
Modeling Insights into *Haemophilus influenzae* Type b Disease, Transmission, and Vaccine Programs

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In response to the 2007–2009 *Haemophilus influenzae* type b (Hib) vaccine shortage in the United States, we developed a flexible model of Hib transmission and disease for optimizing Hib vaccine programs in diverse populations and situations. The model classifies population members by age, colonization/disease status, and antibody levels, with movement across categories defined by differential equations. We implemented the model for the United States as a whole, England and Wales, and the Alaska Native population. This model accurately simulated Hib incidence in all 3 populations, including the increased incidence in England/Wales beginning in 1999 and the change in Hib incidence in Alaska Natives after switching Hib vaccines in 1996. The model suggests that a vaccine shortage requiring deferral of the booster dose could last 3 years in the United States before loss of herd immunity would result in increasing rates of invasive Hib disease in children <5 years of age.

Routine use of *Haemophilus influenzae* type b (Hib) conjugate vaccines has dramatically reduced the incidence of Hib disease in children <5 years of age in numerous populations (1–4). Vaccination programs have also led to herd immunity through reduced Hib transmission, as shown by declines in the prevalence of oropharyngeal Hib colonization among vaccinated children and unvaccinated children and adults (2,4–6). However, even successful vaccination programs have not eliminated Hib colonization (7,8). Thus, the continued success of Hib control programs

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depends on maintaining age-appropriate Hib vaccine coverage. Such coverage can, however, be threatened by changes in vaccine supply, as indicated by the 2007–2009 Hib vaccine shortage in the United States (9,10).

To manage that shortage, the Centers for Disease Control and Prevention and partner organizations recommended that providers defer giving the 12–15-month booster dose to all children except those at high risk for invasive Hib disease (9). This recommendation was based on expert opinion about the predicted effects of a shortage initially expected to last <9 months (9). When it became clear that the shortage would last longer, we sought to develop a model of Hib transmission and disease to predict the effects of continued booster dose deferral and to guide vaccine policy. Such a model could also be useful for optimizing the introduction of Hib vaccines into new populations. Furthermore, it could provide insights into the dynamics of Hib transmission and colonization, which would inform the uncertainty over the types of Hib vaccines that are most appropriate for populations at high risk for invasive Hib disease, such as Alaska Natives (11). We present the model and show its application to various populations and vaccination scenarios.

Methods

Model Structure, Parameters, and Starting Conditions

We developed an age-structured mathematical model to describe Hib transmission, colonization, and disease (Figure 1). The model assumes that populations can be

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divided into mutually exclusive states on the basis of age, Hib antibody levels (high, low, and none), and Hib infection status (susceptible, colonized, and diseased), with an additional state (immune) for infants passively immunized with bacterial polysaccharide immunoglobulin. This model can be expressed as a set of partial differential equations (online Technical Appendix 1, wwwnc.cdc.gov/EID/pdfs/11-0336-Techapp1.pdf), with rate parameters governing the movement of the population between model states. As an example, the age-specific force of infection ($\lambda(a)$) is the rate at which susceptible persons of age a become colonized. We set values for the rate parameters by using published and unpublished data on birth and death rates, Hib colonization and incidence, and Hib vaccine uptake and effectiveness (online Technical Appendix 2, wwwnc.cdc.gov/EID/pdfs/11-0336-Techapp2.pdf).

We tested the model in 3 populations: persons in the United States as a whole; England and Wales; and Alaska Natives (defined as the indigenous residents of Alaska). These populations reflect major diversity in Hib epidemiology and vaccine policy (1,3,4). In the United States, Hib conjugate vaccines were first recommended in 1988 as a single dose for children 18 months of age, and in 1991, they were recommended as a primary series starting at 2 months of

age, with a booster dose at 12–15 months. In England and Wales, Hib conjugate vaccines were introduced in 1992 as a primary series starting at 2 months of age and a 1-time catch-up campaign for children ≤ 4 years of age.

We began the simulations for the US and Alaska Native populations in 1980 and for the England and Wales population in 1985. We used census data to determine the size and age structure of each population. In the starting year, we divided the populations among the model states so that Hib transmission was in or nearly in equilibrium. Modeling and subsequent analyses were all implemented by using SAS version 9.2 (SAS Institute Inc., Cary NC, USA).

Evaluating Model Fit

We verified model fit by using pseudo- R^2 to compare the age-specific point prevalence of Hib colonization from the model with observed prevalence data in the time period before vaccine introduction (4,12–14). In a similar manner, we compared the annual incidence rate of invasive Hib among children <5 years of age from the simulated populations with observed incidence data (1,3,4,15–23).

Effects of Vaccine Shortage in the United States

Before the 2007–2009 vaccine shortage, Merck & Co., Inc. (Whitehouse Station, NJ, USA), and Sanofi Pasteur (Bridgewater, NJ, USA) were licensed to produce Hib vaccines for the United States. The shortage was triggered when Merck recalled certain lots of their Hib vaccine and suspended vaccine production. In Merck's Hib vaccine, the Hib polyribosylribitol phosphate (PRP) polysaccharide is conjugated to *Neisseria meningitidis* outer membrane protein (OMP). PRP-OMP conjugate vaccines induce a strong immune response with a first dose at 2 months of age and are given as a 2-dose primary series (24). In Sanofi Pasteur's vaccine, PRP is conjugated to tetanus toxoid (T). For the primary series, PRP-T vaccines achieve antibody titers comparable to those achieved by PRP-OMP vaccines, but PRP-T vaccines require a 3-dose primary series (24). *Haemophilus b* conjugate (HbOC) vaccine, a third Hib vaccine formerly used in the United States, couples PRP oligosaccharides to CRM₁₉₇ (cross-reacting material 197, a nontoxic mutant of diphtheria toxin). HbOC vaccines have immunogenic properties similar to those for PRP-T and require a 3-dose primary series (24).

For the US population, we modeled the effect of an extended vaccine shortage to explore what might have happened if the shortage had lasted >18 months (10). We first ran the model assuming that vaccine coverage from 2008 onward remained the same as that in 2007 (a complete series scenario). In this scenario, 50% of vaccinated children were assumed to receive PRP-OMP vaccine and 50% PRP-T vaccine, as determined by Merck and Sanofi Pasteur's preshortage Hib vaccine market shares. We then

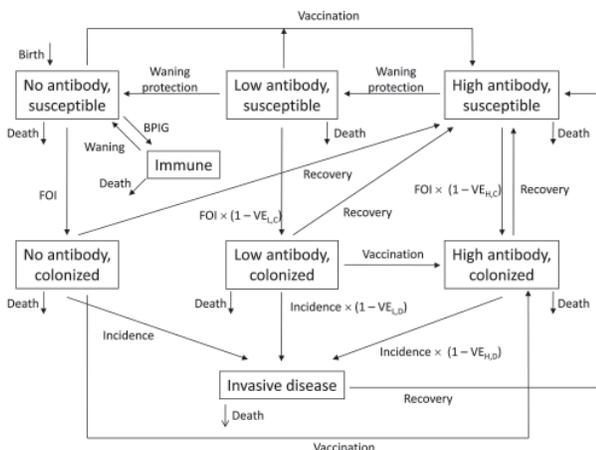


Figure 1. Structure of *Haemophilus influenzae* type b (Hib) simulation model. Persons are born into the no-antibody, disease-susceptible state and can die in any of the model states. Hib-susceptible persons become colonized based on the force of infection (FOI), which is reduced by protection from low ($VE_{L,C}$) or high ($VE_{H,C}$) antibody levels. Persons colonized with Hib develop invasive disease, which is reduced by protection from low ($VE_{L,D}$) or high ($VE_{H,D}$) antibody levels. Colonized and diseased persons recover to the high-antibody, disease-susceptible state. As immunity wanes, susceptible persons move from high to low antibody and from low to no antibody. Some persons are vaccinated and move from no or low antibody states to the high antibody state. For the Alaska Native population, use of bacterial polysaccharide immunoglobulin (BPIG) starting at birth temporarily moves persons to an immune state; as BPIG wanes, immune persons return to the susceptible state. See Technical Appendix 1 (wwwnc.cdc.gov/EID/pdfs/11-0336-Techapp1.pdf) for a formal description of the model structure.

