

REVIEW

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## Impact of meningococcal vaccination on carriage and disease transmission: A review of the literature

Paul Balmer, Cynthia Burman, Lidia Serra, and Laura J. York

Medical Development, Scientific & Clinical Affairs, Pfizer Vaccines, Pfizer Inc, Collegeville, PA, USA

### ABSTRACT

Colonization of the human nasopharyngeal tract by the bacterium *Neisseria meningitidis* is usually asymptomatic, but life-threatening meningococcal disease with a clinical presentation of meningitis, septicemia, or more rarely, gastrointestinal symptoms, can develop. Invasive meningococcal disease (IMD) can be fatal within 24 hours, but IMD is vaccine-preventable. Vaccines used to protect against IMD caused by 5 of the 6 most common serogroups (A, B, C, W, and Y) may also influence carriage prevalence in vaccinated individuals. Lower carriage among vaccinated people may reduce transmission to nonvaccinated individuals to provide herd protection against IMD. This article reviews observational and clinical studies examining effects of vaccination on *N. meningitidis* carriage prevalence in the context of mass vaccination campaigns and routine immunization programs. Challenges associated with carriage studies are presented alongside considerations for design of future studies to assess the impact of vaccination on carriage.

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### Introduction

The only known repository of the gram-negative bacterium *Neisseria meningitidis* is the human nasopharyngeal tract.<sup>1,2</sup> Although bacterial colonization typically does not cause disease, under circumstances that are not completely understood, *N. meningitidis* can invade the bloodstream and cause invasive meningococcal disease (IMD).<sup>1,2</sup> Patients with IMD are most frequently diagnosed with meningitis or septicemia.<sup>3,4</sup> More recently, several serogroup W (MenW) IMD cases in teenagers presented with uncommon gastrointestinal symptoms that included diarrhea, nausea, and vomiting; these cases had a high mortality rate (5 of 15 individuals died within 24 hours of hospitalization).<sup>5</sup> Rapid progression toward fatality is frequent in IMD<sup>6</sup> and is one factor contributing to the seriousness of disease (case fatality rates range from 10% to 40%).<sup>6–8</sup> Moreover, as many as 20% of survivors can experience significant, long-term sequelae, including chronic pain, limb loss, or hearing loss.<sup>9</sup> Although IMD can occur across all ages, incidence is highest in infants <1 year old, adolescents and young adults, and those over age 65 years.<sup>10</sup>

Because of gaps in surveillance, there are currently no reliable global estimates of IMD burden. Estimates from 2001 report more than 1.2 million global annual IMD cases.<sup>11</sup> Furthermore, incidence rates vary widely by geographic distribution, season, and economic development level of a given country; IMD incidence is generally low in industrialized countries ( $\leq 5$  cases per 100,000 people)<sup>1,12,13</sup> and peaks at >1000 cases per 100,000 population in less industrialized countries, such as those within the African meningitis belt.<sup>2,8,14,15</sup>

Transmission of *N. meningitidis* occurs through respiratory secretions passed between individuals in close contact.<sup>16</sup> However, acquisition of *N. meningitidis* typically does not cause disease and often results in asymptomatic colonization of the mucosa of the upper respiratory tract, a phenomenon known as carriage. Importantly, transmission of meningococci often results from close contact with a carrier rather than another individual with IMD, highlighting the importance of asymptomatic carriers in the disease process.<sup>16,17</sup> Among industrialized countries, carriage rates increase gradually through childhood (4.5%), peak during adolescence and young adulthood (23.7%), and then stabilize during adulthood (7.8%).<sup>18</sup> In developing countries, carriage generally peaks in early childhood.<sup>19</sup>

Carriage among individuals attending international mass gatherings such as the Hajj and Umrah can contribute to meningococcal transmission (and possibly IMD) in regions that are not necessarily proximal to the Middle East. Among male Hajj attendees, carriage rates as high as 86% have been reported.<sup>20</sup> From a public health perspective, strategies aimed at lowering carriage of meningococci, such as through vaccination, are the most effective measures for preventing IMD.

Vaccines that provide direct protection against 5 of the 6 major disease-causing meningococcal serogroups (A, B, C, W, and Y) are currently available,<sup>21</sup> and determining the effect of these vaccines on carriage is essential to ascertain their potential impact on disease at the population level. The purpose of this review is to summarize the data evaluating the effect of meningococcal vaccination on carriage.

**CONTACT** Paul Balmer, PhD, Senior Medical Director  [Paul.Balmer@pfizer.com](mailto:Paul.Balmer@pfizer.com)  Pfizer Vaccine Medical Development, Scientific & Clinical Affairs, 500 Arcola Road, Collegeville, PA, USA.

Area of Expertise: Vaccinology

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## Meningococcal carriage: Overview

Carriage is a necessary precursor to IMD and is considered an immunizing event.<sup>2,22</sup> Typically, the transition between carriage and IMD may take place anywhere from 1 day to approximately 2 weeks after acquisition of the bacterium.<sup>2</sup> The factors attributed to the pathophysiology of carriage, such as bacterial attachment to epithelial cells and the eventual invasion of the bloodstream or other epithelial surfaces, are not fully understood.<sup>2</sup>

The meningococcal serogroups associated with carriage are not well defined. Determining the serologic classification of isolates obtained from asymptomatic carriers is complicated by a lack of a protective bacterial capsule on the majority of carriage isolates, thus rendering them nongroupable by serologic methods.<sup>23</sup> Although capsular geno-grouping of *N. meningitidis* may be determined using polymerase chain reaction (PCR)-based methodologies, high levels of plasticity in the target genes of carriage isolates also appear to limit the usefulness of these techniques in carriage surveillance.<sup>24</sup> However, the potential of a whole-genome sequencing approach for accurate genetic characterization of meningococcal carriage isolates has recently been demonstrated.<sup>24</sup> Carriage isolates have also been genetically characterized based on polymorphisms in a subset of housekeeping genes, and groups of related genotypes have been organized into clonal complexes (CCs). In general, CCs of carriage isolates are more heterogeneous than CCs associated with IMD isolates, presumably because of a lack of selective pressure in a carriage microenvironment.<sup>15</sup> However, one European study identified CC23 and CC35 as more frequently associated with carriage.<sup>23</sup>

As with invasive disease, carriage rates vary by age and typically range from 10% to 35%, with rates as high as 55% observed in university students in the United Kingdom.<sup>15</sup> A variety of risk factors have been associated with carriage acquisition and include behaviors linked with social mixing such as dormitory living, sharing utensils or beverages, bar attendance, and smoking.<sup>2,25</sup> Peak carriage rates of meningococci are observed in adolescents and young adults in developed countries<sup>18,26</sup>; thus, this age group is the most likely responsible for transmission of meningococci among the population, particularly if they engage in social mixing behaviors associated with transmission.<sup>27</sup> Consequently, vaccines that prevent meningococcal carriage in adolescents and young adults have the most potential to have an impact on disease across all ages. Notably, in the United Kingdom, the Netherlands, and Italy, mass vaccination of adolescents and young adults with a meningococcal serogroup C conjugate (MCC) vaccine resulted in herd protection in unvaccinated age groups.<sup>28-30</sup> The association between vaccination and carriage reduction is an important component for understanding the public health impact of vaccination.

