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IMMUNISATION COALITION

Pneumococcal conjugate vaccines in children

9:45 am

Declarations

- Member of the NCIRS team that provides scientific technical support to ATAGI and the Department of Health and Aged Care
- NHMRC emerging leadership fellow
- Chair, Enhanced IPD Surveillance Working Group of CDNA

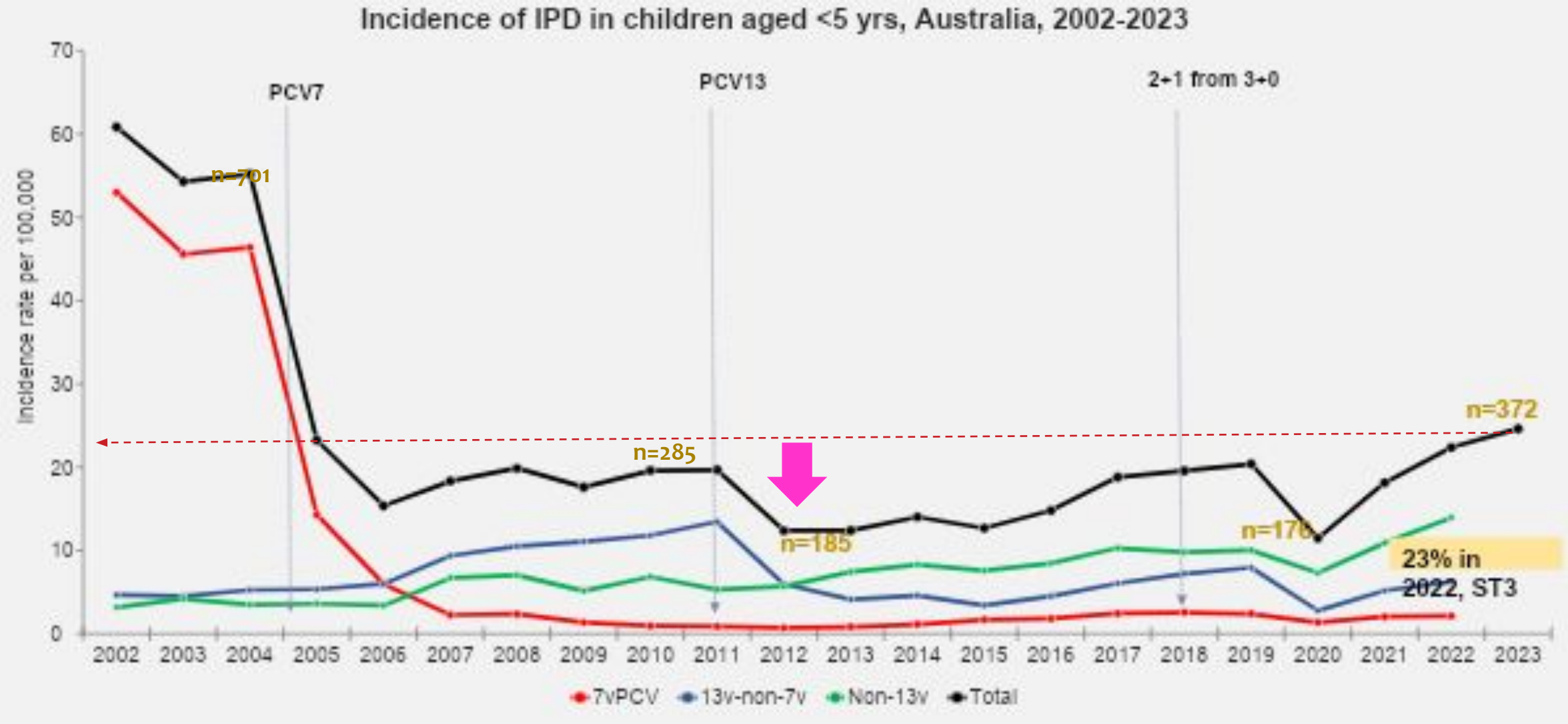
- Views in this talk my own!

