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Incidence of Meningococcal Disease Before and After Implementation of Quadrivalent Meningococcal Conjugate Vaccine in the United States

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IMPORTANCE In 2005, the US Advisory Committee on Immunization Practices recommended routine quadrivalent meningococcal conjugate (MenACWY) vaccine for all adolescents aged 11 to 12 years, and in 2010, a booster dose for adolescents aged 16 years. Measuring the association between MenACWY vaccination and the incidence of meningococcal disease in adolescents is critical for evaluating the adolescent vaccination program and informing future vaccine policy.

OBJECTIVE To describe the association between MenACWY vaccination and the incidence of meningococcal disease in US adolescents.

DESIGN, SETTING, AND PARTICIPANTS In this cohort study, analysis of surveillance data included all confirmed and probable cases of *Neisseria meningitidis* reported to the National Notifiable Diseases Surveillance System from January 1, 2000, to December 31, 2017. Statistical analysis was conducted from October 1, 2018, to August 31, 2019.

EXPOSURES Routine MenACWY vaccination among US adolescents.

MAIN OUTCOMES AND MEASURES Poisson segmented regression analysis was used to model the annual incidence of meningococcal disease among adolescents aged 11 to 15 years and 16 to 22 years before the introduction of the MenACWY vaccine (2000-2005), after the primary dose recommendation (2006-2010), and after the booster dose recommendation (2011-2017); 95% CIs were used to determine significant differences between time periods.

RESULTS The national incidence of meningococcal disease declined from 0.61 cases per 100 000 population during the prevaccine period (2000-2005) to 0.15 cases per 100 000 population during the post–booster dose period (2011-2017). The greatest percentage decline was observed for serogroup C, W, and Y combined (CWY) among adolescents aged 11 to 15 years and 16 to 22 years in the periods after vaccine introduction. Incidence of serogroup CWY meningococcal disease among adolescents aged 11 to 15 years decreased by 16.3% (95% CI, 12.1%-20.3%) annually during the prevaccine period and 27.8% (95% CI, 20.6%-34.4%) during the post–primary dose period ($P = .02$); among adolescents aged 16 to 22 years, the incidence decreased by 10.6% (95% CI, 6.8%-14.3%) annually in the post–primary dose period and 35.6% (95% CI, 29.3%-41.0%) annually in the post–booster dose period ($P < .001$). An estimated 222 cases of meningococcal disease due to serogroup CWY among adolescents were averted through vaccination during the evaluation period.

CONCLUSIONS AND RELEVANCE After introduction of a primary and booster MenACWY dose, the rates of decline in incidence of meningococcal disease due to serogroup C, W, or Y accelerated nearly 2-fold to 3-fold in vaccinated adolescent age groups. Although the MenACWY vaccine alone cannot explain the decline of meningococcal disease in the United States, these data suggest that MenACWY vaccination is associated with reduced disease rates in adolescents.

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Supplemental content

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Meningococcal disease is a serious bacterial infection caused by *Neisseria meningitidis* leading to high rates of death and disability.[1] In the United States, serogroups B, C, and Y cause most meningococcal infections.[2] Although the incidence of meningococcal disease is highest in infants, adolescents and young adults have an increased risk of meningococcal disease as well as the highest rates of oropharyngeal carriage, and thus are considered to be the primary source of *N meningitidis* transmission to other age groups.[3] As a result, adolescents are the primary target group for meningococcal vaccination in the United States.

In 2005, the US Advisory Committee on Immunization Practices (ACIP) recommended that all adolescents aged 11 to 18 years receive a quadrivalent meningococcal conjugate (MenACWY) vaccine, with the first dose to be administered at 11 to 12 years of age.[4] Although the effectiveness of a single MenACWY dose among adolescents was estimated to be 79% in the first year, immunity waned in the 3 to 7 years after vaccination.[5] To help extend protection in older adolescents, in 2010, the ACIP recommended a booster MenACWY dose at 16 years of age.[4] By 2017, estimated coverage of 1 or more dose of MenACWY among adolescents aged 13 to 17 years was 85.1% and of 2 or more doses among those aged 17 years was 44.3%.[6]

The incidence of meningococcal disease in the United States has declined since the late 1990s to current historic lows. This decline began prior to the introduction of the MenACWY vaccine and has been observed across age groups and the primary disease-causing serogroups.[2] Although challenging in this context, measuring the direct association between MenACWY vaccination and disease incidence in adolescents as well as the indirect association in individuals among nonvaccinated age groups through herd protection is critical for evaluating the adolescent vaccination program and to inform future vaccine policy. In this analysis, we evaluate the association between MenACWY vaccination and the incidence of meningococcal disease in the years after both the primary dose and booster dose recommendations in the United States.

