

Cost Effectiveness of Meningococcal Serogroup B Vaccination in College-Aged Young Adults



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Introduction: *Neisseria meningitidis* serogroup B is the most common form of meningococcal infection in young adults in the U.S. Vaccines have recently become available, but it is not clear that the benefits outweigh the costs. The purpose of this study was to assess cost effectiveness and determine potentially favorable conditions for universal vaccination.

Methods: Costs and benefits of universal vaccination at college entry versus no universal vaccination with an outbreak response were estimated in 2018 in the context of a mid-sized U.S.-based 4-year college from both a health sector and a societal perspective. Probability, cost, and utility data were obtained from the published literature. Costs (2015 U.S.\$) and benefits were discounted at 3%. One-way and multivariable probabilistic sensitivity analyses were performed including variations in the specific vaccine used. Further testing of the model's parameters at extremes was used to identify favorable conditions for universal vaccination.

Results: The incremental cost per quality-adjusted life year gained with universal vaccination was \$13.9 million under the health sector perspective and \$13.8 million under the societal perspective, each perspective was compared with a willingness-to-pay threshold of \$150,000 per quality-adjusted life year. Multivariable probabilistic sensitivity analysis showed that universal vaccination was not the preferred strategy for <\$15 million per quality-adjusted life year. Under an extremely favorable model, a universal vaccination strategy became cost effective for vaccine series costing <\$65.

Conclusions: This study demonstrates that universal vaccination at college entry is not cost effective. The rarity of *N. meningitidis* serogroup B contributes to the lack of cost effectiveness for universal vaccination.

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INTRODUCTION

Infection with *Neisseria meningitidis* results in long-term morbidity and high mortality despite improved access to and administration of supportive treatment in critical care settings as well as antibiotic therapies.^{1,2} Established vaccination programs have reduced the incidence of serogroups A, C, W, and Y. As a result, *N. meningitidis* serogroup B (MenB) is now the most prevalent form of meningococcal infection in individuals aged 16–23 years.³ Two Food and Drug Administration–approved MenB vaccines have overcome the high antigenic variability and the need for unique biotechnologic approaches to production.⁴ Their introduction has led to mass MenB vaccination

for college-aged young adults in outbreak settings given the persistent cases of meningococcal infection in this age group and high incidence relative to other population subgroups.⁵

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Despite the critical contributions of vaccination to public health, existing MenB vaccines may not be able to offer a societal health benefit commensurate with their resource use. MenB vaccines’ immunogenicity quickly wanes over time, limiting their ability to provide long-term protection like many other vaccines.⁶ Moreover, the existing vaccine series for MenB are more expensive than previously approved vaccines for other infectious diseases.⁷ Advocates for vaccination argue that the devastating consequences of MenB infection limit the ability to perform cost-effectiveness studies.⁸ The college-aged subpopulation has been specifically identified as a targetable group who would most benefit from vaccine protection given the increased exposure risk and the long life expectancy and large societal contribution of these individuals.⁹ Prior to widespread use of MenB vaccines in adolescents, further work may need to justify the high cost of the vaccine versus the gains accrued to individuals, payers, and society.

The purpose of this study is to assess the cost effectiveness of universal MenB vaccination of entering college students in the U.S. relative to the current standard of care,

where vaccination is an individual decision. This question is addressed from both a health sector perspective that incorporated individual and payer costs and a societal perspective that further accounted for lifetime productivity losses among students experiencing MenB infection.

METHODS

The authors developed a decision tree model using TreeAge Pro 2018, version 18.1, to assess the incremental cost effectiveness and cost per case averted for universal vaccination of incoming students at a mid-sized U.S.-based higher education institution versus no formal vaccination program (current standard of care). This decision point and the resulting risk of MenB infection and associated healthcare events is modeled in Figure 1. All reporting methods described here were adapted from the recommendations of the Second Panel on Cost Effectiveness in Health and Medicine.^{10,11}

Study Population

In order to provide estimates for a real-world setting, this study modeled a hypothetical 4-year U.S.-based liberal arts college with 1,000 students per class and 4,000 faculty and staff in the year