## Methods

PubMed was searched using the following search string: (carriage OR colonization) AND (meningococcal OR meningitidis); filters included human, clinical trial, and date (ie, January 1995 to December 2017).

## Results

Observational and epidemiologic studies that examined carriage prevalence before and/or after vaccination are listed by vaccine serogroup and summarized in Table 1. Vaccine clinical trials with a primary endpoint of carriage or those that had a carriage assessment arm are reported in Tables 2 through 4.

### Observational and epidemiologic studies

#### Serogroup A vaccine

Carriage of serogroup A after vaccination was examined in 3 observational studies, none of which had an unvaccinated control group. Two studies were conducted in Burkina Faso,<sup>31,32</sup> a country that lies within the African meningitis belt and has been prone to high rates of endemic and epidemic meningococcal disease.<sup>33</sup> In 2010, the protein conjugate serogroup A vaccine (PsA-TT, MenAfriVac; Serum Institute of India, Pune, India) was introduced as part of a national immunization campaign, and more than 11 million residents 1 to 29 years old were immunized over a 10-day period.<sup>34</sup> Both carriage studies in this region were cross-sectional surveys targeting those 1 to 29 years old in 3 health districts within Burkina Faso.<sup>31,32</sup> The first follow-up survey was conducted 1 year after vaccination and evaluated 45,847 prevaccination and postvaccination samples.<sup>31</sup> Results demonstrated that serogroup A carriage was completely eliminated up to 13 months postvaccination (prevaccination, 80 carriers; postvaccination, 0 carriers). However, the overall number of carriage isolates detected (any serogroup) increased from 4.0% before vaccination to 7.0% after vaccination (odds ratio [OR], 1.80;  $P < 0.001$ , 95% CI, 1.37–2.38). The majority of the increase was due to increases in carriage of serogroup X (prevaccination, 0.4%; postvaccination, 5.3% [OR, 12.65;  $P < 0.001$ , 95% CI, 6.88–23.25]).<sup>31</sup> The second survey examined carriage 2 years after vaccination and showed similar results.<sup>32</sup> Among the 4964 samples evaluated, the prevalence of serogroup A was 0.02% and was significantly lower 2 years after vaccination compared with prevaccination (OR, 0.05;  $P = 0.005$ , 95% CI, 0.006–0.403).<sup>32</sup> Although serogroup A carriage remained low, marked increases in serogroup W carriage were observed (prevaccination, 0.3%; postvaccination, 6.9%). The emergence of non-serogroup A carriage isolates accounted for the 2-fold increase in total carriage isolates during this 2-year observation period (prevaccination, 4.0%; postvaccination, 7.9%). A limitation of these studies is related to the reliability of participants to disclose their vaccination status; among those considered to be vaccinated, only half were able to present validation (ie, a vaccination card).

A third observational study focused on serogroup A carriage in 3 regions in Chad after the first MenAfriVac mass vaccinations in 2011.<sup>35</sup> Prevaccination samples were collected from 5276 participants aged 1 to 29 years, of which 5001 provided samples postvaccination. Overall, carriage prevalence among the target population before vaccination was low for all typeable isolates. The year before vaccination (13–15 months prior), carriage prevalence was 0.6%, and all samples were serogroup A. In the 2- to 4-month period before vaccination, overall carriage increased to 1.3% with the majority of isolates belonging to serogroup A (0.7%). By 4 to 6 months after vaccination,

Table 1. Observational Studies of Carriage Prevalence Before and After Meningococcal Vaccination.

| Study                                 | Country      | Vaccine                  | Age, y | Enrolled Subjects With Swab Samples | Carriage Isolates  |  | Time Between Assessments | Predominant Clonal Complex     |        | Vaccine Effectiveness (VE)                            |   |
|---------------------------------------|--------------|--------------------------|--------|-------------------------------------|--|--|--------------------------|--------------------------------|--------|---|---|
|                                       |              |                          |        |                                     | Prevaccination % (n)   | Postvaccination % (n)  |                          | Prevaccination Postvaccination | ST-192 |   |   |
| Caugant et al, 2006 <sup>36</sup>     | Uganda       | ACWY polysaccharide      | 2–19   | 750                                 | Total: 1.3 (10) <sup>a</sup>   | Total: 1.9 (14) <sup>b</sup>   | 1 mo                     | ST-4794                        | ST-192 | ND  |   |
| Maiden et al, 2008 <sup>28</sup>      | UK           | MCC protein conjugate    | 15–19  | 14,057–17,770                       | Total: 16.7 (2348) <sup>a,b</sup><br>B: 2.3 (540) <sup>c</sup><br>C: 2.51 (59) <sup>c</sup><br>W: 6.3 (148) <sup>c</sup><br>Y: 5.58 (131) <sup>c</sup> | Total: 17.7 (2931) <sup>b</sup><br>B: 22.76 (667) <sup>c</sup><br>C: 0.72 (21) <sup>c</sup><br>W: 7.51 (220) <sup>c</sup><br>Y: 5.53 (162) <sup>c</sup><br>Total: 18.7 (3320) <sup>b</sup> | 1 year                   | N/A                            | N/A    | ND  |   |
| Ceyhan et al, 2013 <sup>17</sup>      | Turkey       | ACWY protein conjugate   | 15–64  | 296–472                             | Total: 13 (63) <sup>a,d</sup><br>A: 2 (1)<br>B: 14 (9)<br>W: 83 (52)<br>Y: 2 (1)   | Total: 27 (81) <sup>c</sup><br>A: 1 (1)<br>B: 6 (5)<br>W: 91 (74)<br>Y: 1 (1)  | <4 mo <sup>e</sup>       | N/A                            | N/A    | N/A   |   |
| Kristiansen et al, 2013 <sup>31</sup> | Burkina Faso | PsA-TT protein conjugate | 1–29   | 20,326–22,093                       | Total: 3.98 (809) <sup>a,d</sup><br>A: 0.39 (80)<br>B: 0<br>C: 0.02 (4)<br>W: 0.34 (70)<br>X: 0.44 (90)<br>Y: 2.25 (457)<br>NG: 0.53 (108)             | Total: 6.95 (1536) <sup>b</sup><br>A: 0<br>B: 0.01 (1)<br>C: 0.01 (3)<br>W: 0.42 (92)<br>X: 5.33 (1177)<br>Y: 0.86 (191)<br>NG: 0.33 (72)  | 13 mo                    | N/A                            | N/A    | VE against carriage of serogroup A: 100% <sup>f</sup> |   |
|                                       |              |                          |        |                                     |  |  |                          |                                |        |   | VE against carriage of serogroup C at 2 years: 75% (95% CI, 23%–92%)  |
|                                       |              |                          |        |                                     |  |  |                          |                                |        |   | RR (95% CI) postvaccination; year 2: prevaccination<br>B: 1.05 (0.95–1.15), $P = 0.34$<br>C: 0.19 (0.11–0.33), $P < 0.001$<br>W: 1.13 (0.93–1.38), $P = 0.22$<br>Y: 0.97 (0.78–1.20), $P = 0.76$<br>ND<br>OR (95% CI) postvaccination: prevaccination<br>Total: 1.8 (1.37–2.38), $P < 0.001$<br>A: N/A<br>B: N/A<br>C: 0.69 (0.11–4.53), $P = 0.697$<br>W: 1.21 (0.69–2.13), $P = 0.506$<br>X: 12.65 (6.88–23.25), $P < 0.001$<br>Y: 0.38 (0.25–0.57), $P < 0.001$<br>NG: 0.61 (0.41–0.90), $P = 0.014$ |