Key Points

Question What is the association between the quadrivalent meningococcal conjugate vaccination program in adolescents and incidence of meningococcal disease in the United States?

Findings The incidence of meningococcal disease was declining prior to introduction of the vaccine. However, in this cohort study of surveillance data, the rates of decline in incidence of meningococcal disease due to serogroups C, W, and Y accelerated nearly 2-fold to 3-fold in vaccinated age groups, with greater rates of decline in states with high quadrivalent meningococcal conjugate vaccine coverage.

Meaning Although the quadrivalent meningococcal conjugate vaccine alone cannot explain the decline of the incidence of meningococcal disease in the United States, these data suggest an association between vaccination and declining disease rates in adolescents.

Methods

In the United States, surveillance for meningococcal disease is conducted through the National Notifiable Diseases Surveillance System (NNDSS).[7] Data from complementary meningococcal disease surveillance systems were used to complete serogroup information on cases if they were missing from the NNDSS: Active Bacterial Core surveillance ([ABCs], which included 14% of the US population by 2017[8]) and enhanced meningococcal disease surveillance activities (progressively implemented since 2005 to include 98% of the US population by 2017).[9] Because of the low proportion of NNDSS cases with known serogroup from 2000 to 2004 (33%) compared with the higher proportion of cases with known serogroup from 2005 to 2017 (79.8%), these complementary surveillance systems were also used to estimate the national serogroup distribution of cases with unknown serogroup. Analysis of anonymized data collected through routine surveillance systems was determined by human participants' review at the Centers for Disease Control and Prevention to be public health nonresearch; patient consent and institutional review board review was not required.

For cases of meningococcal disease reported from 2000 to 2004, serogroup data from the ABCs (known in 93.9% of cases) was used to estimate the proportion of cases due to serogroup C, W, and Y combined (CWY); serogroup B; or other serogroups in the NNDSS when serogroup was unknown, using a multinomial logistic regression model with patient age group and case year included as covariates. To account for the variability of estimated serogroup proportions, we sampled 10 new sets of parameter estimates using the covariance matrix and parameter estimates from the original multinomial logistic regression model as the variance and the mean of a multinomial normal distribution and then multiplied these serogroup proportions by total cases within the defined subgroups. For cases from 2005 to 2017, NNDSS data alone were used in the multinomial logistic regression model to estimate the proportion of cases by serogroup for cases with unknown serogroup. For both models, we assumed that serogroup was missing at random. Because of increased rates of serogroup B disease in Oregon relative to other states, estimates were derived for Oregon and all other states separately, with cases subsequently compiled to create a national data set, as previously described.[10]

The estimated incidence by case year, patient age group, and serogroup was calculated using population denominators from 2000 to 2017 produced by the US Census Bureau in collaboration with the National Center for Health Statistics.[11] Two MenACWY vaccines were licensed for use in adolescents during the evaluation period: Menactra (Sanofi Pasteur Inc) in 2005 and Menveo (GlaxoSmithKline) in 2010. We estimated vaccination coverage of any MenACWY vaccine from the National Immunization Survey-Teen, an annual survey that estimates clinician-reported vaccination coverage among US adolescents aged 13 to 17 years, using SAS-callable SUDAAN, release 11.0.3 (RTI International).[6] States were grouped into categories based on primary dose MenACWY coverage among adolescents aged 13 to 15 years in 2017 (as a proxy for rate of and level of vaccine uptake) and booster dose coverage among

adolescents aged 16 to 17 years from 2014 to 2017 (as state-level data became available in 2014; data was averaged over 4 years to produce stable state-level coverage results). High MenACWY coverage was defined as 80% or more primary dose coverage and 50% or more mean booster dose coverage. Medium MenACWY coverage was defined as 80% or more primary dose coverage and less than 50% mean booster dose coverage. Low MenACWY coverage was defined as less than 80% primary dose coverage and less than 50% booster dose coverage. No states had primary dose coverage of less than 80% and mean booster dose coverage of 50% or more. Because the ACIP recommended serogroup B meningococcal (MenB) vaccine in adolescents aged 16 to 23 years based on shared clinical decision-making in October 2015 and coverage of 1 or more MenB dose in adolescents was low in 2017 at 14.5% among adolescents aged 17 years,[6,12] we assumed that MenB vaccination had a negligible association with disease rates due to any serogroup.

