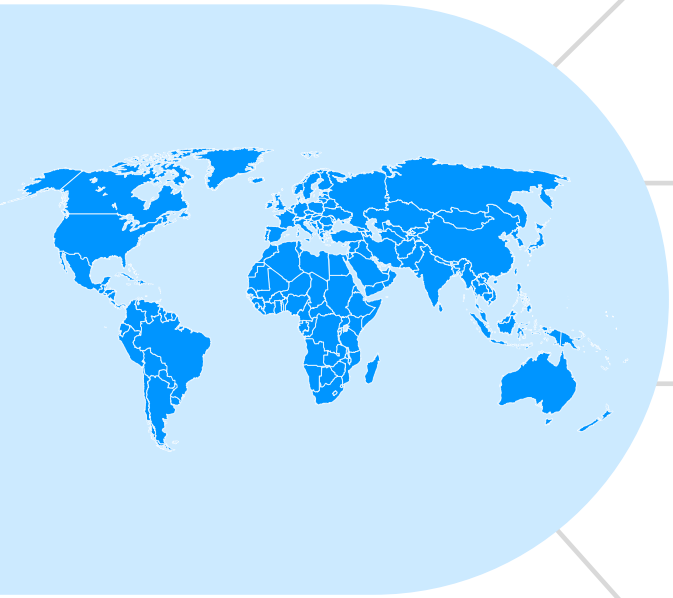
Pneumococcal conjugate vaccine licensure pathways

Lessons for RWE

Pneumococcal Disease Impacts All Age Groups, Primarily Young Children and Older Adults



The most common severe disease in lower respiratory tract infection (LRTI), historically pneumonia, but new data suggest non-pneumonia LRTI may be more common, at least in developed countries

Only a small portion of pneumonia/LRTI is bacteremic; combined with meningitis and sepsis, these three syndromes constitute the majority of invasive pneumococcal disease (IPD), which is relatively uncommon

In children, OM (acute/complicated) also is commonly caused by pneumococcus, but few investigators perform myringotomy, so at present diagnosis and serotype specificity rely on complicated OM

Several other relatively uncommon syndromes caused by pneumococcus: sinusitis, osteomyelitis, UTI, septic arthritis, empyema, cellulitis, endocarditis, peritonitis

ICU, intensive care unit; RSV, respiratory syncytial virus.
*Older adults (≥60 years or ≥65 years).
1. Gettler EB, et al. *Infect Control Hosp Epidemiol.* 2025 May 16;46(6):611–615. doi: 10.1017/ice.2025.88; 2. Wildenbeest JG, et al. *Lancet Respir Med.* 2024;12(10):822-836; 3. Hurley LP, et al. *Vaccine* 2019;37(4):565-570; 4. Rozenbaum MH, et al. *Infect Dis Ther* 2023;12(2):677-685; 5. Li Y, et al. *Infect Dis Ther.* 2023. 12(4):1137-1149; 6. Talbot HK, et al. *Infect Dis Clin Pract* 2016;24(6):295-302; 7. Njue A, et al. *Open Forum Infect Dis.* 2023;10(11):ofad513. doi: 10.1093/ofid/ofad513.

What's the problem?

- Placebo controlled trials not ethical; studies have to compare new product to standard of care
- Regulatory agencies require serotype specific outcomes for license and indications
- IPD by definition has an organism and serotype but is uncommon
- Pneumonia/LRTI requires serotype specific urinary antigen detection assays, which are insensitive
- AOM requires myringotomy, which no one does, or relying on the much less common complicated OM (e.g., AOM with perforation)
- Regardless of syndrome additional serotypes, while important, cause an ever-lower fraction disease
- Even if a study could practically be done, need large area using a single product for sufficient length of time; however, market is becoming ever more fractured with each PCV having a shorter lifecycle

In the CAPiTA RCT, vaccine type IPD and vaccine type community acquired pneumonia (CAP) massively underestimated the benefit of 13-valent pneumococcal conjugate vaccine (PCV13)