|  |              |                               |                     |  |  |  |   |
|--|--------------|-------------------------------|---------------------|--|--|--|---|
| Kristiansen et al, 2014 <sup>32</sup>                    | Burkina Faso | PsA-TT protein conjugate      | 1–29                | 4964   | <p>Total: 7.86 (390)<sup>b</sup><br/>                     A: 0.02 (1)<br/>                     W: 6.85 (340)<br/>                     X: 0.6 (30)<br/>                     Y: 0.2 (10)<br/>                     NG: 0.18 (9)<br/>                     Total: 0.31 (1)<sup>b</sup></p> <p>OR: A: 0.05 (95% CI, 0.006–0.403), P = 0.005</p>  | ST-11  | VE against carriage of serogroup A: 95% <sup>g</sup>      |
| Delbos et al, 2013 <sup>52</sup>                         | France       | MenBvac OMV                   | 1–7                 | 1082   | <p>Total: 2.1 (16)<sup>a,h</sup><br/>                     Total: 0.31 (1)<sup>b</sup></p> <p>OR, 0.15 (95% CI, 0.003–0.95), P = 0.03</p>   | ST-461<br>ST-23<br>ST-32/ET-5<br>ST-174<br>ST-198<br>ST-213<br>ST-41/44<br>N/A   | VE against carriage: 85% <sup>f</sup>                     |
| Soeters et al, 2015 <sup>54</sup> and 2017 <sup>55</sup> | US           | MenB-FHbp recombinant protein | Varied <sup>i</sup> | <p>Prevaccination: 717<sup>j</sup><br/>                     postvaccination: 622–878<sup>k</sup></p> | <p>Round 1<br/>                     Total: 24 (175)<sup>a,d</sup><br/>                     B: 4 (31)<br/>                     C: 1 (8)<br/>                     W: 0 (0)<br/>                     X: &lt;1 (1)<br/>                     Y: &lt;1 (3)<br/>                     NG: 18 (132)</p> <p>Round 2<br/>                     Total: 24 (211)<sup>b</sup><br/>                     B: 4 (36)<br/>                     C: &lt;1 (3)<br/>                     W: 0 (0)<br/>                     X: &lt;1 (2)<br/>                     Y: &lt;1 (4)<br/>                     NG: 19 (166)</p> <p>Round 3<br/>                     Total: 20 (123)<sup>b</sup><br/>                     B: 4 (26)<br/>                     C: 0 (0)<br/>                     W: &lt;1 (1)<br/>                     X: 0 (0)<br/>                     Y: &lt;1 (1)<br/>                     NG: 15 (95)</p> <p>Round 4<br/>                     Total: 21 (130)<sup>b</sup><br/>                     B: 4 (22)<br/>                     C: 0 (0)<br/>                     W: 0.2 (1)<br/>                     X: 1 (5)<br/>                     Y: 0.3 (2)<br/>                     NG: 16 (100)</p> | <p>N/A</p> <p>“Prevaccination” phase: 5–12 d after vaccination;<br/>                     Postvaccination phase<br/>                     Round 2: 2 mo<br/>                     Round 3: 7 mo<br/>                     Round 4: 13 mo</p> | <p>VE against carriage of serogroup B: 0%<sup>g</sup></p> |

(Continued on next page)

Table 1. (Continued)

| Study                           | Country | Vaccine                   | Age, y        | Enrolled Subjects With Swab Samples | Carriage Isolates   |   |                       | Time Between Assessments | Predominant Clonal Complex                           |                            |
|---------------------------------|---------|---------------------------|---------------|-------------------------------------|---|---|-----------------------|--------------------------|--|----------------------------|
|                                 |         |                           |               |                                     | Prevaccination % (n)  | Postvaccination % (n)   | Outcome               |                          | Prevaccination Postvaccination                       | Vaccine Effectiveness (VE) |
| Daugla et al 2014 <sup>35</sup> | Chad    | PsA-TT, Protein conjugate | <1, 1–29, ≥30 | 998–5001                            | Survey 1<br>Total: 0.6 (6) <sup>a,d</sup><br>A: 0.6 (6)<br>W: 0<br>X: 0<br>Other: 0         | Survey 3<br>Total: 0.82 (41) <sup>b</sup><br>A: 0.02 (1)<br>W: 0.02 (1)<br>X: 0.1 (5)<br>Other: 0.68 (34) | 17–21 mo <sup>m</sup> | ND                       | VE against carriage of serogroup A: 97% <sup>g</sup> |                            |
|                                 |         |                           |               | 4278                                | Survey 2<br>Total: 1.3 (56)<br>A: 0.75 (32)<br>W: 0.07 (3)<br>X: 0.1 (6)<br>Other: 3.5 (15) | Survey 2 vs Survey 3 adjusted OR:<br>A: 0.019 (95% CI, 0.002–0.138); P<0.0001                             | 7–9 mo                |                          | VE against carriage of serogroup A: 97% <sup>g</sup> |                            |

MCC = meningococcal serogroup C conjugate; MenB-FHbp = bivalent rLP2086, a recombinant protein meningococcal serogroup B vaccine; N/A = not applicable; ND = not determined; NG = nongroupable; OR = odds ratio; PsA-TT = meningococcal serogroup A conjugate vaccine; RR = rate ratio; ST = sequence type.

<sup>a</sup>Serogroup determined by molecular methods.

<sup>b</sup>Calculated as a proportion of all individuals sampled.

<sup>c</sup>Calculated as a proportion of carriage-positive individuals.

<sup>d</sup>Serogroup determined by agglutination.

<sup>e</sup>≤2 weeks before Hajj and ≥2 weeks after Hajj.

