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Quadrivalent Conjugate Vaccine and Invasive Meningococcal Disease in US Adolescents and Young Adults

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Abstract

IMPORTANCE Beginning in 2005, the US implemented routine immunization of adolescents with a quadrivalent conjugate vaccine (MenACWY) for the prevention of invasive meningococcal disease (IMD).

OBJECTIVES To assess whether MenACWY immunization was associated with a reduced IMD burden among the US adolescent population and how the downward trajectory of IMD that began in the mid-1990s might have evolved in the absence of vaccination efforts.

DESIGN, SETTING, AND PARTICIPANTS In this decision analytical study, a bayesian hierarchical Poisson regression model was developed to investigate the potential trajectory of IMD among US adolescents and young adults without vaccination and evaluate the direct association of vaccination with IMD burden. The model included the entire age-stratified US population and was fitted to national incidence data for serogroups C, W, and Y from January 1, 2001, to December 31, 2021, with stratification by vaccination status for IMD cases.

INTERVENTION Simulated counterfactual scenario of absent vaccination from 2005 to 2021, while retaining the incidence rate of IMD for unvaccinated individuals estimated during model fitting.

MAIN OUTCOMES AND MEASURES The main outcomes were the estimated numbers of IMD cases and deaths averted by MenACWY vaccination among US adolescents and young adults aged 11 to 23 years.

RESULTS Among the entire US population from 2005 to 2021, MenACWY vaccination prevented an estimated 172 (95% credible interval [CrI], 85-345) cases of IMD among US adolescents 11 to 15 years of age and 328 (95% CrI, 164-646) cases of IMD among those aged 16 to 23 years. Absent vaccination, the cumulative incidence of IMD in these age groups would have been at least 59% higher than reported over the same period with vaccination. Using case fatality rates of unvaccinated individuals derived from national data, vaccination averted an estimated 16 (95% CrI, 8-31) deaths among adolescents aged 11 to 15 years and 38 (95% CrI, 19-75) deaths among those aged 16 to 23 years.

CONCLUSIONS AND RELEVANCE This decision analytical model suggests that the MenACWY vaccination program in the US was associated with a reduced burden of meningococcal disease. Without vaccination, the incidence rates per 100 000 adolescents and young adults would have been substantially higher than those observed during the vaccine era.

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Key Points

Question Has the quadrivalent conjugate vaccine (MenACWY) program in the US been associated with a reduced burden of invasive meningococcal disease (IMD) among adolescents?

Findings This decision analytical model found that the MenACWY vaccination program prevented an estimated 500 cases of IMD and 54 deaths among individuals aged 11 to 23 years in the US from 2005 through 2021. Without vaccination, the incidence of IMD would have been at least 59% higher than reported during the vaccine era.

Meaning This study suggests that the MenACWY vaccination program is meaningfully associated with reducing IMD incidence and associated mortality among adolescents and young adults in the US, highlighting its critical role in public health.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Meningococcal infection, caused by the bacterium *Neisseria meningitidis*, is associated with severe disease, most commonly meningitis or sepsis. Long-term sequelae include limb loss, skin scarring, seizures, and neurologic impairment, such as hearing and vision loss, among other disabilities.[1,2] Colonization with *N meningitidis* is common, particularly among older adolescents,[3] and is a substantial source of transmission to others. Twelve serogroups of *N meningitidis* have been identified, but most cases of invasive meningococcal disease (IMD) are caused by serogroups A, B, C, W, X, and Y worldwide.[4] The burden of IMD varies by country and region, ranging from less than 1 case per 100 000 population in some industrialized countries[5] to more than 100 cases during outbreaks in the meningitis belt of sub-Saharan Africa.[6] Although not typically a seasonal disease,[7] most cases tend to occur during the winter and early spring months.[8]