ran the model assuming that the booster dose was deferred for all children starting in 2008 (a no-booster scenario) and that all vaccinated children received PRP-T. Last, we ran the model assuming that the booster dose was deferred starting in 2008 and that primary series coverage decreased by 10 percentage points, as suggested by some coverage surveys during the shortage (25) (a no-booster minus scenario). Again, all children were assumed to receive PRP-T. We compared annual incidence of invasive Hib in children <5 years of age under these 3 scenarios.

For the Alaska Native population we modeled the effect of switching Hib vaccines starting in 2010. During June 1991–1995 and from July 1997 onward, Alaska Native populations received PRP-OMP; during January 1996–June 1997, they received HbOC vaccines. Hib incidence in Alaska Native children rose in 1996–1997 when HbOC was used, prompting a switch back to PRP-OMP (4). During the 2007–2009 shortage, PRP-OMP vaccines from the Strategic National Stockpile were used for Alaska Natives (9). If Merck had not returned its vaccine to the market as expected, Alaska Natives would eventually have had to switch to PRP-T vaccines. To predict the effects of this switch, we compared predicted incidence in children <5 years of age from 2 models: 1 model assumed that PRP-OMP continued to be used from 2010 onward, and the other model assumed that PRP-T was used starting in 2010. We also modeled the effect of 1-time PRP-T booster campaigns, which occurred in conjunction with the switch to PRP-T, for all children 1–4 or 5–10 years of age.

Alternative Approaches to Vaccine Introduction

This model can also be used to explore strategies for introducing Hib conjugate vaccines to new populations. To illustrate this strategy, we modeled hypothetical vaccination programs in 2 populations with the age distribution and transmission patterns of the United States or of the Alaska Native population.

We compared predicted Hib incidence in children <5 years of age in 4 vaccination scenarios in the hypothetical

populations: 1) a primary series starting at 2 months of age and a booster dose at 12–15 months of age; 2) only a primary series starting at 2 months of age; 3) only a single dose at 12–15 months of age; and 4) a primary series at 2 months of age and a 1-time catch-up campaign for children <5 years of age. We assumed the strategies used PRP-T for all vaccine doses, with 90% vaccine coverage achieved within 3 years of vaccine implementation.

Sensitivity Analyses

All model parameters taken from the literature are estimates based on samples of the population, and these estimates have some degree of uncertainty. We conducted detailed sensitivity analyses to determine whether our model conclusions would differ had we used different parameter values (online Technical Appendix 3, wwwnc.cdc.gov/EID/pdfs/11-0336-Techapp.pdf). We ran the model 10,000 times, each time randomly varying 3 parameters, and we looked for individual parameters and combinations of parameters that caused major differences between observed and modeled incidence in children <5 years of age. To test the effect of the rate of recovery from colonization, we also refit the model and ran several vaccination scenarios under extreme values for this parameter.

Results

Model Fit

The model accurately reproduced the observed prevalence of carriage by age group before vaccine introduction for the United States as a whole (pseudo- R^2 0.74) and for Alaska Natives (pseudo- R^2 0.98), the 2 populations for which carriage data were available. The model also accurately reproduced the observed annual incidence of invasive Hib in children <5 years of age in the United States (pseudo- R^2 0.97), in England and Wales (pseudo- R^2 0.91), and among Alaska Natives (pseudo- R^2 0.90) (Figure 2). Of note, the model captured the rise in Hib incidence in the United Kingdom beginning in 1999 and

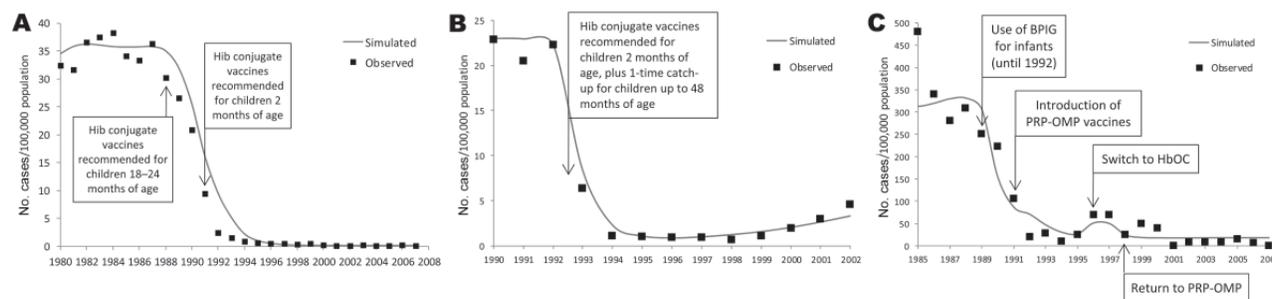


Figure 2. Observed and simulated incidence of invasive *Haemophilus influenzae* type b in children <5 years of age in 3 populations: (A) United States; (B) England and Wales; (C) Alaska Natives. PRP-OMP, Hib polyribosylribitol phosphate polysaccharide conjugated to *Neisseria meningitidis* outer membrane protein; HbOC, *Haemophilus b* conjugate vaccine; PRP-T, polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid.

the rise in invasive disease among Alaska Natives that was associated with the switch to HbOC vaccines in 1996/1997.

Force of Infection

For the United States and England and Wales, the best-fit force of infection suggests that Hib transmission before introduction of vaccine was driven by children 2–4 years of age (Table). Persons of all ages in both populations are primarily colonized through contact with children in this age group. For example, in the United States population, the annual force of infection on children <2 years of age was 36.3 infections/1,000 children, of which 24.3 (66.9%) were caused by children in the 2- to 4-year-old age group.

Furthermore, the model suggests that the dynamics of Hib transmission are different in Alaska Native populations than in the other 2 modeled populations. In Alaska Native populations, most Hib transmission before introduction of vaccine came through contact with children 5–9 rather than 2–4 years of age (Table). A stronger element of assortative mixing was also present, in that children <2 years of age acquired infection from other children <2 years of age, and persons ≥ 10 years of age acquired infection from other persons ≥ 10 years of age.

Model Predictions of Possible Effects of Hib Vaccine Shortage

If the Hib vaccine shortage and deferral of the 12–15 month booster dose in the United States extended indefinitely, the model predicts relatively little change in the incidence of invasive Hib in children <5 of age for the first 3 years under either shortage scenario (Figure 3, panel A). Beginning in 2011, the model predicts that

Hib incidence would increase more substantially in the no-booster shortage scenario (from 0.14 cases/100,000 children in 2007 to 0.72/100,000 in 2012 and 5.7/100,000 by 2020), with slightly greater increases in the no-booster minus shortage scenario.