<sup>f</sup>Vaccine efficacy was not directly included in the published reference and was calculated per Maiden et al *J Infect Dis* 2008<sup>28</sup> using the following equation: VE = 100 x (1 – [rate of carriage in vaccinated individuals/rate of carriage in nonvaccinated individuals]).

<sup>g</sup>Vaccine efficacy was not directly included in the published reference and was calculated using the following equation: VE = 100 x (1 – [rate of carriage in postvaccination sample/rate of carriage in prevaccination sample]).

<sup>h</sup>Data represent unvaccinated and vaccinated children sampled within the same 3-month time period, rather than sampled pre- and postvaccination.

<sup>i</sup>Undergraduate students, graduate students <25 years old, persons in an intimate physical relationship with an undergraduate, and asplenic persons or persons with an immunocompromising condition known to place them at risk for meningococcal disease.

<sup>j</sup>98% (n = 701) of participants had received 1 dose of MenB-FHbp.

<sup>k</sup>In Round 2, 99% (n = 867) of participants had received 1 dose; in Round 3, 81% (n = 501) had received 2 doses; in Round 4, 54% (n = 338) had received 2 doses and 27% (n = 169) had received 3 doses.

<sup>l</sup>Epidemic serogroup A strain.

<sup>m</sup>Time between pre- and postvaccination sampling was 17–21 months, but time between vaccination and postvaccination sampling was 4–6 months.

overall carriage prevalence decreased to 0.8%, and serogroup A carriage decreased to 0.02% (1 subject; 98% difference in serogroup A carriage prevalence between 2–4 months prevaccination and 4–6 months postvaccination [adjusted OR, 0.019, 95% CI, 0.002–0.138]). The majority of postvaccination carriage isolates were non-A, non-W, and non-X by serologic testing.<sup>35</sup>

### Serogroup A, C, W, Y vaccines

Although Uganda is not part of the meningitis belt, outbreaks of serogroup A disease have been reported throughout the country.<sup>36</sup> An immunogenicity trial of a fractional dose of a tetravalent ACWY polysaccharide vaccine in 750 subjects aged 2 to 19 years included a carriage assessment immediately before vaccination and 4 weeks after vaccination.<sup>36</sup> Baseline *N. meningitidis* carriage prevalence was relatively low at 1.3% and increased to 1.9% at 4 weeks postvaccination. Serogroup A carriage was not detected in either prevaccination or postvaccination samples; however, serogroup W (ST-11 strain) carriage was detected postvaccination in 2 participants who were not carriers at baseline. Notably, this was the first detection of this serogroup W strain reported in Uganda, and the infected individuals were vaccinated against this serogroup, albeit with a fractional dose of vaccine. The majority (90%) of those with meningococcal carriage at baseline remained carriers at 4 weeks; among those who were carriers at both assessments, all carried the same isolate at the 4-week evaluation. Most carriage isolates were nongroupable at baseline and at 4 weeks postvaccination. The impact of the MenACWY conjugate vaccine on carriage was also recently analyzed in a cohort of university students in the United Kingdom.<sup>37</sup> Although a shift toward non-encapsulated phenotypes was not observed, serogroup W (ST-11 2013 strain) carriage expanded among the students, indicating possible variations in susceptibility to vaccine-induced immunity.

### Serogroup C vaccine

Before the implementation of routine vaccination, serogroup C was responsible for a substantial portion of meningococcal disease in infants, adolescents, and young adults in the United Kingdom.<sup>38</sup> In 1999, the United Kingdom became the first country to initiate a national immunization campaign focused on serogroup C,<sup>39</sup> and as a result, disease due to serogroup C dramatically decreased in both vaccinated and unvaccinated individuals.<sup>29,40</sup> Serogroup C carriage prevalence in students 15 to 19 years old was assessed in 3 cross-sectional surveys conducted at MCC vaccine introduction in 1999, and 1 and 2, years later (2000 and 2001, respectively).<sup>28</sup> In total, 14,057, 16,482, and 17,770 students participated in surveys 1, 2 and 3, respectively. Vaccine coverage was >90% by 2001. Results demonstrated an increase in total carriage isolates over time (16.7%, 17.7%, and 18.7% in 1999, 2000, and 2001, respectively; rate ratio [2001:1999], 1.12,  $P < 0.001$ ). However, carriage of serogroup C decreased over this same period (2.51%, 0.72%, and 0.48% in 1999, 2000, and 2001); this reduction was significant (rate ratio [2001:1999], 0.19 [95% CI, 0.11–0.33];  $P < 0.001$ ). Carriage prevalence of other serogroups did not change significantly. The endemic strain of serogroup C at the time of vaccination was ST-11, but notably, carriage prevalence of this strain was relatively low (1.83%) when the vaccination campaign was initiated in 1999. After vaccination, prevalence

decreased further to 0.78% in 2000 and 0.21% in 2001 (rate ratio [2001:1999], 0.11 [95% CI, 0.05–0.25];  $P < 0.001$ ), a reduction of 83% and 94% compared with prevaccination levels. Despite the low levels of ST-11 at the time of vaccination, these survey data demonstrated that vaccination significantly reduced carriage of serogroup C and the ST-11 strain.

### Serogroup B vaccines

Globally, serogroup B causes endemic and epidemic disease; some epidemics have been notable for their longevity and the large number of individuals infected.<sup>41–44</sup> Serogroup B has also been responsible for a number of smaller outbreaks, including an outbreak in France in 2000 to 2003<sup>45,46</sup> and several outbreaks at US university and college campuses from 2013 to 2015.<sup>47,48</sup>

Although polysaccharide-based vaccines have been used to target serogroups A, C, W, and Y, similar vaccines targeting serogroup B polysaccharides were not successful because of the structural similarity with  $\alpha(2-8)$ -linked N-acetyl-neuraminic acid on human neuronal cells.<sup>49,50</sup> The first nonpolysaccharide serogroup B vaccines in widespread use were outer membrane vesicle (OMV) vaccines that targeted the surface proteins present on encapsulated meningococci; as such, these vaccines were highly specific for the immunizing antigen and therefore were not effective against disease caused by divergent strains.<sup>49,51</sup> A subsequent strategy targeted either 2 variants of a single conserved surface protein with broad distribution across serogroup B strains, or single variants of several such surface proteins, resulting in the development of 2 recombinant protein serogroup B vaccines, MenB-FHbp (Trumenba<sup>®</sup>, bivalent rLP2086; Pfizer Inc, Philadelphia, PA, USA) and MenB-4C (Bexsero<sup>®</sup>, 4CMenB; GlaxoSmithKline Vaccines, Srl, Siena, Italy). Carriage of serogroup B has been examined in 2 studies (1 observational study and 1 interventional trial) that included an OMV vaccine<sup>52,53</sup> and 1 cross-sectional survey study using the recombinant protein vaccine MenB-FHbp.<sup>54</sup>

