ID 1264728

Systematic Literature Review of PCV13 Effectiveness Against Invasive Pneumococcal Disease in Children Globally

Johnna Perdrizet, MPH,[1*] Iwona Pustulka, MSc,[2] Carol Forbes, PhD,[2] Emily Horn, MSc,[1] Bradford Gessner, MD,[1] Kyla Hayford, PhD[1]

[1]Pfizer Inc. New York, NY, United States; [2]Evidera, London, United Kingdom

*Presenting author

For more information please contact:
Johnna Perdrizet
Pfizer, Inc.
johnna.perdrizet@pfizer.com

INTRODUCTION

- *Streptococcus pneumoniae* is a gram-positive bacterium that can cause a variety of pneumococcal syndromes including invasive pneumococcal disease (IPD), which has declined worldwide from introduction of pneumococcal conjugate vaccines (PCVs), such as PCV7 in 2000 and PCV13 in 2010
- No recent systematic literature review (SLR) of PCV13 vaccine effectiveness (VE) studies has been conducted to evaluate the direct effect of a complete series of PCV13 vaccination across various epidemiologic and geographic settings

OBJECTIVE

- To identify and assess evidence of PCV13 VE against IPD in children worldwide

METHODS

- An SLR was conducted in accordance with methodologies recommended by the Cochrane Collaboration and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist [1,2]
- MEDLINE (In-Process), Embase, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews were searched via Ovid up to November 2021 for observational studies evaluating PCV13 VE against vaccine-type (VT) IPD in children
- PCV13 VE was defined as 1 minus the risk ratio (RR, OR, HR) of VT-IPD among vaccinated versus unvaccinated children using an observational study design
- Two reviewers independently used predefined criteria to select observational studies reporting on VE against VT-type IPD events* (primary outcome: PCV13-type** IPD, secondary outcomes: PCV13 non-PCV7-type IPD, PCV7-type IPD) in children (<18 years) after receiving >1 dose of PCV13 vaccine. No geographical limits or publication date restrictions were applied. Only studies published in English were included
- 1,494 titles/abstracts were screened from which 16 eligible studies [3–16] were included in the SLR

*IPD includes meningitis, septicemia, bacteremia, and bacteremic pneumonia (invasion of the *Streptococcus pneumoniae* bacterium into normally sterile sites of the body [e.g., blood, meninges])
**PCV13 serotypes include 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. PCV7 serotypes include 4, 6B, 9V, 14, 18C, 19F, and 23F. PCV13-unique serotypes include 1, 3, 5, 6A, 7F, and 19A

RESULTS

Study characteristics

- Most studies conducted in Europe (n=8), followed by North America (n=3), Australasia (n=2), Africa (n=2), and Asia (n=1)
- Median age across the included study populations ranged from 8.4 (Inter Quartile Range [IQR]: 5.3–18.9) months–37 (IQR: 17–106) months with the proportion of males ranging from 54%–71%
- Eleven studies reported VE in children who completed a full schedule; of these 11 studies, eight reported PCV13-type VE [4,5,9,11,12,14,15,17], three reported PCV7-type VE [3,11,17], and six reported PCV13 non-PCV7 VE [3,6,9,11,17,18] (**Table 1**)

PCV13 effectiveness for full schedule and after ≥1 dose received

- Eleven studies reported VE in patients who received ≥1 dose of PCV13; of these 11 studies, nine reported PCV13-type VE [3,7,8,11,13,14,16-18], three reported PCV7-type VE [11,17,18], and eight reported PCV13 non-PCV7 VE for children who received at least one dose of PCV13 [3,4,8,10,11,14,17,18]
- PCV13-type, PCV13 non-PCV7-type, and PCV7-type VE estimates were directionally consistent across all studies for fully vaccinated children, and in general had a lower 95% confidence interval >0 except for PCV7-type estimates where few cases were identified, and study power was low. Point estimates of PCV13-type VE were generally higher for fully vaccinated children than those receiving >1 dose (**Table 2**) but definitive conclusions on differences in VE by number of doses could not be assessed due to insufficient study power

PCV13 VE for children aged <13 months

- Six studies reported PCV13-type VE or PCV13 non-PCV7 VE in children aged <13 months (data not shown, available online in Table 3) [3,4,11,13,14,18]
- Among children < 13 months of age, VE of 1 PCV13 dose was significant for 3 outcomes and non-significant for 5 outcomes. VT-IPD VE point estimates were generally higher after 2 or 3 doses compared with 1 dose, but small sample size limited precision of estimates

