Dynamic Transmission Modeling of Pneumococcal Conjugate Vaccine and Potential Dosing Reduction in the United Kingdom

Aaron Lucas, PhD[1]; Michele Wilson, MSPH[1]; Matt Wasserman, MSc[2]; Dylan Jones, PhD[3]; Andrew Vyse, PhD[3]; Mary Slack, FRCPath[4]; Betsy Hilton, MS[5]; Harish Madhava[3]; Raymond Farkouh, PhD[5]

[1]RTI Health Solutions, Research Triangle Park, NC, USA; [2]Pfizer Inc., New York, NY, USA; [3]Pfizer Ltd., UK; [4]School of Medicine, Griffith University, Australia; [5]Pfizer Inc., Collegeville, PA, USA

BACKGROUND

- The public health impact of pneumococcal vaccination has been profound in the United Kingdom (UK), especially in infants and children.
- Invasive pneumococcal disease (IPD) represents the most severe cases of pneumococcal disease. However, a considerable burden of noninvasive pneumococcal disease exists.
- In the UK, the 13-valent pneumococcal conjugate vaccine (PCV13) is administered in a 2 + 1 dosing schedule (2 priming doses followed by a booster dose at 1 year) as part of the routine national immunization program.
- The Joint Committee on Vaccination and Immunisation recently recommended removing the second priming dose from the PCV schedule[1] (i.e., from a 2 + 1 to a 1 + 1 program) and moving the first priming dose to 1 month later. The change was supported by data from a recent randomized controlled trial of 213 UK infants.[2]
- The full utility of a 1 + 1 schedule is not fully understood, and modeling can provide important insight into the impact of a schedule change on both invasive and noninvasive pneumococcal disease.

OBJECTIVE

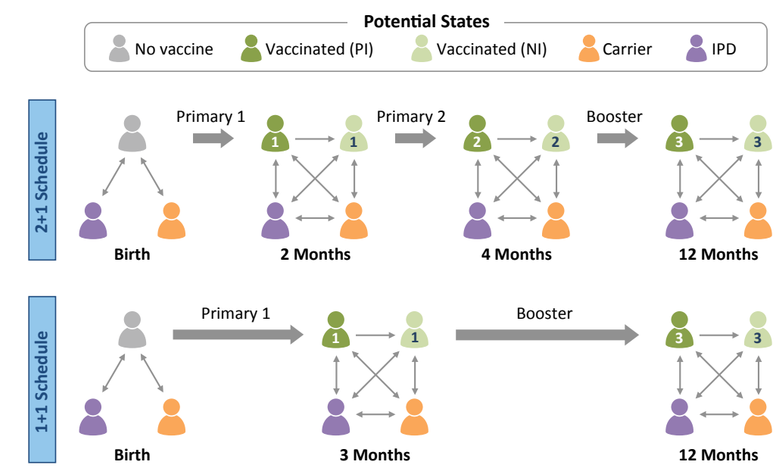
- Using a dynamic transmission model,[3] the objective is to estimate the potential public health impact of moving from a 2 + 1 to a 1 + 1 PCV13 program on the full spectrum of pneumococcal disease in the UK.

METHODS

Model Structure

- A dynamic transmission model developed in MATLAB parameterized using UK serotype-specific IPD surveillance data from 2001 to 2017 (Figure 1).[3]
- Using IPD incidence from the IPD model, we estimated the impact on mucosal disease by applying a multiplier approach[4-6]:
  - Assume a proportional change in incidence of hospitalized pneumococcal community-acquired pneumonia (CAP) and acute otitis media (AOM) relative to the estimated cases of IPD
  - Estimate incidence of CAP and AOM by multiplying the IPD incidence by CAP and AOM multipliers

Figure 1. Model Design and Schedule Shift



NI = nonimmune; PI = partially immune.

Noninvasive Disease Inputs

- We utilized The Health Improvement Network (THIN)[7] data for mild AOM and Hospital Episode Statistics (HES)[8] data for moderate/severe AOM.
- For CAP, we considered only hospitalized pneumonia incidence, and used HES data that were adjusted to account for potential miscoding.[9]
- We assumed 39.8% of overall CAP and AOM are caused by *S. pneumoniae*.[10]
- Age-specific multipliers for pneumococcal CAP and AOM were estimated as the ratio of pneumococcal CAP and AOM to IPD using the most recent year of historical data (Table 1).
- Multipliers assumed constant over the modeled time period to estimate cases of pneumococcal AOM and CAP by multiplying forecasted, age-specific IPD incidence by the age-specific multipliers (Table 1).
- The risk of mortality due to IPD and hospitalized pneumonia were applied to cases of IPD and hospitalized pneumonia to estimate total deaths (Table 2).