Beginning in 2003 in response to a steady expansion of a serogroup B clone in Normandy, France, a progressive vaccination campaign was initiated with an OMV vaccine specific for the outbreak variant (MenBvac, Norwegian Institute of Public Health, Oslo, Norway).<sup>46</sup> The campaign included carriage assessment in children 1 to 7 years old vaccinated with 1 to 3 doses of MenBvac within 2 months of the analysis; a corresponding unvaccinated control group was included as the comparator.<sup>52</sup>

Among 321 vaccinated subjects who received 1 (76.6%), 2 (18.7%), or 3 (4.7%) doses of MenBvac, 1 subject (0.31%) carried a nonvaccine type isolate at 2 months postvaccination. Among the 761 unvaccinated subjects, 16 (2.10%) were carriers of nonvaccine-type isolates at the 2-month assessment. No baseline data were reported, and no subjects in the analysis carried the outbreak clone. Despite a limited number of subjects (all of whom belonged to an age group not typically associated with high carriage rates), the difference in carriage prevalence between vaccinated and unvaccinated subjects was significant (OR, 0.15 [95% CI, 0.003–0.95];  $P = 0.03$ ) and supported the protective effect of MenBvac against serogroup B carriage at 2 months postvaccination. No long-term effects on carriage were assessed.<sup>52</sup>

In response to a 2015 outbreak of serogroup B at a small, private university in the United States, a mass vaccination campaign was initiated that included a carriage evaluation of 717 students aged <25 years.<sup>54</sup> At the time of this observational study, 94.1% (3525/3745) of those eligible had received 1 dose of the recombinant protein vaccine, MenB-FHbp, in the previous 2 weeks. Overall, 25% of subjects were carriers of *N. meningitidis* and 4% carried serogroup B; no subject carried the outbreak strain, and the majority of isolates were nongroupable.<sup>54</sup> Several reasons have been postulated to explain the failure to identify the outbreak strain in this initial study; these included intrinsic properties of the bacteria to resist carriage, efficacy of the vaccine in eliminating carriage isolates within the 1 to 2 weeks between vaccination and evaluation, and a relatively small sample size.<sup>54</sup> Additional carriage evaluations collected samples at 2, 7, and 13 months after the first vaccine dose; as determined by rt-PCR, overall carriage prevalence held steady at 20%–24% through the end of the study, as did MenB carriage, at 4%.<sup>55</sup> The outbreak strain (ST-9069; serogroup B by rt-PCR, nongroupable by slide agglutination) was identified in only 1 participant who was evaluated at months 2 and 7 and had received 2 doses of MenB-FHbp.<sup>55</sup>

Another outbreak among university students in 2015 was caused by the serogroup B ST-32 strain.<sup>56</sup> In response, MenB-4C was initially provided to a small number of students followed by a mass vaccination campaign using MenB-FHbp. An analysis of meningococcal carriage following the campaign examined 4,225 oropharyngeal swab samples from 3,802 participants. During 4 surveys over an 11-month period, prevalence of total meningococcal and MenB carriage remained stable at 11%–17% and 1.2%–2.4%, respectively. Acquisition of meningococcal carriage was identified in 5%–11% of vaccinated subjects; however, a comparison of carriage acquisition among vaccinated and unvaccinated subjects could not be made owing to the small number of vaccine recipients. Most isolates were nongroupable and no participants carried the outbreak strain. After the carriage study began, 3 additional outbreak cases occurred at the university, indicating that the outbreak strain continued to circulate within the campus population but at a prevalence low enough to be undetectable in the carriage study. These results suggest that the duration of carriage of pathogenic strains may be shorter-lived than that of carriage strains.<sup>56,57</sup>

### Clinical trials

In contrast to observational studies of carriage, few clinical trials (interventional clinical studies) have been initiated to evaluate nasopharyngeal carriage as a predefined study endpoint.

### Serogroup A, C, W, Y vaccines

Because of a relatively low level of endemic disease in the United States, vaccination against serogroups A, C, W, and Y is typically not recommended for children younger than 10 years old or adults  $\geq 22$  years old unless they are at increased risk from specific health concerns or travel. However, vaccination is recommended for adolescents 11 to 18 years old because of an increased risk of disease.<sup>10</sup> Meningococcal carriage before and after vaccination with a conjugated ACWY vaccine (MCV4-DT; Menactra, Sanofi Pasteur, Swiftwater, PA, USA) was

examined in 1 field trial as a prospective cohort study conducted in geographically diverse high schools in the United States.<sup>58</sup> Three sequential, cross-sectional surveys for pharyngeal carriage were conducted between 2006 and 2007 in 8 public high schools in Maryland (n = 4) and Georgia (n = 4); 3311 students participated. Free immunization was offered to students at the initial survey at the beginning of the school year (ie, at schools randomized to the vaccination group) or at the third survey at the end of the school year (ie, at schools randomized to the control group). Carriage surveys were performed at 3 points (beginning, middle, and end of the school year), with particular attention to the acquisition of serogroup Y. Generally, carriage prevalence was low for all isolates among the study population. In vaccination schools, carriage prevalence of serogroup Y was 0.35% and 0.32% at the first and third surveys, respectively; in control schools, carriage prevalence was 0.19% and 0.22%. Carriage of all isolates (including nongroupable) was 3.52% and 4.20% at the first and third survey periods in vaccination schools and 2.85% and 3.80% for control schools, respectively. Phenotypically nongroupable strains accounted for most (88%) carriage isolates (Table 2).<sup>58</sup>

The low carriage rates reported in this trial are in accordance with historically low meningococcal disease rates observed in the United States.<sup>7,58</sup> However, authors acknowledged that the low carriage rates, the small analysis population, and technical limitations of the PCR-based serogrouping assay that may have led to sample misclassification precluded meaningful statistical analysis and limited the conclusions that could be drawn regarding carriage reduction in response to vaccination in this setting.<sup>58</sup>

### Serogroup B vaccines

In 2015,<sup>59</sup> the United Kingdom included serogroup B vaccination in the national infant immunization program in response to the disproportionately high rate of disease caused by serogroup B in comparison with other serogroups that cause IMD.<sup>60</sup> In a randomized clinical trial in England, carriage was assessed in 2954 university students 18 to 24 years old before and after administration of 2 doses of MenB-4C (n = 974), 1 dose of MenACWY-CRM (Menveo; GlaxoSmithKline Vaccines, Srl, Siena, Italy; n = 981), or 2 doses of control vaccine (Japanese encephalitis vaccine; IXIARO, Intercell, Vienna, Austria; n = 984; Table 3).<sup>61</sup> Carriage rates were evaluated from 1 month to 1 year after vaccination.

