions of toxin A and toxin B from a nontoxigenic C. difficile host strain. The vaccine (with and without adjuvant) was recently tested in a phase 1 clinical trial and found to be well tolerated, with a clear toxin-neutralizing dose response [28, 29]. This vaccine is currently in phase 2 clinical development for the prevention of primary CDI [30].

Given the size and complexity of C. difficile toxins, an alternative strategy involves the use of recombinant toxin subdomains to produce neutralizing antitoxin antibodies [19, 20]. This approach has a number of advantages related to ease of manufacture and increased stability. It also allows for the inclusion of defined neutralizing epitopes and does not require chemical detoxification, a process that can alter important conformational epitopes. A number of toxin fragments and fusion proteins have been developed. Valneva is developing VLA84, an adjuvant-free genetic fusion of the cell binding domains from toxin A and toxin B, which has demonstrated favorable safety and immunogenicity [31, 32]. A phase 2 study of VLA84 was initiated in 2014 and results are expected in late 2016 [33].
Toxin-based vaccines clearly have the potential to induce strong antitoxin immune responses; however, antibodies directed at the toxins are not likely to prevent colonization of the host. Colonization is a critical step in *C. difficile* pathogenesis and excreted spores can serve as a significant reservoir of *C. difficile* in healthcare facilities and the community. Vaccine efforts directed at cell surface–associated molecules have the potential to reduce or eliminate colonization and thus break the cycle of transmission. While none of these candidates have yet reached the clinic, surface-associated antigens, such as flagellar proteins, S-layer proteins, proteases, and complex polysaccharides have all been studied in animal models as potential vaccine candidates [19, 20].

Models looking at the cost-effectiveness of a *C. difficile* vaccine support its use in certain at-risk populations [34], including people with repeated or anticipated exposures to healthcare facilities and broad-spectrum antibiotics. Vaccination strategies could include vaccinating patients before elective surgical procedures or before patients are admitted into long-term care facilities and nursing homes. There is some evidence that a vaccine could be effective at treating patients with recurrent infections and therefore both therapeutic and prophylactic indications should be considered [35]. Regardless of which vaccine technology takes hold, an effective vaccine against this major nosocomial infection appears to be within reach.

**STAPHYLOCOCCUS AUREUS**

*Staphylococcus aureus* is a human commensal organism and pathogen that can cause many types of infections, ranging from noninvasive skin and soft tissue infections to bacteremia to recalcitrant endocarditis and osteomyelitis. After the introduction of penicillin in 1944 and methicillin in 1959, resistance to both drugs evolved rapidly, and MRSA became endemic in hospitals by the 1980s [36]. While *S. aureus* remains a major cause of community-acquired and healthcare-associated infections, there has been an encouraging decrease in serious, invasive MRSA HAIs over the past decade, likely due to enhanced infection control practices. Nevertheless, an estimated 80 000 invasive MRSA infections and 11 000 related deaths occur annually in the United States [37].

*Staphylococcus aureus* is known for its broad array of virulence factors and host immune evasion mechanisms, and generating protective immunity against invasive *S. aureus* disease has proven challenging. Early efforts with whole-cell live or killed vaccines largely failed to generate protective immune responses [38], so subsequent efforts have focused on purified antigens or toxoids. Many antigens have shown protection in animal models and several have demonstrated safety and immunogenicity in phase 1 clinical trials; however, only 3 candidate vaccines have advanced beyond phase 1 testing.

StaphVAX is a bivalent vaccine, directed against types 5 and 8 capsular polysaccharides (CP5 and CP8), cell surface components that mediate antiphagocytic activity. Early phase 3 studies in end-stage renal dialysis patients conducted by Nabi Biopharmaceuticals showed limited efficacy [39, 40]. A subsequent confirmatory study in hemodialysis patients showed no difference in rates of bacteremia compared with placebo. In addition to inadequate antigen selection, manufacturing quality was cited as a reason for the failure of this trial [40].

Merck’s V710 vaccine candidate is a single recombinant protein IsdB (Iron Surface Determinant B), a cell wall–anchored protein that primarily functions to scavenge iron. This candidate demonstrated excellent protection in multiple animal models as well as encouraging immunogenicity data in early phase human testing. Based on these data, a phase 2b randomized, placebo-controlled trial to evaluate the safety and efficacy of preoperative vaccination with nonadjuvanted V710 in preventing serious *S. aureus* infections in patients undergoing a median sternotomy for cardiothoracic surgery was launched. The study was terminated in 2011 due to lack of efficacy and a significantly higher rate of multorgan system failure–related deaths in members of the vaccinated group who developed *S. aureus* infection [41]. A recent analysis of the data from V710 subjects showed that low prevaccination interleukin 2 levels or undetectable preoperative interleukin 17a levels in subjects who acquired postoperative *S. aureus* infections appeared to be associated with increased mortality. Investigation into data from this trial is continuing, and additional insights into optimal vaccine design will hopefully be gained [42].

The only currently active advanced *S. aureus* vaccine development program is Pfizer’s SA4Ag candidate, which is composed of 4 antigens: clumping factor A, a virulence factor that allows *S. aureus* to bind to fibrinogen; the manganese transporter MntC; CP5; and CP8. Phase 1 studies showed rapid generation of functional antibody that endured at least 12 months [43]. Currently a phase 2b placebo-controlled safety and efficacy study of SA4Ag in adults undergoing elective spinal fusion surgery is under way in the STRIVE trial (*Staphylococcus aureus* Surgical Inpatient Vaccine Efficacy) [44].