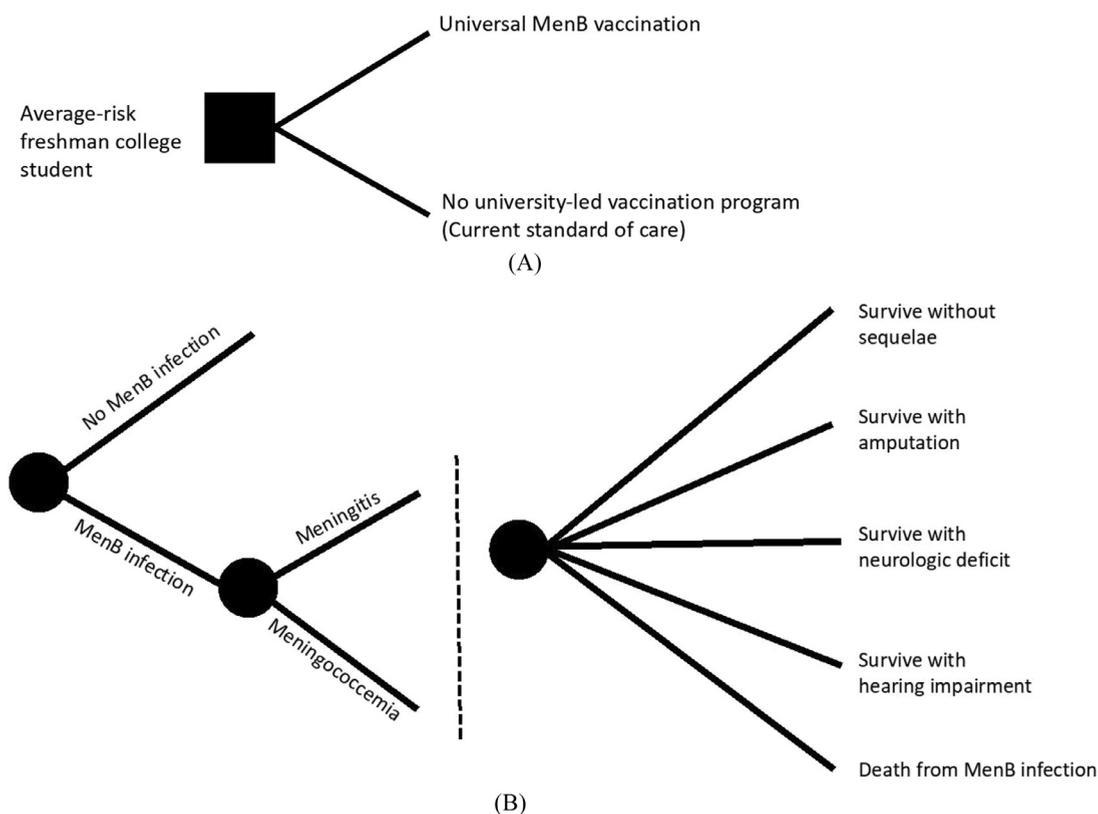


Figure 1. Decision tree model of universal vaccination versus no formal vaccination program in college students (A) and schematized sequelae (B).

Note: To enhance readability, dashed lines represent downstream sequences of identical chance nodes that stem from each of the associated upstream chance nodes.

MenB, *Neisseria meningitidis* serogroup B.

2018. Each individual student was assumed to be at equal risk for MenB infection and to enter college at age 18 years. For the decision to not perform universal preemptive vaccination, it was assumed that a suspected outbreak (i.e., one serogroup-confirmed case) led to a belated universal vaccination campaign of all students, faculty, and staff. Such an aggressive mass vaccination following an outbreak was assumed based on an intended conservative bias favoring early vaccination and the likelihood of many on-campus individuals seeking vaccination independently even if not directly administered as part of an outbreak response. In addition, although the Centers for Disease Control and Prevention (CDC) recommends two to three localized cases before initiating an outbreak response, the authors used a single case to reduce unnecessary model complexity and given that many college administrators may be pressured to initiate an outbreak response after even a single high-publicity case.^{6,12} For the purpose of this model, all students left the institution after 4 years.

