In Small Doses: Missing the Booster Dose in a Reduced Pneumococcal Conjugate Vaccination Schedule

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BACKGROUND

- Pneumococcal conjugate vaccination (PCV) controls both the spread of vaccine serotype (VT) pneumococcal bacteria in populations and the development of invasive and noninvasive VT disease.[1]

- In 2010, the United Kingdom (UK) replaced PCV7 with PCV13 in its infant vaccination program in a 2 + 1 schedule (2 priming doses in infancy + 1 booster dose at 1 year of age).

- Policymakers in the UK are considering modifying the PCV13 schedule from a 2 + 1 to a 1 + 1 schedule by removing the second priming dose.[2,3]

- A previously built dynamic transmission model estimated that the proposed 1 + 1 schedule will increase invasive pneumococcal disease (IPD) across all ages due to reductions in both direct and indirect protection.[4]

- Another measure of the real-world implications of the 1 + 1 schedule is the impact of the schedule to herd protection, or the differential risk of IPD between those who receive the complete schedule versus those who do not.

OBJECTIVE

- To evaluate the differential risk of IPD in children between 1 year and < 2 years of age who miss versus receive the booster dose in a 1 + 1 versus 2 + 1 PCV13 schedule in the UK

METHODS

Model Structure

- Figure 1 displays a visualization of the dynamic transmission model and the dynamics used to estimate nasopharyngeal carriage and IPD dynamics in the UK. The model generates IPD incidence estimates prospectively given the vaccine schedule.

Figure 1. Model Diagram
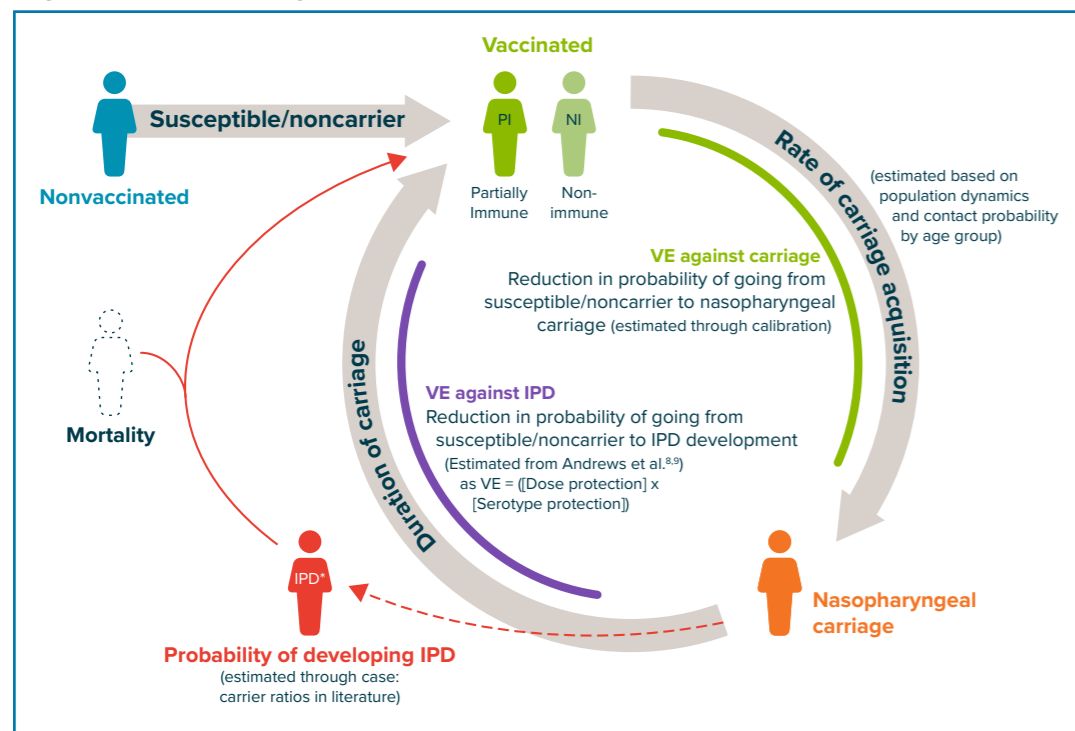
VE = vaccine effectiveness.

- Nasopharyngeal carriage and IPD incidence are stratified into five serotype groups: serotype 19A; serotype 3; PCV13 serotypes excluding 19A, 3, and PCV7 serotypes (i.e., serotypes 1, 5, 7F, and 6A); PCV7 serotypes; and non-vaccine serotypes (NVTs).

- All ages are modeled with inter-age group contact patterns.[5]

Epidemiological Inputs

- Using publicly available estimates (relevant inputs from Wasserman et al.[4] are shown in Table 1) and by estimating various model parameters, the model's resulting IPD incidence was fitted to publicly available routine IPD surveillance data from Ladhani et al.[6] by age group and serotype group.

- Vaccine effectiveness against IPD (VE_{OI}) is calculated as:

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

- VE_c = vaccine effectiveness against carriage; and VE_i = vaccine effectiveness against IPD given carriage acquisition.[8,9]

- The base case assumes that VE_c and VE_i of the first priming dose and booster dose are equivalent between the 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.

