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# Modelling the effect of conjugate vaccines in pneumococcal disease: Cohort or population models?

Baudouin Standaert[a,*], Nadia Demarteau[a], Sandra Talbird[b], Josephine Mauskopf[b]

[a] Baudouin Standaert, GlaxoSmithKline Biologicals, Parc de La Noire Epine, B-1300 Wavre, Belgium
[b] RTI Health Solutions, Research Triangle Park, NC, United States

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ABSTRACT

Cohort and population models estimate vaccine impact on disease events, and yield different estimates in countries with different demographic compositions. We compared administration of the new 10-valent pneumococcal *Haemophilus influenzae*–protein D conjugate vaccine (PHiD-CV) with no vaccination in two countries, the United Kingdom (UK) and Mexico, using two modelling strategies: a cohort model and a population model. The cohort model followed a birth cohort over a lifetime, beginning 10 years after initiation of the vaccine program, when vaccine efficacy steady state had been reached. The population model examined the country-specific population over 1 year, also beginning 10 years after initiation of the vaccine program. Both models included the same age-specific disease rates of meningitis, bacteraemia, pneumonia, and otitis media. The output variables were the numbers of specific events, with and without indirect vaccine effects. Without indirect effects, the cohort and population models produced similar results for both countries (deviation of <20% difference per output measure for most outcomes). The difference between the model types was much greater when indirect vaccine effects were included, especially in Mexico (up to 120% difference). Cohort and population modelling methods produce different results depending on the disease, the intervention, the demographic composition, and the time horizon evaluated. Results from the two model types provide different information about the impact of interventions on events: accumulated vaccine benefit for an individual in a cohort model; vaccine benefit for a whole population at a specific time point in a population model.



## 1. Introduction

Ongoing vaccine programs provide a health benefit at both the individual and the societal level that is sustained long after their initiation [1]. Mathematical models therefore are required to estimate these programs' total impact over time [2]. The results of such modelling exercises are especially important for decision makers at product launch, when only data on efficacy and safety from short-term, randomised clinical trials are available. Such trials are conducted essentially for registration purposes and not for total impact assessment. Modelling uses efficacy data to estimate an intervention's effectiveness in situations closer to reality by integrating epidemiological and local disease-management data [3].

Different modelling approaches exist to evaluate the total impact of new interventions [4]. Each model type has strengths and weaknesses that must be considered when determining which type to select for answering a particular question. In this paper, we discuss and compare two model types—the cohort model and the population model—to answer questions about the total disease impact of a new vaccine program [5,6].

Cohort models follow a fixed number of individuals (i.e., a cohort) from a starting point in time, such as birth year, until a certain endpoint, which may be an event (e.g., death) or a fixed time point. These models evaluate cohorts over time in a cumulative manner, generating accumulated estimates of the effect of a new vaccine program.

Population models, in contrast, evaluate an entire population at specific time points using the total population size and its specific age distribution to estimate the impact of a new vaccine program on total population health during a fixed time period, usually 1 year.

The starting point for a population model is different from that of a cohort model in two ways. First, a population model replicates the demographic composition of the population under study rather than focusing on a representative individual or a cohort (e.g., a cohort at the age the new vaccine is given). Second, a population model attempts to evaluate the prevalence of the disease under study in a two-dimensional setting (over time and across multiple age cohorts). That two-dimensional assessment can be achieved

* Corresponding author at: Health Economics, GlaxoSmithKline Biologicals, Parc de La Noire Epine, B-1300 Wavre, Belgium. Tel.: +32 0 10 85 56 96; fax: +32 0 10 85 91 34.
*E-mail address:* baudouin.a.standaert@gskbio.com (B. Standaert).

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with simple techniques, such as assessment at two different time points, or with more complex, dynamic, time-dependent evaluation processes, such as time-differential equations in dynamic models [7]. Therefore, compared with a cohort model, a population model allows for more comprehensive assessments, over time, of infectious diseases that spread through close contact between individuals or groups within or across age cohorts.

Knowing the differences between the two model types raises questions such as, Will a cohort model and a population model yield different estimates of health outcomes for a new vaccine program; how big can the difference between these estimates be; which factors have the greatest influence on that difference; and how can we best report the results of each model type? Answers to those questions are critical when presenting modelling results to decision makers, as they enable a clearer understanding of the information derived from the selected model type and its correct interpretation.

