Healthcare-associated infections: potential for prevention through vaccination

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Abstract: The challenge of healthcare-associated infections is compounded by the higher incidence of resistant organisms and the decreasing utility of antimicrobial agents. Historic and current vaccines have already contributed to reductions in healthcare-associated infections, and future vaccines have the potential to reduce these infections further. Through examples of bacterial and viral vaccines, this review will attempt to chart the way forward.

Keywords: antimicrobial resistance, healthcare-associated infection, immunization, vaccine immunization

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Introduction

Healthcare-associated infections (HAIs) may be associated with antimicrobial resistance, for example infections caused by Enterobacteriaceae and *Pseudomonas aeruginosa*[1] and *Staphylococcus aureus*.[2] They can be particularly difficult problems in intensive care units,[3] including device-associated infections in intensive care units.[4] HAIs encompass both bacterial and viral infections. Examples of the latter are rotavirus and norovirus acute gastroenteritis acquired in a pediatric unit,[5] and respiratory viruses such as influenza and rhinovirus in the intensive care unit.[6] The rates of healthcare-associated respiratory viral infections may be high: of 7772 laboratory-confirmed cases of respiratory viral infection in a Korean tertiary-care hospital, 22.8% were categorized as having been acquired in hospital, with an overall incidence of 3.9 cases per 1000 admitted.[7] Here, rhinovirus was the most common (30.3%), followed by influenza (17.6%) and parainfluenza (15.6%). Given the tendency of some viral infections such as influenza to predispose to secondary bacterial infections, there is also a connection between antimicrobial resistance and viral infections.

A number of governments and agencies have reviewed the problem of HAIs and antimicrobial resistance. For example, the US Centers for Disease Control and Prevention (CDC) in its HAI Progress Report covers central line-associated bloodstream infections, catheter-associated urinary tract infections, select surgical site infections, hospital-onset *Clostridium difficile* infections and hospital-onset methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia.[8] Point prevalence surveys are also performed.[9] The UK National Institute of Health Research of the Health Protection Research Unit, like other such units, investigates the mechanisms and drivers of antimicrobial resistance,[10] while the World Health Organization has a network of collaborating centers, monitoring and investigating antimicrobial resistance.[11]

Patients with HAIs have an increased risk of death when compared with those without such infections.[12] In this Norwegian study, performed from 2004 to 2011, 19,468 patients were included, 1662 (8.5%) of which had HAIs. Following adjustment for confounding factors, the authors found that patients with HAIs had a significantly increased mortality risk: within 30 days and 1 year, patients with HAIs had an adjusted hazard ratio of 1.5 [95% confidence interval (CI) 1.3–1.8] and 1.4 (95% CI 1.2–1.5) for death, respectively, relative to those without HAIs. Within the healthcare setting, antimicrobial resistance occurs, associated with high antibiotic consumption, critically ill patients and a permanent influx of pathogenic species.[13]

HAIs, and antimicrobial resistance, are not limited to adults, and thereby future opportunities for vaccination are opened – they affect newborns in the first month of life, in the form of late-onset sepsis.[14] Nosocomial pertussis occurs in neonatal units, underlying the importance of pertussis vaccination in healthcare workers.[15] Nor are HAIs limited to facilities in 'first world' cities – they occur in sub-Saharan Africa as well, including the transmission of tuberculosis to healthcare workers,[16] and in Nepal.[3]

Given the decreasing utility of existing antibiotics and the paucity of development of new antibiotics, reviving historic antibiotics to combat antimicrobial resistance is a concept that has gained some traction.[17] The concept that existing vaccines may be put to new uses has been highlighted recently by the retrospective study performed in New Zealand of a serogroup B meningococcal vaccine and observed protection against gonococcal infection.[18]

Why does drug resistance evolve readily but vaccine resistance does not?[19] Both drugs and vaccines impose pressure on pathogen populations and antimicrobial resistance can emerge relatively soon after the introduction of a new drug. Kennedy and Read[19] postulate that it is the ability of vaccines to prevent infections from occurring in the first place that results in fewer opportunities for vaccines to drive variation and resistance.

Vaccines can contribute to solving the problem of antimicrobial resistance in the following ways:[20]

1. Vaccines can reduce the prevalence of resistance by reducing the need for antimicrobial use.
2. They can reduce the impact of antimicrobial resistance by reducing the total number of cases.
3. By reducing the number of pathogens that may be responsible for a particular clinical syndrome, vaccines can permit the use of narrower-spectrum antibiotics.
4. Vaccines can confer herd protection.

The aim of the present review is to describe, through some examples, how past, present and future vaccines can have a positive impact in not only reducing HAIs, but also in reducing antimicrobial resistance. An Ovid Medline search was performed over the period from 2010 using the terms: 'vaccine', 'healthcare-associated infection' and 'antimicrobial resistance'. Studies illustrating important principles of the prevention of HAIs are included.

