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Mathematical model comparisons of potential nontypeable *Haemophilus influenzae* vaccine effects

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Abstract

Vaccines to prevent acute otitis media (AOM) caused by nontypeable *Haemophilus influenzae* (NTHi) are under development. Because NTHi is highly variable and colonization rates are high, special vaccine characteristics and trial designs might be needed. We examined in mathematical models the equilibrium NTHi-caused AOM rate given hypothetical vaccines that generated immunity identical to corresponding maximal naturally acquired immunity. Vaccines were examined with single effects and combinations of immunity affecting (1) AOM rates given colonization (pathogenicity), (2) susceptibility to colonization, and (3) contagiousness given colonization. Percent reductions in AOM across all preschool children were (1) 34%, (2) 31%, (3) 9%, (1&2) 57%, (2&3) 50%, and (1&2&3) 75%. Effects on children in daycare vs. not in daycare were (1) 18 vs. 48%, (2) –1 vs. 57%, (3) 13 vs. 5%, (1&2) 30 vs. 79%, (2&3) 33 vs. 60%, and (1&2&3) 64 vs. 85%. Pure pathogenicity effects (1 alone) will need to be supplemented by transmission effects. The effects of susceptibility (2 alone) are diminished or negative because children protected against colonization have lower levels of immunity to (1) and (3) than unvaccinated children. For trials to predict population effects both colonization and AOM outcomes must be studied and all three effects must be evaluated. This need arises because, unlike *Haemophilus influenzae* type B, high NTHi exposure diminishes cumulative vaccine effects and high colonization rates generate rapid accumulation of natural immunity that alters the indirect effects of vaccine immunity on transmission differently by age and daycare status.

Keywords

Computer simulation; *Haemophilus influenzae*; Mathematical model; Otitis media; Vaccine

1. Introduction

Nontypeable *Haemophilus influenzae* (NTHi) accounts for the majority of localized respiratory tract infections that are caused by *Haemophilus influenzae*. NTHi strains are antigenically divergent and individuals can be re-colonized by different strains and be colonized several times during their childhoods (Faden et al., 1995; Gilsdorf 1998; Gilsdorf et al., 2004; Spinola

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et al., 1986; Trottier et al., 1989). The organism has generated a great disease burden by causing otitis media in children (Paradise et al., 1997; Schappert 1992; Teele et al., 1989). NTHi vaccine development is in progress and several antigens with different protective features have been patented (Bakaletz et al., 1997; Barenkamp 1996; DeMaria et al., 1996; Poolman et al., 2000).

However, there is still controversy about what effects future NTHi vaccines should have. Since NTHi causes diseases mainly in young children while most events of NTHi nasopharyngeal colonization come from older age groups, one might conclude that protection against disease given colonization rather than colonization itself should be the focus of vaccine prevention. However, the experience with *Haemophilus influenzae* type B (HiB) vaccines suggested that indirect effects produced by a vaccine with effects on transmission can be important in disease prevention. Unlike vaccine effects on pathogenicity (disease rates given colonization), vaccine effects on transmission reduce susceptibility and/or contagiousness in vaccinated individuals, and thereby reduce transmission levels in the population where vaccinated individuals mix. The protection produced by reducing exposure to colonization is thus called indirect effects, which benefit both vaccinated and unvaccinated individuals. In comparison, vaccine direct effects result directly from vaccine induced immunity and only exist in vaccinated individuals.

To understand what vaccines are more appropriate for otitis media prevention, an NTHi vaccination program was simulated in a mathematical model and vaccines with different types of effects were compared. The results have implications for future vaccine trial designs. If NTHi vaccination produces significant indirect effects, group randomized trials instead of individually randomized trials may be needed to evaluate NTHi vaccines. The former can capture indirect effects as well as direct effects of vaccination and gain power to detect vaccine effects.

2. Methods

2.1. Mathematical model construction

The mathematical model applied in our analysis, a deterministic compartmental (DC) model, was constructed by Koopman et al (Koopman et al., 2004). It is based on a system of differential equations that parameterize the flow of population between compartments. Each compartment is defined by age group, daycare attendance status, colonization or disease status, and immunity level. Beyond six months of age, colonization and immunity act identically in all age groups. All differences between age groups are due to their differences in exposure or their acquired immunity levels due to their past history of colonization. See the Appendix for a precise formulation of the associated differential equations. The following summarizes the model's major features.

