Vaccine-preventable Clinical versus Radiologically- or Etiologically-Confirmed Disease in Pneumococcal Conjugate Vaccine Efficacy Trials: a Systematic Literature Review and Re-analysis

Kaatje Bollaerts[1], Mark A. Fletcher[2], Jose A. Suaya[2], Germaine Hanquet[1], Marc Baay[1], Lindsay R. Grant[2], Christian Theilacker[2], Thomas Verstraeten[1], Bradford D. Gessner[2]

1. P95 Epidemiology and Pharmacovigilance, B-3000 Leuven, Belgium; 2. Pfizer Inc. WW Medicines Development & Scientific Affairs, Collegeville, PA

ISPPD, 2020. 12th International Symposium on Pneumococci and Pneumococcal Diseases (on-site meeting postponed due to COVID-19 pandemic)
ISPPD 2020 Digital Library, Abstract #: 762. E-poster. June 2020

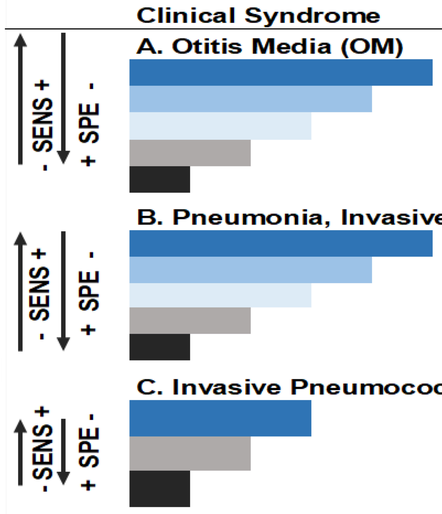
Background and Aim

- Regulatory endpoints for pneumococcal conjugate vaccines (PCVs) routinely include vaccine type (VT) confirmed disease. However, public health decision-making benefits from consideration of all disease prevented regardless of diagnostic or etiological confirmation.
- We aimed to assess the full potential public health impact of vaccines through a systematic literature review and re-analysis of Phase III (efficacy) / Phase IV (effectiveness) vaccine trials.

Methods

- We followed PRISMA guidelines to systematically review the literature for Phase III/IV efficacy trials for several vaccines from 1997 through 2019.
- Data were extracted for endpoints hierarchically organized from most specific to most sensitive within each clinical syndrome.
- For each endpoint, the vaccine-preventable disease incidence (VPDI) (control group minus intervention group incidences) was calculated and VPDI ratios between the most sensitive and most specific outcome were calculated.
- Here we report on PCV trials with otitis media (OM), pneumonia and invasive pneumococcal disease (IPD) as clinical syndromes (Fig. 1).
- Only VPDI ratios involving a clinically diagnosed and a microbiological or radiological endpoint (Fig. 1) are shown [PROSPERO registration, CRD42019145268].

Figure 1. Illustrations of potential levels of endpoints hierarchically organized within clinical syndromes.



Clinical Syndrome	Type	Endpoint
A. Otitis Media (OM)		
	Clinical	OM clinical diagnosis
	Clinical	Confirmed by MEF detection
	Microbiological	Any bacteria identification
	Microbiological	*Sp* identification
	Microbiological	VT *Sp* identification
B. Pneumonia, Invasive and Non-Invasive		
	Clinical	LRTI clinical diagnosis
	Clinical	Pneumonia clinical diagnosis
	Radiological	Confirmed by X-ray (+ inflammatory marker/s)
	Microbiological	*Sp* identification
	Microbiological	VT *Sp* identification
C. Invasive Pneumococcal Disease (IPD) Including Invasive Pneumonia		
	Clinical	IPD or unspec. sepsis clinical diagnosis
	Microbiological	*Sp* identification
	Microbiological	VT *Sp* identification

IPD, invasive pneumococcal disease; LRTI, lower respiratory tract infection; MEF, middle-ear fluid; OM, otitis media; SENS, sensitivity; SPE, specificity; Sp, Streptococcus pneumoniae; VT, vaccine-type

Results

- Eleven articles covering 9 trials met the criteria. In children < 5 years, VPDI ratios ranged from 0.6 to 3.7 for OM (clinical versus VT etiologically-confirmed); from 1.3 to 1.8 for pneumonia (clinical versus radiologically-confirmed); 3.1 and 17.0 for pneumonia (clinical versus bacterial or VT); and 3.8 in one study for IPD (IPD or unspecified sepsis based on ICD-codes to laboratory-confirmed). (Table 1)
- In adults, VPDI ratios ranged from 2.3 to 2.5 for pneumonia (clinical versus VT). (Table 1)

Table 1. Characterization and outcomes of randomized placebo control trials of pneumococcal vaccines.

