

# Letter to the editor: Importance of serum bactericidal activity for estimating the breadth of protection for new meningococcal vaccines

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**To the editor:** Brehony and colleagues [1] recently reported their investigation of six *Neisseria meningitidis* serogroup B (NmB) vaccines by deducing the prevalence of the vaccine components in isolates represented in publicly accessible sequence repositories of NmB. Based on the frequency of exact match of deduced peptide sequences in the databases to at least one component of each vaccine, and by assessing published data, the authors estimated the breadth of strain coverage. Their findings led them to conclude that meningococcal vaccines with multiple antigens would provide greater breadth of coverage against meningococcal disease. However, their evaluation did not incorporate important information about the diversity of factor H binding protein (fHBP) variants and the demonstration of protective immune responses against antigenically diverse MnB invasive disease strains following vaccination with Trumenba. Consequently, the authors' analysis underestimates the potential for vaccine benefit provided by this licensed vaccine. We provide here a description of published data, including results that use the recognised correlate of protection for NmB, serum bactericidal activity measured using serum bactericidal assays performed with human complement (hSBA) [2,3]. This correlation was first validated in large clinical studies using outer membrane vesicle (OMV) vaccines that confer protection via induction of immune response directed against the PorA antigen of NmB [4]. Protection is essentially restricted to strains expressing the matched PorA sequence in the vaccine [5], thus the approach used by the authors to estimate vaccine strain coverage is appropriate for PorA based vaccines, such as the experimental vaccine NonaMen, as described.

However, this approach is not sufficient for estimation of vaccine protection for Trumenba, which was licensed in the United States in 2014. The vaccine is composed

of two lipidated, recombinant fHBPs: 3.45 (subfamily A: A05) and 1.55 (subfamily B: B01). Individual strains of NmB express a single fHBP variant which may be either subfamily A or subfamily B. Preclinical studies demonstrated that hSBA responses induced by a single fHBP were greater against invasive disease strains expressing fHBP of the same subfamily than against those expressing a variant of the other subfamily, and a vaccine that contained one lipidated protein from each subfamily generated antibodies that killed MnB strains regardless of the fHBP variant they expressed [6,7]. In clinical studies in subjects aged 18 months to 62 years, Trumenba (and an earlier formulation of the vaccine) induced hSBA against invasive disease strains that expressed fHBP variants heterologous to the vaccine antigen and represented the antigenic diversity of fHBP [8-14]. These data demonstrate that the bactericidal response elicited by this bivalent single antigen vaccine is directed against a broad and diverse range of fHBP expressed by NmB and is not limited to NmB strains that express fHBP homologous (an exact match) to the vaccine antigens. The hSBA responses were also observed not to be restricted to NmB strains within specific clonal complexes. These data demonstrate the importance of inclusion of hSBA results for assessment of the potential breadth of protection provided by NmB vaccines.

In summary, published data using hSBA, the correlate of protection against *N. meningitidis*, indicate that the breadth of protection for Trumenba is broader than can be extrapolated from reference only to the distribution of the matched vaccine antigens present in disease-causing strains of NmB. While we await direct, post-licensure assessments of vaccine effectiveness against clinical disease, the estimation of potential vaccine benefit should consider results of hSBA assays performed with NmB test strains that express antigens

heterologous to vaccine components, rather than reliance only on exact antigenic sequence matches and assays that do not measure bactericidal activity.

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## Conflict of interest

ASA, JJE, JLP, PB, LJY, and KUJ are all employees of Pfizer Inc.

## Authors' contributions

All authors were involved in drafting or editing the manuscript.

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