Table 1. Vaccine Effectiveness by PCV Serotype Group in Fully Vaccinated Children

Author, year	PCV schedule (country)	Cases vaccinated/ unvaccinated	Controls vaccinated/ unvaccinated	Age group*	Vaccine Effectiveness by PCV Serotype Group, Fully Vaccinated (95% CI)		
					PCV13-type IPD	PCV13 non-PCV7-type IPD	PCV7-type IPD
Latasa 2017[a]	3+1 or 2+1 (Spain)	0/15	4/16	≤10y	100 (NR)	NR	NR
Moore 2016[a]	3+1 (US)	259[g]	1150[g]	≤59m	90.4 (7.6–99)	NR	NR
Van der Linden 2016[b]	3+1 (Germany)	2/13[1]; 2/12[2]; 0/1[3]	33/161[1]; 33/162[2]; 33/163	<24m	91 (61–99)	90 (54–98)[j]	83 (-240–100)
Weinberger 2016[c]	3+1 (Germany)	5/3	29/7	13 to ≤56m	NR	60 (-109–92)[k]	NR
Andrews 2019[g]	2+1 (England)	72/6[2,j]; 76/8[2,k] 40/8[2,l]; 36/6[2,m] NR[3]	508/15[2,j,k,l,m] NR[3]	13m to ≤9y	NR	63.1 (-6.3–87.1)[j] 73.7 (31.1–89.9)[k] 84.8 (58.7–94.4)[l] 79.1 (37.0–93.1)[m]	81.2 (-6.7–96.7)
Andrews 2014[g]	2+1 (England)	13/112	71/56	13 to ≤56m	79 (25–94)[c,n]	NR	NR
Cohen 2017[h]	2+1 (South Africa)	73[i]	403[i]	10 to 59m	NR	100 (91–100)[j]	NR
Su 2016[g]	2+1 (Taiwan)	30[i]	267[i]	2 to 70m	76 (61–85)	NR	NR
Bar-Zeev 2021[a]	3+0 (Malawi)	17[i]	85[i]	<24m	80.7 (-73.7–97.9)	NR	NR
Gidding 2018[d]	3+0 (Australia)	4[1,2]	NR	<7 to 12m	86.0 (61.6–94.9)	85.6 (60.5–94.8)[j,n]	NR
Jayasinghe 2018[a]	3+0 (Australia)	84[c,f]	832[1e] 123[1f]	≥2m	77.9 (56.4–88.8)[e] 59.0 (16.2–88.0)[f]	NR	NR
		17[c,f]	114[1e] 37[1f]	<12m	86.5 (11.7–97.9)[e] 94.4 (71.1–98.9)[f]	NR	NR
		47[1c,1f]; 39[2j]; 9[3e]	500[1c]; 65[1f]; 396[2j]; 64[3e]	12 to 24m	61.8 (-3.3–85.8)[e] 87.1 (-15.7–98.6)[f]	88.7 (72.9–95.3)[j]	75.3 (-10.4–97.0)[e]

VE calculated as 1 – OR × 100% unless otherwise stated; *Minimum age was based on age-eligibility of vaccine schedule; [i]Only N of fully vaccinated cases and controls reported; 1=number of cases/controls for PCV13 type IPD; 2=number of cases/controls for PCV13 non-PCV7 type IPD; 3=number of cases/controls for PCV7 type IPD; [a] Unadjusted; [b] Broome method; adjusted for age and season following the issue of the vaccination recommendation; [c] Adjusted for age and year; [d] VE=(1 – adjusted HR) x 100%; adjusted for comorbidities, maternal characteristics; gestational/delivery characteristics; baby characteristics; geographical characteristics; socio-economic characteristics; and paternal characteristics; [e] Matched case control; [f] Indirect cohort; [g] Adjusted for gender and for all infants and children < or ≥2 years of age within subgroups; diphtheria–tetanus–pertussis vaccination history and influenza vaccination history were put in conditional logistic regression model to estimate the adjusted odds ratio; [h] Adjusted for malnutrition, whether the patient had received 3 doses of diphtheria, tetanus, and pertussis vaccine at 16 weeks of age and maternal education level; [j] Broome method; adjusted for age (2.5–5 m, 6–12 m, 13–17 m, 18–23 m, 2 yrs, 3–4 yrs, ≥5 yrs) and period (years, or for some serotypes 2008–2011, 2012–18); [j] Full Schedule PCV13 non-PCV7; [k] Full Schedule PCV13 non-PCV7 (including serotype 6C); [l] Full Schedule PCV13 non-PCV7 (including serotype 6C and excluding serotype 3); [m] Full Schedule PCV13 non-PCV7 (excluding serotype 3); [n] Full Schedule PCV13 (including serotype 6C)