In the US, the first meningococcal conjugate vaccine (MenACWY) targeting serogroups A, C, W, and Y was recommended in 2005 as a single dose for routine immunization of adolescents aged 11 to 12 years.[9] As there is no infant meningococcal vaccine program, this was the primary dose. A booster dose at 16 years of age was recommended in late 2010[10] to address concerns regarding the waning of vaccine-induced immunity demonstrated at approximately 5 years after receipt of a primary dose.[11,12] Although the MenACWY vaccine has been effective in mitigating the risk of IMD,[12] assessing the population-level association of vaccination with IMD burden has proven challenging, in part due to a decreasing trend in IMD incidence among different age groups that began 8 years before the introduction of the vaccine program (eFigure 1 in Supplement 1). An evaluation of the association between MenACWY vaccination and the incidence of IMD in the US revealed that the introduction of primary and booster doses accelerated the decreasing rates of IMD by up to 3-fold in the vaccinated adolescent age groups.[13] In the period prior to the implementation of vaccination (2000-2005), the mean annual incidence of combined serogroups C, W, and Y disease among adolescents 11 to 15 years of age was estimated at 0.36 cases per 100 000 population, which decreased to 0.12 during the post–primary dose period (2006-2010) and further decreased to 0.01 cases per 100 000 population during the booster dose period (2011-2017). Mbaeyi et al[13] evaluated incidence rates after the implementation of vaccination recommendations and found that rates of decrease were more rapid in the targeted adolescent population; however, rates of decrease in disease were also observed in other age groups. The study, being ecologic in nature, did not evaluate IMD incidence in the absence of vaccination.

In this study, we evaluated the direct association of MenACWY vaccination with the incidence of IMD among adolescents and young adults 11 to 23 years of age. Using a bayesian hierarchical Poisson regression approach,[14] we estimated the age-specific incidence rates of IMD among unvaccinated individuals by fitting the model to national incidence data for serogroups C, W, and Y spanning the years 2001 to 2021 with a parameter associated with the vaccination status of individuals with reported IMD cases. We then simulated a counterfactual scenario in the absence of vaccination by setting the parameter of vaccination to zero, while retaining the estimated incidence rates for unvaccinated individuals across various age groups as determined by model fitting. The counterfactual scenario enabled the estimation of the number of IMD cases prevented by vaccination and allowed the quantification of incidence rates among adolescents and young adults in the hypothetical absence of vaccination.

Methods

Data provided by the US Centers for Disease Control and Prevention (CDC) contained no identifiable personal information; thus, no ethical approval or informed consent was required in accordance with York University research ethics guidelines for program evaluation activities relying on the secondary use of anonymous data. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guideline for decision analytical models and simulated modeling studies.[15]

Data and Inference

The annual incidence of IMD, stratified by serogroups C, W, and Y and by the age groups of younger than 1, 2 to 4, 5 to 10, 11 to 15, 16 to 23, 24 to 49, 50 to 64, and 65 years or older, from 2001 to 2021, was obtained from the CDC (eFigure 1 in Supplement 1). Due to the extremely low rates of serogroup A disease in the US (only 1 case was reported during the study period), this serogroup was omitted from our analysis. We also obtained mortality data associated with IMD from the CDC for the years 2001 to 2021 for all age groups.

Case counts of IMD were further stratified by individuals' vaccination status, which was available at the national level from 2014 onward as part of the CDC's Enhanced Meningococcal Disease Surveillance program. During the period from 2005 to 2013, vaccination status was available only from the CDC's Active Bacterial Core surveillance (ABCs) reports and limited to 10 participating sites.[16] We therefore used a maximum-likelihood approach to infer the status of vaccination among reported cases of IMD occurring in persons 11 to 15 and 16 to 23 years of age. Specifically, we estimated the probability of a reported case of IMD among both unvaccinated and vaccinated individuals. For this inference, we used the reported number of MenACWY vaccine failures that occurred between 2005 and 2008 among 54% of the US population,[17] ABCs incidence data from 2005 to 2013, and National Notifiable Diseases Surveillance System incidence data from 2005 to 2021, as well as the estimated annual vaccine uptake rates among these age groups (eFigures 2 and 3 in Supplement 1).[11,18,19] To estimate vaccine uptake rates, we constructed temporal trends of vaccination with at least 1 dose of the MenACWY vaccine among adolescents aged 11 to 18 years and at least 2 doses of MenACWY vaccine among those aged 11 to 18 years informed by data spanning the years from 2005 to 2022.[18,20] Estimates of the vaccination coverage for age groups 11 to 15 years and 16 to 18 years were then derived from Monte Carlo simulations (eFigures 4 and 5 in Supplement 1). To capture the temporal trend of IMD in the US prior to the implementation of the vaccination recommendations, we used age-stratified incidence rates per 100 000 population reported in the ABCs reports from 2001 to 2004 to extrapolate the number of IMD cases at the national level, adjusting for the population sizes of the age groups and their changes over the years.[21,22]