At baseline, 8% of MenB-4C recipients and 7% of corresponding control recipients were meningococcal carriers. Carriage prevalence at 1 month postvaccination was not significantly different between those receiving MenB-4C or control vaccine (9% and 8%, respectively). By >3 months postvaccination, carriage rates among MenB-4C recipients decreased significantly compared with control vaccine recipients for all *N. meningitidis* isolates (18.2% reduction [95% CI, 3.4–30.8]), serogroup CWY (28.5% reduction [95% CI, 2.8–47.5]), and capsular groups BCWY and CWY (which were identified by genotyping as opposed to serology; 26.6% reduction [95% CI, 10.5–39.9] and 29.6% reduction [95% CI, 8.1–46.0], respectively); notably, carriage rates of capsular group B or disease-associated sequence types of capsular group B did not decrease significantly.<sup>61</sup> Reduced carriage of non-

**Table 2.** *Neisseria meningitidis* Carriage Prevalence Among US High School Students Aged 13–21 Years Vaccinated With MCV4-DT or Control, 2006–2007.<sup>58</sup>

| Enrolled Subjects With Swab Samples             | Carriage Isolates   |  | Time Between Vaccination and Assessment |
|---|---|--|---|
|   | Prevaccination % <sup>a</sup>   | Postvaccination % <sup>a</sup>   |   |
| Round 1: 1731<br>Round 2: 1644<br>Round 3: 1549 | Vaccine Group<br>Round 1<br>Total: 3.52<br>B: 0.35<br>C: 0<br>Y: 0.35<br>NG: 2.83 | Vaccine Group<br>Round 2<br>Total: 3.77<br>B: 0.12<br>C: 0<br>Y: 0.36<br>NG: 3.28<br>Vaccine Group<br>Round 3<br>Total: 4.2<br>B: 0<br>C: 0<br>Y: 0.32<br>NG: 3.87 | 3 mo<br><br><br>6–7 mo                  |
| Round 1: 1543<br>Round 2: 1469<br>Round 3: 1343 | Control Group<br>Round 1<br>Total: 2.85<br>B: 0.19<br>C: 0<br>Y: 0.19<br>NG: 2.46 | Control Group<br>Round 2<br>Total: 2.72<br>B: 0<br>C: 0<br>Y: 0.2<br>NG: 2.5<br>Control Group<br>Round 3<br>Total: 3.80<br>B: 0.15<br>C: 0<br>Y: 0.22<br>NG: 3.43  | 3 mo<br><br><br>6–7 mo                  |

<sup>a</sup>Serogroups determined by serology.  
NG = nongroupable.

serogroup B isolates in MenB-4C recipients may have been due to cross-reaction of protein antigen vaccine components.<sup>61</sup>

Among MenACWY-CRM recipients, 6% were meningococcal carriers at baseline compared with 5% of corresponding controls; at 1 month postvaccination, there was no difference in carriage prevalence across groups (both 6%). However, among MenACWY-CRM recipients, carriage prevalence was significantly lower compared with control vaccine recipients for CWY and Y capsular groups over all time points >2 months postvaccination (27.1% reduction [95% CI, 6.9–42.9] and 26.5% reduction [95% CI, 4.1–43.7], respectively). Although MenB-4C and MenACWY-CRM significantly reduced carriage during the 1-year follow-up compared with controls, neither vaccine had an appreciable effect within the first month after vaccination.<sup>61</sup> These data suggest that the long-term reduction in carriage prevalence may be due to reduced acquisition over time versus nasopharyngeal clearance upon vaccination.

As part of a single-center, blinded, phase 1/2 randomized clinical trial, carriage prevalence was examined in university students aged 17 to 24 years in New Zealand upon receipt of a novel, combination OMV (MeNZB) and MCC (Menjugate<sup>TM</sup>, GlaxoSmithKline, Mississauga, ON, Canada) vaccine.<sup>53</sup> The study included a comparator group that did not receive vaccine. The combination vaccine was prepared by reconstituting a lyophilized MCC vaccine with liquid MeNZB vaccine immediately before dosing.<sup>53</sup> The carriage assessment compared vaccinated (n = 57) and unvaccinated (n = 143–152) subjects at

baseline and at 5 months postvaccination. In unvaccinated subjects, total *N. meningitidis* carriage prevalence at baseline and 5 months postvaccination was similar (19% [95% CI, 13–26] and 22% [95% CI, 15–29], respectively), as was carriage of the serogroup B strain targeted by MeNZB (3% at both time points). Among vaccinated subjects, *N. meningitidis* carriage decreased by approximately 50% during the same period (40% [95% CI, 28–54] and 21% [95% CI, 11–34], respectively), and carriage of the targeted B strain decreased from 4% (95% CI, 0–12) at baseline to 0% (95% CI, 0–6) (Table 4).<sup>53</sup>

## Discussion

From 1995 to 2017, the number of studies examining meningococcal carriage after vaccination was limited. The majority of carriage studies within this period were conducted in association with extensive vaccination campaigns initiated to control outbreaks or high levels of endemic disease, as opposed to smaller, carefully regulated clinical trials. Studies conducted in Africa, where multiple serogroups are endemic and conditions can rapidly escalate to epidemic disease, have provided valuable insight regarding carriage before and after vaccination. Serogroup A carriage decreased following vaccination with PsA-TT, in some cases to undetectable levels. The mass vaccination program was undertaken to curtail rates of IMD caused by serogroup A, without a requirement for effects on carriage; similarly, carriage effects were not a driving factor in the implementation of MCC vaccination in the United Kingdom.<sup>29,39,62</sup> The overall goal of vaccination programs is to reduce transmission across a population. Whereas acute implementation of vaccination breaks the short-term cycle of transmission (as with PsA-TT), implementation in national immunization programs is meant to maintain immunity, and thus protection, in a population. However, variability in sampling techniques, serogrouping methodology, and subject recall of vaccination status may render interpretation difficult for studies affiliated with mass vaccination campaigns.

### Technical considerations for studies evaluating carriage

When evaluating carriage prevalence across studies, several methodologic and technical considerations may influence the interpretation of outcomes. For example, the age at which vaccination occurs varies across studies, with infants being the primary target population in some studies, and adolescents or young adults representing the target vaccination population in other studies. Waning of vaccine effectiveness is exacerbated by younger age,<sup>29</sup> suggesting that a comparison of carriage data in infants versus older children or adolescents may not reflect the true impact of a vaccine on carriage prevalence. Moreover, different age groups exhibit different transmission dynamics: carriage rates in infants in industrialized countries are low and peak in adolescents or young adults,<sup>15,63,64</sup> whereas in developing nations, carriage may be observed more frequently in early childhood than adolescence.<sup>19</sup> Evaluating the effect of vaccination on carriage among an infant target population in a developed country may be difficult because of low baseline carriage rates. In addition, whether vaccination influences



