Dynamic Transmission Modeling to Address Infant Pneumococcal Conjugate Vaccine Schedule Modifications

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BACKGROUND

- Pneumococcal disease is combatted prophylactically through vaccination with pneumococcal conjugate vaccines (PCVs), which protect against acquisition of nasopharyngeal carriage of the bacteria and its presentation as both invasive and noninvasive disease.[1]
- While PCV programs have been implemented successfully throughout the world, infant vaccination programs are crowded, and health care resources are scarce.
- In the United Kingdom (UK), the Joint Committee on Vaccine and Immunisation has recommended reducing the number of priming PCV doses from the existing 2 + 1 schedule to a 1 + 1 schedule.[2,3]

OBJECTIVE

- To present a dynamic transmission model and subsequent evaluation regarding the potential impact of moving to a reduced 1 + 1 schedule in the context of invasive pneumococcal disease (IPD) only.

RESULTS

- The calibration procedure provided a good fit to historical data for vaccine type (VT) disease; recent increases in NVTs at older ages was underestimated but assumed to have little impact on changes in VT disease during a change in schedule (Figure 2).

Base-Case Analysis

- A 1 + 1 program resulted in additional 88 cases of IPD over a 5-year period for all age groups, a 0.4% increase over a 2 + 1 program (Figure 3).
  - The largest net increase occurred at age 65 or older (an increase of 27 additional cases of IPD over 5 years, or 0.2%), and the largest proportional increase was in ages younger than 1 year (18 cases, or 4.0%).
- VT IPD cases contributed 104 cases (2.4% increase) to the net increase in the number of IPD cases (including the decrease of 17 NVT cases). Serotype 19A accounted for the largest increase in IPD (10.9% of incremental cases), with 18 more cases (7.9%) in ages 65+ and 11 (38.9%) more cases at ages 2 or younger.

Figure 2. IPD Incidence for Ages 0 to Less Than 2 Years by Serotype Group From 2001 to 2017: Calibrated vs. Surveillance

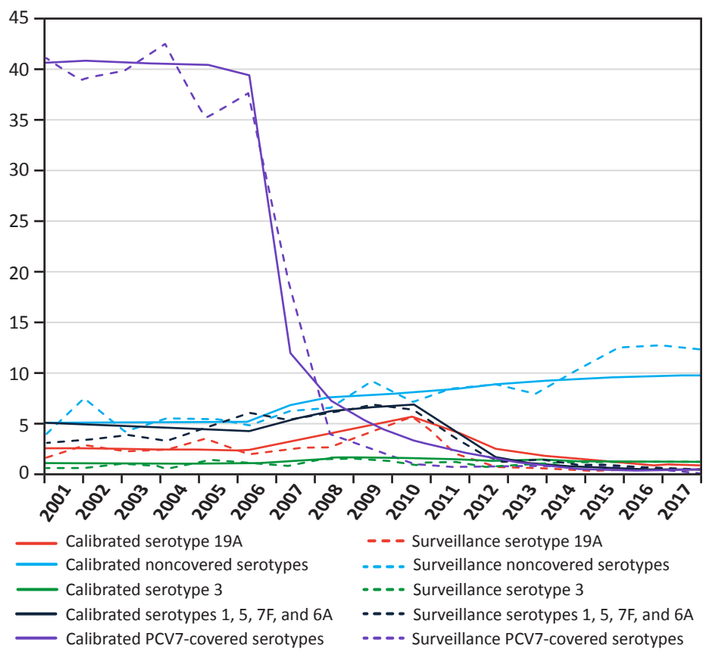
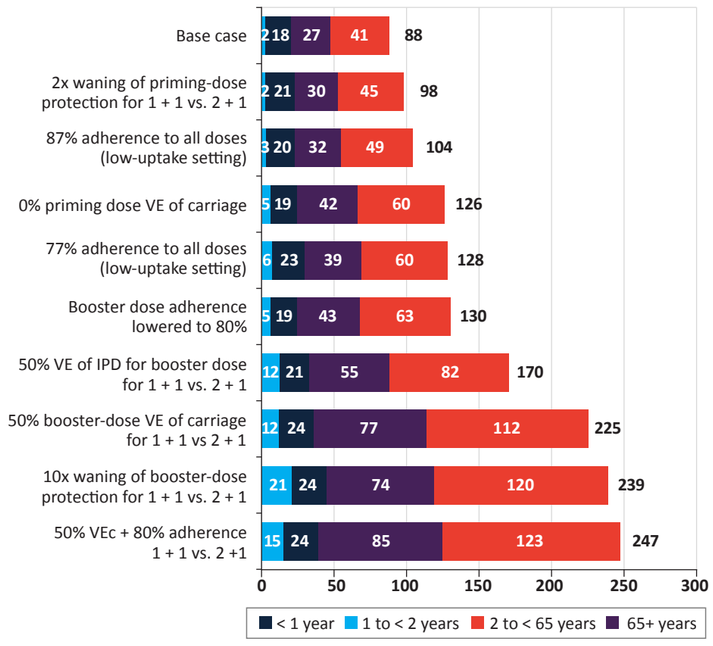


