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Healthy vaccinee bias and MenB-FHbp vaccine effectiveness against gonorrhea

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Abstract

Observational studies demonstrated 30–40% effectiveness of OMV meningococcal serogroup-B vaccines against gonorrhea. To explore whether healthy vaccinee bias influenced such findings, we examined effectiveness of MenB-FHbp, a non-OMV vaccine that is not protective against gonorrhea. MenB-FHbp was ineffective against gonorrhea. Healthy vaccinee bias likely did not confound earlier studies of OMV vaccines.

Summary:

Healthy vaccinee bias likely did not confound earlier studies demonstrating the protective effect of OMV MenB vaccines against gonorrhea.

Keywords

OMV MenB vaccines; gonorrhea; vaccine effectiveness; MenB-4C; MenB-FHbp

Introduction

Declining gonococcal cephalosporin susceptibility has raised the possibility of untreatable gonorrhea in the future (1, 2). New approaches, such as vaccination, are needed as long-term strategies for gonorrhea prevention and control (3). Outer membrane vesicle (OMV) serogroup B meningococcal (MenB) vaccines, which prevent disease caused by *Neisseria meningitidis* serogroup B (NmB), have shown some cross-protection against gonorrhea (3). Reports from Cuba, Norway, and Canada showed reductions in gonorrhea rates after mass

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OMV MenB vaccination campaigns (4–6). Three studies that used STI and OMV MenB vaccine surveillance data from New Zealand, Australia, and the United States showed that OMV MenB vaccines were 30–40% effective against gonorrhea (7–9). This cross-protection may be attributed to the high genetic and antigenic homology (80–90%) between *N. meningitidis* and *N. gonorrhoeae* (10).

MenB-4C (Bexsero®, GSK) is the OMV MenB vaccine currently licensed for use against NmB in the United States (11). MenB-4C is composed of two meningococcal OMV proteins (Porins A and B) and three recombinant meningococcal antigens (Neisserial heparin binding antigen [NHBA], Neisseria adhesin A, and factor H binding protein [fHBP]) (12). Meningococcal OMV proteins and NHBA are conserved and surface-exposed in *N. gonorrhoeae*, suggesting that MenB-4C vaccine-induced antibodies may recognize gonococcal antigenic proteins (10, 13). Murine models have shown that MenB-4C vaccine-induced antibodies cross-reacted with gonococcal antigenic surface proteins and accelerated genital gonococcal clearance (14). Additionally, MenB-4C vaccination produces antibodies in humans that recognize gonococcal antigenic proteins (10). The possible effectiveness of MenB-4C against gonorrhea was supported by a recent U.S.-based study using STI and MenB-4C vaccine surveillance data that demonstrated MenB-4C vaccination effectiveness of 40% against gonorrhea compared to chlamydia (8).

Because the OMV MenB vaccine effectiveness studies against gonorrhea were based on observational data from New Zealand, Australia, and the United States (7–9) and not randomized clinical trials (RCTs), it is theoretically possible that these studies may have been confounded by the healthy vaccinee bias, which may overestimate vaccine effectiveness (15). The healthy vaccinee bias suggests that persons who adopt a preventive behavior (e.g., vaccination) may be more likely to adopt preventive or healthy behaviors and be in better overall health than unvaccinated persons (16). For example, an observational study evaluating vaccine effectiveness against an STI such as gonorrhea without accounting for related STI preventative behaviors may overestimate vaccine effectiveness among vaccinated persons.

Whether the healthy vaccinee bias may have influenced prior observational studies of OMV MenB vaccines can be explored by estimating the effectiveness of MenB-FHbp vaccine (Trumenba®, Pfizer). The Advisory Committee on Immunization Practices has recommended vaccination with a serogroup B meningococcal series for adolescents and young adults aged 16–23 years based on shared clinical decision-making to provide short-term protection against serogroup B meningococcal disease (11). MenB-4C and MenB-FHbp are the two MenB vaccines licensed for use in the U.S. MenB-FHbp has the same clinical indication and recommendation as MenB-4C (10) but is not an OMV vaccine (17) and is not thought to be protective against gonorrhea (18, 19). MenB-FHbp contains recombinant fHBP (17). The gonococcal homolog of fHBP is not surface expressed and does not bind Factor H, a protein vital to gonococcal immune evasion (18, 19). If studies of MenB-4C vaccine effectiveness have been impacted by the healthy vaccinee bias, vaccines such as MenB-FHbp, which do not have an anti-gonococcal effect, would likely also demonstrate a protective effect in observational studies. An observed absence of a protective effect of Men-FHbp would in turn support the validity of the prior observational studies of

OMV vaccines and MenB-4C. The objective of this analysis was to assess the effectiveness of MenB-FHBP vaccine against gonorrhea compared to chlamydia among 16–23-year-old persons diagnosed with gonorrhea or chlamydia in New York City or Philadelphia.