- The model calculates 5-year cumulative VT IPD incidence for children between 1 year and < 2 years of age who miss the booster dose (Inc_{-B}) and receive the booster dose (Inc_B) as the number of new cases per 100,000 person-years for the two populations. The IPD risk ratio (IRR) of the two groups is calculated as the ratio:

$$IRR = \frac{Inc_{-B}}{Inc_B}$$

- The model then compares the IRRs for the 1 + 1 and 2 + 1 schedules to estimate the differential risk of VT IPD for those who receive a booster dose compared with those who receive no booster dose between the two schedules.

Scenario Analysis

- Adherence of the first priming dose is varied from 10% to 50% less than the estimate in Table 1.

- The first priming-dose VE_c is varied from 10% to 50% less than the estimate in Table 1.

- The duration of protection of the first priming dose is varied from 2x (1.9 years protection) to 10x (0.5 year protection) less than that estimated in Table 1.

Table 1. Selected Epidemiological Inputs

Parameter	Value	Source
Vaccine adherence		
First priming dose/ second priming dose/ booster dose[a]	96.7%	Estimated from NHS data (2017)[7]
Duration of immunity (PCV7 and PCV13)		
First priming dose	5.6 years	Calibrated
Second priming dose	11.3 years	Calibrated
Booster dose	11.3 years	Calibrated
PCV effectiveness to IPD (first priming dose, second priming dose, booster dose)		
Serotype 19A	53%, 75%, 74%	Andrews et al., 2011[8,b] Andrews et al., 2014[9,b]
Serotype 3	16%, 34%, 33%	
Serotypes 1, 5, 7F, and 6A	85%, 94%, 93%	
PCV7-covered serotypes	56%, 79%, 93%	
NVT	0%, 0%, 0%	Assumed
PCV effectiveness to carriage (first priming dose, second priming dose, booster dose)		
Serotype 19A	16%, 44%, 49%	Andrews et al., 2011[8] Andrews et al., 2014[9]
Serotype 3	2%, 3%, 18%	
Serotypes 1, 5, 7F, and 6A	53%, 54%, 69%	
PCV7-covered serotypes	15%, 79%, 93%	
NVT	0%, 0%, 0%	Assumed

NHS = National Health Service.

[a]Individuals miss the booster dose with a 3.3% probability. This analysis compares the outcomes of those individuals who miss the booster dose with those who received it.

[b]Adjusted based on dosing time and serotype.

RESULTS

Base-Case Analysis

- We estimate a 5-year cumulative IRR of VT IPD of 1.08 in children between 1 year and < 2 years of age for those who miss versus receive the booster dose in a 2 + 1 schedule (Table 2).

- In a 1 + 1 schedule, this IRR was 1.37, a 27.6% increase in risk compared with the 2 + 1 schedule (Table 2).

- Increases in IRR moving to a 1 + 1 schedule ranged from 44.0% to 48.4% for serotype groups 19A, 1-5-7F-6A, and PCV7. Serotype 3 had a lower increase in IRR compared with other serotype groups but still elicited a positive increase (16.8%) (Table 2).

Table 2. 5-Year Cumulative IRRs (per 100,000) for Children 1 Year to < 2 Years of Age Who Miss Versus Receive the Booster Dose: 1 + 1 Compared With 2 + 1 Schedules

Serotype Group	IRR 2 + 1	IRR 1 + 1	% Increase in Risk Compared With 2 + 1
Serotype 19A	1.11	1.62	45.3%
Serotype 3	1.01	1.18	16.8%
1-5-7F-6A	1.39	2.00	44.0%
PCV7 serotypes	2.32	3.45	48.4%
All VT IPD	**1.08**	**1.37**	**27.6%**

Scenario Analysis

- The increase in the differential risk of VT IPD for children between 1 year and < 2 years of age who miss versus receive the booster dose ranged from 27.6% to 57.5% between the two schedules (Figure 2).

  - The largest increase was seen in scenarios adjusting the duration of protection of the first priming dose.

- Assuming a 0% priming dose efficacy against carriage, based on the immune response in the recent 1 + 1 study,[10] increased the differential risk between the two schedules to 34.8%.