Model population structure—Children in their first 6 months of life are not included in the model since we assume maternal immunity provides complete protection from NTHi colonization. Because the population under age five years is the key population we seek to protect, and because colonization and disease vary strongly by age and daycare attendance status in this group (Alho et al., 1991; Aniansson et al., 1992; Faden et al., 1996; Fleming et al., 1987; Howard et al., 1988; Kero and Piekala 1987; Lundgren and Ingvarsson 1983; Principi et al., 1999; Teele et al., 1989), the population is divided into 9 six-month age groups and in each group they are further divided into those that do and do not attend daycare. Individuals aged over 5 years are divided into two groups: school age group and adult group, which differ in that the school age group has an extra mixing site resulting in higher exposure to colonization. Age composition and daycare attendance by age are similar to those in the U.S. population because we choose developed countries as the target population.

Model contact structure—Most of NTHi transmission occurs through airborne droplets or through direct contact with respiratory secretions, and gathering in places such as daycare centers and schools should facilitate NTHi transmission. Many studies have identified daycare attendance as a factor contributing significantly to the frequent occurrence of NTHi colonization in preschool children (Aniansson et al., 1992; Fleming et al., 1987; Principi et al., 1999). Meanwhile, the prevalence of NTHi nasopharyngeal colonization (called “NTHi prevalence” below) in school children is much higher than in adults (Principi et al., 1999) although the former have even greater immunity (Yamanaka and Faden 1993). For these reasons daycare and school mixing sites are assumed. In total, three mixing sites are assumed: daycare, school, and a general site. All individuals make contacts at the general mixing site but daycare and school children also make contacts at the daycare and school mixing sites, respectively (see Table 2 in the Appendix for contact rates in the three mixing sites).

Natural history of NTHi colonization—See Figure 1 for the natural history of NTHi colonization. Five colonization or disease statuses are assumed: susceptible status, colonization status C_a followed by C_b , disease status following C_b , and colonization status C_c after disease recovery. Colonized individuals recover from C_c if disease occurs but from C_b if not. It's also assumed C_a , C_b , and C_c have the same duration. This structure is consistent with the observation that acute otitis media (AOM) occurs within the context of nasopharyngeal colonization and that ear infection is more readily eliminated by treatment than is nasopharyngeal colonization (Personal communication with Dr. J. Gilsdorf, Medical Center of the University of Michigan). There is no physical meaning to divide colonization period into 2 or 3 equal stages but by doing so the duration of colonization follows a gamma distribution, which has better face validity than an exponential distribution that is implied by one compartment. Throughout the colonization period, contagiousness levels are assumed to be stable disregard colonization or disease status. In addition, neither colonization nor disease events affect contact rates. For simplicity, we only defined a single disease state, AOM. After recovering from colonization individuals become susceptible again but may have higher immunity levels (Figure 1).

Immunity structure—For the purpose of model construction the model was fitted to observed data to obtain values for unknown parameters. Four immunity levels are assumed due to the fact that we did not see improvement of model fit to higher numbers of levels (Figure 1). Generally individuals enter the next higher immunity level after colonization and move down to lower levels due to immunity waning. Those at the highest level remain at that level after colonization. Three types of naturally acquired immunity are assumed, immunity affecting pathogenicity of further colonization (pathogenicity immunity), immunity affecting susceptibility to colonization (susceptibility immunity), and immunity affecting contagiousness of further colonization (contagiousness immunity).

The waning of immunity in the model reflects the dynamics of NTHi strains as well as the biological loss of immunity due to immune system dynamics in the host. Ongoing genetic change in circulating NTHi (Gilsdorf 1998; Lomholt et al., 1993) is one reason individuals lose immunity to NTHi over time. Because the duration of colonization is short compared to immunity duration, for the sake of simplification the waning of immunity causes flows of susceptible instead of colonized individuals to lower immunity levels. We assume the duration of each level of acquired immunity follows an exponential distribution that does not vary with age or immunity level itself. The model's immunity structure implies the duration of maximum naturally acquired immunity follows the same distribution without regard to immunity types.

Model fitting—The DC model was fit to conform to observed data on AOM incidence caused by NTHi (called “AOM incidence” below) by year under age 5 and NTHi prevalence in daycare and non-daycare preschool children, school children, and adults (Koopman et al., 2004). Like

age composition and daycare attendance by age, these data were observed in developed countries.