Bayesian Hierarchical Model

We considered IMD cases and their stratification as a 3-level nested dataset associated with variables of age (a), time strata (t), and vaccination status (ie, number of vaccine doses received; d). Because the data were counts, we used Poisson regression within a bayesian hierarchical approach to model the incidence,[14] expressed by $y_{a,t,d} \sim \text{Pois}\,[\exp(\lambda_{a,t,d})]$, $\lambda_{a,t,d} = \log(P_{a,t,d}) + \rho_a + \beta_t + \delta_d$, and $\beta_t \sim \text{normal}\,(0, \sigma_t)$, where $\exp(\rho_a)$ is the baseline incidence rate for unvaccinated individuals in age group a; β_t is associated with additional contemporaneous covariates capturing the trends in data; $\exp(\delta_d)$ accounts for the incidence rate in vaccinated individuals based on the number of vaccine doses (d) received; and $P_{a,t,d}$ is the population size of age group a, in year t, whose members are immunized with d doses of the MenACWY vaccine.

In this formulation, it is assumed that the risk of disease in unvaccinated individuals is not associated with vaccination and uptake rates. Thus, the model does not consider the indirect (herd) association of vaccination. The parameter δ_d, reflecting vaccine effectiveness, therefore accounts only for the direct association of vaccination given the number of IMD cases among vaccinated individuals and vaccine coverage determined by $P_{a,t,d}$. We used the data stratified by vaccination status (eMethods in Supplement 1) to derive the posterior distributions of δ_1 and δ_2 by considering case counts among those who were vaccinated with only 1 dose and those vaccinated with 2 doses of MenACWY, respectively. These data correspond to vaccine failures among age groups 11 to 15 years and 16 to 23 years (eMethods in Supplement 1). To derive the posterior distribution of ρ_a, we also used case counts among unvaccinated individuals in different age groups. Thus, $\exp(\rho_a + \beta_t)$ represents the incidence rate in the age group a adjusted over time. We assigned noninformative prior distributions to model parameters and estimated their posterior distributions of ρ_a, σ_t, β_t, and

δ_d by running 4 chains, each with 10 000 iterations, using NUTS (No-U-Turn sampler) in Monte Carlo simulations. Convergence of posterior distributions was tested using trace plots and the empirical density of the posterior samples (eFigures 6-9 in Supplement 1). We estimated the mean values and 95% bayesian credible intervals (CrIs) for the posterior distribution of model parameters (eTable in Supplement 1).

To estimate the number of IMD cases averted by vaccination, we set $\delta_d = 0$ to generate a counterfactual scenario without vaccination while sampling from the posterior distributions of ρ_a and β_t estimated from the model fit to observed data from January 1, 2001, to December 31, 2021 (eFigures 10 in Supplement 1). We then calculated the difference between expected cases in the counterfactual scenario ($\delta_1 = \delta_2 = 0$) and the model fit, retaining exp ($\rho_a + \beta_t$) for unvaccinated individuals, and derived 95% CrIs for averted cases as the direct association of vaccination. The model was implemented in the Julia programming language and is available online.[23]

Results

For the entire US population with stratification of ages younger than 1, 2 to 4, 5 to 10, 11 to 15, 16 to 23, 24 to 49, 50 to 64, and 65 years or older, we estimated that between 2005 and 2021, vaccine failures had occurred in 95 individuals, of whom 18 were vaccinated with more than 1 dose of MenACWY (eFigures 2 and 3 in Supplement 1). Fitting the bayesian model to observed data and simulating the counterfactual scenario (**Figure**, A), it was estimated that vaccination of adolescents aged 11 to 15 years averted 172 (95% CrI, 85-345) cases of IMD from 2005 to 2021 among this age group. The number of IMD cases averted among individuals aged 16 to 23 years by the US MenACWY vaccination program during the same period was estimated at 328 (95% CrI, 164-646) (Figure, C).