Measures

Health sector and societal perspectives were analyzed. The health sector perspective included direct medical costs borne by the individual and third-party payers over a 4-year time horizon. The societal perspective included additional costs of lost productivity attributable to premature death and long-term disability from sequelae of MenB infection over the expected lifetime of an entering freshman college student (80 total years of life).¹³ The modeled risk of MenB infection spanned 4 years with an assumed zero risk of infection after leaving college to limit model complexity. This assumption is consistent with current epidemiologic trends reported by the CDC demonstrating a tenfold reduction in risk after the college-aged years.³

Parameter estimates of conditional probabilities were derived from previously published sources (Table 1). Death and hospitalization rates for non-meningococcal causes were assumed to be equal in both decision arms and excluded. Harms contributed by vaccine-associated adverse events were excluded because of the exceptionally low reported incidence.^{22,23}

The MenB risk for this population was calculated based on the annualized incidence of MenB infection in the college-going, 18–24-year-old U.S. population for a 4-year cumulative probability. Estimates of MenB infection in this demographic were obtained from government surveillance data.³ Universal vaccination was estimated to provide 50% reduction in the probability of MenB infection given a moderate to strong initial immunogenicity and then marked reduction at 48 months.^{6,14–16} Herd immunity was not included in this model because of an exploratory sensitivity analysis that demonstrated no change in conclusions with or without community protection. Historical sources reporting the proportion of meningitis (75%) versus meningococemia (25%) were used.^{1,2}

Four clinically significant sequelae of meningococcal infection were included: death, chronic hearing loss, chronic neurologic disorder including epilepsy and intellectual disability, and limb amputation. Probabilities of these sequelae were derived from the historical incidences.^{1,2,17–21} MenB infection was assumed to be clinicopathologically similar to other serogroups for modeling although not true in practice. To reduce model complexity, each of the sequelae was treated as a mutually exclusive event. To account for the overlapping sequelae often present in reality, the

more severe sequelae were over-weighted by using the high-end estimated incidence in the literature whenever possible.

Table 1 summarizes all cost parameters. Vaccine prices were estimated from publicly reported vaccine price lists with a simple average cost of the two available vaccines for two doses.^{7,22,23} Vaccine administration costs were estimated to be 10% in both the preventive setting as well as the outbreak response with variation included in the sensitivity analysis described below.²⁴ The cost of an outbreak included vaccination to all students, faculty, and staff, plus rifampin administration to 20 close contacts. Rifampin was used exclusively in the model as a means of model simplification and relative similarity of healthcare resource utilization regardless of the chemoprophylaxis agent used.

All cases of MenB infection were assumed to be treated with an inpatient hospital admission. Index hospital admission costs were calculated with close monitoring in a critical care setting using National Inpatient Sample charges for healthcare services.²⁵ Meningococcal sequelae were assumed to manifest during the index hospital admission and included additional index hospital admission costs appropriate for each sequelae (Appendix 1, available online). Post-hospital and long-term care costs of sequelae were obtained from previously published reports for each condition.^{26–28}

Productivity losses were assessed using a human capital approach, currently recommended over friction cost methods.¹¹ The effect of using a human capital approach versus a friction cost methodology was tested by sensitivity analysis. Deaths from MenB were valued based on lifetime earnings.²⁹ Because of unavailability of specific estimates, the productivity loss previously reported for severe hearing deficit was applied to all nonfatal sequelae (i.e., amputation, neurologic deficit).²⁷

Quality-adjusted life years (QALYs) were estimated based on age and gender (assumed 50/50 male/female population) Health State Valuations adjustments.³⁰ All deaths from meningitis were assumed to occur at the midpoint of college enrollment (2 years). Disutilities were applied for hospital stay, daily life with an amputation, daily life with a severe hearing deficit, and daily life with a neurologic disorder (Appendix 2, available online).^{31–35} Summative utilities and event-specific disutilities are reported in Table 1. For those with nonfatal sequelae of meningococcal infection, estimated disutility was deducted from the full-life QALY estimate. It was assumed that no reduction in total life expectancy occurred for those with nonfatal sequelae who survived the original infectious episode.