If Alaska Native populations would have had to switch from PRP-OMP to PRP-T vaccine, the model predicts that the incidence of Hib in children <5 years of age would more than double (from 17.9 cases/100,000 children in 2009 to 46.2/100,000 in 2011) (Figure 3, panel B). Given that children 5–9 years of age appear to drive transmission in Alaska Native populations, we modeled the effect of adding a 1-time vaccination campaign for children 5–9 years of age in 2010 to the switch from PRP-OMP to PRP-T vaccine. This model predicts that such a vaccination campaign would keep the incidence of Hib below that for the PRP-T vaccine scenario for 8 years (Figure 3, panel B). The effect of a 1-time booster campaign for children 1–4 years of age was similar (Figure 3, panel B).

Alternative Approaches to Vaccine Introduction

In a hypothetical population with the age distribution and transmission patterns of the United States, the most effective strategy for vaccine introduction would have been to introduce the vaccine as a primary series plus a booster at 12–15 months of age (Figure 4, panel A). Using PRP-T vaccines, we found that this strategy resulted in a rapid decline in incidence and the lowest equilibrium incidence, i.e., 0.22 cases/100,000 children <5 years of age. A strategy of offering only 1 dose of vaccine at 12–15 months of age, without a primary series, was predicted to have nearly as great an effect on Hib incidence, with an equilibrium

Table. Estimated annual prevaccination force of infection from Hib infectious persons to persons with susceptible, no-antibody status and estimated annual prevalence of Hib colonization in 3 modeled populations, stratified by age group*

Susceptible population, age group, y	Hib infections caused by infectious persons/1,000 susceptible persons, by age group, y				Total no. cases
	0–1	2–4	5–9	≥ 10	
United States					
0–1	0.2	24.3	11.6	0.2	36.3
2–4	0.1	77.4	1.4	0.3	79.2
5–9	10.1	136.2	15.5	2.0	163.8
≥ 10	7.0	78.5	9.2	0.8	95.5
Prevalence	1.1%	2.9%	5.3%	3.2%	NA
England and Wales					
0–1	0.6	15.4	10.7	1.7	28.4
2–4	3.1	62.8	11.2	1.9	79.0
5–9	10.1	133.6	16.8	1.9	162.5
≥ 10	6.6	78.4	8.4	2.4	95.8
Prevalence	1.0%	3.0%	4.9%	3.0%	NA
Alaska Natives					
0–1	109.5	5.8	52.3	1.2	168.8
2–4	28.4	15.8	49.2	5.4	98.8
5–9	28.9	144.3	357.8	5.9	536.9
≥ 10	28.4	21.7	80.3	64.7	195.1
Prevalence	5.2%	3.9%	9.9%	4.5%	NA

*Values are no. infections except as indicated. Data are based on Hib simulation model. Hib, *Haemophilus influenzae* type b; NA, not applicable.

incidence of 0.47 cases/100,000 children <5 years of age. Strategies using a primary series only or a primary series with a 1-time catch-up campaign were much less effective, resulting in an equilibrium incidence of 11.0 cases/100,000 children <5 years of age.

In a hypothetical population with the age distribution and transmission patterns of Alaska Natives, the most effective strategy with PRP-T vaccines again would have been vaccinating with a primary series and a booster dose at 12–15 months, which yielded an equilibrium incidence of 50.4 cases/100,000 children <5 years of age (Figure 4, panel B). Both the primary series alone and the primary series with a 1-time catch-up yielded equilibrium incidence rates of 136.2 cases/100,000 children <5 years of age. As with the US population, the strategy of a single dose at 12–15 months of age was superior to a primary series alone, with or without a 1-time catch-up. However, the equilibrium incidence of 101.7 cases/100,000 children <5 years of age was substantially higher than that for the primary plus booster strategy.

Sensitivity Analyses

We found that the model was robust to variations in all parameters except the mean rate of recovery from colonization (online Technical Appendix 3). To see whether conclusions about Hib epidemiology from our model would differ on the basis of the value of this recovery rate, we tried fitting the model assuming a fast and slow recovery rate. The results showed that our conclusions about Hib dynamics and the effect of vaccination programs would be unchanged even under extremely different values for the mean rate of recovery from carriage.

Discussion

We have developed a flexible model of Hib transmission and disease that can be applied to multiple contexts. This model can account for many essential features of Hib epidemiology, including the rapid decline in Hib incidence in the United States after vaccine introduction; the rise in Hib incidence in the United Kingdom 7 years after the catch-up campaign; and the increase in Hib incidence among Alaska Native populations when vaccine was switched from PRP-OMP to HbOC in 1996.

Our model suggests several essential insights into the epidemiology of Hib and into the design of Hib vaccination programs. First, our model suggests that in the United States and England and Wales, Hib transmission is driven by children 2–4 years of age. This is in contrast to prior Hib simulation models, which have suggested that transmission to persons of a given age group primarily occurs from others of the same age group (assortative mixing) (26–28). One model suggests that adults also play a major role across age groups (27). However, those transmission patterns do

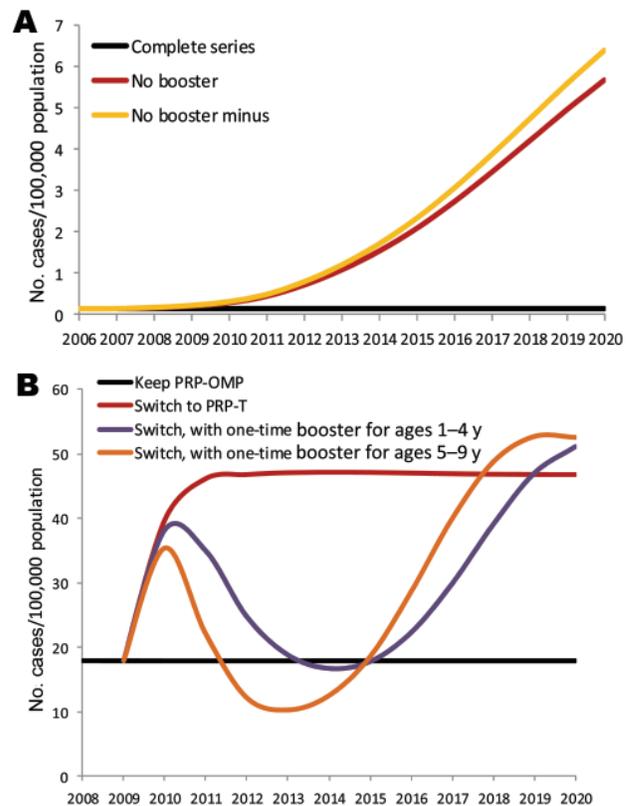


Figure 3. Predicted effects of extended *Haemophilus influenzae* type b (Hib) vaccine shortage on the incidence of invasive Hib disease in the United States (A) and of switching from PRP-OMP to PRP-T vaccine in the Alaska Native population (B). See text for complete description of shortage scenarios. PRP-OMP, Hib polyribosylribitol phosphate polysaccharide conjugated to *Neisseria meningitidis* outer membrane protein; PRP-T, polyribosylribitol phosphate polysaccharide conjugated to tetanus toxoid.

not explain the rapid decline in Hib incidence in the United States in 1988–1990, when Hib conjugate vaccine was only being offered to children 18–24 months of age. During that time, incidence declined even among children <1 year of age, an effect that is only possible if children ≥18 months of age are major drivers of Hib transmission.