Study	Schedule	Numerator				Denominator				Ratio
		Endpoint	Vaccine Group n (py)	Control Group n (py)	VPDI [95% CI] (/1000py)	Endpoint	Vaccine Group n (py)	Control Group n (py)	VPDI [95% CI] (/1000py)	VPDI ratio [95% CI]
Pediatric, otitis media										
Eskola NEJM 2001	3p+1	OM clinical	1251 (1078)	1345 (1085)	80, [-12.3;172.3]	VT Sp	107 (1078)	250 (1085)	131.3, [97;165.5]	0.6 [(a)]
Prymula, Lancet 2006	3p+1	OM clinical	333 (3958)	499 (3882)	44.4, [30;58.9]	VT Sp	60 (3958)	141 (3882)	21.2, [14.1;28.3]	2.1 [1.5;3.0]*
Tregnaghi, PLoS Med 2014	3p+1	OM clinical	254 (9018)	308 (8835)	6.7, [1.5;11.9]	VT Sp	7 (9018)	23 (8835)	1.8, [0.6;3]	3.7 [0.96;10.2]
Pediatric, pneumonia										
Black, PIDJ 2002	3p+1	Pneumonia clinical	1712 (39354)	1804 (39378)	2.3, [-0.6;5.3]	X-ray	327 (39354)	398 (39378)	1.8, [0.5;3.1]	1.3 [-0.49;3.7]
Cutts, Lancet 2005	3p+1	Pneumonia clinical	2172 (9382)	2284 (9191)	17, [2.9;31.1]	X-ray	333 (12808)	513 (12543)	14.9, [10.4;19.4]	1.1 [0.27;1.4]
Kilpi, Vaccine 2018 [(b)]		Pneumonia clinical				X-ray				
<7 mo	2p+1 or 3p+1		398 (40612)	271 (20376)	3.5, [1.7;5.3]		197 (40612)	138 (20294)	1.9, [0.7;3.2]	1.8 [1.14;3.7]*
7-11 mo	2p+1		132 (14831)	82 (7130)	5 [1;9]		69 (14831)	45 (7143)	3.8 [0.9;6.8]	1.3 [0.44;2.9]
12-18 mo	1p+1		88 (8713)	65 (4305)	2.6 [-0.2;5.4]		45 (8713)	39 (4333)	1.6 [-0.4;3.7]	1.6 [-3.6;6.9]
Lucero, PIDJ 2009	3p+0	Pneumonia clinical	1093 (10280)	1080 (10234)	-0.8, [-9.7;8.1]	X-ray	119 (10276)	141 (10240)	2.2, [-0.9;5.3]	N.C.[(c)]
Madhi, CID 2005	3p+0	LRTI clinical	1033 (43338)	1106 (43293)	1.7, [-0.4;3.8]	VT Sp	2 (43338)	6 (43293)	0.1, [0;0.2]	17 [-47.1;>100]
Tregnaghi, PLoS Med 2014	3p+1	Pneumonia clinical	2667 (31480)	2880 (31265)	7.4, [2.7;12]	X-ray + inflammatory marker/s	377 (31480)	450 (31265)	2.4, [0.6;4.2]	3.1 [1.34;8.9]*
Pediatric, IPD										
Palmu, Vaccine 2018 [(b)]	2p+1 or 3p+1	IPD or unspecified sepsis			2.86, [,]	Sp			0.75, [0.3;1.2]	3.8 [(a)(d)]
Adult, pneumonia										
Bonten, NEJM 2015 [(e)]	1d	Pneumonia clinical diagnosis,1st epi	1126 (167874)	1214 (167748)	0.5, [0;1.1]	VT Sp	66 (167874)	106 (167748)	0.2, [0.1;0.4]	2.5 [-0.15;6.21]
Gessner, Vaccine 2019 [(e)]	1d	Pneumonia clinical diagnosis, all epi	1375 (167874)	1495 (167748)	0.7, [0.1;1.3]	VT Sp	70 (167874)	112 (167748)	0.3, [0.1;0.4]	2.3 [0.5;7.6]

Abbreviations: epi: episode, IPD: Invasive pneumococcal disease, LRTI: lower respiratory tract infection, n: number of events/episodes, N.C.: not calculated, OM: Otitis Media, py: person years, Sp: Streptococcus pneumonia, VE: vaccine efficacy, VPDI: vaccine preventable disease incidence, VT: vaccine type, mo: months. (a) Insufficient information to compute confidence intervals, (b) Studies reporting on the same trial, (c) Ratio not calculated as the vaccine preventable disease incidence was negative for the numerator and/or denominator, (d) VPDI ratio was derived from incidences provided in the paper, (e) Studies reporting on the same trial. * Lower limit of 95% Confidence interval > 1.

Discussion/Conclusions

- For all studies and outcomes but one, there was a greater amount of vaccine preventable disease than appreciated by etiologically confirmed outcomes, whether the outcome was OM, pneumonia, or IPD.
- Vaccine technical committees should consider vaccine impact on clinical outcomes when making decisions for use of PCVs.

Contact info: Bradford.Gessner@pfizer.com **Funding Source**: Pfizer Inc. **Conflicts of interest**: KB, TV, MB received consulting fees from Pfizer for the work reported here. GH was paid by P95 for her services. MAF, JAS, LRG, CL and BDG are Pfizer Inc. employees, and as such, they may hold company stock.