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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We used published and unpublished data to set values for the model parameters (Technical Appendix 2 Table 1).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 μg/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 We used published and unpublished data on vaccine coverage by age and year to estimate rates of vaccination (*16–25*) (Centers for Disease Control and Prevention, unpub.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 Value	United States Source(s)	England and Wales Value	England and Wales Source(s)	Alaska Natives Value	Alaska Natives 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	$\delta_{BPIG}(t,a)$	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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