Talk overview

- Serotype epidemiology of pneumococcal disease in Australian children
  - Long term PCV impact
- PCV dose schedule – have we got it right?
  - 2018 schedule change impact
- New PCVs – what to expect?
  - Inferences from immune responses to clinical protection

Serotype epidemiology of pneumococcal disease in Australian children

Impact of successive PCV programs in Australia



Data Source: National enhanced IPD surveillance data, NNDSS, EIPDSWG,CDNA.
Data request ID# 547 (Nov)/2022, May 2023 data extract 2023 data from National Communicable Diseases Surveillance dashboard https://nindss.health.gov.au/pbi-dashboard/
Denominator for rate calculations: ABS estimates Sep 2022 release

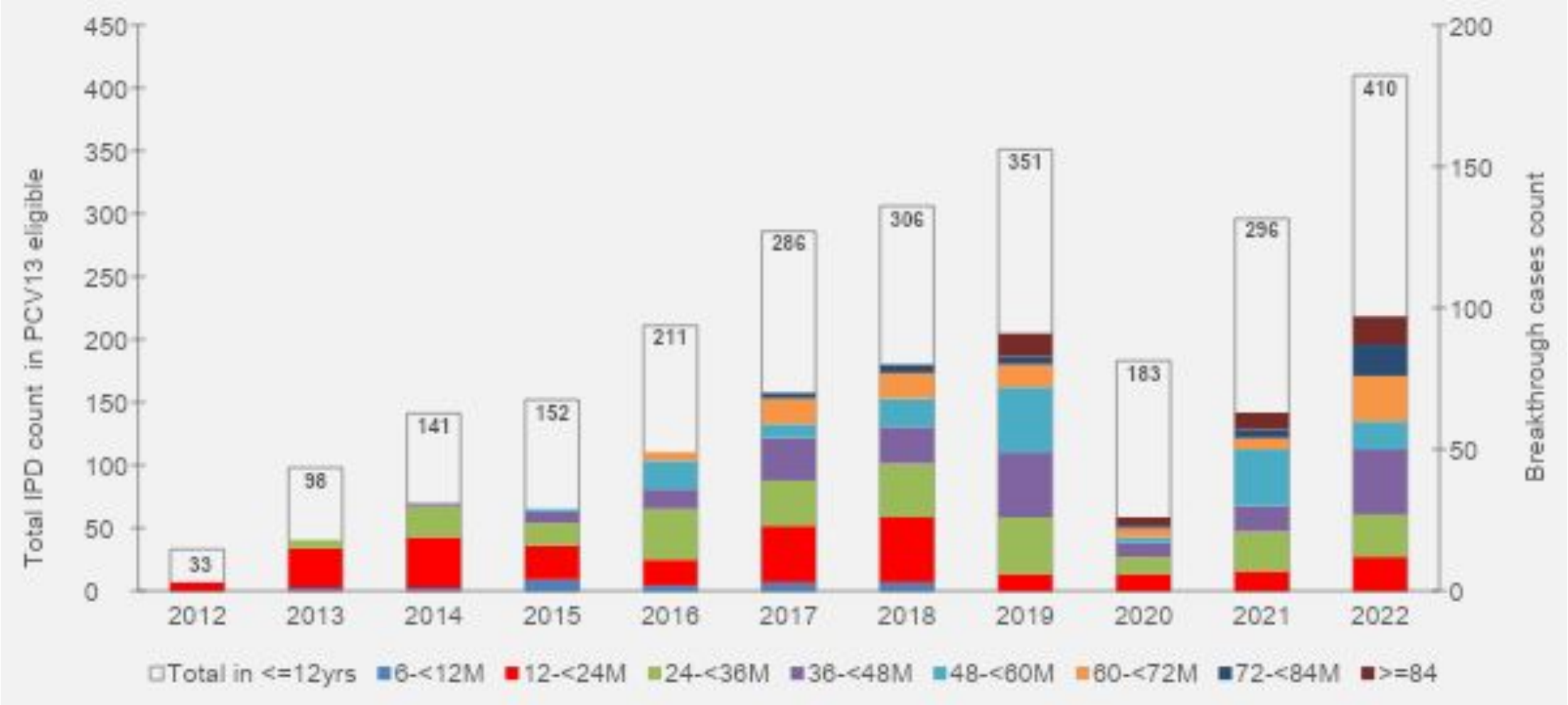
Clinical features of ST3 IPD in paediatric patients in SCH, CHW, RCH & JHH, 2017-18 & 2020-21 (N=47/202)

Clinical feature		Count (%)
Clinical phenotype	Pneumonia*	40 (85%)
	Bacteraemia	5 (11%)
	Meningitis	1 (2%)
	Other	1(2%)
Underlying RFs	Yes†	2(4%)
	No	45 (96%)
ICU admission	Yes	17 (36%)
	No	30 (64%)
Associated viral infections (antecedent/concomitant)	Yes	31 (66%)
	No	16 (34%)

*Empyema n=32, other complications n=5 (incl. Pneumothorax/lung abscess/broncho pleural fistulae, HUS)
†G6PD deficiency + non-accidental brain-injury, Suprasellar pilocytic astrocytoma

PCV dose schedule – have we got it right?