2.2. Levels of naturally acquired immunity

According to model fitting results, each event of colonization reduces pathogenicity by 28%, susceptibility by 48%, and contagiousness by 24%. The maximum level of naturally acquired immunity is $0.62 (=1-(1-0.28)^3)$ for pathogenicity, 0.86 for susceptibility, and 0.56 for contagiousness. Levels of naturally acquired immunity in the model peak at school age. This is consistent with a reported age distribution of NTHi antibody levels (Yamanaka and Faden 1993) and with observed decrease of NTHi prevalence with increasing age (Gunnarsson et al., 2000; Principi et al., 1999). Average immunity levels are lower in adults than in school children because in adults the rate of immunity waning outweighs that of gaining immunity from colonization.

2.3. Vaccine and vaccination

First we compared vaccines with a single type of effects, i.e., vaccines with effects (1) on pathogenicity alone (pathogenicity vaccines), (2) on susceptibility alone (susceptibility vaccines), and (3) on contagiousness alone (contagiousness vaccines). Then comparisons were made for vaccines with combined effects. We assumed that vaccine efficacy levels were proportionate to the maximal levels of the corresponding naturally acquired immunity. For the sake of simplification we further assumed that vaccine efficacy was equal to the corresponding maximal naturally acquired immunity. Type I (relative immunity) vaccine effects were assumed. In other words a vaccine reduced pathogenicity/susceptibility/contagiousness by the same proportion in all vaccinated individuals whether or not they already had such immunity (Chick et al., 2001; Smith et al., 1984). However, it was assumed that immunity in vaccinated individuals cannot be greater than the corresponding maximal naturally acquired immunity. Since our conclusions were to be based on comparisons between different vaccines, for simplicity we assumed that all children received vaccines before six months of age and that full vaccine induced immunity was acquired by six months of age. It was also assumed that vaccine and naturally acquired immunity were both lost at the same rate.

To illustrate immunity in vaccinated individuals, I_p , I_s , and I_c were used to denote the levels of their pathogenicity immunity, susceptibility immunity, and contagiousness immunity, respectively. Since immunity in vaccinated individuals contains two components - naturally acquired and vaccine induced immunity - I_{np} and I_{vp} were used to indicate levels of pathogenicity immunity acquired from natural colonization and vaccination, respectively. Meanwhile, I_{mnp} denotes the maximum level of naturally acquired pathogenicity immunity. Likewise, I_{ns} , I_{vs} , and I_{mns} were used to measure susceptibility immunity and I_{nc} , I_{vc} , and I_{mnc} contagiousness immunity. Given this, $I_p = \min(1-(1-I_{np})^*(1-I_{vp}), I_{mnp})$, $I_s = \min(1-(1-I_{ns})^*(1-I_{vs}), I_{mns})$, and $I_c = \min(1-(1-I_{nc})^*(1-I_{vc}), I_{mnc})$.

2.4. Model analyses

The DC model was constructed and analyzed numerically in Berkeley Madonna® (Macey and Oster 2003). Models without vaccination as well as those with each vaccine were analyzed. For each model, AOM incidence among preschool children was measured at equilibrium. Vaccine effects were measured by the percent reduction of AOM incidence in the model with vaccination, as compared to that without.

3. Results

3.1. Comparisons of vaccines with a single type of effects

As seen in Figure 2, a susceptibility vaccine and a contagiousness vaccine reduced AOM incidence in overall preschool children by 31% and 9%, respectively, less than the value of 35% for a pathogenicity vaccine. For vaccines with effects on susceptibility alone or pathogenicity alone the percentage reduction of AOM incidence was higher in non-daycare preschool children than in daycare children but this was not true for the vaccine with only contagiousness effects. Of note is that the susceptibility vaccine had negative effects in daycare children although of all the three vaccines, it produced the highest effects in non-daycare preschool children. Intensity of exposure accounts for higher effects in non-daycare compared to daycare children. Viewing effects by age helps elucidate the mechanisms through which intensity of exposure acts.

Effects specified by age and exposure are seen in Figure 3. Here we see that the largest effects were in the youngest age groups and that as age progressed, effects fell. The one exception was for contagiousness vaccine effects in children who were in daycare. Both susceptibility and pathogenicity effects were lower and fell faster with age when children were in daycare. Susceptibility effects became negative in higher age groups and these negative effects were reached at considerably younger ages for children in daycare.