Second, our model suggests that Hib transmission dynamics differ across populations. Unlike the findings from the best-fit model for the United States and England and Wales, the best-fit model for the Alaska Native population suggests that transmission is mainly driven by children 5–9 years of age, with some element of assortative mixing. These differences have major consequences for the design of Hib vaccination programs. For example, our model suggests that in the United States and England and Wales, giving 1 dose at 12–15 months of age would be nearly as effective, at a population level, as a full primary series plus a booster at 12–15 months of age.

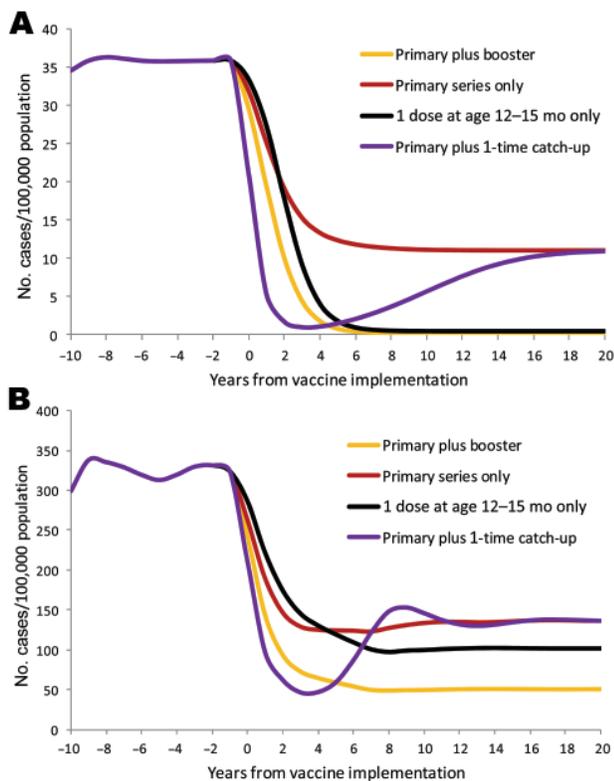


Figure 4. Predicted effects of different vaccination programs on the incidence of invasive *Haemophilus influenzae* type b disease, applied to a population with age structure and transmission dynamics like the United States population (A) and like the Alaska Native population (B).

In contrast, offering only a single dose at 12–15 months would be considerably less effective for the Alaska Native population. Furthermore, PRP-T vaccine was predicted to be much less effective than PRP-OMP vaccine for Alaska Native populations because in Alaska Natives, the force of infection is high even for young infants and PRP-OMP stimulates protective antibodies after the first dose at 2 months of age. A high force of infection in Alaska Native infants is consistent with the observed jump in Hib incidence in Alaska Natives in 1996–1997 with the switch to HbOC vaccine, which does not induce protective antibodies until the third dose at 6 months of age (11). Planning an optimal vaccination program should include some assessment of the Hib transmission dynamics in the target population. Our model can be used to estimate those dynamics from the age-specific prevalence of colonization and age-specific incidence of invasive Hib.

The World Health Organization recommends that all routine infant vaccination programs include conjugate Hib vaccines in infancy, with or without a booster later in life (29). Most countries with Hib vaccination programs

are in line with these guidelines (30). Our study suggests 2 potential practical applications for the design of Hib vaccination programs. First, there may be populations for which a policy of a single dose at 12–15 months of age would reduce invasive Hib nearly as much as would a 3-dose primary series plus a booster. Furthermore, in some populations a single dose at 12–15 months may reduce Hib disease more than a 3-dose primary series without a booster. Additional exploration of the potential utility of a single dose of Hib conjugate vaccine at 12–15 months of age as a complete routine immunization schedule is needed. Second, countries planning to add Hib vaccines to their routine immunization programs could apply this model to local or regional data on Hib disease and colonization to characterize the potential effect of vaccination regimens under consideration.

Our study has a few limitations worth highlighting. First, as with all models, ours necessarily simplifies the underlying reality. We combined all persons ≥ 10 years of age into a single group because Hib colonization and incidence data were insufficient to reliably model more age groups within this broad category. The estimated transmission dynamics for this age group thus represent an average of adolescents and adults and may mask heterogeneity between these groups. Second, a model is only as good as the source data; if the estimates of model parameters from the literature are inaccurate, our model may be inaccurate. We conducted extensive sensitivity analyses to explore this (online Technical Appendix 3), and found that the model is robust to variation in most parameters. The exception is the rate of recovery from Hib colonization. This finding makes sense because duration of infectiousness is a major determinant of disease transmission. However, we are reassured that this sensitivity does not affect our conclusions because using widely varied values for this rate does not change the basic model conclusions. Third, we assume that immunity following natural infection is the same as immunity following vaccination, while, in reality, natural infection may induce longer-lasting protection. Our model could reproduce Hib incidence in England and Wales more accurately than a model that used different parameters for vaccine-induced versus natural immunity (28). This suggests the difference in protection between vaccination and natural infection may not be epidemiologically essential; however, exploring this is a topic for future research.

A strength of our study is that our model is complex enough to successfully model Hib in a variety of populations yet simple enough that the transmission parameters can be estimated from relatively limited carriage and incidence data. A second strength is that, like Leino et al. (27), we used an iterative process to refine initial estimates of the transmission parameters. This process enables greater

flexibility than that available when constraining the matrix to certain combinations of parameters (26) or choosing initial values by hand without further refinement (28).

Our Hib simulation model can be a useful tool for public health planners in countries that are considering implementing Hib vaccination programs and for countries that must respond to Hib vaccine shortages. The model suggests the importance of young children in the transmission of Hib, the need for a dose at 12–15 months of age to maintain herd immunity against Hib disease, and the importance of evaluating Hib transmission dynamics for optimizing vaccine programs.