PCV 13 three-dose breakthrough cases by age group and total IPD in children eligible for 3 doses of PCV13 since program commencement, 2012-2022



Based on national enhanced IPD surveillance data in NNDSS, data access approval #547(Nov)/2022 (May 2023 extract)

Comparison of incidence rates of breakthrough cases in matched cohorts of 3+0* and 2+1† recipient children

Group	Incidence rate (per 100,000)		IRR	95% CIs
	2+1 eligible	3+0 eligible		
All excluding Serotype 3	1.52	3.06	0.50	0.28-0.84
Serotype 3 only	3.04	2.72	1.12	0.71-1.76
Total	4.56	5.78	0.79	0.56-1.09

* Age 12-48 months and disease in 2017 and 2018

† Age 12-48 months and disease in 2019 and 2022 (i.e. excluding 2020-2021)

New PCVs – what to expect?

Immune correlate of protection for inferring clinical efficacy of new PCVs (against VT IPD)

Following development of highly efficacious PCV7

- placebo controlled RCTs to measure VE no longer feasible or ethical to perform

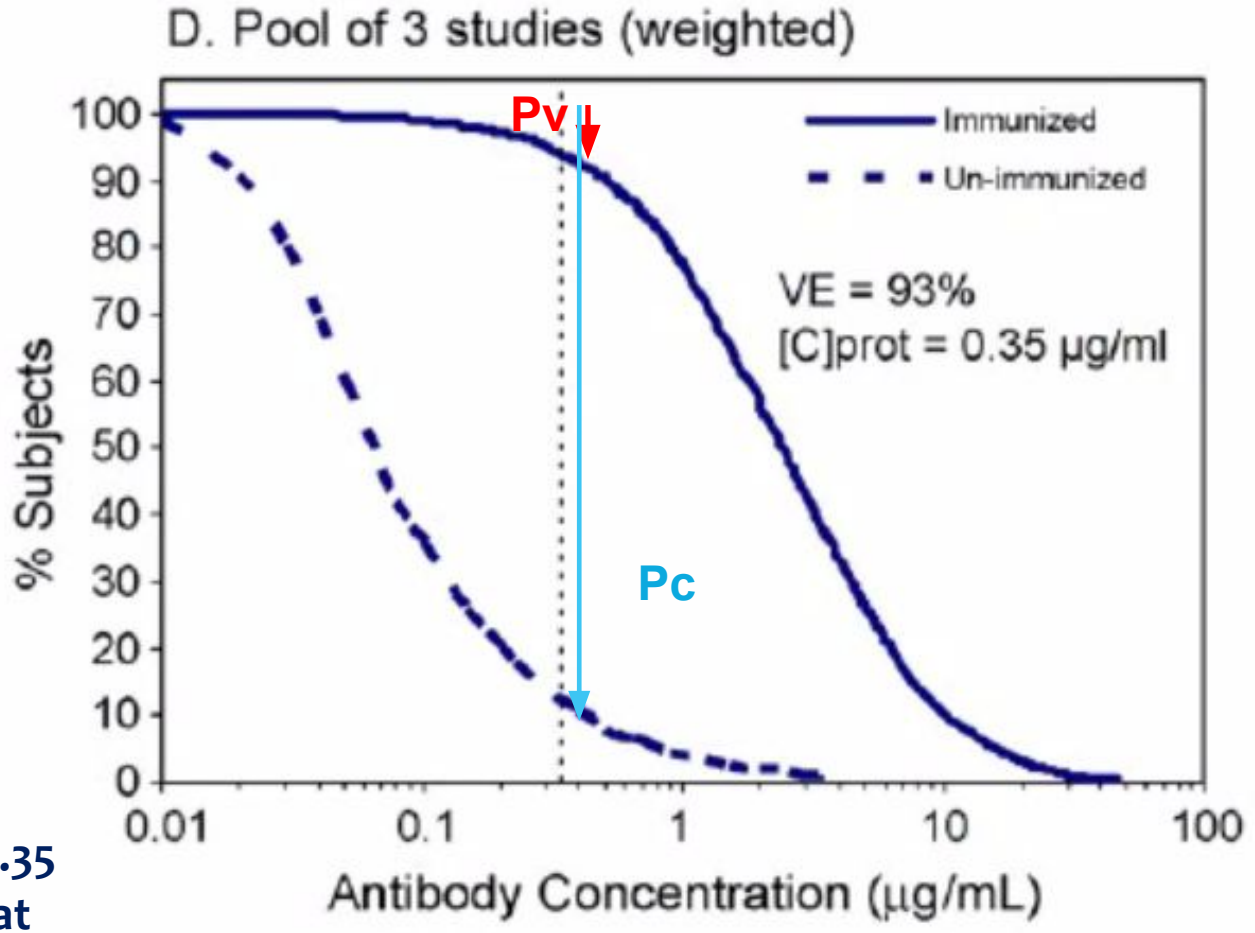
There is an **accepted correlate of protection to infer clinical protection for new PCVs**

