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Review

Vaccines for prevention of group B meningococcal disease: Not your father's vaccines

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ABSTRACT

For decades, there was no licensed vaccine for prevention of endemic capsular group B meningococcal disease, despite the availability of vaccines for prevention of the other most common meningococcal capsular groups. Recently, however, two new vaccines have been licensed for prevention of group B disease. Although immunogenic and considered to have an acceptable safety profile, there are many scientific unknowns about these vaccines, including effectiveness against antigenically diverse endemic meningococcal strains; duration of protection; whether they provide any herd protection; and whether there will be meningococcal antigenic changes that will diminish effectiveness over time. In addition, these vaccines present societal dilemmas that could influence how they are used in the U.S., including high vaccine cost in the face of a historically low incidence of meningococcal disease. These issues are discussed in this review.

1. Introduction

During the past year, two new vaccines to prevent capsular group B meningococcal disease have been licensed. These vaccines are different from other licensed vaccines: the vaccine antigens were identified using reverse vaccinology, they have been unusually painstaking to develop, it has been technically difficult to estimate potential impact, and actual impact will be unusually challenging to monitor post-licensure.

The licensure of these vaccines is an exciting and much-anticipated development. However, many important scientific questions remain unanswered about the potential public health impact that can only be answered post-licensure. In addition, the relatively low incidence of group B disease, in combination with the high cost of the vaccines in the U.S., has raised concern that these vaccines may not be widely used.

In this review, I will give a brief overview of meningococcal disease epidemiology and the two licensed group B vaccines and then discuss some salient scientific and societal issues that may influence their impact and how widely they will be used. This is meant to be an overview of some of the challenges in vaccine prevention of group B meningococcal disease; reviews of group B vaccines themselves have been published elsewhere [1–3]. Although the vaccines are technically not exclusively group B vaccines because the proteins they employ are present in meningococci independent of capsular group, for simplicity I refer to them as group B vaccines throughout this review.

2. Background

2.1. Meningococcal disease and epidemiology

Neisseria meningitidis is a major cause of meningitis and other invasive bacterial infections globally. There are 12 known meningococcal polysaccharide capsular groups yet six, namely A, B, C, W, X, and Y cause almost all infections. The case fatality rate is around 10–15% and permanent sequelae are common [4–7]. Transmission of *N. meningitidis* occurs through contact with respiratory secretions of colonized persons; pharyngeal carriage rates vary widely by time and geography but typically are highest in adolescents and young adults [8–11].

Because of both the naturally dynamic nature of meningococcal disease epidemiology and the introduction of conjugate vaccines, the epidemiology of meningococcal disease has changed dramatically over the past few years. In the U.S., there has been a huge decline in the incidence of meningococcal disease since

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an incidence peak in the mid-1990s. The prevalence of meningococcal carriage among U.S. high school students has also declined [11,12]. Most of the decline in incidence was natural because it preceded the routine use of quadrivalent conjugate vaccine in 11–18 year olds in 2005 [13]. In addition, the incidence of group B infections has also declined, which would not have been influenced by conjugate vaccine [6]. The reasons for the decline are unknown but are likely multifactorial, variable by geographic location, and non-independent, and include reductions in both active and passive tobacco smoking, changing patterns of antibiotic use, use of influenza vaccines, declines in meningococcal carriage, and lack of development of novel antigenic variants among virulent strains to which the population is not immune. The incidence of meningococcal disease is naturally cyclical and it is unknown whether the incidence will increase in the future.

As a result of this natural decline and the routine use of quadrivalent conjugate vaccines in adolescents, the current annual burden of meningococcal disease in the U.S. is at historically low levels, approximately 0.14 cases per 100,000 population, in contrast to the most recent peak of 1.3 cases per 100,000 population in 1997. Meningococcal disease incidence is approximately ten-fold higher in the U.K. than in the U.S. [14].

In the U.S., approximately a third of all cases are caused by group B. However, the proportion varies by age group, with two thirds of cases among infants under 1-year-old and 39–45% of cases among 11–22 year olds being caused by group B [15]. During 2010–2012, there were an estimated 48–56 annual group B cases among 11–24 year olds, down from 161 during 1997–1999 [7]; the case fatality rate in this age group is approximately 10%, somewhat lower than for groups C and Y. About a third of cases among 18–23 year olds occur among persons attending college, a high-risk group that historically was targeted for meningococcal immunization in the U.S. [16–18]. University-associated outbreaks, traditionally caused by group C strains, are now predominantly caused by group B and are becoming relatively common [19,20]. Since 2013, there have been group B outbreaks at Princeton University, University of California-Santa Barbara, Providence College, and University of Oregon.