Statistical analysis was conducted from October 1, 2018, to August 31, 2019. Poisson segmented regression analysis was used to measure the association of MenACWY vaccination among adolescents aged 11 to 15 years and 16 to 22 years, as well as indirect associations in other age groups. We assumed that the annual case counts followed a Poisson distribution and used the logarithm of the US population as an offset. We estimated the annual percentage change in meningococcal disease incidence by age group before MenACWY vaccine introduction (2000-2005), after the primary dose recommendation (2006-2010), and after the booster dose recommendation (2011-2017), as well as by state-level MenACWY coverage categories. Other MenACWY coverage thresholds than those described above were also assessed; while annual percentage change varied by coverage threshold selected, overall trends were similar. Thus, only results for the above-described coverage categories are presented. We included year as a continuous covariate in the model and added 2 additional continuous covariates to test for significant changes in the slope, or the rate of change in incidence, between time periods. The 95% CIs were calculated, and a 2-tailed $P < .05$ was used to determine significant differences in the annual percentage change in incidence between groups and time periods. The number of cases due to serogroup CWY averted through MenACWY vaccination among adolescents was estimated by subtracting the annual number of cases observed during the postvaccination periods from the estimated number of cases if the rates of reduction in incidence observed during the prevaccination period had remained constant. Analyses were conducted using SAS, version 9.4 (SAS Institute Inc).

Results

Descriptive Epidemiology

From 2000 to 2017, a total of 19 207 cases of meningococcal disease were reported in the United States: 10 556 cases (0.61 cases/100 000 population) during the prevaccine period from 2000 to 2005, 5251 cases (0.35 cases/100 000 population) during the post-primary dose period from 2006 to 2010, and 3400 cases (0.15 cases/100 000 population) during the post-booster dose period from 2011 to 2017. Incidence declined in all age groups and for serogroups CWY and B during the evaluation period (eTable 1 in the Supplement).

Although the greatest absolute reductions in incidence due to serogroup CWY were among infants younger than 1 year, adolescents experienced the greatest percentage reductions in incidence due to serogroup CWY during the postvaccination periods. During the post-primary dose period from 2006 to 2010, vaccine-eligible adolescents aged 11 to 15 years had a 67.0% reduction in incidence due to serogroup CWY compared with the prevaccine period. During the post-booster dose period, vaccine-eligible adolescents aged 11 to 15 years experienced an 88.8% reduction in serogroup CWY incidence, and those aged 16 to 22 years experienced a 77.2% reduction in serogroup CWY incidence (eTable 1 in the Supplement).

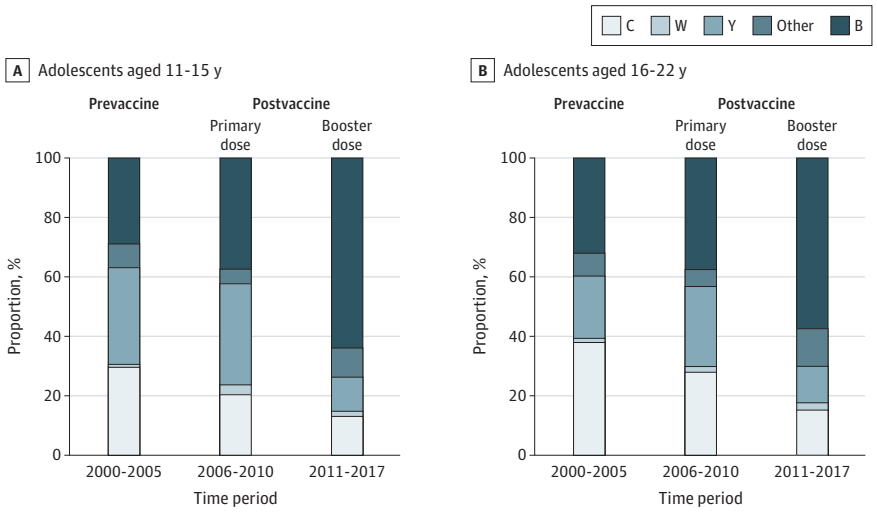
The proportion of total cases that were due to serogroup CWY declined among adolescents aged 11 to 15 years from 62.2% before vaccination to 27.9% in the post-booster dose period. Among adolescents aged 16 to 22 years, the proportion of cases due to serogroup CWY declined from 60.1% before vaccination to 30.6% in the post-booster dose period (**Figure 1**; eTable 1 in the Supplement). These declines were observed for both serogroups C and Y, the predominant vaccine-preventable serogroups during the evaluation period; the proportion of cases due to serogroup W remained stably low (Figure 1). In contrast, the serogroup distribution among other age groups remained relatively consistent during the evaluation period despite declines in incidence (eTable 1 in the Supplement).