All costs were adjusted to 2015 U.S. dollars based on most common dates of existing literature and 3% per year discounting was applied to future costs and future QALYs.

Statistical Analysis

One-way sensitivity analysis was performed of all parameter estimates to identify those most likely to affect overall results. Having identified the college-aged incidence of MenB infection and vaccine price as disproportionately sensitive estimates by one-way sensitivity analysis, an extreme outlier model was constructed, with all cases of MenB infection leading to hospitalization and immediate death to determine a conservative threshold of MenB infection incidence and vaccine prices where reconsideration of cost effectiveness may be indicated (Appendix 4, available online; Figure 1). MenB incidence was modeled across a range based on observed real-world MenB infection rates from <10 times to >10 times the current MenB incidence in U.S. college students.^{3,36}

Table 1. Conditional Probabilities, Costs (US\$2015), and Utilities for Cost-Effectiveness Analysis Comparing Universal MenB Vaccination Versus Standard of Care

Parameter	Estimate	SD	Distribution	Reference
Probabilities				
Risk of meningococcal infection				
4-year probability of MenB infection in the absence of vaccination	9.2×10^{-6}	$2.8 \times 10^{-6,a}$	Beta	3
Probability of meningococemia if infected ²	0.25	0.075 ^a	Beta	1, 2
Vaccine efficacy				
Effectiveness of vaccine	0.5	0.075 ^b	Beta	6, 14–16
Natural history of meningococcal infection				
Probability of amputation, meningitis/meningococemia	0 / 0.0325	0 / 0.00975 ^a	Beta	1, 2, 17–21
Probability of death, meningitis/meningococemia	0.1 / 0.4	0.03 / 0.12 ^a	Beta	1, 2, 17–21
Probability of hearing loss if meningitis only	0.0547	0.01641 ^a	Beta	1, 2, 17–21
Probability of chronic neurodeficit if meningitis only	0.1245	0.03735 ^a	Beta	1, 2, 17–21
Costs^d				
Cost of vaccination				
Cost of vaccination per person	323.81	48.57 ^b	Gamma	7, 22, 23
Costs associated with treating an outbreak	2,590,480	388,572 ^b	Gamma	7, 22, 23, 24
Acute hospitalization				
Baseline costs of hospitalization for meningitis/meningococemia	19,959 / 25,240	2,993 / 3,786 ^b	Gamma	25
Additional costs of hospitalization with amputation	81,772	40,000	Gamma	25
Additional costs of hospitalization with hearing loss	2,928	439 ^a	Gamma	25
Additional costs of hospitalization with neurologic deficit	8,775	1,316 ^b	Gamma	25
Long-term health sector costs				
Intermediate- and long-term costs of amputation	427,313	213,657 ^c	Gamma	26–28
Intermediate- and long-term costs of hearing loss	129,327	64,663 ^c	Gamma	26–28
Intermediate- and long-term costs of neurologic deficit	502,173	251,087 ^c	Gamma	26–28
Productivity (human capital lost)				
Productivity costs of amputation, neurodeficit, or hearing loss	706,409	658,847 ^b	Gamma	27
Productivity costs of early death	851,775	127,766 ^b	Gamma	29
Utilities^d				
QALYs from decision point				
Early death from MenB	1.85	0.2775	Normal	30
Full life	25.9	3.885	Normal	30
Disutilities from surviving MenB infection with sequelae				
Amputation	11.93	5.965	Normal	31–35
Chronic hearing loss	3.19	1.595	Normal	31–35
Neurologic disability	1.51	0.755	Normal	31–35
MenB hospitalization	0.02	0.01	Normal	31–35

^aSD: $\pm 30\%$ of estimate. SDs in other literature were not routinely reported and inconsistent among sources.

^bSD: $\pm 15\%$ of estimate. SDs in other literature were not reported.

^cSD: $\pm 50\%$ of estimate. SDs in other literature were not routinely reported, inconsistent among sources, and projected to long term with assumed increased variability.