Despite tremendous efforts, the results of clinical trials have largely been disappointing. The potential reasons for these failures include (but are not limited to) complex pathogenic mechanisms of the bacterium, including extensive strain and antigenic variability, colonization and biofilm formation; immune evasion; unclear correlates of protection in humans; and the lack of predictive animal models [45–47]. An additional factor that can complicate decisions to invest in a *S. aureus* vaccine is determining the optimal target population(s). Surveillance data can help to provide models of which target populations could benefit the most from such a vaccine [48].

Data from multiple failed vaccine programs have clearly demonstrated that innate and T cell–mediated immunity are key aspects of a protective immune response against *S. aureus*. Current research efforts are focused on further characterizing
the pathogenesis and host immune response to identify new antigenic targets; design of multicomponent vaccines that would generate functional opsonizing antibodies and robust T cell–mediated immunity; development of more representative animal models; and the use of novel adjuvants to augment antibody production and to steer the T-cell response toward a protective adaptive immune response. These additional data and tools enhance the likelihood that a safe and efficacious *S. aureus* vaccine can be developed. Ultimately, a vaccine will form only part of the multitargeted armamentarium, in addition to other interventions including passive immunotherapy and antimicrobials.

**GRAM-NEGATIVE HAIs**

HAIs caused by resistant gram-negative bacteria, including CRE and multidrug-resistant *Acinetobacter* and *P. aeruginosa*, are becoming increasingly prevalent. *Pseudomonas aeruginosa* is the only one of these gram-negative species for which a vaccine candidate, IC43, has progressed beyond phase 1 clinical development. The results from a phase 2/3 clinical trial of IC43 in ICU patients requiring mechanical ventilation, conducted in Europe, are expected soon [49]. No *Klebsiella* vaccine candidates have reached the clinic, and only 1 extraintestinal *Escherichia coli* vaccine candidate is known to be in the early stages of clinical development [50]. The variable capsular polysaccharides of *Klebsiella pneumoniae* and *E. coli* limit their potential as vaccine targets. Recent studies suggest that *K. pneumoniae* and *E. coli*–derived extracellular vesicles are potential vaccine candidates, providing new directions for vaccine development [51, 52]. Early translational research on possible *Acinetobacter* vaccines are mainly focused on antigen selection, immune correlates of protection, and animal models for safety and efficacy evaluation [53].

**CANDIDA**

Systemic candidiasis is a common infection in immunocompromised individuals and occurs predominantly as a consequence of high-risk medical procedures and exposure to broad-spectrum antibiotics. Currently there are 2 vaccine candidates in phase 2 testing for *Candida* infections; however, these candidates are being developed for vulvovaginal candidiasis [54, 55] and may not be effective for systemic disease. Interestingly, one of these vaccines, NVD-3, targets an epitope shared by *Candida* and *S. aureus*, demonstrating the possibility of cross-kingdom protection [56].

**PASSIVE IMMUNIZATION**

As vaccine approaches have met with challenges, increasing attention is being paid to the use of monoclonal antibodies (mAbs) to prevent HAIs in targeted patient populations. The mAbs for *C. difficile*, *S. aureus*, and *P. aeruginosa* are currently in phase 2 and/or phase 3 clinical testing in high-risk patient populations [57], and there are companies pursuing the discovery and development of antibodies for uropathogenic *E. coli*, *Klebsiella*, and *Acinetobacter*. mAbs are attractive because they do not require an adaptive immune response and therefore can work well in immunocompromised patients. In addition, mAbs have the potential for therapeutic use as well as prophylactic use. The early 2000s saw several unsuccessful *S. aureus* mAb development efforts targeting the same cell-surface constituents as early vaccine candidates [58, 59]. Most of the mAbs currently in clinical development for *C. difficile* and *S. aureus* infections target toxins, and are therefore antivirulence strategies that may mitigate disease without driving resistance but may also require traditional antibiotics to alleviate bacterial burden. The current *Pseudomonas* candidates target both cell-surface components and virulence factors. Clinical trials for both prophylactic and therapeutic indications are challenging to design and expensive to conduct, so the recent increase in public and private investment in the development of mAbs is promising.

**DISCUSSION**

As antibiotic resistance and antibiotic-associated HAIs increase, it is imperative to develop multiple prevention and treatment modalities. While the potential of vaccines to prevent HAIs is clear, for most pathogens there are significant challenges. *Clostridium difficile* is the only urgent or serious resistant threat for which an effective vaccine may become available in the next couple of years. While there are vaccines in phase 1 and 2 testing for other HAI pathogens, vaccine development is a high-risk endeavor, and several *S. aureus* vaccine candidates have already failed in phase 2/3 testing. To advance the development of new vaccines, it will be necessary to conduct and translate basic research on correlates of protection and to adopt strategies to enhance vaccine responses in elderly and immunocompromised populations. In particular, the role of the mucosal immune response against CDI requires more investigation. It is also important to harness technological advances such as reverse vaccinology, structure-based vaccine design, novel adjuvants that can promote protective T-cell responses, and novel delivery methods, such as nanoparticles, to address these challenges. Furthermore, other prophylactic immune interventions such as mAbs have an important role to play in reducing HAIs and antibiotic use in healthcare settings. Despite the challenges involved in developing vaccines and other prophylactic immune interventions, they are a promising potential addition to the arsenal of tools to combat this major public health problem.

**Notes**

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