An understanding of the dynamics behind these patterns should guide our pursuits of NTHi vaccines and our design of NTHi vaccine trials. In the following we will present additional figures that help explain these patterns in Figure 3. We now consider three dynamic systems phenomena that contribute to these patterns:

1. Indirect effects accrue to children not because they were vaccinated, but because their contacts were vaccinated. These indirect effects are greater in children in daycare because they were exposed to more vaccinated children.
2. The amount of immunity acquired through natural colonization is lowered by vaccination that reduces NTHi circulation.
3. The accumulation of natural immunity in the unvaccinated children diminishes the difference in their immunity levels from those of vaccinated children.

Since the indirect effects of vaccines acting only on pathogenicity in our model are negligible, almost the entire drop with age in pathogenicity vaccine effects is due to phenomenon number 3 in the above list. The faster decrease trend as well as the lower pathogenicity effects in daycare children (Figure 3b) as compared to children not in daycare (Figure 3a) can be explained by more natural colonization in daycare. For contagiousness vaccines, the increase of vaccine effects by daycare attendance (Figure 2) is accounted for by phenomenon number 1 because these vaccines only produce indirect effects on AOM occurrence.

In Figure 4 we also see an important phenomenon that arose when vaccines had effects only on susceptibility to colonization. By protecting children from colonization, naturally acquired pathogenicity immunity was considerably decreased. This is part of the explanation for why pure susceptibility vaccines had negative effects at higher ages. Another part of the explanation can be seen in Figure 5. Just as pure susceptibility vaccines diminished the natural acquisition of immunity to pathogenicity, they also reduced the natural acquisition of immunity to contagiousness. A final part of the explanation for the age patterns of pure susceptibility vaccines is seen in Figure 6. In the daycare setting due to high transmission levels naturally acquired colonization quickly raises immunity levels to susceptibility to the same levels that can be achieved with a susceptibility vaccine. The reduced levels of naturally acquired immunity to pathogenicity and contagiousness together with the minimal difference between

susceptibility immunity levels in vaccinated and unvaccinated children caused pure susceptibility vaccines to have a negative effect at higher ages.

Figure 6 also shows that even though contagiousness vaccines reduced levels of susceptibility immunity, these effects were quite small compared to the effects of susceptibility vaccines on contagiousness immunity. The reason is that the effects on colonization levels by a pure contagiousness vaccine were small as indicated in Figure 2.

Now let us explain why in Figure 3 the effects of a pure contagiousness vaccine rose with age for children in daycare. Contagiousness effects of vaccines reduce the force of infection for everyone, vaccinated and unvaccinated alike, regardless of their level of pathogenicity or susceptibility immunity. Thus everyone gets the same relative benefits from contagiousness effect vaccines. Thus when looking at Figure 5, one must not think of the benefits being greater at a younger age just because the difference of contagiousness immunity between the vaccinated and unvaccinated is greater at a younger age. The benefits of the contagiousness vaccine are the same across all age groups and the percentage reduction in Figure 3 would be constant across all ages except that other differences come into play. These other factors are naturally acquired immunity levels to susceptibility and pathogenicity. As seen in Figures 4 and 6, the reduction in population level immunity for both of these was minimal for contagiousness vaccines. But for daycare children the relative reductions were far greater at the youngest ages than at the higher ages under 5. This accounts for the rise in contagiousness effects seen in Figure 3. In contrast for non-daycare children, the gap between immunity levels for pathogenicity and susceptibility mainly increased at first and then slightly decreased. This can also be seen to be directly reflected in the shape of the percentage reduction from the pure contagiousness effect vaccine.

3.2. Comparisons of vaccines with different effect combinations

As seen in Figures 2 and 7, compared to pure pathogenicity vaccines or pure susceptibility vaccines, the combination of pathogenicity and susceptibility effects considerably increased vaccine population effects in both daycare and non-daycare children. Adding contagiousness effects to pathogenicity effects, however, significantly raised vaccine efficacy only in daycare children as they are the only ones heavily exposed to vaccinated children. In the daycare setting, contagiousness effects slightly exceeded susceptibility effects in enhancing pathogenicity effects despite the fact that vaccines reduced contagiousness by 56% while they reduced susceptibility by 86%. The reason for this greater effect of contagiousness reduction is seen in the previously presented differences in the deficit of susceptibility induced by contagiousness vaccines as compared to the deficit in contagiousness induced by susceptibility vaccines. Because contagiousness vaccines induce a deficit in both pathogenicity and susceptibility immunity, only vaccines with all the 3 effects can significantly reduce daycare AOM incidence. Note that in daycare settings even though the sum of pure susceptibility effects and pure contagiousness effects was small (Figure 2), a combined susceptibility and contagiousness effect vaccine produced much larger effects than a pure pathogenicity vaccine (Figure 7). The former vaccine also produced larger effects in both daycare and non-daycare children than a vaccine with combined pathogenicity and contagiousness effects (Figure 7).