CAPITA Population[1]					Extrapolation to The Netherlands 2008 - 2012	
Outcomes	Placebo-Group Incidence Rate Per 100K[a]	% Vaccine Efficacy	95% CI	Vaccine-Preventable Disease Incidence Rate Per 100K[a]	Total Number of Outcomes Per Year[b]	Total Number of Preventable (assuming 5 years of protection)[c]
Hospital-treated Outcomes						
Vaccine type IPD	20	76	48 to 89	14.9	598	2,266
Vaccine type CAP	67	38	14 to 55	25.1	2,028	3,802
Radiologically-confirmed CAP	559	6.7	-4 to 16	37.4	16,974	5,686
Clinical CAP	891	8.1	-1 to 16	72.2	27,049	10,955
Hospital and Community-treated Outcomes						
Clinical CAP	3,370	7.4	0 to 14	250	102,293	37,849
LRTI including CAP	12,890	4.4	0 to 9	570	391,264	86,078

a per 100,000 person years of observation
b Calculated from placebo group incidence rate per 100,000 multiplied by population of adults ≥65 years in Netherlands (3.04 million)
c Calculated from VPDI per 100,000 x population of adults ≥65 years in Netherlands (3.04 million) x 5 years ÷ 100,000

VT-CAP = vaccine-type community-acquired pneumonia; VT-IPD = vaccine-type invasive pneumococcal disease; LRTI = lower respiratory tract infection; PCV13 = 13-valent pneumococcal conjugate vaccine; 100K = 100,000; CAPiTA = Community-Acquired Pneumonia Immunization Trial in Adults

1. Gessner BD, et al. *Vaccine* 2019;37:5777-87. 2. van Werkhoven CH, et al. *Clin Microbiol Infect.* 2020;Sep 22;S1198-743X(20)30560-7.

Solution: immunogenicity non-inferiority

- Regulatory agencies globally agreed to license new PCVs based on non-inferiority of IgG levels to early generation products.
- Pediatric PCV13/PCV20
  - NI vs. PCV13: percent of subjects with IgG concentration >=0.35ug/ml
  - NI vs. PCV13: IgG GMCs after last infant/priming dose
  - NI vs. PCV13: IgG GMCs after toddler/booster dose
  - New serotypes evaluated based on NI vs. lowest responding non-Spn3 in PCV7/PCV13
  - Totality of data
- Pediatric PCV15
  - NI vs PCV13: IgG GMCs after toddler/booster dose
  - New serotypes evaluated based on superiority to PCV13 (that is, nothing)
  - Totality of data
- Adult PCV15, PCV20, PCV21
  - NI vs PCV13/PCV20: OPA responses after a single dose.
  - Totality of data

This solution addresses many of the issues for this congress

- Recognizes that placebo-controlled or any RCT not always feasible for licensure
- Recognizes that clinical endpoints are not necessary for licensure
- Accepts that immunologic responses may be sufficient for licensure
- Accepts role of observational or pragmatic RCT via post—authorization confirmatory (PAC) studies
- Allows for serotype specific data
  - VE against disease will always be product aggregate
  - VE will vary based on serotype distribution over place/time