Bacterial infections

S. aureus vaccination

Rationale. The increased risk of transmission of MRSA in the healthcare setting has been well established.[21,22] Factors identified in the 2002 Graffunder and Venezia study[22] which were independently associated with MRSA infection, and which provide clues as to how and when a future *S. aureus* vaccine could be used, are previous hospitalization (within the last 12 months), longer length-of-stay before infection, previous surgery, enteral feedings, macrolide use and levofloxacin use.

A study of antibiotic exposure and other risk factors for antimicrobial resistance in commensal *S. aureus* found that in a population with no recent antibiotic usage, the prescription behavior of the general practitioner affects the odds for carriage of a resistant *S. aureus*.[23] In this study, of the 6093 *S. aureus* isolates, 77% showed resistance to at least one antibiotic and 7.1% exhibited multidrug resistance, including 1.3% with MRSA. The authors reported higher multidrug resistance rates in participants working in the healthcare setting or in nurseries. Participants working in healthcare or nurseries had a 1.7 to 1.9 times higher risk for carrying a multidrug-resistant *S. aureus* than those not working in those settings.

Modeling. The studies by Graffunder and Venezia,[22] Caffee and colleagues,[21] and van Bijnen and colleagues[23] provide some insights into the potential for vaccinating healthcare workers against *S. aureus* in the future and the potential, in turn, of preventing transmission from healthcare workers to patients. The healthcare worker is an obvious target for vaccination against *S. aureus*. What is more difficult to anticipate is when an individual will become a patient, especially a hospitalized patient, and therefore when an individual should be pre-emptively vaccinated against *S. aureus* in anticipation of becoming a patient.

Modeling is a useful exercise, in anticipation of how a *S. aureus* vaccine would be used, were it to be licensed and deployed.[24] The authors simulated stochastic susceptible–infected–recovered dynamics on social networks, based on observations in a

hospital in Tokyo, in an exploration of different containment strategies directed against nosocomial infections. In relation to *S. aureus* and the possibility of vaccination, the modeling showed that prioritizing medical doctors, rather than nurses or patients, was more effective. They also found that vaccinating healthcare workers with a high frequency of connectivity to pairs of individuals would be a superior approach over vaccinating healthcare workers with simply a large connectedness to other individuals.

Examples of vaccines. A robust T-cell response is thought to be one of the key requirements for an effective vaccine against *S. aureus*.[25] Other desired attributes are the ability to induce antibodies to neutralize toxins and the ability to induce antibodies to neutralize cell wall-anchored (CWA) proteins. The authors go on to list virulence factors that have the potential to be included in vaccines:

1. Membrane damaging toxins
2. CWA proteins
3. Clumping Factor A
4. Clumping Factor B
5. Fibronectin-binding proteins
6. SasX
7. Protein A
8. Iron regulated surface proteins.

Some other principles of *S. aureus* vaccine development include:[26]

1. Protection in animal models has not translated into protection in humans;
2. Antitoxins have worked well in other gram-positive infections;
3. Benefits of using multiple antigens;
4. The organism can evade human host defenses;
5. Some MRSA strains are more virulent than other strains;
6. Staph vaccines may cause harm due to an 'immune-priming' process; and
7. Reducing severity of disease and decreasing the cost/length of hospital stay may be achievable.

C. difficile *vaccination*

Rationale. The risk factors for *C. difficile* infection include those having received antimicrobial therapy within the previous 3 months, those having received multiple antibacterial agents, those 65 years of age and older, those with severe underlying illness including immunocompromise, those with certain gastrointestinal conditions, those in the intensive care unit and those with prolonged hospitalization.[27]

Modeling. It is possible that a *C. difficile* vaccine will be the first vaccine specifically licensed for the prevention of HAI. Modeling of transmission of *C. difficile* assists in defining potential vaccination strategies.[28,29] The ability to vaccinate individuals in the period leading up to their elective admission to hospital would provide a degree of confidence that the admission might not be prolonged by a bout of diarrheal disease. There would also be the potential for indirect protection of other patients, by virtue of the decreased likelihood of transmission. It may also be possible to vaccinate staff.