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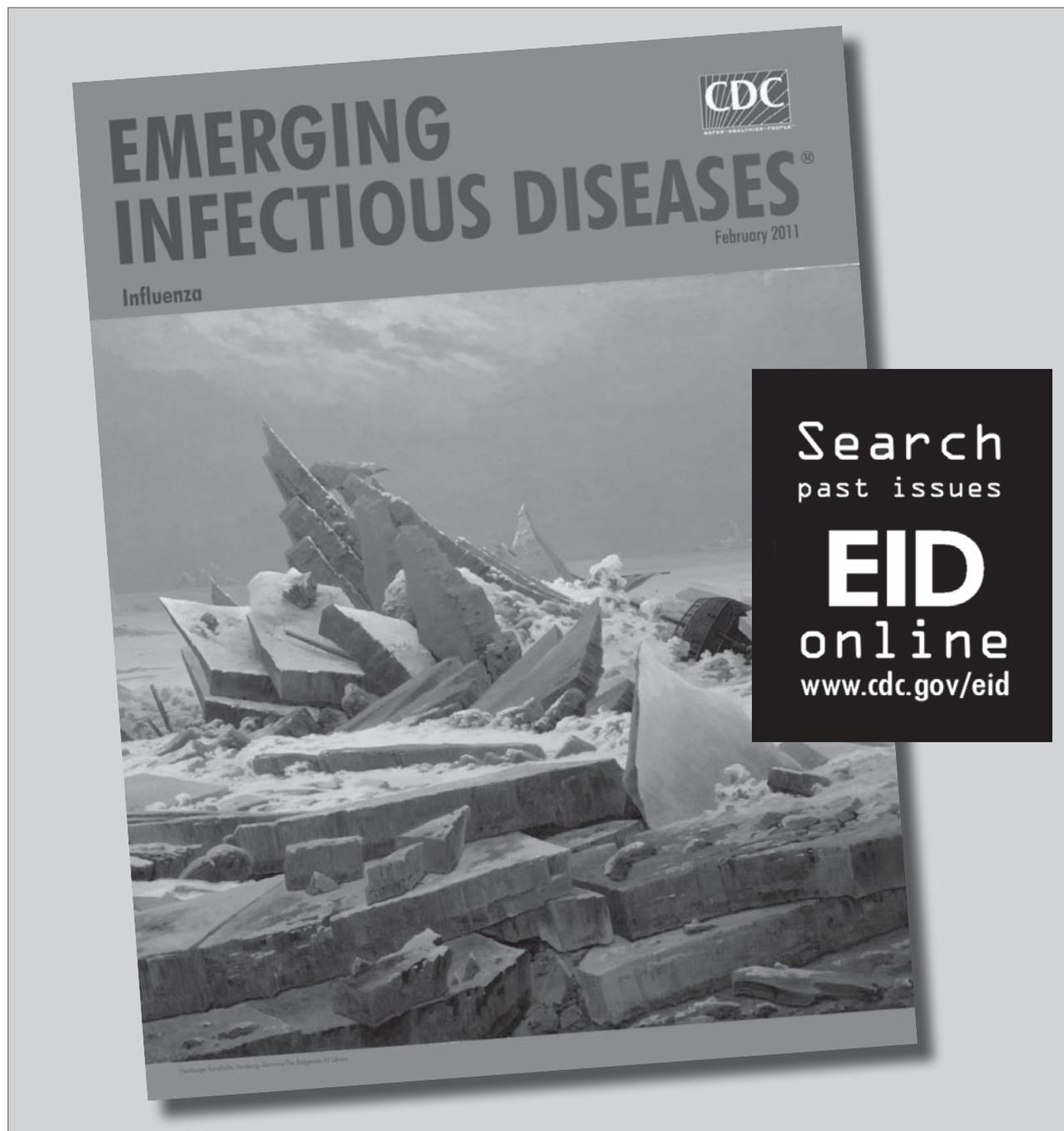
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Modeling Insights into *Haemophilus influenzae* Type b Disease, Transmission, and Vaccine Programs

Technical Appendix 1

Model Structure

The following set of partial differential equations defines the rates at which the simulated population moves between model states:

$$\frac{\partial NS}{\partial t} + \frac{\partial NS}{\partial a} = \mu(t, a)X(t) + \omega_L LS(t, a) + \omega_{BPIG} I(t, a) - \mathbf{I}(t) + \lambda(t, a) + \gamma(t, a)\varepsilon(a) + \delta_{BPIG}(t, a)\bar{NS}(t, a)$$

$$\frac{\partial I}{\partial t} + \frac{\partial I}{\partial a} = \delta_{BPIG}(t, a)NS(t, a) - \omega_{BPIG} I(t, a)$$

$$\frac{\partial NC}{\partial t} + \frac{\partial NC}{\partial a} = \lambda(t, a)NS(t, a) - \mathbf{I}(t) + \rho_C + \sigma(a) + \gamma(t, a)\varepsilon(a)\bar{NC}(t, a)$$

$$\frac{\partial LS}{\partial t} + \frac{\partial LS}{\partial a} = \omega_H HS(t, a) - \mathbf{I}(t) + \omega_L + \lambda(t, a)(1 - \alpha_L) + \gamma(t, a)\varepsilon(a)\bar{LS}(t, a)$$

$$\frac{\partial LC}{\partial t} + \frac{\partial LC}{\partial a} = \lambda(t, a)(1 - \alpha_L)LS(t, a) - \mathbf{I}(t) + \rho_C + \sigma(a)(1 - \beta_L) + \gamma(t, a)\varepsilon(a)\bar{LC}(t, a)$$

$$\frac{\partial HS}{\partial t} + \frac{\partial HS}{\partial a} = \rho_C [NC(t,a) + LC(t,a) + HC(t,a)] - \rho_D D(t,a) + \gamma(t,a)\varepsilon(a) [NS(t,a) + LS(t,a)] - [\mu(t) + \omega_H(a) + \lambda(t,a)(1 - \alpha_H)] \overline{HS}(t,a)$$

$$\frac{\partial HC}{\partial t} + \frac{\partial HC}{\partial a} = \lambda(t,a)(1 - \alpha_H)HS(t,a) + \gamma(t,a)\varepsilon(a)[NC(t,a) + LC(t,a)] - [\mu(t) + \rho_C + \sigma(a)(1 - \beta_H)] \overline{HC}(t,a)$$

$$\frac{\partial D}{\partial t} + \frac{\partial D}{\partial a} = \sigma(a) [NC(t,a) + (1 - \beta_L)LC(t,a) + (1 - \beta_H)HC(t,a)] - [\mu(t) + \rho_D] \overline{D}(t,a)$$

In which:

- NS, NC, LS, LC, HS, HC, D, and I are population states, where N=No antibody, L = Low antibody, H = High antibody, S = Susceptible, C = Colonized, D = Diseased, and I = Immune; X(t) is the total population.
- $\mu(t,a)$ and $v(t)$ are time-dependent birth and death rates, respectively. Birth rate also depends on age as individuals are only born into the age=0 group
- ω_L is the rate at which low antibody wanes to no antibody and $\omega_H(a)$ is the age-dependent rate at which high antibody wanes to low antibody
- $\lambda(t,a)$ is the time- and age-dependent force of infection
- $\gamma(t,a)$ is the time- and age-dependent rate of vaccination, and $\varepsilon(a)$ is the age-dependent vaccine take rate
- $\sigma(a)$ is the age-dependent rate of invasive disease among colonized persons
- α_L and α_H are the efficacy of low and high antibody at preventing colonization
- β_L and β_H are the efficacy of low and high antibody at preventing invasive disease
- ρ_C and ρ_D are the rates of recovery from colonization and invasive disease, respectively
- $\delta_{BPIG}(t,a)$ is the time- and age-dependent rate of BPIG use (for Alaska Native populations only), and ω_{BPIG} is the rate of waning of BPIG protection.

Modeling Insights into *Haemophilus influenzae* Type b Disease, Transmission, and Vaccine Programs

Technical Appendix 2

Model Parameters and Implementation

Model Parameters

We used published and unpublished data to set values for the model parameters (Technical Appendix 2 Table 1). Parameters assumed to be constant across populations include rates of recovery from colonization and disease, the proportion of vaccinations that induce high antibody levels (the vaccine “take rate”), the rate at which antibody levels wane, and the protective efficacy of low and high antibody levels against colonization and disease. We used studies of the duration of *Haemophilus influenzae* type b (Hib) colonization (1–3) and disease (4) to determine the rates of recovery from colonization and disease. We estimated the vaccine take rates based on antibody responses to Hib vaccination (5,6), assuming antibody titers of <0.15 $\mu\text{g/mL}$ post-vaccination indicate lack of response. Rates of antibody waning were estimated from antibody titers at different time points post-vaccination and from prior Hib modeling studies (5,7). We estimated protection against colonization and disease associated with low and high antibody levels from studies of vaccine effectiveness (8–10).