Methods

Data source and variables

We replicated an approach we used previously to examine vaccine effectiveness of MenB-4C against gonorrhea (8). We identified all reported gonococcal and chlamydial infections in the STI surveillance records of the New York City Department of Health and Mental Hygiene (NYCDOHMH) and the Philadelphia Department of Public Health (PDPH) among persons 16–23 years between January 1, 2016–December 31, 2018. We classified infections for which a person was diagnosed with gonorrhea but not chlamydia as "gonococcal mono-infections" and for which a person was diagnosed with chlamydia but not gonorrhea as "chlamydial mono-infections." We linked individual STI records to health department immunization registry records to obtain data on MenB-FHbp vaccination status, age at vaccination, dates of vaccination, and number of MenB-FHbp doses received. We then determined whether each STI occurred before or after the first MenB-FHbp vaccination date or had occurred in unvaccinated persons to determine the MenB-FHbp vaccination status at the time of each infection.

We obtained person-level socio-demographic data and infection-level STI and MenB-FHbp vaccination data. The Advisory Committee on Immunization Practices recommends two doses of MenB-FHbp administered at 0 and 6 months to adolescents and young adults aged 16–23 years who are not at increased risk for MenB on the basis of shared clinical decision-making (11). For this analysis, we considered receipt of ≥1 MenB-FHbp dose as vaccinated because of the low prevalence of receipt of two doses of MenB-FHbp vaccine in this sample. Because STI and vaccination data were obtained at the infection level, we classified vaccination data in relation to each STI. We assumed post-vaccination immunity started 30 days after receipt of the first vaccine dose (20). For this analysis, STIs that occurred ≥30 days after the date of the first MenB-FHbp dose were categorized as occurring after vaccination. STIs that occurred before vaccination, among MenB-FHbp-naïve persons, or occurred <30days after first MenB-FHbp dose were categorized as STIs occurring among unvaccinated persons. The analytic dataset included vaccination category of each gonococcal or chlamydial mono-infection at each STI occurrence. We excluded gonococcal-chlamydial co-infections, STI and vaccination data where only MenB-4C vaccine was administered, or where MenB-FHbp and MenB-4C vaccines were administered to the same person from this analysis.

Analysis

We calculated frequencies of socio-demographic characteristics of persons using person-level data. Using infection-level data, we compared the prevalence of gonococcal mono-infections in the vaccinated group to gonococcal mono-infections to the unvaccinated group. We selected chlamydial mono-infections as the comparison group; characteristics and STI testing of persons diagnosed with chlamydia are relatively similar to those of persons with

gonorrhea, thus minimizing bias, particularly from possible differences in STI testing or screening between groups. We calculated unadjusted and adjusted prevalence ratios (UPR and APR, respectively) and 95% confidence intervals (CI) using log-binomial regression with generalized estimating equations to account for correlations between multiple STI infections over time per person. We included significant variables ($p \leq 0.05$) in bivariate analyses in the multivariable model. The multivariable model included MenB-FHbp vaccination category as the independent variable and race/ethnicity, gender, and jurisdiction as covariates. MenB-FHbp vaccine effectiveness was calculated as 100×(1-APR). Statistical significance was set at $p \leq 0.05$. All analyses were done using SAS 9.4. Human subjects review at CDC and the Institutional Review Board (IRB) of the NYC DOHMH determined this project was non-research and therefore exempt from further review. The IRB of PDPH reviewed and approved this project.

Results

Of 96,235 eligible persons aged 16–23 years with a diagnosis of gonorrhea or chlamydia during 1/1/16–12/31/2018, most were female (66.3%) and non-Hispanic Black (56.2%); however, race/ethnicity data were missing for 34.5% of persons (Table 1). Overall, 1.6% were vaccinated with MenB-FHbp. Among 134,983 STI cases recorded among 96,235 persons, 87.1% were chlamydial mono-infections and 12.9% were gonococcal mono-infections. MenB-FHbp vaccination was not significantly associated with gonococcal mono-infections (UPR=0.89, 95% CI=0.76–1.06) in bivariate analysis (Table 2). After adjusting for race/ethnicity, gender, and jurisdiction, no association between MenB-FHbp vaccination and gonococcal mono-infections was observed (APR=0.97, 95% CI=0.79–1.19).