**Table 3.** *Neisseria meningitidis* Carriage Prevalence Among University Students 18–24 Years Old Before and After MenB-4C and MenACWY Vaccination.<sup>61</sup>

| Vaccine group                       | Positive Isolates <sup>a</sup> |               |               | Carriage Rate Reduction, % (95% CI) |
|-------------------------------------|--------------------------------|---------------|---------------|-------------------------------------|
|                                     | MenB-4C % (n) <sup>b</sup>     | MenACWY % (n) | Control % (n) |                                     |
| Baseline                            | N = 976                        | N = 984       | N = 986       |                                     |
| A, B, C, W, Y                       | 33 (326)                       | 34 (334)      | 31 (303)      | N/A                                 |
| A                                   | 0                              | 0             | 0             | N/A                                 |
| B                                   | 9 (92)                         | 10 (100)      | 9 (86)        | N/A                                 |
| C                                   | 0 (3)                          | 0 (3)         | 0 (3)         | N/A                                 |
| W                                   | 2 (20)                         | 2 (20)        | 1 (10)        | N/A                                 |
| Y                                   | 7 (70)                         | 7 (67)        | 7 (68)        | N/A                                 |
| Disease-associated capsular B       | N = 974                        |               | N = 984       |                                     |
| Baseline                            | 8 (78)                         |               | 7 (72)        | N/A                                 |
| 1 month postvaccination 2           | 9 (87)                         |               | 8 (75)        | 18.2 (–73.3–19.4)                   |
| Serogroup A, C, W, or Y (combined)  |                                | N = 981       | N = 984       |                                     |
| Baseline                            |                                | 6 (58)        | 5 (49)        | N/A                                 |
| 1 month postvaccination 2           |                                | 6 (57)        | 6 (58)        | 10.5 (–34.2–40.3)                   |
| >2 months postvaccination 1         |                                | N = 3520      | N = 3504      |                                     |
| Capsular groups CWY                 |                                | 9 (333)       | 11 (388)      | 27.1 (6.9–42.9)                     |
| Capsular group Y                    |                                | 7 (261)       | 9 (325)       | 26.5 (4.1–43.7)                     |
| >3 months postvaccination 2         | N = 2489                       |               | N = 2576      |                                     |
| <i>N. meningitidis</i>              | 32 (797)                       |               | 34 (885)      | 18.2 (3.4–30.8)                     |
| Capsular group B                    | 9 (233)                        |               | 10 (262)      | 15.6 (–11.0–35.9)                   |
| Disease-associated capsular group B | 9 (214)                        |               | 9 (237)       | 12.6 (–15.9–34.1)                   |
| Capsular groups B, C, W, Y          | 18 (449)                       |               | 21 (539)      | 26.6 (10.5–39.9)                    |
| Capsular groups C, W, Y             | 9 (216)                        |               | 11 (277)      | 29.6 (8.1–46.0)                     |
| Capsular group Y                    | 7 (178)                        |               | 9 (228)       | 25.1 (–0.2–44.0)                    |

N/A = not applicable.

<sup>a</sup>*N. meningitidis*-positive samples were identified via culture and biochemical confirmation; isolates were also characterized by genogroups, serogroups, and sequence types. Non-serogroupable isolates were evaluated by PCR (reported as combined or individual capsular groups).

<sup>b</sup>Capsular group B isolate typing was based on multilocus sequence typing.

meningococcal clearance among adolescents who are already carriers at immunization is not clear.

The prespecified endpoints of carriage clinical studies vary, clouding the interpretation of trends in carriage isolate evolution. Some studies evaluate carriage by general meningococcal identity, others evaluate serogroup, and yet others categorize results by specific CCs; these differences in data presentation render interpretation and comparison of multiple datasets challenging. Moreover, seroagglutination as a method to identify the serogroup of nasopharyngeal isolates is potentially subject to variable interpretation, as this method relies on the technical expertise of the microbiologist performing the assay. PCR-based analyses, although not infallible, may offer a more consistent means to determine serogroup. Whole genome sequencing is also increasingly used to fully characterize invasive and noninvasive meningococcal isolates.<sup>65,66</sup> Considering that many carriage isolates do not express capsule and would be considered nongroupable in a seroagglutination assay, molecular

methods provide crucial information regarding CCs associated with circulating carriage isolates, which may shift stochastically or in response to vaccine implementation.

Studies evaluating vaccine impact on carriage prevalence versus reduction in acquisition rates measure different facets of colonization and should not be compared directly. Carriage prevalence data may be obtained readily in cross-sectional studies, whereas tracking acquisition rates requires a more complicated and costly strategy of following the same subjects over time. Moreover, variation in the time after vaccination at which sampling is performed can further confound interpretation of vaccine effects on carriage. Time points as brief as 2 months and as long as 2 years have been reported in carriage studies (Table 1). Given the changing selective pressures that can occur during study windows (especially in the context of a mass vaccination program), true vaccine impact on carriage may be difficult to discern.

Time of year may also be a factor in the interpretation of carriage study data. When assessing carriage prevalence

**Table 4.** *Neisseria meningitidis* Carriage Prevalence After Combination Meningococcal Serogroup B and C Vaccine in Healthy University Students Aged 17–24 Years.<sup>53</sup>

|                            | Subjects   |                        |         |                 |        |              |                        |         |                 |       |
|----------------------------|------------|------------------------|---------|-----------------|--------|--------------|------------------------|---------|-----------------|-------|
|                            | Vaccinated |                        |         |                 |        | Unvaccinated |                        |         |                 |       |
|                            | N          | <i>N. meningitidis</i> |         | Outbreak Strain |        | N            | <i>N. meningitidis</i> |         | Outbreak Strain |       |
| % (n)                      |            | 95% CI                 | % (n)   | 95% CI          | % (n)  |              | 95% CI                 | % (n)   | 95% CI          |       |
| Baseline                   | 57         | 40 (23)                | 28%–54% | 4 (2)           | 0%–12% | 152          | 19 (29)                | 13%–26% | 3 (4)           | 1%–5% |
| 5 months postvaccination   | 57         | 21 (12)                | 11%–34% | 0 (0)           | 0%–6%  | 143          | 22 (31)                | 15%–29% | 3 (4)           | 1%–7% |
| Carriage rate reduction, % |            | 48%                    |         | 100%            |        |              | –16%                   |         | 0%              |       |

in Africa, for example, the seasonality of disease in this region should be considered,<sup>67</sup> as the sampling period could override the observed effects of vaccination on carriage. Carriage assessment during the dry period, when the bacterium may be less likely to circulate, could result in lower apparent prevalence compared with the wet period.<sup>67</sup> Thus, decreases in carriage observed during dry periods may actually occur independently of vaccination status. Therefore, the evaluation of prevaccination and postvaccination samples collected during different seasons in Africa may be biased and not reflective of the true impact of vaccination. With a 4-week sampling window between baseline and postvaccination assessment, potential confounding effects of seasonality on carriage were bypassed in the tetravalent polysaccharide vaccine study conducted in Uganda.<sup>36</sup> However, the small number of subjects ( $n = 750$ ) and the low baseline carriage prevalence (2.0%) hampered development of statistically meaningful conclusions from this study.