The remaining model parameters were allowed to vary across populations. We estimated birth and death rates from vital statistics data (11–15). We used published and unpublished data on vaccine coverage by age and year to estimate rates of vaccination (16–25) (Centers for Disease Control and Prevention, unpub. data). To implement vaccination in the model, we assume that vaccination with the primary series takes effect at the completion of the primary series. That is, vaccination is treated as a single event that takes place at four months (PRP-OMP) or six months (PRP-T, HbOC) of age. We assume that single doses given after the first year of life take effect at the time of vaccination.

To parameterize the age- and time-specific force of infection ($\lambda(t,a)$) we first partitioned the population into four age classes: 0 to <2 years of age; 2 to <5 years of age, 5 to <10 years of age, and ≥ 10 years of age. The force of infection on susceptibles in age class i is then:

$$\lambda(t,i) = \sum_{j=1}^4 c_{ij} * Y_j(t) * p_{ij}$$

where j represents the four age classes, c_{ij} is the rate at which susceptibles in age class i contact persons in age class j ; Y_j is the proportion of persons in age class j who are infectious; and p_{ij} is the probability of transmission from j to i given contact between susceptible and infectious persons (26). The terms c_{ij} and p_{ij} can be combined into a single transmission coefficient, β_{ij} . The collection of β_{ij} values forms a Who Acquires Infection from Whom (WAIFW) matrix. To estimate the WAIFW matrix in the United States and Alaska Native populations we first tried a wide variety of possible matrices, varying the degree of assortative mixing and the relative importance of each age group; for each matrix we ran the model to equilibrium and determined which matrix gave the best fit between observed and predicted age-specific prevalence of colonization prior to the introduction of Hib vaccines (22,27–29). We then took the best-fit matrix and used maximum likelihood estimation (MLE) to refine the matrix parameters and get the best fit to the observed prevalence of colonization (Technical Appendix 2 Table 2).

Finally, to estimate the age-specific rate at which disease develops in colonized persons, we used data on the incidence of invasive Hib by age (22,30) and the duration of Hib disease to estimate the point prevalence of invasive Hib in each population. We then computed the age-specific ratio of Hib colonization prevalence to Hib disease prevalence. We fit a variety of functions to this ratio and chose the function with the best fit to the data based on the Akaike Information Criteria. We then use MLE to refine the parameter values for the best fitting function to best match the age-specific incidence of disease in each population.

For the England and Wales population, insufficient data are available on the prevalence of Hib colonization by age to estimate the WAIFW matrix and rate of disease among colonized persons. We assumed the rate of disease among colonized persons was the same as in the United

States population and adapted the United States WAIFW matrix to England and Wales age-specific Hib incidence (31) by using MLE.

To account for the use of bacterial polysaccharide immunoglobulin (BPIG) to passively immunize Alaska Native infants during July 1, 1989–April 30, 1992, we added an additional Immune model state. Newborns receiving BPIG (23) move to the Immune state and return to the No antibody, Susceptible state as BPIG wanes.

Implementation

We divided the population into $n = 520$ age groups, by week of age from birth to age 10 years. We treated persons ≥ 10 years of age as a single age group because little data exist on age-specific Hib colonization and incidence for persons ≥ 10 years of age. Within each age group, the set of partial differential equations that govern the model reduces to a set of ordinary differential equations. To run the model, we moved the population between the model states within each age group using the ordinary differential equations. We then incremented time by one week and aged the population by moving individuals from age n to age $n + 1$, with newborns entering the model at age $n = 0$.

Calculating the Force of Infection

After fitting the models, we calculated the age-specific force of infection in each population by running the models and determining the simulated age-specific point prevalence of Hib carriage just prior to vaccine implementation. We multiplied the WAIFW matrix by the age-specific prevalence of carriage to get the age-specific force of infection.

Technical Appendix 2 Table 1. Values and sources for parameters used in the model, by population*

Parameter name	Parameter symbol†	United States		England and Wales		Alaska Natives	
		Value	Source(s)	Value	Source(s)	Value	Source(s)
Rate of recovery from colonization	ρ_C	2.1759/y	(1–3)			Same for all populations	
Rate of recovery from disease	ρ_D	33.2067/y	(4)			Same for all populations	
Proportion of vaccines inducing immunity	$\varepsilon(a)$						
Vaccine at <1 year of age		0.99	(5)			Same for all populations	
Vaccine at ≥ 1 year of age		1	(6)			Same for all populations	
Protection of high antibody against colonization	α_H	0.96	(9)			Same for all populations	
Protection of high antibody against disease	β_H	0.98	(8)			Same for all populations	
Protection of low antibody against colonization	α_L	0	(10)			Same for all populations	
Protection of low antibody against disease	β_L	0.9	(8)			Same for all populations	
Rate of waning from high to low antibody	$\omega_H(a)$		(5,7)				
<1 year of age		4.9987/y				Same for all populations	
1–1.99 years of age		0.3287/y				Same for all populations	
≥ 2 years of age		0.1983/y				Same for all populations	
Rate of waning from low to no antibody	ω_L	0.0939/y	(5,7)			Same for all populations	
Force of infection from outside population‡	part of $\lambda(t,a)$	0.0005/y	(32)			Same for all populations	
Birth rate per 1,000 population	$\mu(t,a)$	15.236/y	(14)	12.40/y	(12,13)	Varies over time	(14)
Death rate per 1,000 population	$\nu(t,a)$	8.713/y	(11)	10.64/y	(12,13)	Varies over time	(11,15)
Rate of disease among colonized: $x + ye^{-z \times \text{age}}$	$\sigma(a)$						
x		2.25×10^{-6}	MLE	2.25×10^{-6}	MLE	3.50×10^{-5}	MLE
y		0.002614	MLE	0.002614	MLE	0.01591	MLE
z		1.0446/y	MLE	0.02002/wk	MLE	0.0371/wk	MLE
Rate of Hib vaccination	$\gamma(t,a)$	Varies over time	(16–19)	Varies over time	(20,21)	Varies over time	(22,25)
Rate of BPIG use in newborns	$\delta_{\text{BPIG}}(t,a)$	Not used		Not used		Varies over time	(23)
Rate of waning of BPIG	ω_{BPIG}	Not used		Not used		Varies by age and time§	(23)

*MLE, maximum-likelihood estimation; Hib, *Haemophilus influenzae* type b; BPIG, bacterial polysaccharide immunoglobulin.

†Corresponds to symbols used in Technical Appendix 1 (wwwnc.cdc.gov/EID/pdfs/11-0336-Techapp1.pdf).

‡Force of infection from within the population is found in Table 2 of the article.

§Time-varying because the number of doses of bacterial polysaccharide immunoglobulin varied over time.

Technical Appendix 2 Table 2. Final Who Acquires Infection from Whom matrices for the United States; England and Wales; and Alaska Native populations*

United States population

		Age group of infectious persons (j), y			
		0–1	2–4	5–9	≥10
Age of susceptible persons (i), y	0–1	0.02	0.83	0.22	0.01
	2–4	0.01	2.66	0.03	0.01
	5–9	0.96	4.68	0.29	0.06
	≥10	0.66	2.70	0.17	0.03

England and Wales population

		Age group of infectious persons (j), y			
		0–1	2–4	5–9	≥10
Age of susceptible persons (i), y	0–1	0.05	0.51	0.22	0.06
	2–4	0.29	2.08	0.23	0.06
	5–9	0.97	4.43	0.34	0.06
	≥10	0.63	2.60	0.17	0.08

Alaska Native population

		Age group of infectious persons (j), y			
		0–1	2–4	5–9	≥10
Age of susceptible persons (i), y	0–1	2.11	0.15	0.53	0.03
	2–4	0.55	0.40	0.50	0.12
	5–9	0.56	3.68	3.61	0.13
	≥10	0.55	0.55	0.81	1.43

*Matrix values are the product of (the annual rate at which persons of age group i encounter persons of age group j) and (the probability of transmission given contact between susceptible in age group i and infectious in age group j).