Discussion

MenB-FHbp vaccination was not protective against gonorrhea in adjusted and unadjusted analyses. This finding suggests that the healthy vaccinee bias was unlikely to have confounded the effectiveness of MenB-4C and other OMV MenB vaccines against gonorrhea as seen in prior observational studies. Rather, the high genetic similarities between gonococcal and meningococcal OMV proteins and NHBA and the anti-gonococcal antibodies that MenB-4C vaccines produce may explain the reduced gonococcal risk in vaccinated persons (10, 14). Data from population-level studies and immune responses in murine models (4–8, 14) provide evidence to support RCTs that evaluate the efficacy of MenB-4C vaccine against gonorrhea. Ongoing RCTs in populations with elevated incident gonorrhea rates will provide efficacy data critical to understanding anatomic-site specific MenB-4C vaccine efficacy (21, 22) and mechanism of vaccine-induced anti-gonococcal immune responses (22, 23).

There are limitations to this analysis. Because we did not systematically screen persons at all potentially infected anatomic sites, but relied on surveillance data, misclassification bias is possible as infections might have been acquired before vaccination but detected after vaccination. There may also have been missed, incomplete, or incorrect matches between the STI surveillance registry and the immunization information system. Although, the small prevalence of vaccinated persons (1.6%) in this sample may have also reduced

the power to detect a difference, we do not think this is the case because of the biological plausibility of MenB-4C vaccine effectiveness against gonorrhea and the growing body of vaccine effectiveness from various studies (8, 9). We defined vaccination as receipt of ≥1 MenB-FHbp dose which may explain the lack of observed MenB-FHbp effectiveness. However, a single MenB-4C dose was still effective against gonococcal mono-infection (8). Approximately one-third of responses for the race variable was missing and so the association with gonococcal mono-infection should be interpreted with caution.

In conclusion, the absence of observed effectiveness of MenB-FHb against gonococcal mono-infection supports the validity of the prior observational studies demonstrating modest effectiveness of OMV MenB vaccines against gonorrhea. RCTs examining the protective effect of MenB-4C vaccines against gonorrhea are essential to understanding its feasibility and prospect as an effective vaccine against gonorrhea.

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Table 1.

Socio-demographic, vaccination, and sexually transmitted infection characteristics among 16–23-year-old persons with a diagnosis of gonococcal mono-infection or chlamydial mono-infection — New York City and Philadelphia (2016–2018), N=96,235 persons (134,983 STI episodes)

Variable	N	%
Race/ethnicity		
Black, non-Hispanic	35,419	36.8
Hispanic	14,666	15.2
Other[1]	7,890	8.2
White, non-Hispanic	5,085	5.3
Missing	33,175	34.5
Gender		
Male	32,428	33.7
Female	63,751	66.3
Transgender	26	<1.0
Missing	30	<1.0
Ever received MenB-FHbp vaccine		
Yes[2]	1,500	1.6
No	94,735	98.4
Jurisdiction		
New York City	64,718	67.2
Philadelphia	31,517	32.8

[1] Asian, American Indian, Native Hawaiian/Pacific Islander, other race, or two or more races

[2] Receipt of ≥1 dose of MenB-FHbp vaccine

Table 2.

Association between MenB-4C vaccination and gonococcal mono-infection compared to chlamydial mono-infection— New York City and Philadelphia (2016–2018) (N=134,983 STI episodes)

Variable	UPR	95% CI	APR	95% CI
MenB-FHbp vaccination status				
Vaccinated[1]	0.89	0.76–1.06	0.97	0.79–1.19
Unvaccinated	1.00		1.00	
Race/ethnicity				
Black, non-Hispanic	0.96	0.90–1.02	0.94	0.88–1.01
Hispanic	0.73	0.68–0.78	0.72	0.67–0.79
Other[2]	0.80	0.74–0.86	0.79	0.71–0.86
White, non-Hispanic	1.00		1.00	
Gender				
Male	2.36	2.29–2.43	2.70	2.60–2.81
Female	1.00		1.00	
Jurisdiction				
New York City	0.74	0.71–0.76	1.07	1.02–1.11
Philadelphia	1.00		1.00	

UPR=Unadjusted prevalence ratio

APR=Adjusted prevalence ratio

CI=Confidence interval

[1]Receipt of ≥1 dose of MenB-FHbp vaccine

[2]Asian, American Indian, Native Hawaiian/Pacific Islander, other race, or two or more races