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Vaccines for *Acinetobacter baumannii*: Thinking “out of the box”

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We are indeed fortunate that modern medicine continues to offer advancements that promise better and longer lives. Delivering on that promise depends on our ability to effectively prevent and treat bacterial infections that frequently arise as complications of medical interventions. *Acinetobacter baumannii* has emerged as a “successful” pathogen due to its ability to readily survive in the nosocomial environment and to display myriad mechanisms of antibiotic resistance¹. Infections caused by this organism are becoming extremely difficult to prevent and treat, jeopardizing the safety of hospitalized patients. Since infection control strategies have yielded limited benefit against the spread of *A. baumannii*, and new antibiotics active against multidrug resistant *A. baumannii* will not be available in the very near future, unconventional approaches are urgently needed to counter the threat posed by this pathogen.

Vaccines have long helped to reduce the burden of bacterial infection but, until now, have only seldom targeted nosocomial pathogens. In a commentary recently written by Pachon and McConnell, a cogent argument for the development of a vaccine to protect against *A. baumannii* is advanced. Guided by knowledge of the clinical syndromes caused by *A. baumannii*, the authors identify key populations that may benefit from prophylactic vaccination, such as patients supported by mechanical ventilation or who have sustained burns, and military personnel at risk for war-related trauma. The unpredictability of these events is recognized on economic grounds as an obstacle to plan an eventual immunization strategy. Furthermore, such a strategy must be balanced with the time required to achieve protective and durable immunity. In terms of developing an effective vaccine, the importance of selecting appropriate antigens is reviewed, including outer membrane and biofilm associated proteins, polysaccharides, and inactivated whole cells. In their analysis, Pachon and McConnell are careful to recognize obstacles that may stand in the way of a future vaccine against *A. baumannii*.

1. Is a vaccine a realistic hope against *A. baumannii*?

Unique challenges are readily foreseeable in developing such a vaccine. The ability of *A. baumannii* to cause infections in various anatomic sites, ranging from the central nervous system and urinary tracts in hospitalized patients with invasive devices, to severe respiratory and skin and soft tissue infections, suggests the presence of diverse virulence factors^{2,3}.

This feature of *A. baumannii*, as well as the MDR phenotype, indicates that its genome readily participates in horizontal gene transfer⁴. Therefore, protection from a single component vaccine targeting resistance or virulence determinants may be transient and elusive, and effectiveness may vary according to strain type and genotype. Nevertheless, a vaccine that targets even a limited number of *A. baumannii* strains may still prove useful. In the case of other nosocomial pathogens such as *Staphylococcus aureus* and community acquired pathogens such as the influenza virus and *Streptococcus pneumoniae*, mathematical models suggest that even a partially effective vaccine that favors susceptible strains may have an impact in limiting infections by antibiotic resistant strains⁵.

2. Who would be candidates for a vaccine?

Patients vulnerable to *A. baumannii* are often elderly, suffer multiple comorbidities, and are functionally impaired. Chronic inflammation and putative deficiencies in antigen presentation, humoral and cellular immunity may lead to poor vaccine responses⁶. This is especially true of the chronically ill patients residing in long-term care facilities who are exposed to the epidemic of MDR *A. baumannii* in the United States. In this regard, *A. baumannii* is not different from other infectious diseases agents that disproportionately impact the debilitated and the elderly. Therefore, strategies that are under investigation for vaccines against influenza and pneumococcal disease in these populations may prove useful in a future vaccine against *A. baumannii*. Perhaps the simplest approach to increase vaccine efficacy in the elderly is to increase the dose that is administered⁷. Although randomized controlled trials demonstrated an increase in the level of antibody response induced by high dose influenza vaccine, and pneumococcal conjugate vaccine^{8,9}, whether higher antibody titers translate into protective immunity and a lower incidence of infection remains to be seen. The use of Toll-like receptor (TLR)-ligands as adjuvants also offers exciting prospects to enhance the potency of vaccines administered to the elderly and chronically ill¹⁰.

Extensive surgery, severe trauma, burn injury and war have been associated with *A. baumannii* infection, making patients with these conditions candidates for a vaccine against *A. baumannii*. After severe trauma and burn injury the immune system suffers profound alterations with simultaneous increased expression of classical inflammatory, antiinflammatory and adaptive immunity genes¹¹. Additionally, physical injury related to these events may increase the expression of T-helper 2 lymphocytes which cause impaired cell mediated immunity and may disable critical components of protection against *A. baumannii*¹². Macrophage activation may suffer, impairing the host defense against *A. baumannii* infection through decreased phagocytosis and secretion of cytokines, which in turn may limit the recruitment of neutrophils to the site of infection and impair the clearance of *A. baumannii*^{13,14}.