Immunogenicity as licensure endpoint has many nuances and deficiencies

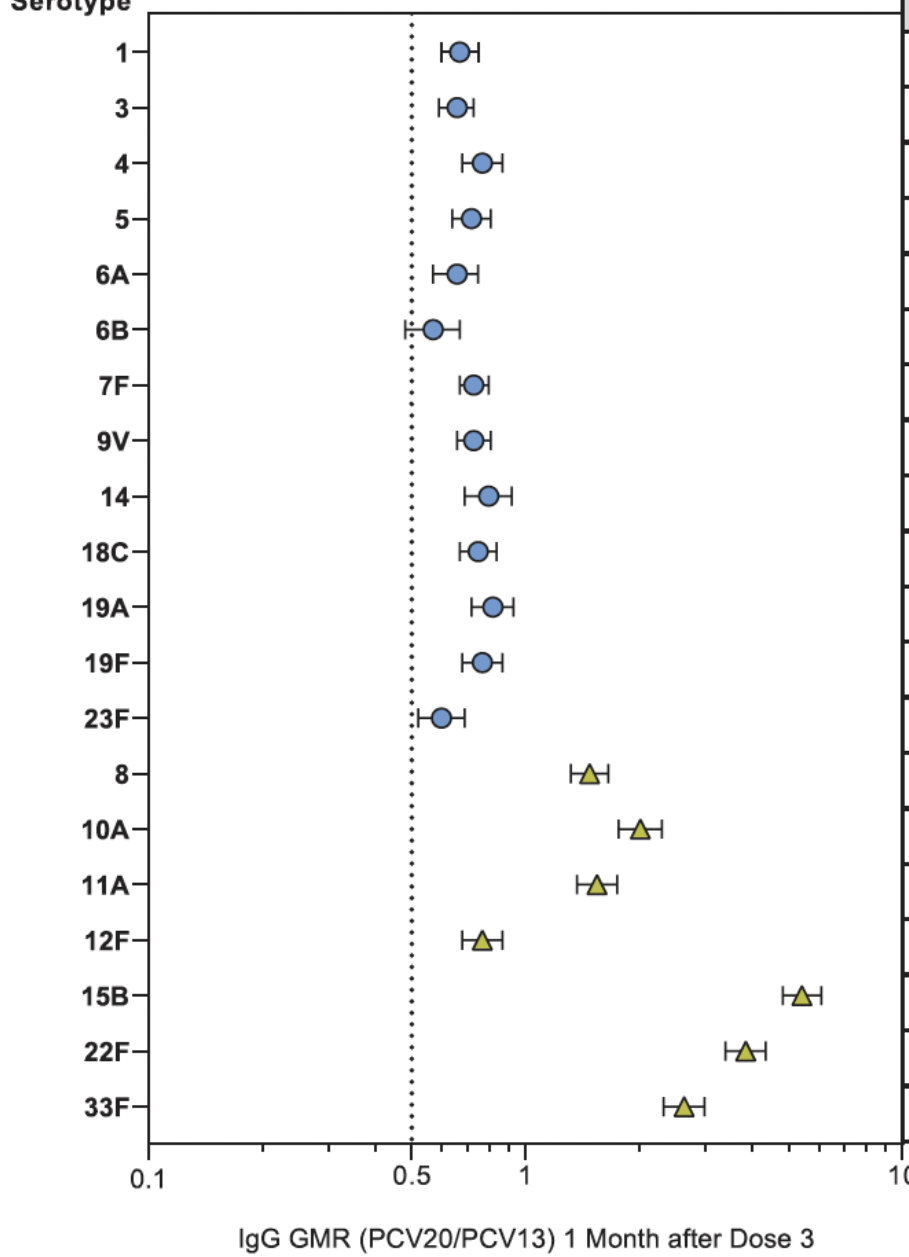
- Immunologic responses accepted because of bridge to an RCT with clinical outcome
- License indications based on those supported by original PCV7 or PCV13 RCTs: peds/adult IPD, peds OM (just original PCV7 serotypes), adult CAP
- Not a true correlate of protection, either for children or adults
  - Focus on circulating IgG ignores systemic innate and cellular immunity and role of other IgG subclasses; ignores all mucosal antibody responses
  - Original 0.35 ug/ml threshold was based on three trials in very different populations (Navajo, enrollees in Kaiser, South Africans) that gave different individual thresholds; was based on a 2-4-6 month schedule; was an aggregate of the 7 serotypes in PCV7
  - Even if IgG GMCs are considered predictive of protection for every serotype, the level at which protection eventually diminishes is unknown
- Some schedules – e.g., 2+1 or 1+1 in pediatrics – are based on reduction in carriage/transmission yet regulatory agencies will not consider carriage reduction/prevention as a regulatory or confirmatory endpoint and no immunogenicity correlate or surrogate exists

Immunogenicity as licensure endpoint has many nuances and deficiencies

- Even if over a small age window (e.g., PCV20 post dose 2nd to toddler dose), regulatory agencies have refused to license vaccines that miss NI criteria for some serotypes even while showing clear evidence of putatively protective levels for new serotypes
- No agreement on totality of data and what constitutes a performance that's too poor; can be arbitrary and based on the specific license application reviewer assigned
- Unclear how to interpret NI comparisons of new technologies, which may not even be based on IgG response to capsular polysaccharide
- To maintain license/indications, some reg. agencies require large-scale post-authorization studies that may not be feasible.
  - EU requires studies in both pediatrics/adults demonstrating VE against IPD
  - FDA – as part of accelerated approval for new PCV20 serotypes against vaccine serotype CAP – required large observational study