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Technical Appendix 3

Sensitivity Analyses

Rationale

As shown in Technical Appendix 2 Table 1 (wwwnc.cdc.gov/EID/pdfs/11-0336-Techapp2.pdf), our *Haemophilus influenzae* type b (Hib) simulation model uses published research studies to define values many of the model parameters such as birth and death rates; protective effects of low and high antibody levels; and rates of recovery from colonization and disease. The true population values of these parameters are unknown; we merely have point and interval estimates of these parameters based on samples from the population. For example, the vaccine take rate parameter (the proportion of vaccinations that induce protective immunity) in persons ≥ 1 year of age comes from Käyhty et al. (reference 6 in Technical Appendix 2), where all 34 persons ≥ 1 year of age achieved protective antibody levels after vaccination with Hib conjugate vaccine. Thus, our modeled estimate for the vaccine take rate in persons ≥ 1 year of age is 1.0. However, with a sample size of 35 persons, a vaccine take rate as low as 0.9 would not be inconsistent with these data.

For modeling purposes, we must select a single value for each parameter, and in each case we choose the best estimate from the available data (typically the mean). However, the true parameter value in the population may be different from the value we choose for the model. To properly interpret the model results, it is essential to assess how sensitive the model is to the specific parameters values we chose. Returning to the above example of the vaccine take rate, we want to know whether our conclusions from the model would be different if we had used a take rate of 0.9 rather than 1.0. In this Technical Appendix we present detailed sensitivity analyses of our Hib simulation model. The goal of these analyses is to determine whether the conclusions of

our model depend on the specific parameter values used, or whether the model is robust to the uncertainty in the estimates of these parameters. This includes robustness to the specific values for individual parameters and for combinations of parameters.

Approach

The model uses 15 parameters that have been defined based on published studies. The model also includes parameters for the force of infection and the incidence of disease among the colonized, which were estimated as part of the model fitting process (Technical Appendix 2). We restricted our sensitivity analyses to the parameters based on the literature. Inference about the force of infection is part of the purpose of the model, and varying the values of the model output would not inform us about the sensitivity of the model to the other parameters.

For each of 15 parameters based on published studies, we define the point estimate and its SE from the published studies. The point estimates were used in the primary analysis as described in the main manuscript. Here, we make use of the SEs to explore how sensitive the model is to each of the 15 parameters and to combinations of the parameters.

For the sensitivity analyses, we ran 10,000 iterations of the simulation model on the United States population. In each iteration, we randomly selected 3 parameters to vary. We randomly sampled a value for each of those three parameters from a distribution defined by the parameter's point estimate and SE. We then ran the United States model from 1980 through 2000 using the sampled values of the three parameters and the point estimates for all remaining model parameters. We determined the predicted incidence of invasive Hib in children <5 years of age in 1987 (the last year before vaccination was started) and in 2000 for each iteration of the model.

For each of the 15 parameters, we then calculated the mean and SD of the mean for the modeled incidence in 1987 and 2000 across all iterations of the model where that parameter was allowed to vary. For any individual parameter, a large SD indicates that the model is sensitive to the value of that parameter. In contrast, a small SD indicates that the model is robust to the uncertainty in the estimation of that parameter.

The model may also be sensitive to certain combinations of parameters without being highly sensitive to the individual parameters. To explore this possibility, we looked at all two-way and three-way combinations of parameters, again calculating the SD of the mean incidence in 1987 and 2000 for all iterations where those parameters were varied together.

Results of Sensitivity Analyses

The observed annual incidence of invasive Hib per 100,000 children <5 years of age was 36.3 in 1987 and 0.23 in 2000. Across iterations, the mean modeled incidence matches the observed incidence in these years closely (Technical Appendix 3 Table 1). However, at first glance, it appears that the model is sensitive to the particular values of all the parameters. The SD of the predicted annual incidence per 100,000 in 1987 was ≥ 8.4 for all parameters. For example, when death rate was allowed to vary along with any other 2 parameters, the modeled incidence in 1987 had a mean of 36.1 and an SD of 8.7, which is a high degree of variability.

However, closer examination of the data shows that the variability is predominantly due to a single parameter: the rate of recovery from colonization (ρ_C). The SD for incidence in 1987 across iterations where ρ_C was varied is 23.8, which is an extreme amount of variability. The high SD in estimated incidence from varying the other parameters was largely due to iterations where ρ_C was varied along with the other parameters. When the variability of the remaining parameters was examined only among iterations where ρ_C was fixed (set to the mean), the SD was much smaller, never larger than 1.6 for incidence in 1987. Thus, we conclude that the model is highly sensitive to the value of ρ_C , and highly robust to the remaining individual parameters.

We further examined all 2-way and 3-way combinations of the parameters, excluding iterations where ρ_C was also varied. The SE for estimated incidence in 1987 was never >2.3 for any pairs or triads of parameters, and never >0.03 for incidence in 2000. This finding indicates that there were not pairs or triads of parameters to which the model is highly sensitive.

Additional Analyses

Because the model is highly sensitive to the rate of recovery from colonization, we further explored whether changes in this parameter would impact our conclusions from the model. We chose two extreme values for ρ_C — a fast recovery rate 2 SE higher than the mean value and a slow recovery rate 2 SD lower than the mean recovery rate. The mean (SE) duration of colonization from the literature was 0.46 years (168 days), which corresponds to ρ_C of 0.0417 recoveries per week among the colonized (references 1–3 in Technical Appendix 2). Two SE above this was a recovery rate of 0.0547 recoveries per week, corresponding to an average

duration of colonization of 128 days. Two SE below was a recovery rate of 0.0336 recoveries per week, an average duration of 208 days.

For each of the extreme values of ρ_C , we refit the “who acquires infection from whom” (WAIFW) matrix for the United States population. We compared the WAIFW matrices generated from the mean, extreme low, and extreme high rates of ρ_C to see whether our conclusions about the relative role of each age group for Hib transmission differs depending on the modeled value of ρ_C . In addition, we tested whether our conclusions about the impact of different vaccination strategies would differ based on the modeled rate of ρ_C . For this, we ran the United States model under three scenarios: using a primary series only, using a primary series and a booster, and using a single dose at 12–15 months only.

We found that the specific value used for ρ_C does not affect the conclusions we draw based on our model. Across all 3 values of ρ_C , our model suggests that children 2–4 years of age are the key drivers of Hib transmission in the United States (Technical Appendix 3 Table 2). Furthermore, across all 3 values of ρ_C our model suggests that using a single Hib dose in the second year of life would reduce Hib incidence more than a primary series in infancy with no booster dose (Technical Appendix 3 Figure).

Summary

Although the specific values of the model parameters must be defined from estimates of these values that are measured with uncertainty, this uncertainty does not impact our model’s conclusions. Other than the rate of recovery from colonization, any reasonable values for the model parameters alone or in combination can be substituted into the model without impacting the model output’s fit to observed incidence data. The model can be fit using a wide range of values for the rate of recovery from colonization and still result in similar conclusions about the epidemiology of Hib and the impact of Hib vaccination programs.