4. Discussion

We have illustrated complexities in the population effects of vaccines against NTHi that we hope will lead investigators to take new approaches to their evaluation. These complexities emerge because high colonization rates cause immunity levels to rise quickly across preschool ages. This diminishes the differences in immunity levels between vaccinated and unvaccinated individuals and generates population level feedbacks between naturally acquired immunity and

vaccine effects on susceptibility, contagiousness, and pathogenicity. These feedbacks will play an important role in the population effects of an NTHi vaccine and should not be ignored.

Three phenomena we list clearly explain our results. Summarizing these from the results section, these are (1) indirect effects, (2) vaccine caused reduction in acquisition of natural immunity, and (3) rapid displacement of vaccine effects by naturally acquired immunity. A major value of this paper is to make clear the need to consider these in designing vaccines and vaccine trials.

If we had a vaccine with a very strong pathogenicity effect and no effect on susceptibility or contagiousness, the complex feedbacks between naturally acquired immunity and vaccine effects would not come into play. Such a vaccine would not alter the circulation of NTHi that generates naturally acquired immunity. All of its effects would be direct effects on the vaccinated individuals. But our calculations indicate that the benefits from a vaccine with purely pathogenicity effects would be limited if the vaccine does not stimulate more immunity than natural colonization. Even if every child was fully vaccinated with a pure pathogenicity effect vaccine before they lost their maternal immunity, AOM rates from NTHi would fall only 34% in preschool children. We show that adding susceptibility effects to that vaccine increased the reduction to 57%, and a vaccine that combined all 3 effects could reduce AOM rates by 75%.

Any NTHi vaccine is likely to affect susceptibility or contagiousness. Experience with the HiB vaccine supports that notion. HiB effects on transmission were purely positive because of the low colonization rates with Type B *Haemophilus influenzae*. But our analysis has uncovered the potential for the reduction in susceptibility to colonization from NTHi vaccines to increase susceptibility to disease given colonization and to increase the contagiousness of colonization in the higher preschool years. We found that a vaccine that has the same effect on susceptibility to colonization as maximal naturally acquired immunity would only reduce preschool AOM rates by 31% even if perfectly administered. In daycare children the effects would actually be negative. Major reasons for this overall low effect and negative effect in daycare children are decreased population levels of pathogenicity and contagiousness immunity.

An important inference from our work is that we should pursue development of vaccines that have all three vaccine effects. Note that even though immunity from colonization or vaccine in our model reduces contagiousness much less than it reduces susceptibility, adding contagiousness effects to susceptibility effects in a vaccine made a great contribution to overall vaccine effects. There are two reasons for this. The first is that susceptibility effects alone generate a significant deficit in contagiousness immunity. The second is more subtle and relates to equilibrium dynamics. Contagiousness and susceptibility effects make quantitatively equal contributions to reducing the basic reproduction number (R_0) (Simon and Koopman 2002). Above the critical level for sustaining infectious agent circulation, however, adding one source of immunity has a greater effect in the presence of the other source of immunity than in its absence. That is because there is a convex relationship between the amount of immunity already present and the effects of immunity on colonization prevalence. This is manifest in the classic equation $\text{Prevalence} = 1 - 1/R_0$. The same percentage reduction in R_0 has a larger effect on prevalence if something else has already lowered the value of R_0 .

To separately evaluate pathogenicity effects and transmission effects of NTHi vaccines, one can measure both AOM and colonization as outcomes in individually randomized trials that are designed not to have important indirect effects on placebo recipients. But we have shown that indirect effects could be important, especially in daycare children. All contagiousness effects are indirect and these are not detected in standard individually randomized trials. The contacts of vaccine recipients could be studied to pick up such effects. Group randomized

designs, however, offer an approach that can detect indirect effects and that allow for better prediction of population effects of vaccination programs (Halloran et al., 1991; Halloran and Struchiner 1991; Hayes et al., 2000; Longini et al., 2002; Longini et al., 1998). We believe that serious consideration should be given to group randomized trials in daycare centers as both the most cost-effective way to detect useful vaccine effects and the best way to quantify each of the separate vaccine effects.