- **having both VE and Ab data in the same population enabled this from PCV7 efficacy trials enabled this**

RCDC created of pooled IgG data from 3 PCV trials

VE=1 - (Pv/Pc)
When VE is known,
[C]prot= IgG concentration in the RCDC corresponding to Pv/Pc value of that VE

Standard practice to interpret the IgG concentration of 0.35 µg/mL as the correlate of protection against IPD, with that same Cp used for all serotypes

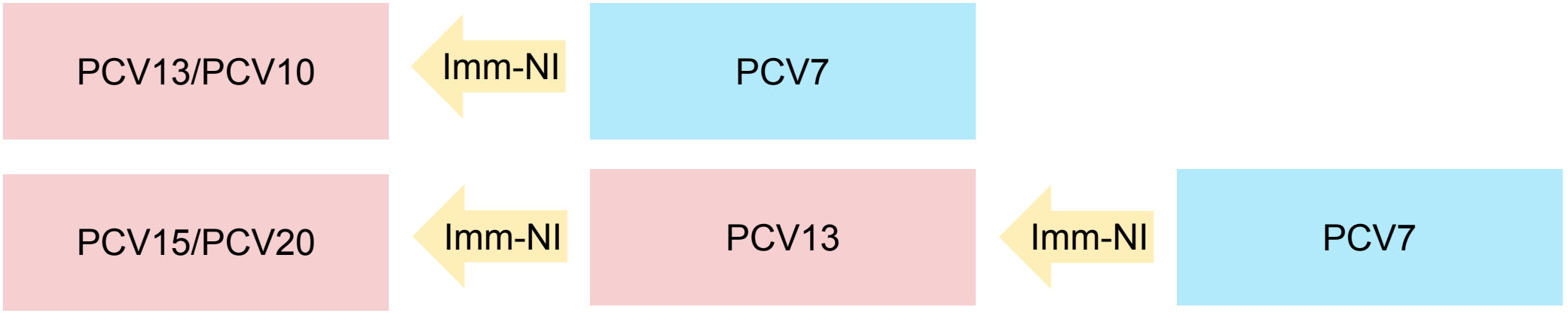


Siber, G. R. et al. Estimating the protective concentration of anti-pneumococcal capsular polysaccharide antibodies. Vaccine 25, 3816–3826 (2007).

Immune bridging to efficacy for new PCVs

Cp based rationale for approving of new PCVs is

- If new product is **non-inferior to licensed product** that **equates to similar clinical efficacy**



- For PCV15/20: 'bridge-to-bridge' approach

'Downward drift of efficacy': 'by approving vaccines based on noninferiority to a prior vaccine, which itself was justified based on non-inferiority, it is possible that subsequent vaccines could be accepted despite having inferior immunogenicity to an originally licensed vaccine.'

