AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology

COMMENTARY

Unveiling New Aspects of Meningococcal Carriage and Disease Prevention

Magnus Gottfredsson

Department of Infectious Diseases, Landspitali University Hospital, and Faculty of Medicine, School of Health Sciences, University of Iceland, Reykjavik, Iceland

Recently, two protein-based vaccines have been approved for the prevention of invasive meningococcal disease caused by *Neisseria meningitidis* serogroup B (MenB). It is therefore important to study carefully if and how these pathogens respond to widespread vaccination. Traditionally, meningococci have been classified on the basis of capsular phenotypes, but variable levels of capsule expression can influence the results, mainly among MenB strains. In this issue, Jones and colleagues (J Clin Microbiol 54:25–34, 2016, http://dx.doi.org/10.1128/JCM.01447-15) compare whole-genome sequencing to traditional phenotypic methods of classifying meningococci. They demonstrate that for MenB in particular, sequencing-based methods are far superior to traditional methods, especially when it comes to characterizing carriage isolates. This has important implications for future surveillance.

The use of highly immunogenic protein-conjugated capsule-specific vaccines against *Neisseria meningitidis* serogroups A, C, W, and Y has lowered the incidence of invasive meningococcal disease (IMD) in several countries over the past 10 to 15 years. Nevertheless, IMD remains a significant cause of morbidity and mortality, especially in children and young adults worldwide. Meningococci, including *N. meningitidis* serogroup B (MenB), are commonly carried in the throats of asymptomatic young people (1). It is believed that carriage strains are the main source of outbreaks of IMD, although the mechanisms involved are poorly understood. The development of an effective vaccine against the MenB capsule has been hampered by the low immunogenicity of the B capsular polysaccharide. In addition, structural similarities exist between the serogroup B polysaccharide capsule and neural cell adhesion molecules, raising concerns about the potential cross-reactivity to neural tissues of antibodies elicited by such a vaccine (2). Development of a vaccine based on the serogroup B capsule has thus been deemed unfeasible, although no indication of increased neurologic effects has been observed following natural infections with MenB (3).

In 2000, a seminal study was published where whole-genome sequencing (WGS) of a virulent MenB isolate was performed in order to identify potential vaccine candidates (4). By using this "reverse vaccinology" approach, the investigators identified proteins that are expressed at the bacterial surface, are conserved across a range of strains, and induce an effective antibody response (4). The results provided the foundation for the subsequent development of novel protein-based vaccines; two such vaccines have recently been licensed.

The former of the two, Bexsero (Novartis Vaccines and Diagnostics) is a four-component vaccine directed against MenB (4CMenB). It includes a combination of recombinant *N. meningitidis* proteins, the NHBA fusion protein (derived from the *Neisseria* heparin-binding antigen), NadA (derived from neisserial adhesin A), the fHbp fusion protein (derived from factor H-binding protein), and outer membrane vesicles containing the PorA P1.4 protein, produced by the fermentation of New Zealand MenB strain NZ98/254 (5). Importantly, these proteins are not specific to serogroup B and thus one intriguing question relates to their ability to lower the rate of meningococcal carriage, irrespective of serogroups. 4CMenB was licensed in the United States in January 2015 for use in persons 10 to 25 years old. Approval of the vaccine was based on the demonstration of an immune response, as measured by serum bactericidal activity against three MenB strains representative of the strains prevalent in the United States. However, the effectiveness of the vaccine against diverse serogroup B strains has not been confirmed (5). Among college students in the United Kingdom, the vaccine has been shown to reduce carriage across serogroups (6).

Trumenba (Pfizer), or MenB-FHbp, another vaccine against MenB that was licensed by the U.S. FDA in October 2014, is composed of two recombinant lipidated factor H-binding protein (fHbp) variants from MenB, one from fHbp subfamily A and one from subfamily B (A05 and B01, respectively) (7). According to the FDA grading of recommendations assessment, development, and evaluation, both vaccines received overall evidence type 2 (moderate level of evidence) for use in outbreak settings and type 3 (low level of evidence) for use in persons at increased risk of serogroup B meningococcal disease (8). The Advisory Committee on Immunization Practices in the United States has recommended the use of MenB vaccines among persons ≥10 years old who are at increased risk of IMD caused by this serogroup. This includes those with complement deficiencies, anatomic or functional asplenia, or routine exposure to meningococci in the laboratory and those who are at an increased risk because of a disease outbreak (category A recommendation). Additionally, vaccine series may be administered to adolescents and young adults 16 to 23 years old to provide short-term protection against most strains of

Accepted manuscript posted online 18 November 2015

Citation Gottfredsson M. 2016. Unveiling new aspects of meningococcal carriage and disease prevention. J Clin Microbiol 54:2–4. doi:10.1128/JCM.02776-15.

Editor: D. J. Diekema

Address correspondence to magnusgo@landspitali.is.

MenB (category B recommendation). The preferred age range for vaccination against MenB is 16 to 18 years (9).