^dAll values discounted to present at 3% per year.

MenB, *Neisseria meningitidis* serogroup B; QALY, quality-adjusted life year.

The total cost of a vaccine series from current prices down to zero was also included.

All of the deterministic base parameters described above were incorporated into a multivariable probabilistic sensitivity analysis using probability ranges described in Table 1, including beta

distributions for conditional probabilities and gamma distributions for costs. Utilities were assumed to be normally distributed based on summated utilities consistently >0 with adequate sampling to justify a normal distribution.³⁷ The probabilistic distribution of incremental cost-effectiveness ratios was assessed with a

Table 2. Expected Values of Base Case Cost Effectiveness Comparing Universal MenB Vaccination for College Students to Standard of Care

Perspective	EV cost (US\$, 2015)	Incremental EV cost	EV effectiveness (QALYs)	Incremental EV effectiveness	ICER (\$/QALYs)	Cost per case averted
Health sector perspective						
Universal vaccination	324.25	299.53	25.89998	0.0000215	13,899,861	65,116,255
Standard of care	24.72		25.89996			
Societal perspective						
Universal vaccination	325.55	298.24	25.89998	0.0000215	13,839,796	64,834,867
Standard of care	27.31		25.89996			

EV, estimated value; ICER, incremental cost-effectiveness ratio; MenB, *Neisseria meningitidis* serogroup B; QALYs, quality adjusted life years.

10,000-iteration Monte Carlo simulation plotted with a willingness-to-pay threshold of \$150,000 per QALY, as is currently accepted for interventions within the U.S. by both the WHO and expert consensus.^{38,39} Comparative effectiveness across a wide range of willingness-to-pay thresholds up to \$30 million per QALY was ultimately included because of the high cost of vaccination relative to its incidence.

For the assessment of costs in real-world implementation, health sector costs of universal vaccination were compared with outbreak-only vaccination at the college campus level. The probability-weighted expected value of an outbreak response was calculated as the total estimated cost of an outbreak times the probability of an outbreak on an individual college campus. Health sector costs and societal costs were also assessed per case averted.

RESULTS

For both the health sector and societal perspectives, not having a formalized MenB vaccination program was more cost effective than universal vaccination in college-aged individuals with a willingness-to-pay threshold of \$150,000 per QALY (Table 2). From the campus-level health sector perspective, vaccinating each entering class of college students per year would cost \$323,810 per campus. By contrast, an outbreak for a campus that would only universally vaccinate after an infected case was identified would cost \$2,590,480 per campus. However, the probability-weighted expected value of an outbreak would only cost \$23.83 per campus. With the low incidence of MenB even among high-risk populations, such as U.S. college students, and published evidence that vaccine efficacy quickly wanes over time,^{3,6} a universal vaccination program would reduce the number of cases/mid-sized campuses affected in 4 years from 9.2 cases per 1,000 campuses to 4.6 per 1,000 campuses.

The incremental cost per QALY gained with universal vaccination was \$13.9 million under the health sector perspective and \$13.8 million under the societal perspective each compared with a willingness-to-pay threshold of \$150,000 per QALY. Multivariable probabilistic sensitivity analysis demonstrated that universal vaccination was not the probability-weighted preferred strategy up