Absent vaccination, the cumulative incidence of IMD in these age groups would have been at least 59% higher than reported over the same period with vaccination. Based on the counterfactual scenario, the mean incidence rate of IMD per 100 000 population for combined serogroups C, W, and Y among adolescents aged 11 to 15 years would have been 0.17 (95% CrI, 0.08-0.35) from 2006 to 2010, 0.08 (95% CrI, 0.04-0.17) from 2011 to 2017, and 0.05 (95% CrI, 0.03-0.11) from 2018 to 2021 in the absence of vaccination (**Table**). Compared with the incidence rates of 0.12 per 100 000 population estimated during the primary dose period of 2006 to 2010 and 0.01 per 100 000 population estimated during the booster dose period of 2011 to 2017,[13] our estimates reveal elevated IMD rates without vaccination (Figure, B). Among those aged 16 to 23 years (Figure, D), the incidence rate of IMD per 100 000 population would have been 0.27 (95% CrI, 0.13-0.56) from 2006 to 2010, 0.13 (95% CrI, 0.07-0.28) from 2011 to 2017, and 0.09 (95% CrI, 0.04-0.18) from 2018 to 2021 in the absence of vaccination. Our estimate for 2006 to 2010 among this age group is comparable with the previously estimated rate of 0.31 per 100 000 population in the presence of vaccination.[13] However, the mean annual rate of IMD per 100 000 population of 16- to 23-year-olds in the counterfactual scenario was higher than the rate of 0.07 estimated for the booster dose period of 2011 to 2017.[13]

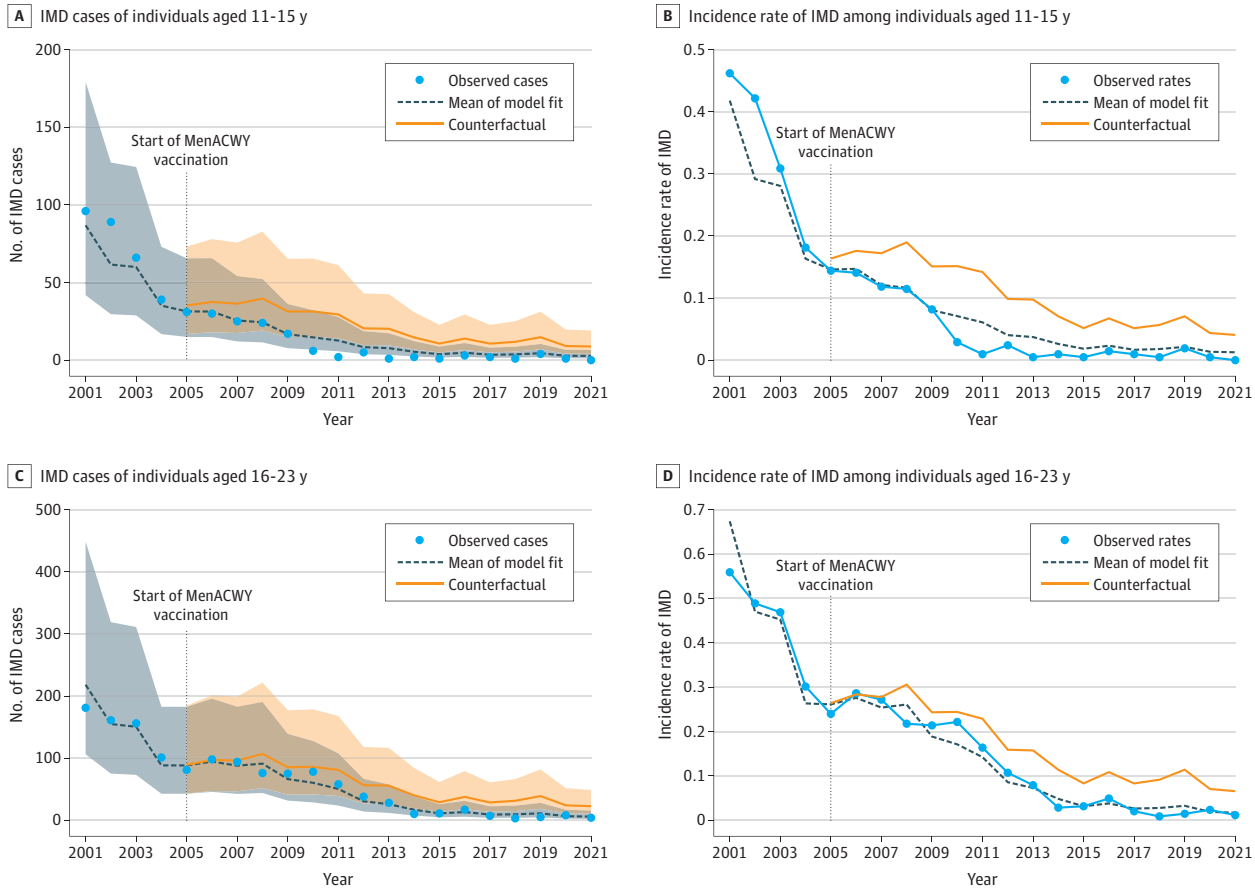
The case fatality rates associated with serogroups C, W, and Y were calculated to be 9.1% among unvaccinated individuals aged 11 to 15 years and 11.6% among unvaccinated individuals aged 16 to 23 years. Applying case fatality rates to additional cases of IMD in the counterfactual scenario, we estimated that primary and booster doses of MenACWY vaccines prevented 16 (95% CrI, 8-31) deaths among adolescents aged 11 to 15 years and 38 (95% CrI, 19-75) deaths among those aged 16 to 23 years.