Technical Appendix 3 Table 1. Mean and SD of predicted annual incidence per 100,000 persons in 1987 and 2000 from the Hib simulation model, where the value of the listed parameter was randomly sampled from its distribution*

Parameter	Incidence among all iterations where the parameter was sampled				Incidence excluding iterations where recovery from colonization was varied			
	1987		2000		1987		2000	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Birth rate	35.8	8.4	0.16	0.04	35.6	0.9	0.15	0.01
Death rate	36.1	8.7	0.16	0.03	35.7	0.8	0.15	0.01

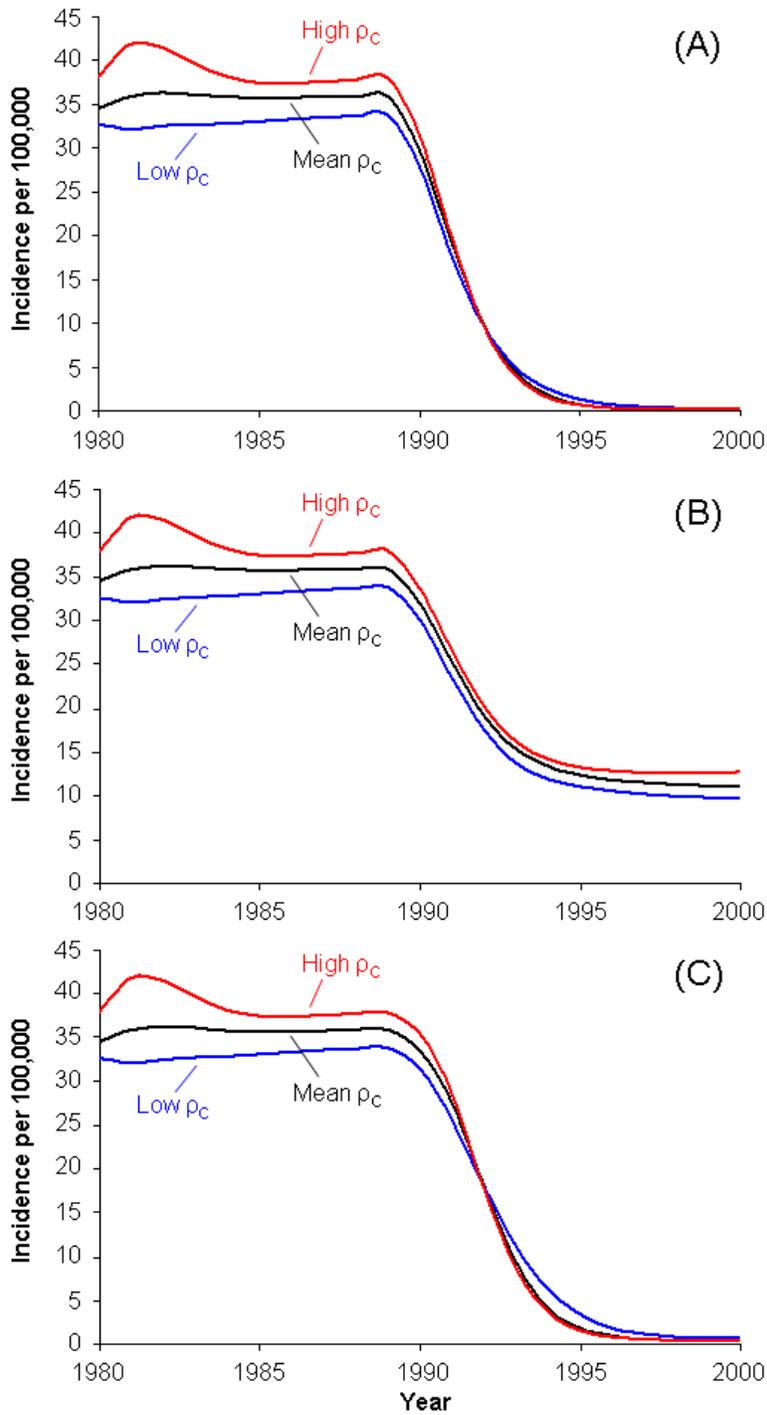
Parameter	Incidence among all iterations where the parameter was sampled				Incidence excluding iterations where recovery from colonization was varied			
	1987		2000		1987		2000	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Vaccine take rate								
Age <1 year	35.9	8.8	0.16	0.03	35.6	0.8	0.15	0.01
Age ≥1 year	36.3	8.6	0.17	0.04	35.7	0.8	0.16	0.02
Outside force of infection	36.5	9.7	0.16	0.03	35.7	0.8	0.15	0.01
Rate of recovery from colonization	39.5	23.8	0.18	0.09	NA	NA	NA	NA
Rate of recovery from disease	36.1	9.5	0.16	0.03	35.7	0.7	0.15	0.01
Rate of waning from low to no antibody	36.5	9.6	0.16	0.04	35.6	0.8	0.15	0.01
Rate of waning from high to low antibody								
Age <1 year	36.3	8.8	0.16	0.04	35.7	0.7	0.15	0.01
Age 1 year	36.2	9.3	0.16	0.04	35.7	0.8	0.15	0.01
Age ≥2 years	36.5	9.5	0.16	0.03	35.7	0.8	0.15	0.01
Protection of low antibodies against colonization	35.1	9.4	0.14	0.03	34.7	1.6	0.14	0.02
Protection of low antibodies against disease	36.2	9.2	0.16	0.03	35.7	0.8	0.16	0.02
Protection of high antibodies against colonization	36.4	8.4	0.16	0.03	35.8	0.9	0.15	0.01
Protection of high antibodies against disease	36.3	9.1	0.16	0.04	35.7	0.8	0.15	0.01

*Hib, *Haemophilus influenzae* type b; NA, not applicable.

Table 2. Estimated “who acquires infection from whom” matrix in the United States population using three values for the rate of recovery from colonization*

Mean recovery rate (0.0417 recoveries per week)					
		Age group of infectious persons (j) ,y			
		0–1	2–4	5–9	≥10
Age group of susceptible persons (i), y	0–1	0.02	0.83	0.22	0.01
	2–4	0.01	2.66	0.03	0.01
	5–9	0.96	4.68	0.29	0.06
	≥10	0.66	2.70	0.17	0.03
Extremely low recovery rate (0.0336 recoveries per week)					
		Age group of infectious persons (j) ,y			
		0–1	2–4	5–9	≥10
Age group of susceptible persons (i), y	0–1	0.76	0.19	0.30	0.01
	2–4	0.01	2.15	0.02	0.01
	5–9	0.22	3.34	0.38	0.08
	≥10	0.12	1.94	0.23	0.02
Extremely high recovery rate (0.0547 recoveries per week)					
		Age group of infectious persons (j) ,y			
		0–1	2–4	5–9	≥10
Age group of susceptible persons (i), y	0–1	0.22	1.03	0.27	0.01
	2–4	0.55	3.33	0.03	0.02
	5–9	1.76	5.59	1.46	0.08
	≥10	1.93	31.10	0.74	0.03

*Matrix values are the product of (the annual rate at which persons of age group i encounter persons of age group j) and (the probability of transmission given contact between susceptible in age group i and infectious in age group j)



Technical Appendix 3 Figure. Predicted effects of different Hib vaccination strategies on incidence of Hib in children <5 years of age, in a United States-like population, under different assumptions about the rate of recovery from colonization (ρ_c). (A) Vaccination with primary series and booster dose; (B) Vaccination with primary series only; (C) Vaccination with a single dose at 12–15 months of age only.