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PERSPECTIVES

If Not Now, When? Nonserotype Pneumococcal Protein Vaccines

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The sudden emergence and global spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have greatly accelerated the adoption of novel vaccine strategies, which otherwise would have likely languished for years. In this light, vaccines for certain other pathogens could certainly benefit from reconsideration. One such pathogen is *Streptococcus pneumoniae* (pneumococcus), an encapsulated bacterium that can express >100 antigenically distinct serotypes. Current pneumococcal vaccines are based exclusively on capsular polysaccharide—either purified alone or conjugated to protein. Since the introduction of conjugate vaccines, the valence of pneumococcal vaccines has steadily increased, as has the associated complexity and cost of production. There are many pneumococcal proteins invariantly expressed across all serotypes, which have been shown to induce robust immune responses in animal models. These proteins could be readily produced using recombinant DNA technology or by mRNA technology currently used in SARS-CoV-2 vaccines. A door may be opening to new opportunities in affordable and broadly protective vaccines.

Keywords. *Streptococcus pneumoniae*; pneumococcus; pneumococcal vaccines; conjugate vaccines.

The success of coronavirus disease 2019 (COVID-19) vaccines has brought to question the approach to development of vaccines against other infectious diseases. Dr. Eric Lander, Director of the Office of Science and Technology Policy, is proposing the United States have a vaccine ready within 100 days of identifying the next pandemic outbreak [1]. As vaccine development for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has demonstrated, rapid deployment of vaccines for new pathogens can benefit from new technologies in design and delivery. However, vaccines for older, well-known pathogens have generally remained unchanged since the time of their introduction. The time may now be auspicious to reconsider how older, traditional vaccines may yield to improved versions derived from novel, alternative approaches. Vaccines for *Streptococcus pneumoniae* (pneumococcus) are prime examples of old and well-trodden approaches that are long overdue for reformulation in light how the field of host–pathogen interactions has progressed.

Pneumococcus is an opportunistic bacterial pathogen in humans that consists of >100 antigenically and biochemically distinct serotypes [2], most of which can cause human disease [3]. It remains the leading cause of community-acquired pneumonia and is a major cause of global mortality, particularly in young children [4]. Capsular polysaccharide (CP) is an important pneumococcal virulence factor and the basis for serotype classification. Variation in the linkage and monosaccharide composition of the CP defines the antigenicity of individual serotypes. Immunization with CPs associated with invasive disease protects in a very narrow, capsule-specific manner. Additionally, CP-based vaccines have 2 (among others) significant shortcomings: (1) there are >100 serotypes and (2) CP alone is poorly immunogenic in very young children who are at high risk for infection [5].

The immune system processes polysaccharide protein conjugate vaccines as peptide antigens and subsequently produces polysaccharide responses that more closely resemble those induced by proteins. Early in the 20th century, polysaccharides were found to be more immunogenic when covalently linked to a carrier protein [6]. This observation led to the licensing of a conjugate vaccine against *Haemophilus influenzae* type B (Hib) in 1990 for the United States. Conjugate vaccines for meningococcus and pneumococcus became available in the United States in 1999 and 2000, respectively. The Hib vaccine has been extremely effective, practically eliminating *H. influenzae* type B meningitis from young children in the United States. Meningococcal conjugate vaccines have been effective against the 4 serogroups contained in those vaccines. However, unlike these encapsulated pathogens, the diversity of pneumococcal serotypes that

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Table 1. Pneumococcal Vaccines

Vaccine	Manufacturer	Serotypes Included	Format
Pneumovax	Merck	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F	Purified polysaccharide
Prevnar 13	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F	Oligosaccharides conjugated to CRM_{197}
Prevnar 20	Pfizer	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, 33F	Oligosaccharides conjugated to CRM_{197}
Vaxneuvance	Merck	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F	Oligosaccharides conjugated to CRM_{197}

Prevnar 20 and Vaxneuvance have been approved by the FDA but are not commercially available.

Abbreviation: FDA, US Food and Drug Administration.

cause human disease is much greater, making conjugate approaches to vaccines extremely complex and costly.

Increasing numbers of pneumococcal serotypes have been identified since the introduction of the first pneumococcal conjugate vaccine (PCV) in 2000 (Table 1). Pfizer recently won approval for a third-generation PCV from the US Food and Drug Administration (FDA) [7]. This PCV has 20 serotype-specific CPs conjugated to the Diphtheria CRM_{197} Protein. The vaccine covers the most common 20 serotypes associated with invasive pneumococcal disease (IPD) and pneumococcal pneumonia. In addition, Merck has announced FDA approval of a 15-valent conjugate vaccine [8]. Shortly after the release of the first-generation 7-valent PCV in 2000, it became evident that this vaccine applied selective pressure to shift IPD to serotypes not contained in the 7-valent vaccine [9, 10]. Thus, serotypes 19A, 7F, and 6C, which were not contained in the 7-valent PCV, became a more frequent cause of IPD. This phenomenon of serotype replacement has now twice led to increases in the valency of PCVs in an effort to keep chasing the latest pneumococcal epidemiology [11]. In addition, the 13-valent PCV was ineffective against serotype 3, which remains the most common cause of IPD in the United States. Consequently, the complexity and cost of PCVs have increased in parallel.

We are now 21 years on with the development PCV. The current PCVs have been highly effective against IPD serotypes contained in the vaccine. This success is the reason for expanding the PCVs. However, cost prohibits the use of PCVs in much of the developing world, and it is only through philanthropic endeavors that PCVs have been available to global populations at high risk for IPD.

The current strategy of conjugating increasing numbers of CPs to develop PCVs that are ever more complex continues to put pressure on pneumococcus, at least in the near term. Selective removal of capsular types from the upper respiratory tract by vaccine-induced immune responses creates niches that will be filled, largely, by nonvaccine serotypes [12]. Whether these serotypes have the capacity to cause invasive disease to the same extent as serotypes in the vaccine is a question that remains to be answered. However, if history teaches us anything, we should be very circumspect about dismissing these currently uncommon serotypes. A highly desirable alternative to conjugate vaccines would be a nonpolysaccharide pneumococcal vaccine with broad coverage against all pneumococcal serotypes. There has long been interest in and growing support for developing such a vaccine based on pneumococcal proteins. Pneumococcal proteins with vaccine potential have been extensively studied [13] and proposed as vaccine candidates based on their distribution among all capsule types and their ability to elicit protective immune responses against systemic infection in animal models. Such a vaccine would likely be immunogenic in young children, be less expensive to produce, and elicit strong immunological memory at least of the magnitude seen with conjugated CP. Further, it could be possible to formulate an mRNA vaccine coding for a protein or multiple proteins similar to those currently available for SARS-CoV-2.

An alternative approach to pneumococcal vaccines stands to greatly reduce the disease burden, particularly in the developing world. Nonetheless, development of a new vaccine in the presence of an effective vaccine will face some hurdles. Conjugate vaccines have proven highly effective against carriage and invasive infection for the specific serotypes they target. Additionally, there has always been reluctance to consider antigens other than polysaccharide for encapsulated pathogens. Clearly, PCVs have had an impact on pneumococcal disease in developed countries. However, it is time to step up to approaches that are more affordable and can cover a wider variety of serotypes without constant reformulation and associated complexity and cost. Much like efforts to develop a universal flu vaccine, producing a noncapsular pneumococcal vaccine with broad coverage has far-reaching implications. If not now, when?

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