Direct Vaccine Association in Adolescents

By Poisson segmented regression analysis, the estimated incidence of serogroup CWY meningococcal disease among adolescents aged 11 to 15 years decreased by 16.3% (95% CI, 12.1%-20.3%) annually during the prevaccine period and 27.8% (95% CI, 20.6%-34.4%; $P = .02$) during the post-primary dose period; the rate of decrease remained stable during the post-booster dose period (**Figure 2**A; eFigure and eTable 2 in the Supplement). States with high and medium MenACWY coverage experienced larger reductions in serogroup CWY disease incidence during the post-primary dose period compared with states with low MenACWY coverage (Figure 2B; eTable 3 in the Supplement). During the post-booster dose period, no cases due to serogroup CWY were observed among adolescents aged 11 to 15 years in states with high coverage. In states with low MenACWY primary dose coverage, there was no significant change in incidence reduction between time periods (Figure 2B; eTable 3 in the Supplement). From 2006 to 2017, an estimated 66 (95% CI, 8-144) cases of meningococcal disease due to serogroup CWY were averted through vaccination among adolescents aged 11 to 15 years.

Among adolescents aged 16 to 22 years, the incidence of serogroup CWY disease decreased by 10.6% (95% CI, 6.8%-14.3%) annually in the post-primary dose period and 35.6% (95% CI, 29.3%-41.0%; $P < .001$) annually during the post-booster dose period (**Figure 3**A; eFigure and eTable 2 in the Supplement), while the annual incidence of serogroup B disease slightly increased. States with high MenACWY coverage

Figure 1. Estimated Serogroup Distribution by Time Period—United States, 2000-2017



A, Adolescents aged 11 to 15 years. B, Adolescents aged 16 to 22 years. Nongroupable accounts for the majority of cases with "other" serogroup.

had the greatest percentage declines in serogroup CWY disease incidence during the post-booster dose period, although this difference was not significant (Figure 3B; eTable 3 in the Supplement). From 2011 to 2017, an estimated 156 (95% CI, 92-239) cases of meningococcal disease due to serogroup CWY were averted through vaccination among adolescents aged 16 to 22 years.

Indirect Associations in Individuals in Unvaccinated Age Groups

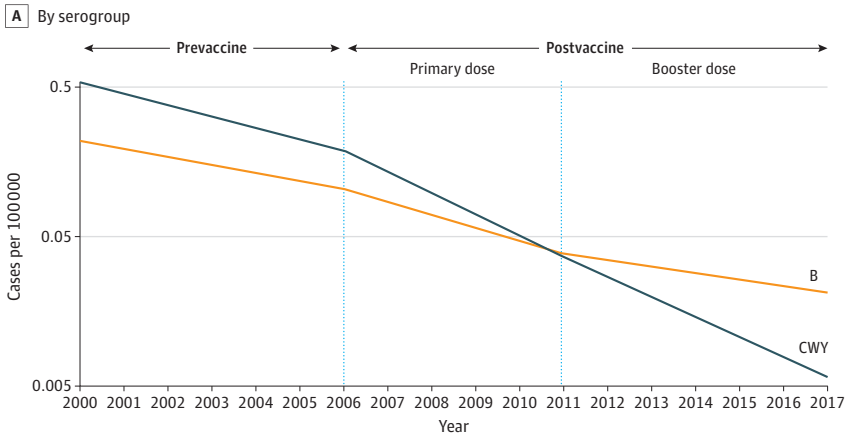
Among individuals in unvaccinated age groups, the annual percentage decline in serogroup CWY disease incidence during the post-primary dose period did not change significantly compared with the prevaccine period (**Figure 4**; eFigure and eTable 2 in the Supplement). However, during the post-booster dose period, annual percentage reductions in serogroup CWY disease incidence, which were significantly different than those observed for serogroup B, were observed in infants younger than 1 year and in adults 65 years or older. For all unvaccinated age groups, annual percentage decreases in serogroup CWY disease incidence during the post-booster period were larger for states with high vs medium vs low MenACWY coverage, although the results were not consistently significant (eTable 3 in the Supplement).