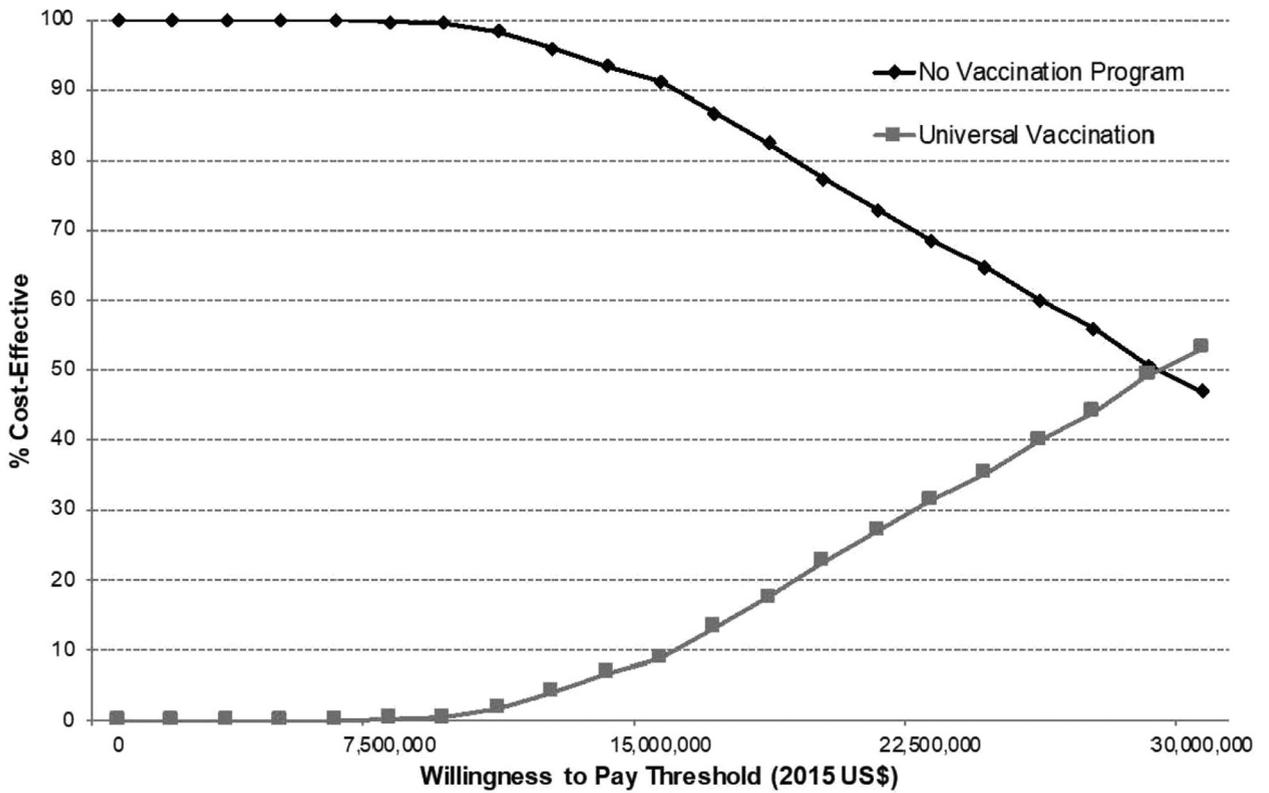
to a willingness-to-pay threshold of \$28.2 million per QALY and \$15.0 million per QALY under the health sector and societal perspectives, respectively (Figure 2). Sensitivity analysis of these findings using a friction cost approach demonstrated a <1% difference in resulting estimates (Appendix 3, available online).

Potential extremes of real-world variation in MenB with a simplified model (Appendix 4, available online; Figure 1) and one-way sensitivity analysis of MenB incidence demonstrated a universal vaccination strategy becoming cost effective at a 4-year cumulative risk of 4.6 cases per 100,000 individuals (Appendix 4, available online; Figure 2). Under this same extreme model, a universal vaccination strategy became cost effective for vaccine series pricing <\$65 (Appendix 4, available online; Figure 3). In the more conservative model used throughout the rest of this manuscript, the breakeven price for a vaccine series was \$28 or a 4-year cumulative risk rising to 10.3 cases per 100,000 individuals.