Table 2. Vaccine Effectiveness by PCV Serotype Group in Children Receiving ≥ 1 dose

Author, year	PCV schedule (country)	Cases vaccinated/ unvaccinated	Controls vaccinated/ unvaccinated	Age group*	Vaccine Effectiveness by PCV Serotype Group, ≥1 dose received (95% CI)		
					PCV13-type IPD	PCV13 non-PCV7-type IPD	PCV7-type IPD
Moore 2016[a]	3+1 (US)	259[g]	1150[g]	Median: 21 (IQR: 11–37)m	86 (75.5–92.3)	87 (76.7–93.1)	NR
Van der Linden 2016[b]	3+1 (Germany)	25/55[1]; 23/43[2] 2/12[3]	194/43[1]; 194/43[2] 33/16[3]	0–23m	86 (74–93)	82 (66–91)	94 (78–99)
Weinberger 2016[c]	3+1 (Germany)	18/29[1]; 15/23[2] 3/6[3]	99/18	2.5 to ≤5m	89 (76–95)[d]	88 (73–95)[e]	91 (60–98)
Guevara 2016[f]	3+1 (Spain)	3/6[1]; 3/5[2]	44/19[1]; 44/14[2]	Up to 59m	94 (42–100)	92 (27–99)	NR
Andrews 2019[g]	2+1 (England)	136/134[2,h]; 218/152[2,e]	1262/136[2,h,e]	2.5m to <9yrs	NR	74.2 (62.6–82.2)[h] 65.9 (52.3–75.7)[e]	NR
Andrews 2014[g]	2+1 (England)	105/55	330/80	2.5 to ≤56m	NR	73 (57–83)[h]	NR
Deceuninck 2015[i]	2+1 (Canada)	10[g]	NR	2–48m	86 (62–95)	NR	NR
Domínguez 2017[j]	2+1 (Spain)	29/85[1]; 9/50[1d] 31/70[2]; 9/33[2k]	189/298[1]; 112/175[1d] 165/253[2]; 74/113[2k]	7–59m	75.8 (54.1–87.2) 95.8 (84–98.9)[d]	64.2 (31.9–81.2) 95.7 (75.7–99.3)[k]	NR
		10/31[1]; 6/22[1d] 9/22[2]; 5/13[2k]	82/121[1]; 63/86[1d] 55/86[2]; 36/51[2k]	7–23m	80.7 (45.3–93.2) 95.5 (54.5–99.5)[d]	54.3 (-37.7–84.8) 90.1 (34.8–98.5)[k]	NR
		19/54[1]; 3/28[1d] 22/48[2]; 4/20[2k]	107/177[1]; 49/89[1d] 165/253[2]; 38/62[2k]	24–59m	75.3 (45.4–88.9) 97.1 (79.8–99.6)[d]	66.9 (28.6–84.7) 95.3 (64–99.4)[k]	NR
Miller 2011[a]	2+1 (England & Wales)	35/35[1d]	72/22[1d]	2.5 to <24m	78 (40–92) 70 (30–87)[d, g]	NR	NR
Tomczyk 2018[l]	2+1 (Dominican Republic)	NR	NR	4.8–17.4m	67.2 (2.3–90)	NR	NR
Jayasinghe 2018[a]	3+0 (Australia)	107[i1m,1n]; 88[i2] 49[i2o]; 19[i3]	1070[i1m]; 167[i1n] 880[i2]; 432[i2o]; 190[i3]	2–42m	71.3 (48.3–84.0)[m] 75.6 (46.4–88.9)[n]	71.5 (44.9–85.2) 69.4 (25.3–87.5)[o]	70.4 (-8.0–91.9)
		51[i1m,1n]	510[i1m] 71[i1n]	12–24m	58.8 (-10.9–84.7)[m] 87.4 (-13.6–98.6)[n]	NR	NR
		34[i1m,1n]	340[i1m] 73[i1n]	<12m	77.4 (47.3–90.3)[m] 82.2 (52.9–93.3)[n]	NR	NR
		NR	NR	0–24m	NR	72 (45–85)	NR