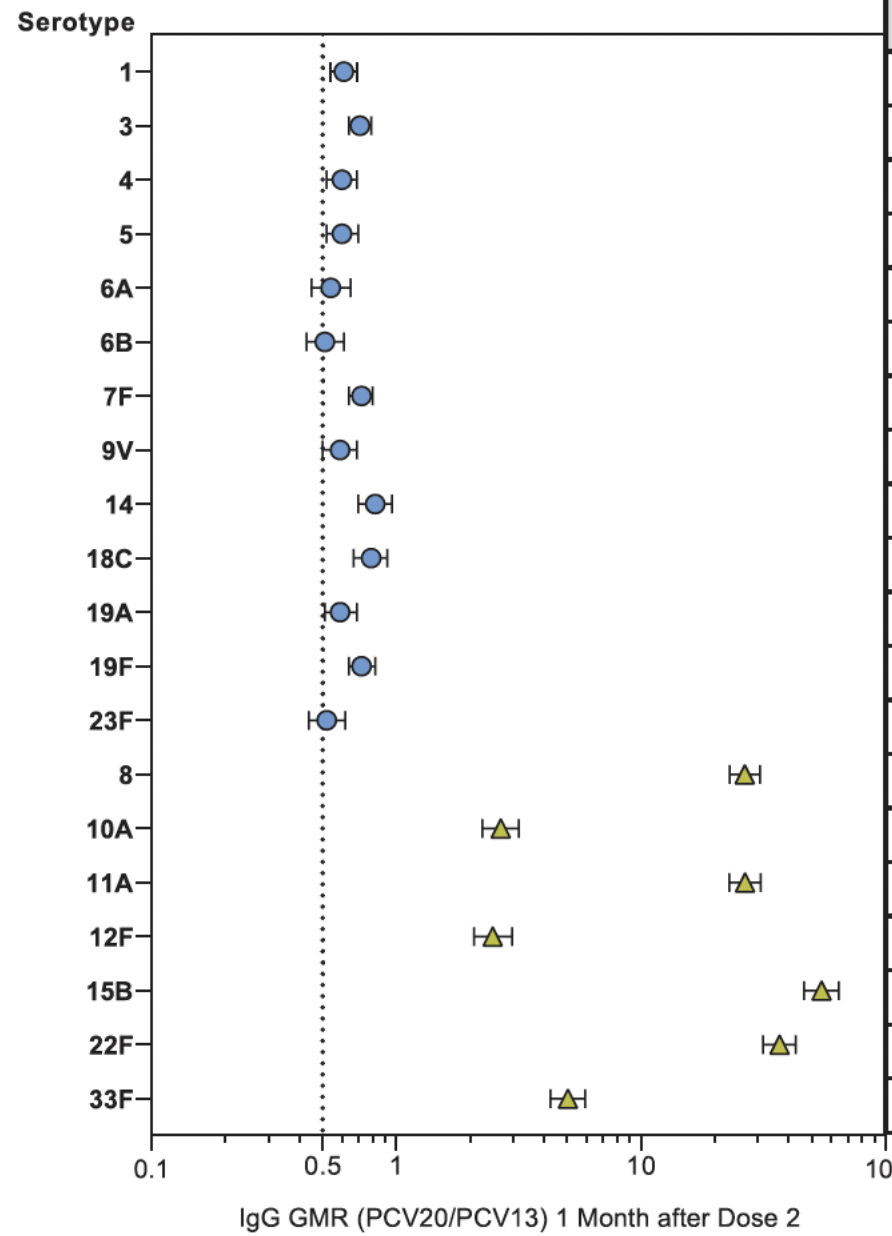
PCV20 vs. PCV13 pediatrics in 2+1 for Europe