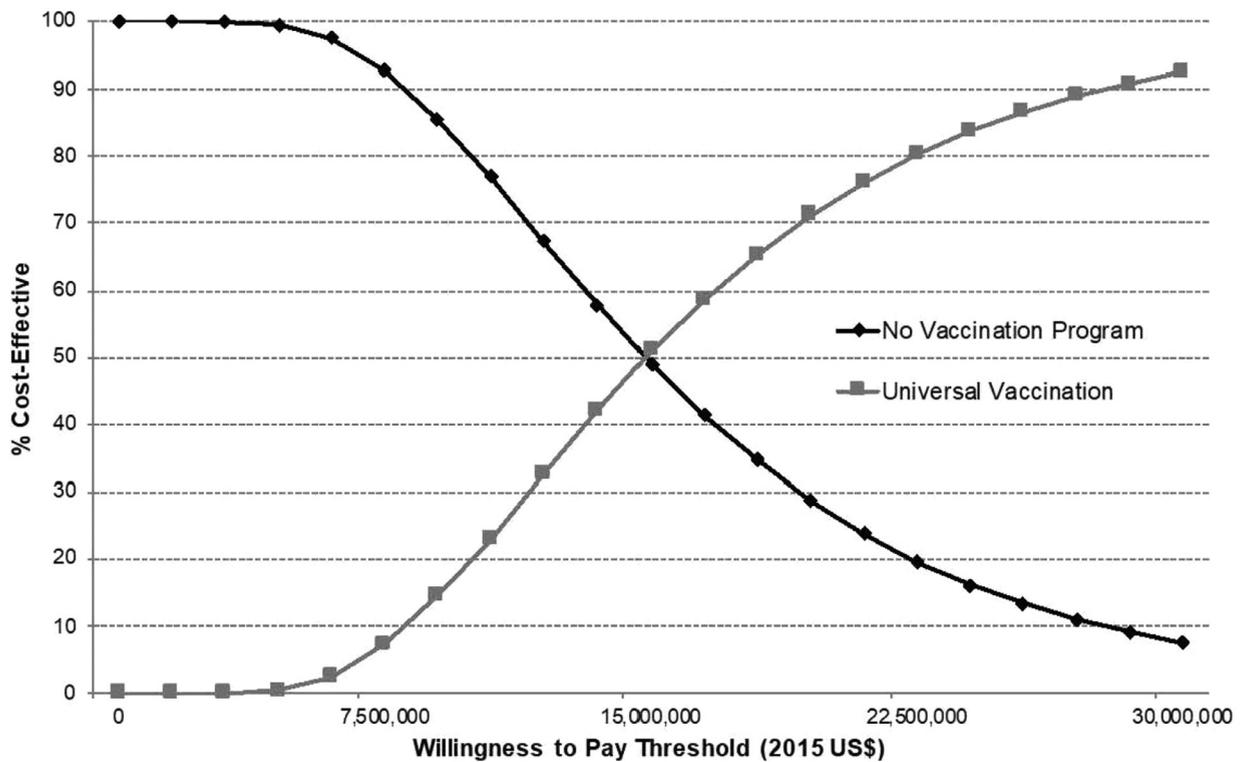
DISCUSSION

The purpose of this study was to assess the cost effectiveness of universal MenB vaccination among those entering college in the U.S. These results demonstrate that universal MenB vaccination at entry to college is not cost effective at any accepted willingness-to-pay threshold. Even under a series of conservative assumptions including the high cost of pan-campus vaccination in response to an outbreak, a decision maker's willingness-to-pay would need to be more than ten times greater than standard assumptions for MenB vaccination to be a cost-effective decision for the payer/payee or for society at large. In the context of a resource-constrained health system, these results reject current advocacy for broader MenB vaccination of college-bound adolescents.

Rates of meningococcal disease in the U.S. have decreased by more than 75% in the last decade, and population-based protection afforded by tetravalent vaccines have been an important contributor to this trend.^{40,41}



(A)



(B)

Figure 2. Cost-effectiveness acceptability curve comparing universal vaccination with no formal vaccination program for college students using a health sector perspective (A) and a societal perspective (B).

Currently, serogroup B meningococcal infections represent more than half of all meningococcal cases that occur each year in the U.S among adolescents and young adults.^{3,40} The unique antigenic variability of serogroup B *N. meningitidis* has historically inhibited vaccine development, but two approved MenB vaccines offer a new opportunity for enhanced meningococcal protection. Unfortunately, the short-term immunogenicity of these vaccines and low disease incidence limits the benefit from these technologic advances.⁶ Currently, the CDC's Advisory Committee on Immunization Practices maintains a Category B recommendation for MenB vaccination in adolescents and young adults, supporting its use in the context of individualized decision making. This recommendation effectively represents an intermediate state in between a Category A recommendation for the widespread use of a vaccine and a recommendation to not use a vaccine.