Discussion

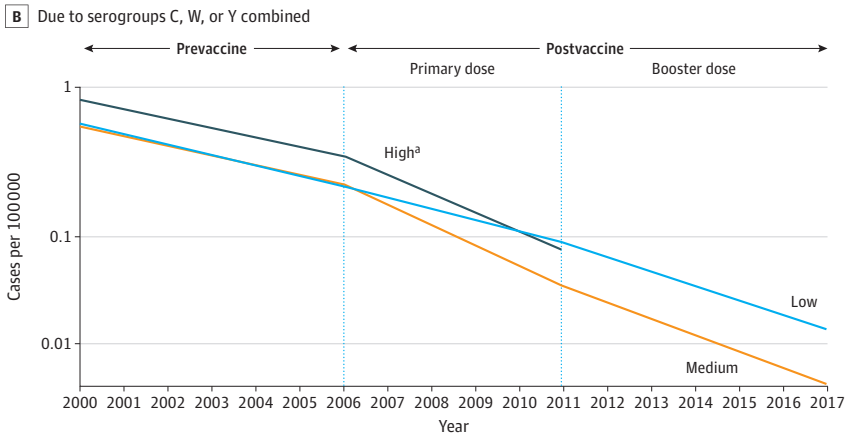
From 2000 to 2017, a sustained decline in the incidence of meningococcal disease was observed among all age groups and for the major disease-causing serogroups in the United States; these declines began prior to the introduction of the adolescent MenACWY vaccination program. However, the rates of decline in incidence accelerated nearly 2-fold to 3-fold in vaccinated age groups, from approximately 16% to 27% or 28% after the introduction of a primary MenACWY dose among adolescents aged 11 to 12 years and from 11% or 15% to 36% after introduction of a booster dose in adolescents aged 16 years. Furthermore, among all age groups, adolescents experienced the greatest percentage decline in incidence and the greatest reduction in the proportion of cases due to serogroup CWY. The trends in greater declines in serogroup CWY disease incidence in states with higher MenACWY coverage suggest that these declines may be vaccine related as opposed to natural evolutionary changes alone. We estimate that 222 cases of meningococcal disease due to serogroup CWY have been averted through vaccination of adolescents from 2006 to 2017. Although the number of cases of meningococcal disease averted is modest compared with other vaccination programs in the United States,[13] preventing meningococcal disease is important from a public health perspective because of the consequences of the infection on the individual and community.

Given the low overall booster dose coverage observed, it is difficult to separate the association between the addition of the booster dose at age 16 years and residual primary dose immunity in an aging adolescent cohort on the incidence of meningococcal disease in older adolescents. Immunogenicity and observational studies demonstrate waning immunity 3 to 5 years after MenACWY primary vaccination; booster vaccination elicits an anamnestic response, with evidence of greater immune persistence to serogroups C, W, and Y after the booster dose compared with the primary dose.[5,14-19] Although both primary and booster MenACWY vaccination were likely associated with substantial reductions in incidence of meningococcal disease in adolescents, higher incidence in older adolescents, potential indirect associations in other age groups after introduction of the booster dose, and the greatest declines in incidence among both younger and older adolescents in states with the highest booster dose coverage (irrespective of primary dose coverage) suggest that vaccinating older adolescents may be the most efficient vaccination strategy if high coverage can be achieved.

Figure 2. Estimated Log Annual Incidence and Annual Percentage Change in Meningococcal Disease Incidence Among Adolescents Aged 11 to 15 Years—United States, 2000-2017



Period	Serogroup	
	CWY % (95% CI)	B % (95% CI)
2000-2005	-16.3 (-20.3 to -12.1)	-11.8 (-18.6 to -4.4)
2006-2010	-27.8 (-34.4 to -20.6)	-18.0 (-26.2 to -8.9)
2011-2017	-26.5 (-39.0 to -11.4)	-9.5 (-20.8 to 3.4)



Period	Serogroups CWY by state-level MenACWY coverage[b]		
	Low coverage % (95% CI)	Medium coverage % (95% CI)	High coverage % (95% CI)
2000-2005	-17.2 (-25.9 to -8.6)	-16.2 (-18.1 to -10.4)	-15.7 (-25.9 to -4.9)
2006-2010	-18.6 (-33.0 to -3.0)	-30.8 (-39.3 to -21.3)	-30.0 (-45.1 to -7.7)
2011-2017	-23.0 (-45.1 to 3.0)	-25.3 (-39.3 to -3.9)	-100.0 (-100 to -0)

A, By serogroup. B, Due to serogroup C, W, or Y combined (CWY) by state-level quadrivalent meningococcal conjugate (MenACWY) vaccine coverage. Vertical axis shows the incidence rates transformed from the log scale.