In practice, the susceptibility of meningococci following vaccination with these novel protein-based vaccines will be determined by the presence and level of antigen expression at the bacterial surface, as well as the titer of complement-binding antibodies directed against those antigens. It has been shown that the expression of the four meningococcal vaccine antigens used in 4CMenB can change over time in the same individual (1). Therefore, the long-term success of the new vaccines likely depends on their ability to suppress meningococcal colonization and the generation of virulent escape mutants among the colonizing meningococcal strains. Recent studies using a meningococcal antigen typing system suggest that the recent coverage of 4CMenB against European invasive isolates may be close to 78% (10).

In contrast to invasive strains, those found among asymptomatic carriers may not express a capsule, despite having the requisite capsular genes, because of phase variation. This makes the standard phenotypic (antibody-based) methods less sensitive for strain characterization. This lack of sensitivity has potential implications for the surveillance of meningococcal carriage following vaccination with the novel MenB vaccines. In this issue, Jones and coworkers present the results of their comparative study of phenotypic and genotypic approaches to *N. meningitidis* capsule typing (11). The investigators looked at invasive ($n = 97$) and carriage ($n = 93$) isolates from different populations, geographic locations, and time periods. Overall, the agreement between phenotypic and genotypic methods was good for the invasive strains. On the other hand, 35 (38%) of the carriage isolates had a complete *cps* operon and 44 (47%) were capable of expressing a capsule according to the sequence analysis and in theory should be serogroupable by phenotypic methods. However, phenotypic methods correctly identified the serogroups of only 17 to 19 (39 to 43%) of the 44 strains. No genetic clues were provided as to the mechanism involved among organisms with an intact *cps* operon that did not seem to express a capsule. Interestingly, the phenotypic methods performed poorly when it came to the MenB isolates, correctly identifying only 4 to 6 of 17 serogroup B carriage strains. Thus, antibody-based methods seem to be inherently insensitive for the characterization of these strains, which could be the source of outbreaks. It would be of interest to analyze the data from this study with respect to the presence of the genes encoding NHBA, NadA, and fHbp. Similarly, the data of Jones et al. (11) could also provide clues as to why MenB strains, in particular, seem to express their polysaccharide capsule less avidly during carriage. This could be the result of a combination of phase variation and deletions or insertions in the *cps* locus. The WGS data generated by the investigators, along with additional data from other collections of isolates, could potentially give a more detailed picture of this phenomenon. Performing WGS is becoming more economically feasible as the cost continues to fall, gradually replacing reverse transcription-PCR and multilocus sequence typing. Indeed, the analysis and interpretation of sequence data are becoming more significant rate-limiting steps in meningococcal genomics than the cost of sequencing. As an added benefit of these endeavors, further studies incorporating WGS coupled with transcriptomics and proteomics may shed some light on the pathogenic mechanisms involved in IMD, although the lack of a good animal model still poses a constant challenge to basic research in this field.

With the introduction and use of the two new MenB vaccines on a large scale, monitoring studies will be of great importance in assessing their effects on carriage, meningococcal population structure, vaccine antigen variants, and herd immunity. Currently, studies in the United Kingdom indicate that 31 to 34% of young university students carry meningococci in their throats, 9 to 10% carry MenB, and 7% carry serogroup Y (6). As of September 2015 in the United Kingdom, babies born on 1 July 2015 are offered 4CMenB as part of the routine immunization schedule and a catch-up campaign will be offered to babies born on 1 May or later (12). The vaccine will be given at 2, 4, and 12 months of age (13). Simultaneously, The Meningitis Research Foundation Meningococcus Genome Library in the United Kingdom will perform WGS of invasive strains for epidemiological surveillance (12, 14). This is crucial for effective control and understanding of the evolutionary trends resulting from vaccination (14). Information on meningococcal population structure and vaccine antigen variants will, it is hoped, become available in close-to-real time, facilitating genomic pathogen surveillance and improving our responses to this devastating infection.