Examples of vaccines. A number of trials are under way for investigational *C. difficile* vaccines.[30] For example, the *C. difficile* Vaccine Efficacy (Clover) trial is a phase III, placebo-controlled, randomized, observer-blinded study to evaluate the efficacy, safety and tolerability of a genetically modified, chemically treated recombinant full-length toxin A/toxin B vaccine in adults 50 years of age and older [ClinicalTrials.gov identifier: NCT03090191]. The subjects are receiving three doses of the vaccine (or placebo) and being followed for three years. In another study, subjects are being assessed after one, two and three doses of a formalin-inactivated full-length toxin A/toxin B intramuscular vaccine administered at 0, 7 and 30 days [ClinicalTrials.gov identifier: NCT01887912]. In a third program, a vaccine designated VLA84, a genetic fusion of the truncated cell-binding domains of toxin A and toxin B, is being tested.[31]

Acinetobacter baumannii *vaccination*

Rationale and modeling. The predominant clinical features of *Acinetobacter baumannii* infection are sepsis and pneumonia, and modeling has been performed for both sepsis[32,33] and for pneumonia.[34] Vaccination would need to be targeted at individuals at risk of exposure (predominantly the healthcare setting), those with underlying medical and surgical factors that increase their risk, taking account of the prevalence of multiresistant strains.[35]

Examples of vaccines. Both single antigen and multicomponent approaches have been adopted

for developing vaccines against *A. baumannii*.[36,37] The active immunization trials include whole-cell vaccines and pure protein-based vaccines. The single antigen candidates include: the outer membrane protein OmpA, the membrane transport Ata, the biofilm-associated protein Bap, the K1 capsular polysaccharide and the membrane-associated polysaccharide poly-N-acetyl-β-(1-6-glucosamine). However, a single antigen approach may be suboptimal, due to antigenic variation and differences in target antigen expression. By contrast, inactivated whole cells, outer membrane complexes and outer membrane vesicles have been utilized in multicomponent strategies.

The McConnell group has demonstrated that vaccination with outer membrane complexes elicits rapid protective immunity to multidrug-resistant *A. baumannii*.[38] They reported that a single dose of the vaccine was able to be protective as soon as 6 days following immunization.

Development of prophylactic vaccines against *A. baumannii* is advancing along several fronts. A live attenuated strain, deficient in thioredoxin (DELTAtrx mutant), was protective in a lethal challenge study in mice.[39]

Streptococcus pneumoniae *vaccination*

Pneumococcal vaccines have a global impact on pneumococcal infection, as a result of widespread vaccination.[40] Perhaps less-well recognized is the potential impact that pneumococcal vaccination could have in the healthcare facility setting. In an acute care setting in London, UK, a cluster of three cases of pneumococcal infection occurred over a 5-day period.[41] The authors suspected nosocomial transmission because of very recent hospitalization and also because of identical and unusual antimicrobial resistance. The three patients – a 60-year-old female, a 76-year-old female and a 73-year-old male – all appear to have contracted pneumococcal infection originating in the wife of the male patient. The pneumococcal isolates were all serotype 9V and had indistinguishable antibiotic susceptibility patterns. The cluster not only highlights the difficulties of attributing pneumococcal infection to nosocomial spread, but also emphasizes the utility of pneumococcal vaccination, especially in the elderly.

Neisseria gonorrhea *vaccination*

Maternal transmission of gonococcal infection remains a problem in developing countries.[42] This results in morbidity in both the mother and the baby. In this Ethiopian study, there was a high level of antimicrobial resistance in the gonococcal isolates. A solution to this may emerge from a study performed in New Zealand, which suggests that an outer membrane vesicle meningococcal vaccine known as MENZ-B may have a 31% effectiveness against gonorrhea (95% CI 21–39%).

Viral infections

Influenza vaccination

In a small study of nurses, in which there was a 100% response rate, a self-administered questionnaire was distributed among nurses over 4 months of a winter season.[43] Out of 145 nurses, 89 (61%) reported that they had continued working while unwell with a flu-like illness. The most common reason for influenza vaccine uptake by the nurses who had been vaccinated for the current season was (1) the belief that they were personally at risk of influenza because of the nature of their work (80%); and (2) the belief that they were at risk of transmitting influenza to their patients. Although 72% of the nurses were aware of the CDC recommendations for influenza vaccination of at-risk populations (including healthcare workers), only 21% had actually been vaccinated. In a larger study of healthcare workers in Italy, 830 completed a survey.[44] Beliefs about the safety of influenza vaccine and the increased risk of contracting influenza were two of a number of drivers of the adherence or otherwise of healthcare workers to influenza vaccination. While both of these studies have limitations, such as size or convenience sampling, nevertheless a conclusion that can be made is that improvements in healthcare worker influenza vaccination have the potential to decrease the risk of healthcare-associated influenza infection, especially in susceptible patient populations.