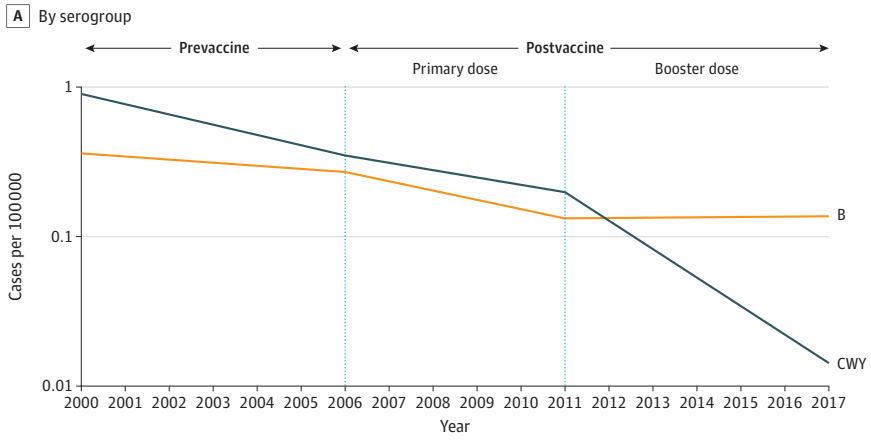
[a] No cases due to serogroup CWY reported in states with high coverage during the post–booster dose period.

[b] Categorized based on primary dose MenACWY coverage in adolescents aged 13 to 15 years during 2017 and mean booster dose coverage among adolescents aged 16 to 17 years during the period from 2014 to 2017 (low, primary dose coverage <80% and mean booster dose coverage <50%; medium, primary dose coverage ≥80% and mean booster dose coverage <50%; high, primary dose coverage ≥80% and mean booster dose coverage ≥50%).

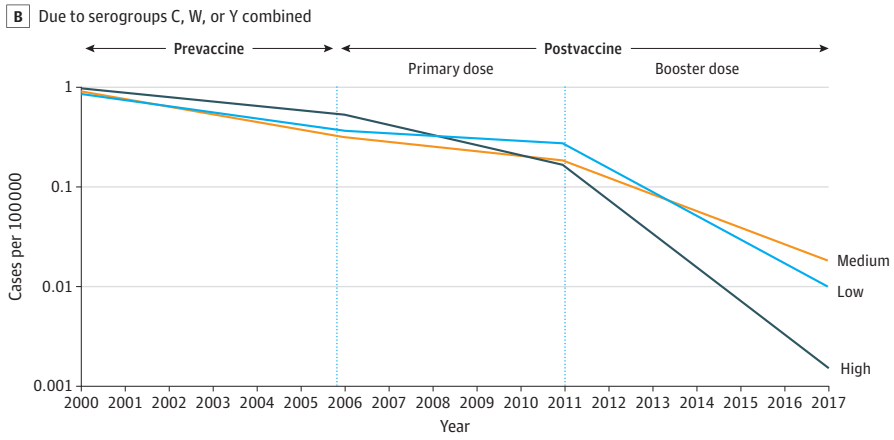
Vaccination of adolescents has been proposed as a strategy to reduce meningococcal disease incidence among other age groups through herd protection given that adolescents have the highest rates of meningococcal carriage and are considered to be the primary transmitters to other age groups.[3,20] Although vaccination with monovalent meningococcal conjugate vaccines against serogroup A and C has been demonstrated to reduce oropharyngeal meningococcal carriage and induce herd protection to unvaccinated persons,[21,22] evidence is limited for MenACWY vaccines, to our knowledge.[23-25] In our analysis, we observed faster rates of decline in serogroup CWY incidence in infants and older adults in the post-booster dose period compared with pre-booster dose periods, with trends in greater reductions in states with higher MenACWY coverage. However, it may be too early to conclude that these increased incidence reductions in unvaccinated groups are primarily due to herd protection from adolescent vaccination; further increases in booster dose coverage will be useful to better assess the association between adolescent MenACWY vaccination and disease rates in other age groups.