An issue rarely considered among the studies reported here is the extent to which naturally occurring nasopharyngeal colonization by non-disease-causing Neisserial species affects the analysis of carriage following vaccination against *N. meningitidis*. Preferential colonization by competing bacteria within the nasopharynx may be a confounding variable in carriage analyses. When purposely introduced through inoculation, *N. lactamica* colonization was able to reduce meningococcal carriage by mechanisms that include displacing resident bacteria as well as inhibiting colonization by new isolates.<sup>68</sup>

Clinical studies assessing carriage as an endpoint are relatively uncommon compared with observational carriage studies. Several factors may contribute to this disparity, including anticipated low carriage rates and difficulty recruiting a sufficient number of subjects to produce statistically robust data. Two studies cited difficulty in recruiting participants: in a study conducted in university students in the United Kingdom, a slow enrollment rate from one university necessitated a protocol amendment that allowed students from another university to be recruited.<sup>68</sup> In the MCV4 vaccination study in Maryland and Georgia high schools, authors note that lower-than-expected enrollment prevented statistically robust evaluation of MCV4 effects on carriage.<sup>58</sup> This study also noted genetic changes in strains (strain evolution) or strain replacement, which may have yielded sampling errors leading to the misclassification of some isolates.<sup>58</sup>

Compounding suboptimal enrollment and sampling errors, lower-than-expected baseline carriage rates can also hamper achievement of statistically meaningful results in carriage studies. In the MCV4 study in high school students, the majority (88%) of carriage isolates were phenotypically nongroupable, and serogroup B carriage was not detected at all at the Maryland study site, which was unexpected.<sup>58</sup> However, the MCC study in the United Kingdom demonstrated that a large study population can overcome lower-than-expected carriage prevalence. Even though prevalence of serogroup C and the ST-11 strain was low compared with other isolates, the study demonstrated a statistically significant decrease in carriage of this serogroup and CC after MCC vaccination.<sup>28</sup>

### Vaccine impact on meningococcal carriage

The reduction in vaccine-type serogroup carriage that was demonstrated after implementation of MenAfriVac and MCC in vaccination campaigns<sup>28,32</sup> was unintentional but beneficial and similar to observations made after broad implementation of pneumococcal conjugate vaccines (PCV). After the introduction of 7- and 13-valent PCV, vaccine-type carriage decreased significantly, ultimately reducing transmission and thus disease in unvaccinated individuals via herd protection.<sup>69,70</sup> Implementation of MenAfriVac led to a remarkable decrease or elimination of serogroup A carriage in all age groups.<sup>35</sup> Similarly, 3 European countries introducing MCC observed herd protection in unvaccinated age groups, suggesting tangible vaccine impact.<sup>26,28,30</sup> Most evidence that conjugate vaccines have an impact on carriage comes from studies affiliated with mass vaccination. Carriage studies conducted in the form of clinical trials are thus far rare; a randomized clinical trial evaluating carriage after MenACWY or MenB-4C vaccination in university students in England reported significant reductions in carriage 3 months after the second vaccine dose.<sup>61</sup> The study of high school students in the United States who received MenACWY vaccination concluded that carriage rates were lower than expected, with nongroupable strains representing almost 90% of isolates.<sup>58</sup> The differences in study design and conclusions between these studies highlight the challenges associated with carriage evaluation.

Study data assessing the impact of MenB vaccination on serogroup B carriage are less clear than those for serogroups A and C. Whereas serogroup A and C carriage has been well studied because of their association with successful vaccination campaigns (and thus large study populations), MenB vaccines have been implemented less frequently and generally in smaller populations. Three prominent studies evaluated MenB carriage after vaccination with MenB OMV (in children aged 1–7 years in France),<sup>52</sup> MenB-FHbp,<sup>54</sup> or MenB-4C<sup>61</sup> (both in university students). Only 1 individual vaccinated with MenB OMV was a carrier (serogroup not determined), whereas 16 children in the unvaccinated group were carriers (5 carried MenB). Among the university students, 4% ( $n = 31$ ) of those immunized with MenB-FHbp were carriers of MenB at baseline; a follow-up evaluation has not yet been published. Among those receiving MenB-4C, lower carriage prevalence was observed beginning only at 3 months after the second vaccine dose and applied to capsular groups B, C, W, and Y, rather than solely to group B. Additional studies are needed to generate a more accurate picture of MenB carriage before and after vaccination with protein-based or OMV MenB vaccines.

The first efficacious meningococcal vaccines were developed from purified capsular polysaccharide.<sup>71</sup> Although effective for short-term protection, herd immunity is not observed with polysaccharide-only vaccines because they are T cell-independent and rely on humoral immune responses.<sup>21</sup> The longer-term success observed with conjugate vaccines (eg, MCC) has been attributed to their ability to reduce carriage via herd immunity.<sup>28</sup> Although the underlying mechanisms of immunity are not yet fully understood, conjugate vaccines are associated with high antibody levels and their impact on carriage may result from movement of antibodies from serum to

the nasopharynx.<sup>72</sup> The OMV and MenB protein vaccines may elicit herd immunity through the same mechanisms as conjugate vaccines. In addition, a whole-cell vaccine against *Streptococcus pneumoniae* induces Th17 responses, allowing for protection against colonization.<sup>73</sup> If meningococcal vaccines elicit such responses, the protection against colonization would likely impact herd immunity.

### Future studies of meningococcal vaccination impact on carriage

Meningococcal carriage will be assessed in a phase 4, randomized, double-blind study conducted in 45,000 Australian secondary school students  $\geq 14$  years of age who will receive 2 doses of MenB-4C (Australian New Zealand Clinical Trials Registry ID: ACTRN12617000079347; ClinicalTrials.gov Identifier: NCT03089086).<sup>74,75</sup> Samples will be collected within 12 months postvaccination among MenB-4C recipients and an unvaccinated control group; control subjects will receive MenB-4C at month 12. Carriage prevalence within 1 year of vaccination will be determined for all serogroups; the study is anticipated to conclude in June 2019. Carriage studies are valuable tools that support accurate epidemiological profiles, and should aim to generate statistically robust, comprehensive data.

### Conclusions

The impact of meningococcal vaccination on carriage of specific serogroups has been evaluated in large, observational studies associated with regional or national vaccination campaigns. Carriage of serogroups A and C was significantly reduced within approximately 1–2 years of respective MenA and MenC vaccine implementation, a conclusion based on evaluation of thousands of samples. Carriage studies of other single serogroups or serogroup combinations after corresponding vaccine implementation should, ideally, provide a similar volume of data and quality of evidence as the MenA and MenC studies. However, carriage studies for other serogroups are often not of sufficient size to provide robust statistical power. Additional large, rigorously controlled studies are needed to better understand the true impact of meningococcal vaccination on carriage prevalence.

### Disclosure of potential conflicts of interest

All authors are employees of Pfizer Inc and may hold stock.

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