Figure 2. Scenario Analysis: Percentage Increase in 5-Year Cumulative VT IPD IRR of Children Aged 1 Year to < 2 Years of Age Who Miss Versus Receive the Booster Dose When Varying First Priming Dose Parameters: 1 + 1 Compared With 2 + 1
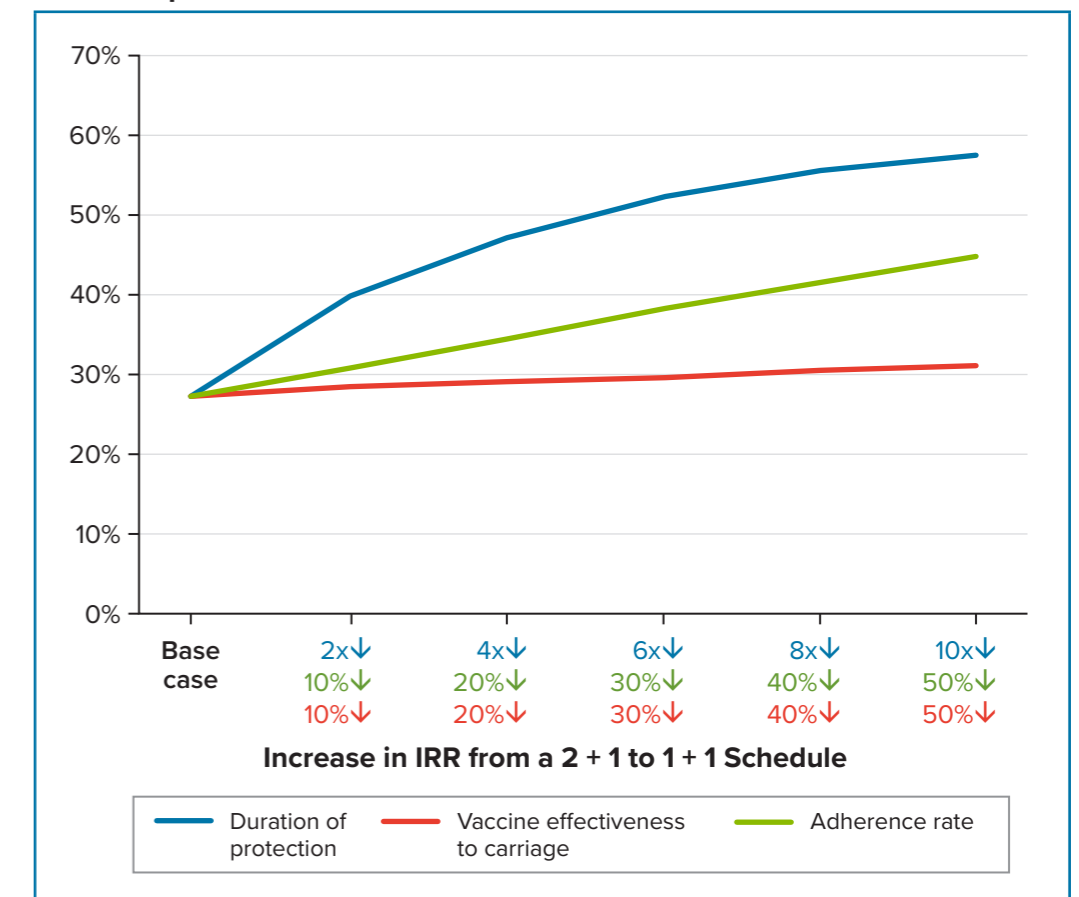
Data labels reflect how the first priming dose parameters change relative to the estimates in Table 1. Percentages with a downward arrow indicate a percentage reduction relative to the estimates in Table 1. Numbers adjacent to a multiplication sign signify that the parameter was that many times less than the estimate in Table 1 (e.g., 2x = 2 times less than the estimate in Table 1).

STRENGTHS AND LIMITATIONS

- Strengths

  - Model fit was strongly aligned with UK observed data for < 2-year-olds

  - Results were robust to scenario analyses.

- Limitations

  - Uncertainty around 1 + 1 effectiveness and risk of carriage in the first year of life

  - Computational limitations require assumptions restricting the number of compartments

DISCUSSION AND CONCLUSIONS

- Based on model results, switching to a 1 + 1 schedule could increase the differential risk of VT IPD in younger age groups who miss versus receive the booster dose. This is particularly important in areas where booster dose compliance is low, such as in large metropolitan areas.[11]

- Given the uncertainty regarding the duration of protection of the first priming dose, this differential risk in a 1 + 1 schedule may be substantially greater than the model predicts.

- Decision makers should consider that eliminating priming dose in the current 2 + 1 schedule may not only increase the disease burden for the entire UK population[4] but may also disproportionately impact vulnerable populations, especially in areas where booster dose adherence is lower than others.

REFERENCES

1. Waight PA, et al. Lancet Infect Dis. 2015 May 31;15(5):535-43.

2. Joint Committee on Vaccination and Immunisation. https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation.

3. Flasche S, et al. PLoS Med. 2015 Jun 9;12(6):e1001839.

4. Wasserman M, et al. Epidemiol Infect. 2018;146(14):1797-806.

5. Mossong J, et al. PLoS Med. 2008 Mar 25;5(3):e74.

6. Ladhani SN, et al. Lancet Infect Dis. 2018 Jan 26. https://www.sciencedirect.com/science/article/pii/S1473309918300525.

7. Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables.

8. Andrews N, et al. PloS One. 2011 Dec 2;6(12):e28435.

9. Andrews NJ, et al. Lancet Infect Dis. 2014 Sep 30;14(9):839-46.

10. Goldblatt D, et al. Lancet Infect Dis. 2017 Nov 22. pii S1473-3099(17)30654-0.

11. Jones et al., 2018.

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