The robustness of these inferences from our work to realistic inconsistencies with the simplifying assumptions in our model needs to be considered. Both the data and the theory underlying our model are weak. The conformation of contacts in the real world is more complex and could be different from that employed in our model. The natural history of colonization, disease, and immunity might be different from that in our model. We have calculated effects from the three different types of immunity in our model from very limited data (Koopman et al., 2004) and the true effects might be different.

Standard sensitivity analyses provide some limited reassurance regarding the robustness of our inferences. Table 1 presents a sensitivity analysis relevant to assumptions about the distribution of times until vaccine acquired immunity is lost and to waning rates. But more sensitivity analyses should be pursued. In particular it would be useful to relax our simplifying assumptions about natural immunity and its waning. In reality many distinct bacterial variants with diverse immune cross reactions between strains are circulating. Our model assumes one continuously varying homogeneous agent. It also assumes that the vaccine is always adjusted to changes in the mix of NTHi variants that are circulating. Vaccines that are not so perfectly adjusted might help select for variants that displace the variants to which the vaccine is most specifically directed. This will alter the population effects of vaccination in ways that cannot be assessed with our model. Individual based stochastic models are needed to address this and other realistic complexities in NTHi immunity that might be considered.

Even without further robustness assessment, however, the results of our analysis indicate that NTHi vaccine trials should not be simple individual randomization trials. To justify simple randomized trials, new data and new model analyses would have to counter the issues we have raised.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

The natural history of NTHi colonization and naturally acquired immunity. The arrows point the direction of transition from one status to another. The word susceptible indicates a status without NTHi colonization. Pathogenicity/Susceptibility/Contagiousness: one minus immunity affecting pathogenicity/susceptibility/contagiousness; $\gamma/\theta/\chi$: one minus pathogenicity/susceptibility/contagiousness immunity acquired through each event of colonization. n : immunity level, larger values indicates higher immunity levels. C_a : the initial stage of colonization; C_b : the later stage of colonization followed by either recovery or disease; D : disease stage; C_c : colonization stage after disease recovery. C_a , C_b , and C_c have the same duration. Most colonized individuals recover from C_b but some develop disease after C_b .

Fig. 2.
Percentage reduction of NTHi-caused AOM incidence in preschool children by vaccines with a single type of effects administered before losing maternal immunity.

Fig. 3. Percentage reduction of NTHi-caused AOM incidence by age groups among non-daycare (top) and daycare (bottom) preschool children as the result of vaccination before losing maternal immunity.

Fig. 4. Equilibrium immunity on pathogenicity with and without vaccination by age groups among non-daycare (top) and daycare (bottom) preschool children.

Fig. 5. Equilibrium immunity on contagiousness with and without vaccination by age groups among non-daycare (top) and daycare (bottom) preschool children.

Fig. 6. Equilibrium immunity on susceptibility with and without vaccination by age groups among non-daycare (top) and daycare (bottom) preschool children.

Fig. 7.

Percentage reduction of NTHi-caused AOM incidence in preschool children by vaccines with combined effects administered before losing maternal immunity. Note: the legend in the figure indicates vaccine types, e.g., “Pathogenicity+Contagiousness” represents a vaccine inducing immunity affecting both pathogenicity and contagiousness.

Table 1

Sensitivity of vaccine population effects^a to different assumptions about the duration of vaccine induced immunity

Types of Vaccines (Represented by types of vaccine induced immunity)	Baseline	Varying Distributions of Immune Duration		Varying Average Immune Duration	
		Gamma with 1 ^b	Gamma with 2 ^b	Decreased by 20% ^c	Increased by 20% ^c
Pathogenicity Only	34%	35%	35%	34%	35%
Susceptibility Only	31%	32%	32%	30%	31%
Contagiousness Only	9.0%	9.3%	9.3%	8.9%	9.1%
Pathogenicity +Susceptibility	57%	57%	58%	56%	58%
Pathogenicity +Contagiousness	43%	44%	44%	43%	43%
Susceptibility +Contagiousness	50%	52%	52%	48%	51%
Combination of the 3 Types	75%	75%	75%	75%	75%

^aPopulation effects were measured by percentage reduction of NTHi-caused AOM incidence in preschool children.

^bGamma with 1 (or 2): using a gamma distribution with shape parameters 1 (or 2). At baseline the duration of vaccine induced immunity follows a gamma distribution with shape parameters 3.

^cThe average duration of vaccine induced immunity was decreased or increased by 20%. At baseline the average duration is equal to that of maximum naturally acquired immunity.