3. Should a vaccine afford durable protection?

Under those circumstances, an immunogenic vaccine could be potentially undermined by the ability of *A. baumannii* to evade immune surveillance while provoking a destructive immune response. The possibility of such a scenario is illustrated by the recent experience with a vaccine directed against *S. aureus*, which did not reduce the rate of *S. aureus*

infections and may have caused worse outcomes when administered to patients soon after they underwent cardiovascular surgery¹⁵. A clear explanation for this phenomenon is not evident, but it can be speculated that the “original antigenic sin” of vaccination constrains subsequent immune responses after infection¹⁶. Similarly, data obtained by Wertheim *et al.* show that although *S. aureus* nasal carriers have a higher risk of developing *S. aureus* bacteremia, non-carriers with *S. aureus* bacteremia had a higher mortality risk¹⁷. Whether a vaccine against *A. baumannii* could have a negative impact on the morbidity of infection remains to be established. Given the transient nature of many of the conditions cited herein (trauma, surgery, burn, war casualties), the need for durable immunity may not be as great.

4. Can a vaccine be developed and implemented effectively?

An essential element in the development of a vaccine against *A. baumannii* is sufficient investment by manufacturers. A profit incentive needs to be apparent to justify that investment. Additionally, the economic incentive of vaccines has to exceed that from curative treatments (i.e., antibiotics). The United States Centers for Disease Control and Prevention estimate that 12000 patients are infected yearly with MDR *A. baumannii*, resulting in approximately 500 deaths¹⁸. This means that the market for antibiotics against MDR *A. baumannii* is very small, potentially favoring vaccines. Nevertheless, some analyses based on a higher prevalence of MDR *A. baumannii* suggest that a novel, single-pathogen agent focused on *A. baumannii* could prove beneficial and maintain costs below the usual thresholds used to define cost-effective therapies (\$50000/quality adjusted living years (QALY))¹⁹. Furthermore, under the current paradigm, antibiotics tend to have a broad spectrum of activity and target more than one organism, expanding their potential market. In fact, mathematical models simulating the decision-making process of regulators and payers result in lower justifiable prices for vaccines and in lower incentives in vaccine development²⁰. Not surprisingly, there is an apparent absence of investors who believe that an active vaccine approach is feasible, and thus all translational effort seems to be directed towards passive approaches.

Legitimate concerns exist about how to conduct the requisite large-scale clinical trials needed to prove the efficacy of a vaccine targeting *A. baumannii*. As mentioned above, the estimates of the burden of *A. baumannii* infection vary widely. For instance, when active surveillance for colonization with MDR *A. baumannii* was assessed among patients admitted to a medical intensive care unit in Maryland, United States, a prevalence of less than 1% was documented²¹. On the other hand, another study in Maryland focusing on patients both on acute care and long-term care facilities identified MDR *A. baumannii* in 34% of all mechanically ventilated patients²². Therefore, special care has to be devoted to site and patient selection, and inclusion and exclusion criteria, in order to recruit sufficient numbers of patients in a time-efficient manner. Although the introduction of rapid molecular diagnostic tests to determine the presence of MDR *A. baumannii* and other bacteria of interest may expedite the screening process and play a pivotal role in future vaccine trials, such applications still need further development in order to gain widespread use.

5. “Out of the box”

Notwithstanding these obstacles, the time is right for new approaches to mitigate the threat posed by *A. baumannii* to hospitalized patients. At the beginning of the global MDR *A. baumannii* epidemic, vaccines were regarded as a potential response to that particular challenge²³. Pachon and McConnell are preparing the field for a vaccine that protects against *A. baumannii* infection and colonization. They are compelled by the crisis of multidrug resistance among nosocomial pathogens, to think “out of the box”. We applaud these efforts. Similar exercises may also serve as the starting point to advance therapies against MDR pathogens by ushering new concepts of “combination chemo-immuno-therapy”: antibiotics coupled to vaccines, or antibodies conjugated with radioisotopes^{24,25}. Reverse vaccinology and harnessing advances in genomics, proteomics and bioinformatics may yield interesting targets²⁶. Lastly, modulating inflammation and enhancing phagocytosis may prove important²⁷. Regardless of the route followed, novel research directions are needed as we exhaust conventional options in our battle against MDR *A. baumannii*. Time may run out faster than we think.

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