Among a number of ways of improving healthcare worker influenza vaccination rates, the compliance of healthcare workers with vaccination programs is regarded as important, and the decision by healthcare workers not to be vaccinated should be documented.[45]

In those aged 50 years and older, influenza vaccination can result in significant reductions in the risk of laboratory-confirmed influenza hospitalizations, as shown in a US CDC study performed in 2010–2011 as part of the Emerging Infections Program surveillance.[46] The vaccine effectiveness against hospitalization was 56.8% (95% CI 34.1–71.7%) and for the age group 75 years and older, this remained at a similar level of 57.3% (95% CI 15.9–78.4%).

Influenza vaccination can offer substantial protection against hospitalization, even in years in which there is a degree of antigenic drift.[47]

Hepatitis B virus

Nosocomial transmission of hepatitis B virus has been documented since at least the early 1980s,[48,49] although the phenomenon was described more frequently and in ever more surprising forms in the 1990s.[50] Hepatitis B vaccines have not only resulted in global reductions in the burden of liver disease caused by hepatitis B virus, but also have conferred protection in the healthcare setting, especially for healthcare workers.[51] The importance of widespread community-based hepatitis B vaccination is highlighted by the recognition that some patients in healthcare facilities, such as those receiving hemodialysis, respond poorly to the vaccine, and thus depend on herd protection.[52]

Rotavirus

Rotavirus is considered an important cause of HAIs.[53] In the study by Cunliffe and colleagues, rotavirus was found to be responsible for 31% of healthcare-associated gastroenteritis cases. However, a 13-year study of infants and children in the UK, to assess the impact of routine rotavirus vaccination in the community, demonstrated not only a reduction in community-acquired rotavirus gastroenteritis, but also an 83% (95% CI 66–92%) reduction in healthcare-associated rotavirus gastroenteritis.[54]

Norovirus

Noroviruses are a recognized cause of nosocomial outbreaks of viral diarrheal disease,[5] as well as being endemic in some countries. Airborne spread in addition to direct contact has been reported in nosocomial outbreaks.[55] Environmental samples collected during outbreaks have been documented as containing norovirus.[56] Candidate vaccines include virus-like particles (VLPs), subviral particles or viral vectors.[57] These have the potential to have an impact not only in the community, but also in reducing the burden of diarrheal disease in the healthcare facility setting.

Therapeutic vaccines

Efforts are underway to develop therapeutic vaccines for chronic hepatitis B virus infection.[58] The authors note the considerable genetic diversity of hepatitis B virus and cite this as a challenge in the development of effective vaccines – a vaccine that is protective against one genotype may not be protective against other genotypes. They describe as another obstacle the lack of convenient *in vitro* infection systems and animal models. The authors list the major areas of endeavor, in the development of therapeutic vaccines against hepatitis B virus:

1. Recombinant peptide-based vaccines
2. DNA-based vaccines
3. Viral vector-based vaccines
4. Cell-based vaccines.

For *A. baumannii*, passive immunization with DELTAtrxA-immune sera provided protection against lethal systemic challenge in mice.[39] Anti-OMC antisera was shown to be highly protective, suggesting that vaccine antisera has the potential to treat established infections, including those caused by pan-resistant clinical isolates.[59] The same group showed that passive immunization with serum raised against inactivated cells protects mice from subsequent infection.[33]

Future directions

Strategies for developing new vaccines. Various approaches are being adopted for the development of effective vaccines against HAIs. For example, bacterial whole-cell vaccines, auxotrophic for D-glutamate, have been generated for *A. baumannii, P. aeruginosa* and *S. aureus*.[60] A classical polysaccharide approach is also being used to develop vaccines against *A. baumannii*.[61] The authors report that capsular polysaccharide-induced antibody provided 55% protection against challenge in an animal model. Combinatorial approaches using pan-genomics, core genomics, proteomics and reverse vaccinology are also being used to develop vaccines against *A. baumannii*.[62] *In silico* analysis

predicts the outer membrane putative pilus assembly protein FilF of *A. baumannii* to be protective.[63] A bacterial 'superglue' approach to develop VLPs as vaccine uses genetic fusion of SpyTag or SpyCatcher to the N-terminus and/or C-terminus of a phage capsid protein to form a stable, nonaggregated VLP.[64] Mixing of spy-VLPs with different vaccine antigens fused to SpyCatcher or SpyTag results in the formation of antigen-VLP complexes with coupling efficiencies ranging from 22% to 88%.

For hepatitis B virus, vaccination against which is problematic in patients with chronic kidney disease, an investigational vaccine with a toll-like receptor 9 agonist adjuvant (HBsAg-1018) appeared to be more sero-protective than a standard vaccine.[65]

Finally, clinical trials and modeling will be required to ascertain exactly who should receive vaccines for the prevention of HAIs and when they should receive such vaccines.

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Conflict of interest statement

E. David McIntosh is an employee of Takeda Pharmaceuticals International AG. The company is developing vaccines against dengue virus, Zika virus, norovirus, poliomyelitis and influenza.

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