Figure 3. Base-Case and Scenario Analysis Results: Incremental IPD Cases Over 5 Years



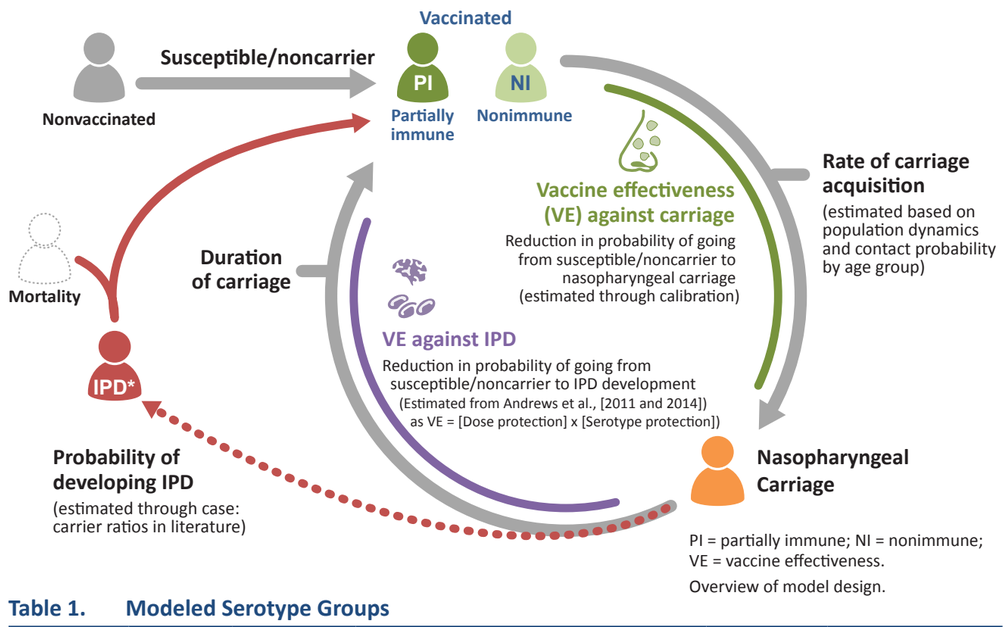
METHODS

Model Structure

- Figure 1 displays a visualization of the model used to estimate carriage and IPD in the UK.
- Carriage and IPD incidence are stratified into five serotype groups (Table 1) and 13 age groups according to the UK population distribution at the start of the model (Table 2).
- Base case compares continuing a 2 + 1 program (priming at 2 months and 4 months + booster at 12 months) versus a 1 + 1 schedule (priming at 3 months + booster at 12 months) starting in 2018.

Epidemiological Inputs

Figure 1. Model Diagram



PI = partially immune; NI = nonimmune; VE = vaccine effectiveness.

Overview of model design.

Table 1. Modeled Serotype Groups

Serotype groups					
	Serotype 19A	Serotype 3	PCV13 serotypes excluding 19A and 3 (i.e., serotypes 1, 5, 7F, and 6A)	PCV7 serotypes	Noncovered serotypes (NVTs)

Table 2. Modeled Age Groups

Age groups < 14 months	0-1 months		2 months	3 months	4 months	5-11 months	12-13 months
Age groups ≥ 14 months	14-23 months	2-4 years	5-17 years	18-34 years	35-49 years	50-64 years	65+ years