Table 1. Additional Epidemiologic Parameters

	IPD Distribution[a]		IPD Multipliers[b]		
Age Group	Bacteremia	Meningitis	CAP	Mild AOM	Moderate/ Severe AOM
< 2	65.2%	34.8%	7.1	146.0	**10.6**
2-4	86.9%	13.1%	22.4	601.5	**33.5**
5-17	90.5%	9.5%	14.0	618.2	**39.7**
18-34	91.0%	9.0%	16.7	N/A	**N/A**
35-49	91.2%	8.8%	17.6	N/A	**N/A**
50-64	92.9%	7.1%	21.6	N/A	**N/A**
65+	97.6%	2.4%	38.6	N/A	**N/A**

NA = not applicable.

[a] Source: Melegaro and Edmunds.[11]

[b] Estimated using IPD data[12,13] and CAP and AOM data.[7,8]

Table 2. Disease-Related Case-Fatality Ratios

Age Group (Years)	Bacteremia	Meningitis	Hospitalized Pneumonia
0 to < 2	0.036	0.036	**0.003**
2 to 4	0.038	0.038	**0.002**
5 to 17	0.069	0.069	**0.012**
18 to 34	0.145	0.145	**0.031**
35 to 49	0.171	0.171	**0.051**
50 to 64	0.222	0.222	**0.091**
65+	0.342	0.342	**0.171**

Source: Melegaro and Edmunds.[11]

Scenario Analysis

- To capture the uncertainty surrounding the implementation and effectiveness of a 1 + 1 schedule, we considered a series of scenario analyses that varied assumptions of the vaccine effectiveness, waning, and adherence of both the primary and booster doses in the 1 + 1 schedule.

RESULTS

Base-Case Analysis

- Base-case results show an increase of more than 8,777 cases of pneumococcal disease, and 241 deaths over a 5-year period (Table 3).

Table 3. Base-Case Results Over a 5-year Horizon

Parameter	2 + 1 Schedule	1 + 1 Schedule	Differences in Number of Cases
Outcomes			
Total cases	1,605,397	1,614,173	8,777
IPD	23,638	23,725	88
AOM			
0 to < 2 years old	133,363	136,392	3,029
2 to < 5 years old	170,465	171,427	961
5 to < 18 years old	624,442	627,189	2,747
All ages	928,270	467,504	6,738
CAP			
0 to < 2 years old	6,056	6,194	138
2 to < 5 years old	6,017	6,051	34
5 to < 18 years old	13,337	13,395	59
18 to < 35 years old	41,422	41,582	160
36 to < 50 years old	57,444	57,647	204
51 to < 65 years old	104,109	104,413	304
65+ years old	425,104	426,158	1,054
All ages	653,489	655,440	1,951
Deaths			
IPD	5,857	5,873	17
Hospitalized pneumonia	86,522	86,746	224

Scenario Analysis

- In scenario analyses (Table 4), reducing to a 1 + 1 schedule was predicted to incur 8,777-27,807 additional cases of pneumococcal disease and 249-743 more deaths across all age groups over the 5-year period.
- Assumptions regarding the booster-dose vaccine effectiveness and duration of protection in a 1 + 1 schedule had the largest impact on incidence.
- 0% priming-dose efficacy against carriage, based on the immune response in the recent 1 + 1 study[2], increased the number of cases of pneumococcal disease by 34.1%.