In this paper, we compare outcomes derived from a cohort model and a population model in two countries with different demographic structures, in the area of an infectious disease that can be prevented by vaccination. We studied pneumococcal disease caused by *Streptococcus pneumoniae*, a pathogenic bacterium that can affect children and adults, causing pneumonia, upper respiratory tract infections such as acute otitis media (AOM), and invasive infections such as meningitis and bacteraemia [8]. Pneumococcal disease is concentrated in children aged younger than 5 years and in elderly patients (older than 75 years) [9], and its incidence varies between countries [10]. We studied the United Kingdom (UK) and Mexico. The UK has a relatively stable population structure, but the proportion of elderly persons is increasing. Mexico is a good example of a young, dynamic, emerging country, with a relatively high proportion of young people in its demographic composition. The vaccine investigated was the new 10-valent pneumococcal *Haemophilus influenzae*–protein D conjugate vaccine (PHiD-CV), which was approved by the European Medicines Agency on March 30, 2009. PHiD-CV offers protection against 10 serotypes, plus additional protection against nontypeable *H. influenzae* from the carrier protein, which may be especially important in AOM [11]. Previous evaluations of pneumococcal vaccines have typically used cohort modelling [12]. In this paper, we demonstrate that both cohort and population models may be needed to present a clearer and more comprehensive picture of the vaccine's potential, especially for this disease type and in countries with rapid time-dependent changes in demographic structure.

## 2. Methods

### 2.1. Population model

The structure of the population model is described in detail in a companion paper in this supplement (Talbird et al. [13]); only a brief overview is presented here. The population model was derived from a previously published model developed for Canada [5,14] and constructed in Microsoft Excel (Microsoft Corporation, Redmond, WA). The population was subdivided into 123 age groups (monthly from birth to 23 months and yearly thereafter). Each age group comprised a number of individuals based on the current demography of the country under study. Within that structure, the frequency of the disease under study and its short- and long-term impact on morbidity and mortality were simulated for each age group using a decision tree that highlighted the proportion of subjects having different rates and severity of acute disease events and different rates of long-term sequelae.

In contrast to cohort models, the 1-year cross-sectional population model did not include natural death rates by age group. Instead, the population model made the simplifying assumption that the entire population (based on population statistics, which usually report values for the middle of the year) was at risk for pneumococcal disease (and disease-related death) that year. Therefore, only disease-related deaths by age group within the 1-year time frame were considered.

**Table 1**
Cumulative number of person-years at risk in the United Kingdom and Mexico with a cohort model or a population model.

| | UK | | Mexico | |
|---|---|---|---|---|
| | Person-years at risk | % | Person-years at risk | % |
| Cohort model | 59,316,000 | | 152,061,000 | |
| Population model | 60,587,000 | | 106,682,000 | |
| Difference | 1,270,000 | 2% | 45,379,000 | 42% |

UK = United Kingdom.

Vaccination effects were measured over a 1-year time frame at vaccine efficacy steady-state level, a hypothetical future year occurring sufficiently long after the initiation of a program involving vaccination of a single age cohort each year for the vaccine's effect on the prevalence of events to have become constant over time. In our example, it was assumed that the vaccine efficacy steady-state level was reached 10 years after its initiation because of the assumed 10-year duration of efficacy of the vaccine, with full efficacy for 3 years and then waning efficacy for the next 7 years. The population age distribution at steady state was assumed to be equal to the age distribution in 2006 for each country.

Indirect effects, including herd protection and serotype replacement, are carryover effects of vaccination beyond the direct protection conferred on the vaccinated population. Herd protection reflects the reduced attack rate in both vaccinated and unvaccinated individuals because of fewer susceptible individuals in the population; serotype replacement reflects the increase in pneumococcal serotypes that are not countered by a vaccine and therefore can become more prevalent and cause more disease. Herd protection and serotype replacement (which together constitute the net indirect vaccine effect) were incorporated into the model by altering the incidence of invasive pneumococcal disease in all age cohorts in both vaccinated and unvaccinated individuals according to published data estimating the net indirect effects observed after the introduction of the 7-valent pneumococcal conjugate vaccine (PCV-7) [15,16]. (See Talbird et al. [13] for a more detailed explanation of net indirect vaccine effect.) Indirect effects were applied only to invasive disease and are not included for pneumonia and AOM.

### 2.2. Cohort model

The cohort model, also developed in Microsoft Excel for ease of access, used a Markov design. The model followed a single birth cohort over a lifetime with a cycle time of 1 month over the entire time horizon. In total, the cohort was followed for approximately 1200 cycles, or 100 years. The disease frequency was adjusted by age for each cycle number in the model. Management of the disease followed the same decision-tree structure as in the population model; however, the cohort model included a branch for natural death (Fig. 1). Modelling natural death is essential in cohort modelling because a single cohort is followed over time as it ages. The natural mortality of the cohort (i.e., deaths from all other causes unrelated to pneumococcal disease) was taken from all-cause mortality rates in national databases expressed for monthly age groups. Herd protection and serotype replacement effects were estimated from the same published data used for the population model [15,16], applying a reduction in incidence of invasive pneumococcal disease (net indirect effect) in the cohort at all ages as a fixed value at vaccine efficacy steady state. Thus, the cohort model began its evaluation 10 years after vaccine initiation. As in the pop-