VE calculated as 1 – OR × 100% unless otherwise stated; * Minimum age was based on age-eligibility of vaccine schedule; [i] Only N of cases and controls who received ≥1 dose reported; 1 = number of cases/controls for PCV13 type IPD; 2 = number of cases/controls for PCV13 non-PCV7 type IPD; 3 = number of cases/controls for PCV7 type IPD; [a] Unadjusted; [b] Broome method; adjusted for age and season following the issue of the vaccination recommendation; [c] Adjusted for age and year; [d]≥1 dose PCV13 (including serotype 6C); [e] ≥1 dose PCV13 non-PCV7 (including serotype 6C); [f] Adjusted for sex and parental income level; [g] Adjusted for age (2.5–4.49, 4.5–7.99, 8–12.99, 13–17.99, 18–23.99 months) and period (2010, 2011); [h]≥1 dose PCV13 non-PCV7 (including serotype 6C and excluding serotype 3); [i] Adjusted for age, year, season and underlying medical conditions including asthma and severe prematurity; [j] Adjusted for all demographic, clinical and epidemiological variables; [k] ≥1 dose PCV13 non-PCV7 (excluding serotype 3); [l] Adjusted for low weight-for-age Z score (i.e. malnutrition) and home built of wood (i.e. socioeconomic proxy); [m] Case Control; [n] Indirect Cohort; [o] ≥1 dose PCV13 non-PCV7 (excluding serotype 19A)

DISCUSSION

- Children fully vaccinated with PCV13 (3+1, 2+1, or 3+0) have a high level of direct protection against vaccine-type IPD with limited variability attributable to geography
- Although PCV13 VE tended to be higher for fully vaccinated children and in a 3+1 schedule, data were insufficient to make definitive conclusions
- VE of a single PCV13 dose for children <13 months of age varied substantially
- Limitations included the observational nature of included studies, possibility of unmeasured confounding, and variability in VE methods. Heterogeneity between studies including the presentation of data prevented more formal meta-analyses

CONCLUSIONS

- **Substantial VE against vaccine-type IPD was observed for children receiving the full PCV13 vaccination schedule**
- **As higher-valent PCVs are licensed based on immunogenicity endpoints, estimating real world VE under different dosing schedules and age groups will be important**

REFERENCES

1. Higgins, J., et al. 2020; Available from: https://training.cochrane.org/handbook/archive/v6.1.
2. Page, M.J., et al., BMJ, 2021. **372**: p. n71.
3. Andrews, N., et al., Vaccine, 2019. **37**(32): p. 4491-4498.
4. Andrews, N.J., et al., The Lancet Infectious Diseases, 2014. **14**(9): p. 839-46.
5. Bar-Zeev, N., et al., The Lancet Global Health, 2021. **9**(7): p. e989-e998.
6. Cohen, C., et al., The Lancet Global Health, 2017. **5(3)**: p. e359-e369.
7. Deceuninck, G., et al., Vaccine, 2015. **33**(23): p. 2684-9.
8. Dominguez, Á., et al., PLOS ONE, 2017. **12**(8): p. e0183191.
9. Gidding, H.F., et al., Vaccine, 2018. **36**(19): p. 2650-2656.
10. Guevara, M., et al., Euro Surveill, 2016. **21**(14).
11. Jayasinghe, S., et al., Clinical Infectious Diseases, 2018. **67**(3): p. 367-374.
12. Latasa, P., et al., Vaccine, 2017. **35**(40): p. 5381-5387.
13. Miller, E., et al., The Lancet Infectious Diseases, 2011. **11**(10): p. 760-8.
14. Moore, M.R., et al., The Lancet Respiratory Medicine, 2016. **4**(5): p. 399-406.
15. Su, W.J., et al., Pediatric Infectious Disease Journal, 2016. **35**(4): p. e124-33.
16. Tomczyk, S., et al., Clinical Infectious Diseases, 2016. **62**(9): p. 1119-25.
17. van der Linden, M., et al., PLoS ONE [Electronic Resource], 2016. **11**(8): p. e0161257.
18. Weinberger, R., et al., Vaccine, 2016. **34**(18): p. 2062-5.

DISCLOSURE

This study was sponsored by Pfizer Inc.