The impact of a meningococcal protein-based serogroup B vaccine on serogroup W invasive disease in children.

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Neisseria meningitidis, which causes invasive meningococcal (IMD) disease, is an 'accidental pathogen': despite a lifestyle dependent on asymptomatic colonisation of the human pharynx, it paradoxically remains a globally important cause of morbidity and mortality [1]. While all age groups may be affected, IMD prevalence is highest in young children and adolescents [2]. Controlling IMD is challenging due to its unpredictable occurrence and the diversity of meningococci, which is exacerbated by high rates of horizontal genetic exchange within the species [3].

Acapsulate meningococci are common in carriage, but very rarely invade, with almost all IMD caused by organisms expressing one of six of the twelve known capsular polysaccharides, corresponding to serogroups A, B, C, W, X, and Y. In addition, some meningococcal lineages, identified as clonal complexes, are much more likely to cause IMD and are known as the 'hyperinvasive' meningococci [1]. Horizontal genetic exchange confers on meningococci an ability to change capsular group, leading to the emergence and global spread of hyperinvasive meningococci with different serogroup:clonal complex (cc) combinations [3]. For example, C:cc11, B:cc11, and W:cc11 meningococci have all caused epidemics and pandemics in the past 100 years [4].

Since the 1990s, major advances have been made in IMD prevention and control by the implementation of conjugate-polysaccharide vaccines that target serogroups A, C, W, and Y (MenACWY vaccines) [5]. Unfortunately, conjugate B polysaccharide vaccines have not been developed to date, as the polysaccharide is structurally identical to the polysialic acid decorating human fetal neural cells, leading to poor immunogenicity and a theoretical risk of autoimmunity [6,7]. Consequently, protein-based vaccines have been developed as an alternative approach. The licenced multi-component, protein-based recombinant vaccine

4CMenB (Bexsero®) is composed of (i) the MeNZB outer membrane vesicle (OMV) vaccine containing, among other constituents, porin PorA P1.4 [8], combined with (ii) three recombinant outer membrane proteins (factor H binding protein, fHbp; Neisserial adhesin A, NadA; and Neisserial Heparin Binding Antigen, NHBA). The four major proteins are thought to play a principal role in generating immunity, with the contribution of the other OMV components incompletely characterised [9].

All meningococci, and indeed other *Neisseria* including the gonococcus, potentially contain one or more of the 4CMenB vaccine major and minor components. This leads to the tantalising question of the extent to which this, and other, protein based B vaccines, can provide wider protection i.e. to be 'universal' meningococcal or even gonococcal vaccines. Laboratory data suggest that at least a degree of cross-protection exists, as 4CMenB-induced antibodies are bactericidal against a hyperinvasive meningococcal W:cc11 global outbreak strain [10]. There is also a suggestion of some effectiveness of the meningococcal B OMV vaccine used during the New Zealand meningococcal epidemic, (MeNZB) against gonococcal infection [11].

The implementation of MeNZB and 4CMenB in national programmes has enabled investigations of their impact by post-implementation disease surveillance. One such study, providing evidence of an impact of 4CMenB immunisation on serogroup W IMD in the United Kingdom (UK), is presented by Ladhani et al in their paper "First real world evidence of meningococcal group B vaccine, 4CMenB, protection against meningococcal group W disease; prospective enhanced national surveillance, England"[12]. This analysis is especially valuable as the authors have endeavoured to distinguish the direct impact of 4CMenB in infants with the anticipated herd immunity impact arising from a concomitant conjugate

MenACWY immunisation programme in adolescents [13]. This is important as (i) most asymptomatic meningococcal transmission in the UK is in adolescents and (ii) a major part of the success of the monovalent meningococcal conjugate polysaccharide vaccines globally has been their exceptionally strong herd immunity effect: a direct consequence of their impact on the carriage of capsulate organisms [5].

The direct effect of an estimated 69% reduction in group W IMD in cohorts fully-vaccinated with 4CMenB is very large for a non-specific effect, comparing favourably with the 75% reduction of group B IMD estimated in the same cohorts [14]. Although this degree of direct protection is impressive, there was an even greater estimated impact on infant group W IMD from the herd immunity consequent from the adolescent MenACWY vaccine program. Herd immunity resulting from meningococcal conjugate polysaccharide vaccines was first shown following the MenC conjugate vaccine program, introduced in the UK in 1999 [15] to combat a C:cc11 epidemic [16, 17]. Monovalent conjugate meningococcal A vaccines have also been shown to generate herd immunity through their impact on carriage of A:cc5 meningococci [18]; however, to our knowledge, Ladhani *et al.* provide the first convincing published evidence for a herd immunity effect for the quadivalent MenACWY conjugate vaccine.

Due to the naturally dynamic nature of epidemics caused by hyperinvasive meningococci, there is some uncertainty around the estimates by Ladhani *et al.*, which consequently analysed a conservative and an extreme scenario. Further, vaccine impact is dependent, not only on the presence of vaccine antigens, but also on their expression, which may change over time, potentially as a consequence of vaccine pressure. While W:cc11 meningococci frequently express antigens immunologically cross-reactive with 4CMenB components, this

is not true for serogroup W meningococci belonging to other clonal complexes. Fortunately, the W:cc11 meningococci causing the pandemic during the UK introduction of the meningococcal ACWY and 4CMenB vaccines was susceptible to immune responses elicited by both vaccines. Consequently, the impressive vaccine impact measured may be optimistically high with respect to protection against all serogroup W IMD. Ultimately, however, Ladhani *et al.* indicate that both meningococcal ACWY and 4CMenB were effective in preventing cases of group W IMD in young children. This impact is clinically significant as W:cc11 IMD is: (i) associated with a higher case fatality rate than other capsular groups; (ii) more difficult to diagnose, due to non-classical presenting symptoms; and (iii) associated with more severe disease syndromes [4].

When the 4CMenB vaccine infant program was introduced in the UK, the Joint Committee on Vaccination and Immunisation anticipated that a 4CMenB program might also protect infants against W:cc11 [13]. This anticipation has been substantiated, supporting a broader protection against IMD by 4CMenB immunisation. As 4CMenB does not affect carriage of capsulate meningococci, and cannot therefore generate a herd immunity effect [19], direct protection against other disease causing serogroups is an important finding. These data will contribute to cost effectiveness evaluation of introduction of meningococcal B vaccine programs globally.

The protein-based meningococcal vaccine developed by Pfizer (Trumenba®) contains two variants of the outer membrane protein, fHbp, one of which is also included in 4CMenB [20]. The fHbp gene has been shown to be present in all meningococcal C isolates from meningococcal C cases in the USA, suggesting this vaccine may also be effective in protecting against IMD caused by meningococci with diverse capsular serogroups. Although

the focus of the evaluation of this vaccine to date has been on group B disease, there is the potential for a bivalent fHBP vaccine to provide broader protection [21].

A single vaccine against all meningococcal groups causing disease remains an attractive ultimate goal. Of continuing interest is the generation of evidence of impact on other serogroups classically associated with disease including not only A, C, Y, and X, but also emerging groups more rarely associated with disease, such as group E [22]. Ladhani *et al.* were unable to interrogate these other capsular groups, due to the low numbers of cases in the UK, but this may prove possible in other settings. In conclusion, as clinical trial development of combination ACWY+B meningococcal vaccines progresses, existing meningococcal B vaccines may offer direct protection beyond their design remit against a range of IMD-associated hyperinvasive meningococci.

Potential Conflicts of Interest

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