Discussion

The continuous decrease in the incidence of IMD across all age cohorts in the US since its last peak in the mid-1990s has posed challenges in assessing the association of MenACWY vaccination with IMD

burden among adolescents. Although vaccination efforts appear to have accelerated this downward trend,[13] there has been a lack of exploration into the potential trajectory of IMD incidence in the absence of vaccination. In this study, we used a bayesian hierarchical regression model to investigate this trajectory among age groups eligible for adolescent vaccination and to estimate the number of IMD cases prevented over a span of 17 years (2005-2021). Our analysis revealed that without vaccination, an additional 500 cases of IMD would have occurred among individuals aged 11 to 23 years, with approximately 66% of them being among those aged 16 to 23 years. As reported,[16] the incidence rate of IMD among older adolescents was also higher with vaccination, which could partly be associated with a considerably lower uptake rate of the booster dose compared with the primary dose. Vaccination coverage with a single dose of MenACWY among adolescents aged 11 to 15 years

Figure. Model Fit and Simulated Counterfactual Scenario



Model fit (dark blue dashed line) to observed data (light bue dots) with 95% credible intervals (shaded areas) for vaccine-eligible age groups 11 to 15 years (A) and 16 to 23 years (C). The counterfactual scenario without vaccination is shown by the orange line. Annual incidence rates of invasive meningococcal disease (IMD) per 100 000 population of age groups 11 to 15 years (B) and 16 to 23 years (D). Incidence rates were adjusted for the population size over the study period. MenACWY indicates quadrivalent conjugate vaccine for invasive meningococcal disease.

Table. Estimated Incidence Rates per 100 000 Population of Adolescents and Young Adults for Different Time Periods in the Counterfactual Scenario Without Vaccination

	Incidence rates without vaccination (95% CrI)	
Time period	Aged 11-15 y	Aged 16-23 y
2006-2010	0.17 (0.08-0.35)	0.27 (0.13-0.56)
2011-2017	0.08 (0.04-0.17)	0.13 (0.07-0.28)
2018-2021	0.05 (0.03-0.11)	0.09 (0.04-0.18)

Abbreviation: CrI, credible interval.

increased from 13% in 2005 to approximately 81% in 2021 (eFigure 4 in Supplement 1). Although the uptake of the booster dose among those aged 16 to 23 years has increased since its introduction in 2010, it remained less than 60% in 2021 (eFigure 5 in Supplement 1).

During the vaccine era between 2005 and 2021, there were 846 IMD cases reported among adolescents and young adults aged 11 to 23 years (eFigure 1 in Supplement 1). Absent vaccination, the incidence of IMD in this population would have been at least 59% higher over the same period. When considering age groups separately, the incidence of IMD without vaccination would have been 110% higher among adolescents aged 11 to 15 years and 47% higher among those aged 16 to 23 years compared with the reported 155 and 691 cases of IMD, respectively, after the implementation of vaccination during the aforementioned period.

A previous study estimated that, from 2006 to 2017, vaccination among adolescents aged 11 to 15 years prevented 66 (95% CI, 8-144) cases of IMD due to serogroups C, W, and Y.[13] For the same period, our assessment indicated that 137 (95% CrI, 68-275) cases were averted within this age cohort. In addition, the antecedent study also inferred that, during the booster period from 2011 to 2017, vaccination averted 156 (95% CI, 92-239) cases of IMD due to serogroups C, W, and Y among individuals aged 16 to 22 years.[13] Our evaluation, which extended to include 23-year-olds during the same period, estimated 171 (95% CrI, 86-338) cases of IMD prevented. Overall, our cumulative projection of 308 is a 1.4-fold increase of the previous estimate of 222.