Additional factors besides vaccination were likely associated with the marked declines in the incidence of meningococcal disease observed in all age groups and for the primary disease-causing serogroups. Improvements in environmental conditions, such as reduced crowding, may be a factor. In addition, as smoking is a risk factor for meningococcal carriage and disease, one possible associated factor is decreased rates of smoking and secondhand smoke exposure, although

Figure 3. Estimated Log Annual Incidence and Annual Percentage Change in Meningococcal Disease Incidence Among Adolescents Aged 16 to 22 Years—United States, 2000-2017



Period	Serogroup	
	CWY % (95% CI)	B % (95% CI)
2000-2005	-14.6 (-17.0 to -12.1)	-4.7 (-8.4 to -0.9)
2006-2010	-10.6 (-14.3 to -6.8)	-13.3 (-17.4 to -9.0)
2011-2017	-35.6 (-41.0 to -29.3)	0.5 (-4.4 to 5.8)



Period	Serogroups CWY by state-level MenACWY coverage[a]		
	Low coverage % (95% CI)	Medium coverage % (95% CI)	High coverage % (95% CI)
2000-2005	-15.8 (-20.7 to -10.6)	-14.9 (-18.0 to -11.8)	-8.4 (-15.3 to -0.9)
2006-2010	-8.1 (-12.6 to 0.8)	-10.4 (-15.0 to -5.4)	-23.5 (-35.2 to -9.8)
2011-2017	-38.1 (-49.6 to -24.0)	-31.9 (-38.4 to -24.6)	-56.7 (-79.2 to -9.9)

A, By serogroup. B, Due to serogroup C, W, or Y combined (CWY) by state-level quadrivalent meningococcal conjugate (MenACWY) vaccine coverage. Vertical axis shows the incidence rates transformed from the log scale.

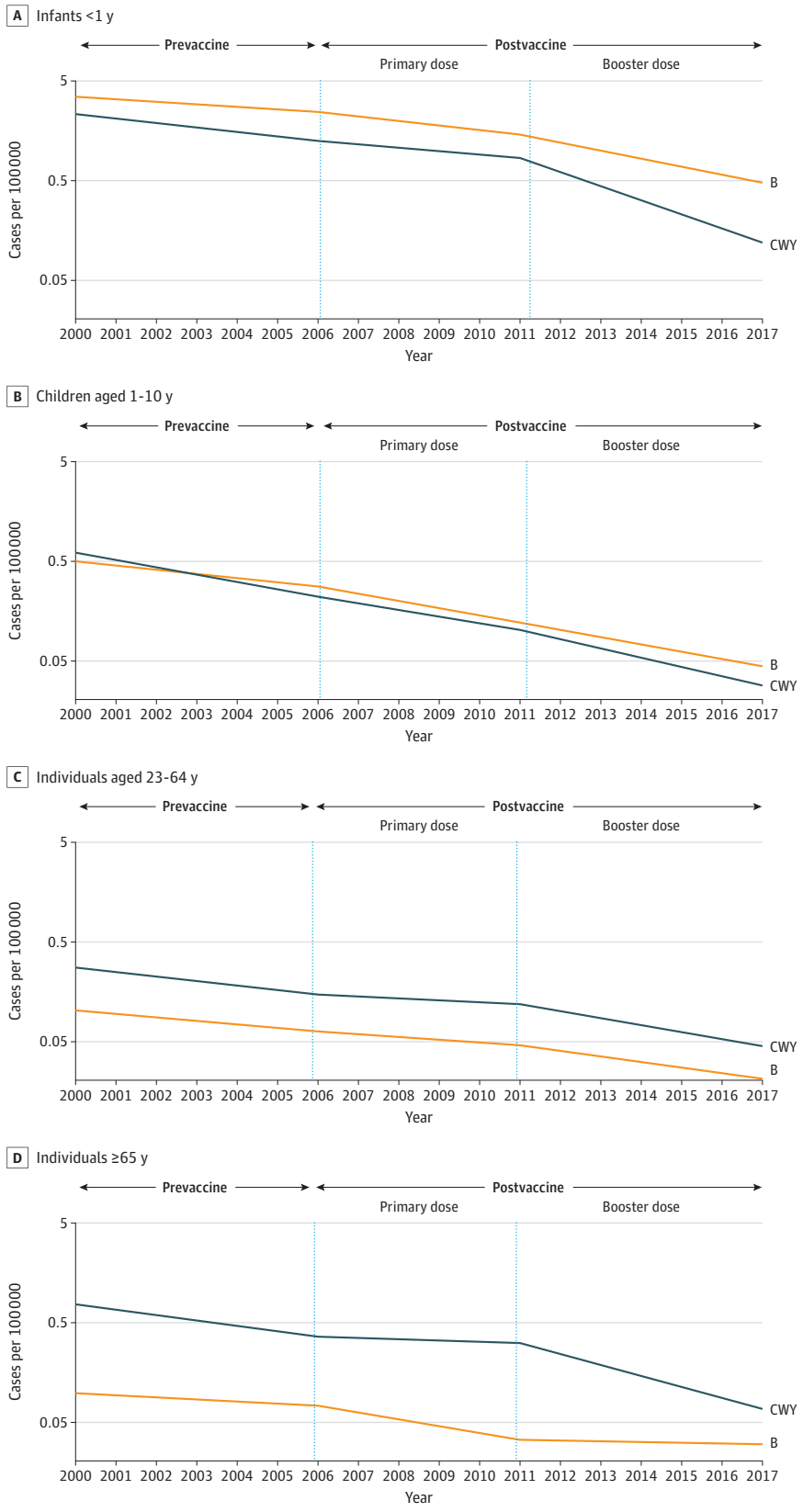
[a] Categorized based on primary dose MenACWY coverage in adolescents aged 13 to 15 years during 2017 and mean booster dose coverage among adolescents aged 16 to 17 years during the period from 2014 to 2017 (low, primary dose coverage <80% and mean booster dose coverage <50%; medium, primary dose coverage ≥80% and mean booster dose coverage <50%; high, primary dose coverage ≥80% and mean booster dose coverage ≥50%).