Table 4. Scenario Analysis Results: Difference in Number of Cases Over 5 Years (2 + 1 Schedule vs. 1 + 1 Schedule)

Scenario	IPD	CAP	AOM	Deaths
Base case	88	1,951	6,738	241
80% adherence to booster dose	131	3,026	9,599	380
50% booster-dose VE of carriage	225	5,330	15,954	677
50% VE of IPD for booster dose	171	3,910	13,193	488
10× waning of booster-dose protection	238	5,429	22,140	658
50% VE_c + 80% adherence	247	5,849	17,492	743
0% priming-dose VE of carriage	127	2,933	8,711	372
2× waning of priming-dose protection	98	2,156	7,677	265
87% adherence (low uptake setting)	105	2,332	8,418	286
77% adherence (low uptake setting)	128	2,827	10,631	345

VE = vaccine effectiveness; VE_c = vaccine effectiveness against carriage.

Results presented are the incremental outcomes of a 1 + 1 schedule compared with a 2 + 1 schedule.

STRENGTHS AND WEAKNESSES

- Strengths
  - Model fit was strongly allied to UK observed data.
  - Results were robust to all sensitivity analyses.
  - Considers impact beyond only IPD.
- Weaknesses
  - Uncertainty around 1 + 1 effectiveness against carriage.
  - Limited data exist on the risk of carriage in the first year of life.
  - Computational limitations require assumptions restricting the number of compartments.

DISCUSSION AND CONCLUSIONS

- Based on the model assumptions, switching to a 1 + 1 schedule will substantially increase disease burden.
- The results likely are conservative as they are based on a paradigm of relatively low vaccine-type pneumococcal transmission, a paradigm that has been called into question given that vaccine serotypes continue to circulate and for some serotypes circulation may be increasing.[14-16]
- Results demonstrate that only considering IPD in a 1 + 1 schedule greatly underestimates cases of pneumococcal disease and the health care impact of removing a dose from a PCV program.
  - Scenario analyses confirm that the success of a 1 + 1 schedule is sensitive to the effectiveness of the revised schedule against carriage.
- The modified schedule reduces direct protection contemporaneously with early onset OM during the first year of life, which has been shown to be important in reducing recurrent OM and antibiotic usage.
  - This may have additional consequences on antimicrobial resistance due to a higher prevalence of complex OM cases. An increase in cases of resistant disease could have wider implications beyond the pneumococcus.[17]

REFERENCES

1. Joint Committee on Vaccination and Immunisation. https://www.gov.uk/government/groups/joint-committee-on-vaccination-and-immunisation. 2. Goldblatt D, et al. Lancet Infect Dis. 2017 Nov 22. 3. Lucas A, et al. Presentation at: 11th International Symposium on Pneumococci and Pneumococcal Diseases. April 15-19, 2018. 4. Thorrington D, et al. BMC Med. 2018a Feb 8;16(1):13. 5. Thorrington D, et al. PLoS One. 2018b;13(2):e0192640. 6. van Hoek AJ, et al. Vaccine. 2012;30(50):7205-13. 7. In Practice Systems and IMS Health. https://www.ucl.ac.uk/pcph/research-groups-themes/thin-pub/database. 8. NHS Digital. http://www.content.digital.nhs.uk/catalogue/PUB22378. 9. Daniel P, et al. British Thoracic Society Adult Community Acquired Pneumonia (CAP) Audit Report National Audit Period: 1 December 2014-31 January 2015. 10. Bewick T, et al. Thorax. 2012 Jun 1;67(6):540-5. 11. Melegaro A, Edmunds WJ. Vaccine. 2004;22(31-32):4203-14. 12. Waight PA, et al. Lancet Infect Dis. 2015 May 31;15(5):535-43. 13. Collins S, et al. Presentation at: 10th International Symposium on Pneumococci and Pneumococcal Diseases (ISPPD). June 26-30, 2016. 14. Lewnard JA, et al. Clin Infect Dis. 2017;65(11): 1853-61. 15. Dagan R, et al. Lancet Infect Dis. 2016;16(4): 480-92. 16. Isturiz R, et al. Expert Rev Vaccines. 2017;16(10):1007-27. 17. Lipsitch M, Siber GR. MBio. 2016 Jul 6;7(3):e00428-16.

CONTACT INFORMATION

For more information contact:

Matt Wasserman

Pfizer Inc.
235 42nd Street
New York, NY 10017Phone: +1.919.316.3731
Phone: +1.212.733.6884
E-mail: Matt.Wasserman@pfizer.com

Presented at: International Symposium on Pneumococci & Pneumococcal Diseases (ISPPD) April 15-19, 2018, Melbourne, Australia

Funding for this research was provided by Pfizer