The estimates of averted IMD cases reported here are likely conservative, given that our model considers only the direct association of vaccination with IMD cases by analyzing case counts by vaccination status. Previous studies highlighted the importance of herd immunity in routine immunization programs and provided evidence for the use of the MenACWY vaccine to confer indirect (herd) protection.[24-27] Further studies, using dynamic models, could quantify the reduction in transmission and circulation of *N meningitidis* serogroups due to the indirect benefits associated with vaccination.

Limitations

Our study has several limitations. Although we considered data stratified by vaccination status in different age groups, the risk of disease for unvaccinated individuals is implicitly associated with the indirect outcomes of vaccination. Thus, our analysis may still underestimate the benefits associated with vaccination among adolescents and young adults. Given the nature of data, we were not able to distinguish the benefits associated with vaccination by the number of vaccine doses received. The model assumes that the effectiveness of the MenACWY vaccination in preventing IMD is the same for each serogroup, when the extent of protection is likely serogroup dependent.[12] Serogroups C and Y were the most prevalent during the analyzed period, for which the effectiveness of 1 dose of MenACWY vaccine has been estimated at 77% and 51%, respectively, with overlapping confidence intervals.[12] Thus, our analysis may underestimate the number of IMD cases averted during the years when serogroup C was highly prevalent relative to serogroup Y, while potentially overestimating cases averted during the years when serogroup Y was dominant. The model considers covariates of age, time, number of vaccine doses, and vaccination status of individuals with reported cases but does not account for other potential exogenous confounders or the geographic distribution of cases. For vaccination coverage, we treated adolescent age groups as a homogeneous population without considering race, ethnicity, socioeconomic status, health insurance status,[28] or regional disparities,[29] which could introduce selection bias into our analysis. Although we were unable to address these factors using IMD data, they could be associated with vaccination uptake and may, therefore, influence the risk of disease and outcomes. For stratification by vaccination status prior to 2014, we used an optimization method to infer the status of IMD cases reported at the national level based on data and information available from the ABCs sites. In this process, we assumed that the risk of disease was homogeneous temporally, geographically, and within each age group. Our model does not account for local or time-dependent variations in the incidence rate that might describe an outbreak scenario; however, because such outbreaks occur sporadically and account for a small

proportion (approximately 5%) of IMD cases across all age groups in the US,[30] our results would still be relevant at the national level.

Conclusions

In this decision analytical model study, we provided additional evidence that vaccination against serogroups A, C, W, and Y of *N meningitidis* was associated with a reduced burden of IMD among adolescents and young adults in the US. Given the severity of the disease and its potential lifetime sequelae, any decrease in vaccine uptake or in the level of protection within the US population could become a public health concern, especially during the high-risk period of late adolescence and early adulthood. In light of the ongoing discussions regarding potential changes to the adolescent meningococcal vaccine schedule for both primary and booster doses,[31] additional studies are needed to accurately quantify the association of altering schedules with incidence rates and the overall burden of disease across different age demographics.

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Author Contributions: Dr Moghadas had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Statistical analysis: Wells, Shoukat, Moghadas.

Obtained funding: Shin, Moghadas.

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Supervision: Moghadas.

Conflict of Interest Disclosures: Mr Shin reported being a Sanofi employee during the submitted work. Ms Langevin reported being a Sanofi employee and holding Sanofi shares/stock options during the conduct of the study. Dr Langley reported receiving grants from GSK paid to employer for conduct of research, grants from Moderna paid to employer for conduct of vaccine studies, grants from Sanofi paid to employer for conduct of vaccine studies, and grants from Pfizer paid to employer for conduct of vaccine studies outside the submitted work; and serving as senior medical advisor for the Meningitis Foundation of Canada. Dr Galvani reported receiving personal fees from Sanofi Pasteur during the conduct of the study. Dr Moghadas reported receiving personal fees from Sanofi during the conduct of the study. No other disclosures were reported.

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SUPPLEMENT 1.

eFigure 1. Trends in Meningococcal Disease Caused by Serogroups A, C, W, and Y in the US by Age Groups From 2001 to 2021
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SUPPLEMENT 2.
Data Sharing Statement