A

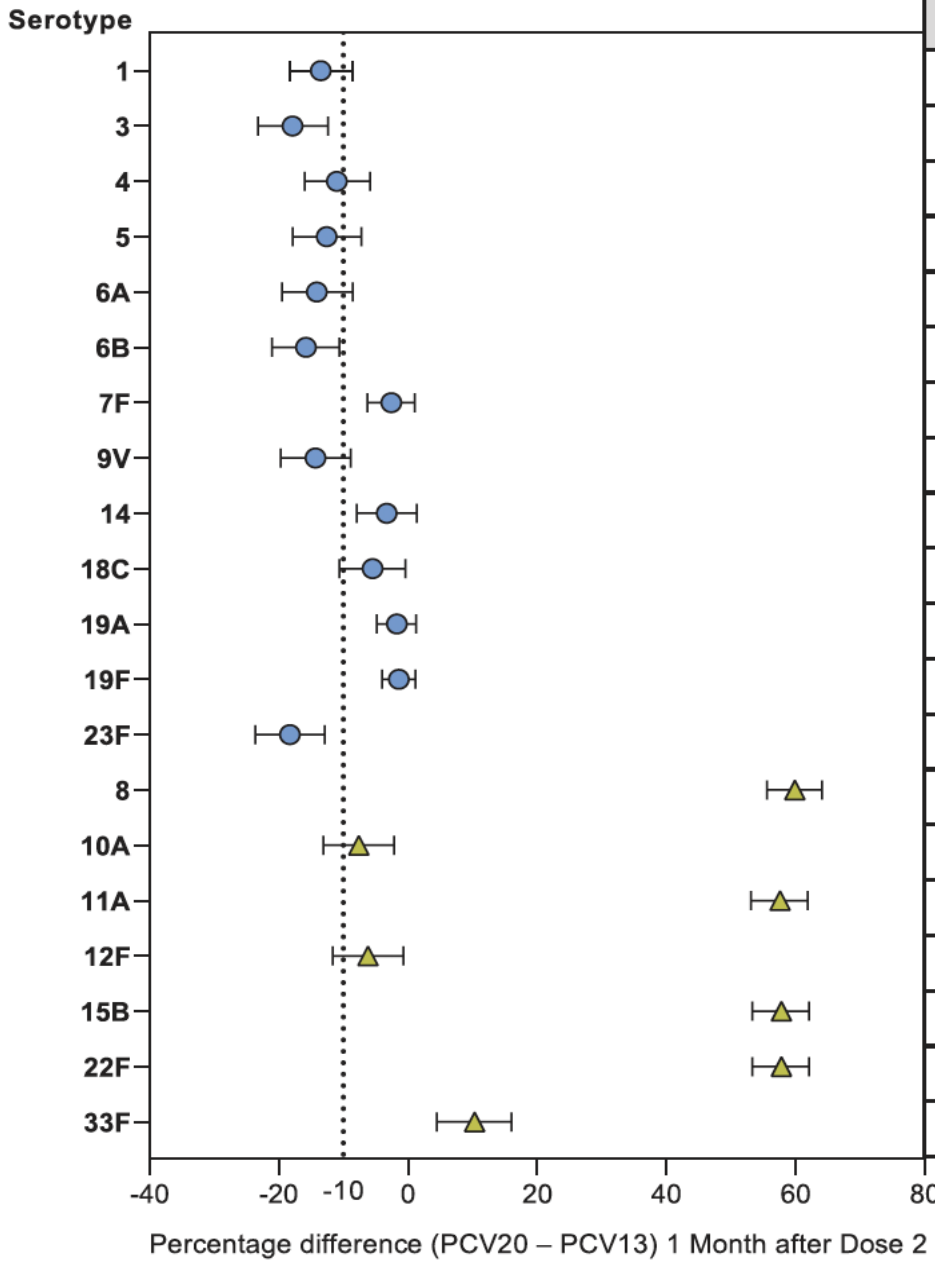


PCV20		PCV13	
N	GMC	N	GMC
494	1.71	502	2.53
494	0.72	502	1.09
494	4.11	502	5.36
494	1.74	502	2.41†
494	7.75	501	11.82
494	2.64	501	4.63
494	3.61	502	4.93
494	3.68	502	5.04
493	4.52	501	5.66
494	2.71	502	3.61
494	4.51	502	5.49
494	6.19	502	8.08
494	2.64	502	4.40
495	3.57	501	0.03*
495	4.86	502	0.01*
495	3.74	502	0.02*
495	1.86	502	0.01*
495	13.09	502	0.02*
495	9.27	502	0.00*
495	6.37	501	0.01*

B



	PCV20		PCV13	
	N	GMC	N	GMC
1	566	0.57	562	0.93
3	566	0.41	562	0.58
4	566	0.55	562	0.92
5	566	0.34	562	0.56
6A	566	0.45	562	0.84
6B	564	0.03	561	0.06†
7F	566	1.02	562	1.41
9V	566	0.45	562	0.77
14	565	1.05	562	1.28
18C	566	0.69	562	0.87
19A	566	0.67	562	1.13
19F	566	2.21	562	3.06
23F	566	0.13	562	0.25
8	567	1.62	561	0.02*
10A	567	0.16	562	0.02*
11A	567	1.62	562	0.02*
12F	567	0.15	562	0.01*
15B	566	3.33	562	0.04*
22F	567	2.25	562	0.01*
33F	566	0.31	562	0.03*