- By estimating various model parameters (Table 3), resulting IPD incidence was fit to publicly available routine IPD surveillance data from Ladhani et al.[4] (by age group and serotype group).
- Vaccine effectiveness (VE) against IPD is calculated as:

$$VE_{OI} = 1 - (1 - VE_c)(1 - VE_i)$$

  - VE_{OI} = VE against IPD; VE_c = VE against carriage; and VE_i = VE against IPD given carriage acquisition.[9,10]
- Base case assumes that the VE_c and VE_i of the first priming dose and booster dose are equivalent between 2 + 1 and 1 + 1 programs. As such, the only difference in the 1 + 1 program is the delayed receipt of the first priming dose and the lack of a second priming dose.
- Three factors drive the risk of carriage and IPD:
  - Contact pattern of individuals[11]
  - Force of infection (the likelihood of carriage acquisition after contact with a carrier)
  - Immunity level (VE and duration of protection)

Table 3. Epidemiological Inputs

Parameter	Value
Birth rate[5]	12 per 100,000 per year
General mortality rate[6]	0.15-43.20 per 1,000 per year
Vaccine adherence: 1st primary dose/ 2nd primary dose/booster dose[7]	96.7%
Probability of IPD given carriage acquisition[8]	
Serotype 19A	20 per 100,000 acquisitions
Serotype 3	9 per 100,000 acquisitions
Serotypes 1, 5, 7F, and 6A	28 per 100,000 acquisitions
PCV7-covered serotypes	22 per 100,000 acquisitions
NVT[a]	2 per 100,000 acquisitions
Duration of carriage among carriers (weeks)[8]	
Serotype 19A	12.6
Serotype 3	6.2
Serotypes 1, 5, 7F, and 6A	7.4
PCV7-covered serotypes	14.2
NVT[a]	6.2
Duration of protection (PCV7 and PCV13) (years)	
1st primary dose[a]	5.6
2nd primary dose[a]	11.3
Booster dose[a]	11.3
PCV effectiveness against IPD (1st dose, 2nd dose, booster)[9,10]	
Serotype 19A	53%, 75%, 74%
Serotype 3	16%, 34%, 33%
Serotypes 1, 5, 7F, and 6A	85%, 94%, 93%
PCV7-covered serotypes	56%, 79%, 93%
NVT[b]	0%, 0%, 0%
PCV effectiveness against carriage (1st dose, 2nd dose, booster)[9,10]	
Serotype 19A	16%, 44%, 49%
Serotype 3	2%, 3%, 18%
Serotypes 1, 5, 7F, and 6A	53%, 54%, 69%
PCV7-covered serotypes	15%, 79%, 93%
NVT[b]	0%, 0%, 0%

NHS = National Health Service. [a]Calibrated; [b]Assumed.

Calibration

- Unknown input parameters were estimated such that the modeled IPD incidence curves approximated historical IPD surveillance as closely as possible.[4,12]

Scenario Analysis

- A number of scenarios were tested on VE, adherence, and duration of protection.

STRENGTHS AND LIMITATIONS

- Strengths:
  - Using a compartmental model design that is common in this disease area.[14-16]
  - Capturing granularity in the impact on carriage acquisition and disease by modeling several age and serotype groups.
  - Accounting for the historical effects of switching from PCV7 to PCV13 and considering both IPD and carriage separately.
  - Considering vaccine characteristics (peak vaccine effectiveness, waning rate, etc.) separately for each dose.
  - Fitting the model to UK surveillance data allows calibration with greater certainty and measurability.
- Limitations:
  - Uncertainty surrounding vaccine effectiveness and waning, variation of carriage duration and invasiveness rates by age, and risk of carriage and disease in the first year of life may understate benefit of a 2 + 1 program in the base case.
  - Assumes carriage of one serotype at a time, a potentially conservative approach that underestimates carriage prevalence from co-colonization.
  - Modeled historical carriage prevalence similar to van Hoek et al.[13], but differences in carriage over time may significantly influence model results.

CONTACT INFORMATION

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DISCUSSION AND CONCLUSIONS

- Eliminating a priming dose from the UK schedule could cause 88 to 247 additional cases of IPD over a 5-year period.
  - Base case led to the smallest increase; any assumptions that do not hold would result in greater increase in disease.
- Increases in pneumococcal pneumonia and acute otitis media are projected to be even greater.[17]
- Scenario analyses suggest vaccine efficacy against carriage and the duration of its protection are the most sensitive parameters; clinical data to inform these are needed.
- Recent epidemiologic trends in the UK raise further concerns about the shift to a 1 + 1 schedule. Existing assumptions that the eradication of carriage in younger age groups results in sustained herd effect may not hold true if other mitigating dynamics are occurring.

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