Group B strains are also responsible for a substantial proportion of meningococcal disease cases in many other countries. In those in which monovalent group C vaccines have been introduced, group B disease has become a predominant cause of meningococcal disease. For example, over 80% of cases in the U.K. and Australia are caused by group B strains [21,22].

2.2. Meningococcal polysaccharide and conjugate vaccines

Until very recently, all meningococcal vaccines in routine use have been either capsular polysaccharide or capsular polysaccharide-protein conjugate vaccines. Meningococcal polysaccharide vaccines have been available for decades; the advent of polysaccharide–protein conjugate vaccines has been more recent. Polysaccharide vaccines are limited by lack of efficacy in infants and lack of substantial herd protection. Therefore, polysaccharide vaccines were generally used for control of outbreaks and epidemics and immunization of high-risk persons [23]. Given the immunologic superiority of conjugate vaccines, over the past 15 years they have been replacing polysaccharide vaccines and have been introduced into the routine immunization programs of many countries [24,25].

There are multiple licensed conjugate vaccines that variably cover capsular groups A, C, W, and Y. Until recently, however, a glaring problem with the meningococcal vaccine armamentarium has been the lack of vaccines to prevent group B disease. This is because the group B polysaccharide polysialic acid structure, α-2,8-linked N-acetylneuraminic acid, is antigenically similar to human neural tissue, which has raised concerns about its use as a vaccine antigen. Therefore, group B vaccine development has focused on antigenic meningococcal outer membrane proteins and has lagged far behind the conjugate vaccines [26].

Over the past 15 years, meningococcal conjugate vaccines have had an impressive impact in countries that have introduced them. For example, monovalent capsular group C conjugate vaccines have led to huge reductions in group C disease in the United Kingdom and other countries [27–29]. MenAfriVac, a monovalent group A conjugate vaccine that is being introduced at a price of $0.40 per dose into the meningitidis belt of sub-Saharan Africa, has already had a dramatic impact on the epidemiology of group A disease [30–32].

A substantial proportion of the public health impact of meningococcal conjugate vaccines has been mediated through herd protection that results from vaccine-induced reductions in pharyngeal carriage [33]. For example, monovalent group C conjugate vaccines led to a 66% and 75% reduction in group C carriage in U.K. adolescents by one to two years, respectively, after mass immunization [34,35]. Similarly, MenAfriVac led to a dramatic reduction in group A carriage when high vaccine coverage rates were achieved in African villages [36]. Vaccine-induced reductions in carriage have generally been accompanied by large reductions in the incidence of meningococcal disease among the unimmunized [37].

2.3. Group B vaccines

Outer membrane vesicle vaccines, in which the outer membrane protein PorA is the primary antigen, have been used to control outbreaks of group B disease for many years [38,39]. However, immunity to these vaccines is specific to the outbreak strain PorA type and they are therefore not useful for prevention of the antigenically very diverse strains that cause endemic group B disease [40,41]. Therefore, efforts to develop group B vaccines have focused on relatively conserved antigenic outer membrane proteins.

There are two recently licensed group B vaccines; both utilize meningococcal outer membrane proteins as their antigens. Antigenic discovery was accomplished through reverse vaccinology, a process that began over 15 years ago with the mining of the meningococcal genome for possible vaccine targets [42,43]. Both vaccines exhibit substantial reactogenicity but are considered to have an acceptable safety profile. Licensure was based on safety and immunogenicity; no efficacy data are available for either vaccine because of the difficulty in conducting a clinical trial for a low-incidence infection. Immunogenicity was determined using serum bactericidal assays with human complement as an immunologic marker of protection, which have been validated for tailor-made outer membrane vesicle-based vaccines that use PorA as the main antigen [38,44,45].

One vaccine, (4CMenB, Bexsero, Novartis, whose vaccine business, excluding influenza, was recently acquired by GlaxoSmithKline) is licensed for infant and adolescents in Europe, Canada, Australia, and elsewhere and in the U.S. as a two-dose schedule for 10–25 year olds. It is a cocktail of one variant each of factor H binding protein (FHbp), NadA, *Neisseria* heparin binding antigen (NHBA), and the outer membrane vesicles that contain the New Zealand outbreak strain PorA serosubtype P1.4. The second vaccine (rLP2086, Trumenba, Pfizer), which is licensed in the U.S. as a 3-dose schedule for ages 10–25 years, utilizes one variant of lipidated FHbp from each of the two FHbp subfamilies.

FHbp is an important meningococcal virulence factor that binds human factor H, which down-regulates the alternative complement pathway. FHbp has been described as a conserved antigen but exhibits substantial antigenic diversity and has been classified into two sub-families or 3 variant groups, each with many subvariants; antibody response is sub-family specific [46,47]. FHbp