REFERENCES

1. **Gasparini R, Comanducci M, Amicizia D, Ansaldi F, Canepa P, Orsi A, Icardi G, Rizzitelli E, De Angelis G, Bambini S, Moschioni M, Comandi S, Simmini I, Boccadifuoco G, Brunelli B, Giuliani MM, Pizza M, Panatto D.** 2014. Molecular and serological diversity of *Neisseria meningitidis* carrier strains isolated from Italian students aged 14 to 22 years. J Clin Microbiol **52:**1901–1910. http://dx.doi.org/10.1128/JCM.03584-13.
2. **Finne J, Leinonen M, Mäkelä PH.** 1983. Antigenic similarities between brain components and bacteria causing meningitis. Implications for vaccine development and pathogenesis. Lancet **ii:**355–357.
3. **Gottfredsson M, Reynisson IK, Ingvarsson RF, Kristjansdottir H, Nardini MV, Sigurdsson JF, Schneerson R, Robbins JB, Miller MA.** 2011. Comparative long-term adverse effects elicited by invasive group B and C meningococcal infections. Clin Infect Dis **53:**e117-24. http://dx.doi.org/10.1093/cid/cir500.
4. **Pizza M, Scarlato V, Masignani V, Giuliani MM, Aricò B, Comanducci M, Jennings GT, Baldi L, Bartolini E, Capecchi B, Galeotti CL, Luzzi E, Manetti R, Marchetti E, Mora M, Nuti S, Ratti G, Santini L, Savino S, Scarselli M, Storni E, Zuo P, Broeker M, Hundt E, Knapp B, Blair E, Mason T, Tettelin H, Hood DW, Jeffries AC, Saunders NJ, Granoff DM, Venter JC, Moxon ER, Grandi G, Rappuoli R.** 2000. Identification of vaccine candidates against serogroup B meningococcus by whole-genome sequencing. Science **287:**1816–1820.
5. **Food and Drug Administration.** 2015. Highlights of prescribing information for Bexsero. Food and Drug Administration, Silver Spring, MD. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM431447.pdf. Accessed 4 November 2015.
6. **Read RC, Baxter D, Chadwick DR, Faust SN, Finn A, Gordon SB, Heath PT, Lewis DJ, Pollard AJ, Turner DP, Bazaz R, Ganguli A, Havelock T, Neal KR, Okike IO, Morales-Aza B, Patel K, Snape MD, Williams J, Gilchrist S, Gray SJ, Maiden MC, Toneatto D, Wang H, McCarthy M, Dull PM, Borrow R.** 2014. Effect of a quadrivalent meningococcal ACWY glycoconjugate or a serogroup B meningococcal vaccine on meningococcal carriage: an observer-blind, phase 3 randomised clinical trial. Lancet **384:**2123–2131. http://dx.doi.org/10.1016/S0140-6736(14)60842-4.
7. **Food and Drug Administration.** 2015. Highlights of prescribing information for Trumenba. Food and Drug Administration, Silver Spring, MD. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM421139.pdf. Accessed 4 November 2015.
8. **Centers for Disease Control and Prevention.** 2015. Grading of recommendations assessment, development, and evaluation (GRADE): use of serogroup B meningococcal (MenB) vaccines in persons at increased risk

for serogroup B meningococcal disease. Centers for Disease Control and Prevention, Atlanta, GA. http://www.cdc.gov/vaccines/acip/recs/grade/mening-serogroup-b.pdf. Accessed 4 November 2015.

9. **MacNeil JR, Rubin L, Folaranmi T, Ortega-Sanchez IR, Patel M, Martin SW.** 2015. Use of serogroup B meningococcal vaccines in adolescents and young adults: recommendations of the Advisory Committee on Immunization Practices, 2015. MMWR Morb Mortal Wkly Rep **64:**1171–1176. http://dx.doi.org/10.15585/mmwr.mm6441a3.
10. **Vogel U, Taha MK, Vazquez JA, Findlow J, Claus H, Stefanelli P, Caugant DA, Kriz P, Abad R, Bambini S, Carannante A, Deghmane AE, Fazio C, Frosch M, Frosi G, Gilchrist S, Giuliani MM, Hong E, Ledroit M, Lovaglio PG, Lucidarme J, Musilek M, Muzzi A, Oksnes J, Rigat F, Orlandi L, Stella M, Thompson D, Pizza M, Rappuoli R, Serruto D, Comanducci M, Boccadifuoco G, Donnelly JJ, Medini D, Borrow R.** 2013. Predicted strain coverage of a meningococcal multicomponent vaccine (4CMenB) in Europe: a qualitative and quantitative assessment. Lancet Infect Dis. **13:**416–425. http://dx.doi.org/10.1016/S1473-3099(13)70006-9.
11. **Jones CH, Mohamed N, Rojas E, Andrew L, Hoyos J, Hawkins JC, McNeil LK, Jiang Q, Mayer LW, Wang X, Gilca R, De Wals P, Pedneault L, Eiden J, Jansen KU, Anderson AS.** 2016. Comparison of phenotypic and genotypic approaches to capsule typing *Neisseria meningitidis* using invasive and carriage isolate collections. J Clin Microbiol **54:**25–34. http://dx.doi.org/10.1128/JCM.01447-15.
12. **Meningitis Research Foundation.** 2015. MenB (meningococcal B) vaccine. Meningitis Research Foundation, Bristol, United Kingdom. http://www.meningitis.org/menb-vaccine. Accessed 4 November 2015.
13. **National Health Service.** 2015. The NHS vaccination schedule. National Health Service, Redditch, United Kingdom. http://www.nhs.uk/Conditions/vaccinations/Pages/vaccination-schedule-age-checklist.aspx. Accessed 4 November 2015.
14. **Hill DM, Lucidarme J, Gray SJ, Newbold LS, Ure R, Brehony C, Harrison OB, Bray JE, Jolley KA, Bratcher HB, Parkhill J, Tang CM, Borrow R, Maiden MC.** 2015. Genomic epidemiology of age-associated meningococcal lineages in national surveillance: an observational cohort study. Lancet Infect Dis **15:**1420–1428. http://dx.doi.org/10.1016/S1473-3099(15)00267-4.