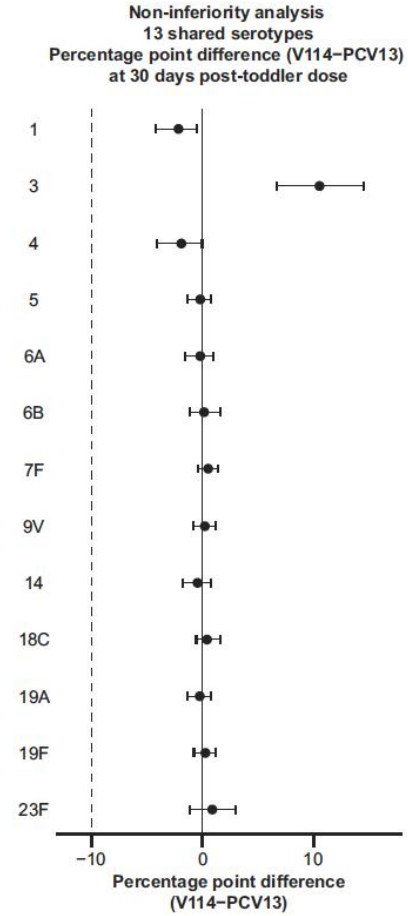


PCV20		PCV13	
N	%	N	%
566	70.7	562	84.2
566	58.0	562	75.8
566	68.6	562	79.5
566	63.4	562	76.0
566	59.5	562	73.7
564	20.7	561	36.5†
566	87.6	562	90.2
566	60.2	562	74.6
565	78.6	562	81.9
566	71.0	562	76.5
566	92.2	562	94.0
566	94.3	562	95.7
566	23.5	562	41.8
567	96.5	561	2.9*
567	28.9	562	2.7*
567	94.2	562	2.0*
567	30.3	562	0.2*
566	94.3	562	8.5*
567	94.4	562	2.0*
566	46.8	562	2.7*

PCV15 vs. PCV13 pediatrics in 2+1 for Europe

	V114			PCV13		
Pneumococcal serotype	% ≥0.35	n		% ≥0.35	n	Difference (95% CI)
1	96.8	500		99.0	525	−2.2 (−4.3, −0.6)
3	92.8	500		82.3	525	10.5 (6.6, 14.6)
4	96.6	500		98.5	523	−1.9 (−4.0, 0.0)
5	99.4	500		99.6	524	−0.2 (−1.4, 0.8)
6A	99.2	500		99.4	523	−0.2 (−1.5, 1.0)
6B	99.2	500		99.0	523	0.2 (−1.2, 1.5)
7F	100.0	500		99.6	525	0.4 (−0.4, 1.4)
9V	99.8	499		99.6	525	0.2 (−0.8, 1.2)
14	99.2	500		99.6	523	−0.4 (−1.7, 0.7)
18C	99.8	500		99.4	525	0.4 (−0.6, 1.5)
19A	99.6	500		99.8	523	−0.2 (−1.3, 0.7)
19F	99.8	500		99.6	524	0.2 (−0.8, 1.2)
23F	97.8	497		96.9	521	0.9 (−1.2, 3.0)

13 shared serotypes



	V114			PCV13		
2 serotypes	% ≥0.35	n		% ≥0.35	n	Difference (95% CI)
22F	99.4	500		5.4	520	94.0 (91.6, 95.8)
33F	99.2	500		2.0	510	97.2 (95.4, 98.4)

Additional serotypes in V114

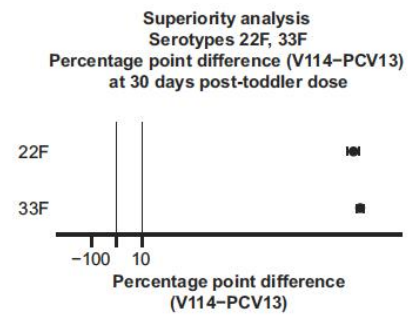
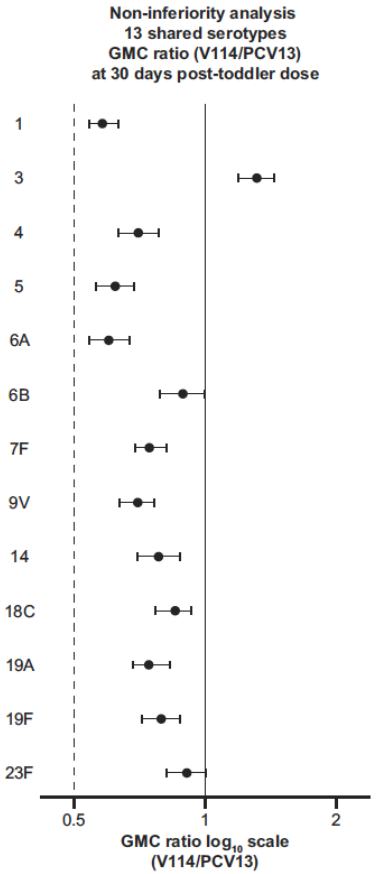