rates of e-cigarette use have increased recently in US adolescents.[26-29] In addition, changes in social mixing patterns among teens, such as decreases in bar and pub attendance and intimate kissing, have been implicated in reduced meningococcal carriage rates in the United Kingdom.[30] Furthermore, fluoroquinolones and other antibiotics that clear meningococcal carriage are widely used,[31] although the short-term association of antimicrobial treatment with the dynamic nature of meningococcal carriage makes this an unlikely major factor.

Limitations

Our analysis has several limitations. First, our analysis is ecologic in nature and without a contemporaneous control. Thus, it is difficult to determine what would have occurred in the absence of vaccination or to separate the association between vaccination policy from any temporal trends in meningococcal disease incidence rates. However, we were able to compare the rate of decline in serogroup CWY incidence with that of serogroup B among adolescents as well as assess changes in incidence in those in unvaccinated age groups, who are also subject to the nonvaccine-related stochastic changes in meningococcal disease incidence. In addition, the proportion of cases with unknown serogroup was high during the early years of this evaluation. However, this limitation is mitigated by the high quality of serogroup information in the ABCs system that was used to extrapolate to national estimates during the prevaccination period.

Figure 4. Estimated Log Annual Incidence in Meningococcal Disease in Nonadolescents by Age Group and Serogroup—United States, 2000-2017



A, Infants younger than 1 year.
B, Children aged 1 to 10 years.
C, Individuals aged 23 to 64 years.
D, Individuals 65 years or older.
Vertical axis shows the incidence rates transformed from the log scale.

In addition, meningococcal disease detection may be more sensitive in recent years because of the increased availability of polymerase chain reaction–based confirmation methods in the United States. However, this surveillance bias would lead to an underestimation in the association between vaccination and incidence and, thus, is unlikely to affect the interpretation of our results. Furthermore, while the lack of decline in serogroup B disease incidence in adolescents and young adults during the period from 2015 to 2017 supports our assumption that MenB vaccination was not associated with incidence of meningococcal disease due to any serogroup,[32] we cannot rule out a potential association. Finally, MenACWY booster dose coverage may be underestimated in our analysis, particularly among adolescents aged 16 years who had not received the booster dose at the time of the coverage survey but who went on to receive it later, as well as among older adolescents who received the booster dose at 18 years or older, further limiting the interpretation of our results on the association of state-level vaccination coverage on meningococcal disease incidence.

Conclusions

Measuring the association between MenACWY vaccination and disease rates is challenging in the setting of historically low meningococcal disease incidence and declining incidence rates prior to vaccine introduction. Although reductions in meningococcal disease incidence in the United States are likely multifactorial, this evaluation demonstrates that MenACWY vaccination is associated with declining meningococcal disease incidence in adolescents and potentially in infants and older adults. MenACWY vaccination of adolescents may have the potential for even greater benefit in settings with higher meningococcal disease incidence. Further efforts are needed to increase MenACWY booster dose coverage among adolescents aged 16 years to achieve the full benefits of the vaccination program and to further assess the potential for herd protection of individuals in other age groups. Continued monitoring of meningococcal disease incidence in the setting of MenACWY and MenB vaccination will be important to guide future meningococcal vaccine policy.

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Acquisition, analysis, or interpretation of data: Mbaeyi, Pondo, Blain, Yankey, Potts, Shang, MacNeil.
Drafting of the manuscript: Mbaeyi, MacNeil.
Critical revision of the manuscript for important intellectual content: All authors.
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Supervision: Cohn, Hariri, MacNeil.

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