These results demonstrate that despite the poor prognosis of MenB infection and reasonable nominal cost of MenB vaccination, the extreme rarity of MenB infection even among its second modal peak in college-aged individuals make vaccination not cost effective. Vaccinating 100,000 college students would prevent fewer than five cases of MenB. Such a small population-wide benefit makes support of vaccination economically untenable even when accounting for individual costs, payer costs, community outbreak costs, and productivity lost by society.

Given the lack of cost effectiveness that was observed for MenB vaccination under current epidemiologic trends, it was also tested under what conditions universal MenB vaccination may warrant further consideration. The one-way sensitivity analysis highlighted that the incidence of MenB may be a particularly critical assumption to the analysis described above. For the last part of this study, extremes of MenB disease incidence were tested for the effect on conclusions. First, all other constraints were relaxed that may limit the favorability of MenB vaccination to create a conservative model for predicting a reconsideration threshold (Appendix 4, available online; Figure 1). For example, for this extreme case, it was assumed that any case of MenB infection would result in hospitalization and immediate death with a lifetime of associated productivity loss and QALYs. It was also assumed that current MenB vaccines were perfectly effective, leading to zero cases of MenB in the targeted population. Even under such favorable conditions, a rate of MenB cumulative risk during college would have to be 4.6 cases per 100,000 students for universal vaccination to be cost effective under a willingness-to-pay threshold of \$150,000 per QALY. This incidence rate is five times higher than the historically stable rate observed in the U.S. and 50% greater than the

infection rate observed in Ireland, the highest reported in industrialized countries.³⁶ Recognizing this threshold is important for the public health community and highlights the importance of ongoing long-term surveillance.

Extremes of vaccine price were also considered as part of the sensitivity analysis. Using the same simplified model as for MenB incidence sensitivity analysis, MenB vaccination should be further considered when vaccine series pricing is less than \$65. In the more conservative model, the price of the vaccine series would have to drop to less than \$28. This threshold is substantially below the \$324 average current price of meningococcal vaccine series and does not materially impact the conclusions in this study but may be an important consideration in the future if the cost of MenB vaccines dramatically decreased.

Limitations

These findings have important limitations when considering MenB vaccination in other contexts. The CDC recommends certain high-risk groups for vaccination that include those exposed to an MenB outbreak as well as those with underlying immune system dysfunction.⁵ The model population in this analysis is composed of exclusively average-risk college-aged individuals. Higher-risk individuals who would likely disproportionately benefit from vaccination were excluded. In the related case of outbreak response, inadequate data currently exists to assess the utility of immediate vaccination when an outbreak occurs. Current outbreak vaccination practices were incorporated in the standard of care arm to model a real-world response. However, there is also limited data on how current outbreak responses are implemented in terms of which vaccine is used, compliance with intermediate-term follow-up vaccination, and antibiotic prophylaxis selected. These unknown factors have been simplified in the model reported here by assuming similar usage as in the universal vaccination case. Finally, and most importantly, these findings cannot address one's personal decision making when considering vaccination. For any individual, the decision to vaccinate is whether to spend a few hundred dollars today for short-term protection from a disease that they will not likely contract with devastating consequences if they are. It is well known that individual decision makers are excessively loss averse,⁴² and it may be consistent with an individual's risk preferences to risk a relatively small amount of income for even imperfect peace of mind.

CONCLUSIONS

Despite the safety and short-term efficacy of MenB vaccination, the extreme low incidence of MenB and high cost of vaccination prevent universal vaccination of college-aged individuals from being a cost-effective strategy.

Based on economic modeling, the standard of care should remain: no formal vaccination program with an outbreak response as needed. However, ongoing epidemiologic surveillance is necessary and universal vaccination should be reconsidered if rates of MenB infection markedly increase in the college-aged population.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at <https://doi.org/10.1016/j.amepre.2018.09.020>.

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