Fig. 3. Proportions of participants with IgG ≥0.35 µg/mL at 30 days post-toddler dose. Forest plot depicts the difference in proportions with IgG ≥0.35 µg/mL with the corresponding 95% CIs. N range 497–500 for V114 and 510–525 for PCV13. CI, confidence interval; IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

	V114			PCV13		
Pneumococcal serotype	GMC	n		GMC	n	GMC ratio (95% CI)
1	1.28	500		2.20	525	0.58 (0.54, 0.63)
3	0.85	500		0.65	525	1.31 (1.20, 1.43)
4	1.41	500		2.00	523	0.70 (0.63, 0.78)
5	2.08	500		3.35	524	0.62 (0.56, 0.68)
6A	3.21	500		5.36	523	0.60 (0.54, 0.67)
6B	4.56	500		5.12	523	0.89 (0.79, 1.00)
7F	2.78	500		3.74	525	0.74 (0.69, 0.81)
9V	2.14	499		3.07	525	0.70 (0.64, 0.76)
14	5.35	500		6.83	523	0.78 (0.70, 0.87)
18C	2.10	500		2.48	525	0.85 (0.77, 0.92)
19A	4.74	500		6.38	523	0.74 (0.68, 0.82)
19F	4.08	500		5.18	524	0.79 (0.72, 0.87)
23F	1.58	497		1.77	521	0.90 (0.81, 1.00)

13 shared serotypes



	V114			PCV13		
2 serotypes	GMC	n		GMC	n	GMC ratio (95% CI)
22F	500	6.06		0.09	520	68.34 (61.73, 75.65)
33F	500	3.28		0.07	510	48.99 (44.45, 54.01)

Additional serotypes in V114

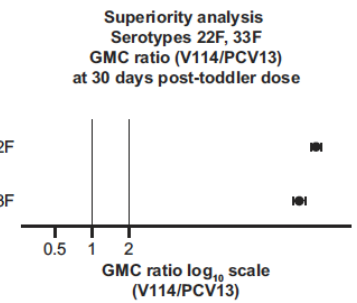


Fig. 4. IgG GMCs at 30 days post-toddler dose. Forest plot depicts the V114/PCV13 GMC ratios with the corresponding 95% CIs. N range 497–500 for V114 and 510–525 for PCV13. CI, confidence interval; GMC, geometric mean concentration (μg/mL); IgG, immunoglobulin G; PCV13, 13-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine.

Some consequences

- US FDA
  - PCV20 has indication for
    - IPD against all 20 serotypes with no PAC for age 6+ weeks
    - Pneumonia against 20 serotypes for age 18+ years thru accelerated approval requiring large-scale, multi-year, confirmatory trial
    - OM for original PCV7 serotypes for age 6 weeks to 5 years
  - PCV15 has indication for
    - IPD against all 15 serotypes for age 6+ weeks
  - PCV21 has indication for
    - IPD against all 21 serotypes for age 18+ years
    - Pneumonia against 21 serotypes for age 18+ years thru accelerated approval requiring large-scale, multi-year, confirmatory trial
- EU EMA
  - Did not license PCV20 in a 2+1 schedule
    - Some countries ignored EU
    - Some countries could not legally ignore EU
  - PAC required to reconsider 2+1
  - PAC required for IPD
- Some countries that ordinarily would use EU as reference elected to use other countries (e.g., Australia) so as to have 2+1 schedule licensed locally

Potential solutions

- Change the goalposts: e.g., primary outcome as post-toddler dose
- Change acceptable outcomes
  - Carriage
  - All-cause outcomes
- Identify true correlates of protection
- Combination of pragmatic and observational post-licensure studies