-Public Summary Document on PCV15 use in children submission- March 2023 PBAC Meeting
https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2023-03/files/pneumococcal-conjugate-vaccine-15-valent-adsorbed-psd-03-2023.pdf

Correlates of protection actually varies by serotype

	Vaccine effectiveness (95% CI)	Predicted vaccine effectiveness at 0·35 µg/mL ELISA cutoff*	Calculated correlate of protection in µg/ml for ELISA* (95% CI)	Calculated correlate of protection in titres for opsonophagocytic antibody* (95% CI)
PCV13				
1	84% (54 to 95)	96%	0·78 (0·47 to 1·68)	4 (4 to 8)
3	26% (−69 to 68)	97%	2·83 (1·16 to ∞)	39 (14 to ∞)
6A†	98% (64 to 99·8)	90%	0·16 (0·08 to 1·05)	4 (4 to 824)
7F	91% (70 to 98)	98%	0·87 (0·40 to 1·80)	769 (373 to 1502)
19A	67% (33 to 84)	95%	1·00 (0·60 to 2·47)	48 (15 to 234)
5	..	89%	..	..
Extra serotypes in PCV13 (plus 6C)	73% (55 to 84)	97%	1·19 (0·97 to 1·64)	..
Extra serotypes in PCV13 (plus 6C), excluding 3	80% (65 to 89)	97%	1·04 (0·68 to 1·42)	..
All PCV7 serotypes	90% (34 to 98)	98%	0·59 (0·34 to 2·45)	..
All PCV13 serotypes, (plus 6C)	75% (58 to 84)	97%	0·98 (0·77 to 1·25)	..
All PCV13 serotypes (plus 6C), excluding 3	82% (68 to 89)	97%	0·81 (0·70 to 1·10)	..
PCV7				
4	97% (65 to 99·8)	98%	0·35 (0·20 to 1·17)	70 (52 to 329)
6B	58% (3 to 82)	31%	0·16 (0·08 to 2·54)	97 (4 to 1003)
9V	70% (−25 to 93)	86%	0·62 (0·19 to ∞)	201 (4 to ∞)
14	98% (88 to 99·5)	98%	0·46 (0·25 to 1·12)	4 (4 to 92)
18C	96% (81 to 99)	83%	0·14 (0·09 to 0·40)	4 (4 to 284)
19F	75% (37 to 90)	96%	1·17 (0·62 to 4·62)	430 (260 to 909)
23F	78% (23 to 94)	60%	0·20 (0·08 to 1·50)	231 (4 to 890)
All PCV7 serotypes	82% (72 to 89)	93%	0·63 (0·51 to 0·79)	..

Calculated correlates of protection are based on the estimates of vaccine effectiveness estimates for the measure defined as at least two doses given before age 12 months or one dose given on or after age 12 months. PCV=pneumococcal conjugate vaccine.* Calculations based on the proportion above the cutoff from 1 month post-second dose samples from studies of PCV13 and PCV7. †Includes cases typed as 6A/C.

Table 3: Predicted vaccine effectiveness at the 0·35 µg/mL correlate of protection and calculated correlates of protection for ELISA and opsonophagocytic antibody assays

This UK study calculated Cp for individual STs in PCV13 by applying Siber et al method

- to RCDCs of IgG responses for each ST from PCV13 trials and ST specific vaccine effectiveness from post-licensure studies
- **results showed significant differences between these Cp by ST**
- **Such that the aggregate correlate is likely imprecise**

Andrews, N. J. et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. Lancet Infect. Dis. 14, 839–846 (2014).

PCV15 vs PCV13 immunogenicity trial data, proportions above IgG of ≥0.35 mcg/mL post dose 3 in a 2+1 schedule

- For 11/13 common STs 15v lower however meets pre-defined NI
- ST3 higher how it would translate to superior clinical protection is uncertain

Table 8: Proportions of Participants with IgG Response Rates ≥0.35 mcg/mL in Toddlers Administered a 3-Dose Regimen (Protocol 025)

Pneumococcal Serotype	VAXNEUVANCE (N=588)	Prevenar 13 (N=591)	Percentage Point Difference* (VAXNEUVANCE - Prevenar 13) (95% CI)*
	Observed Response Percentage (m/n)	Observed Response Percentage (m/n)	
13 Shared Serotypes†			
1	96.7 (521/539)	99.4 (534/537)	-2.8 (-4.7, -1.3)
3	92.0 (496/539)	83.8 (450/537)	8.2 (4.4, 12.2)
4	95.7 (516/539)	97.9 (524/535)	-2.2 (-4.5, -0.1)
5	99.1 (534/539)	100.0 (535/535)	-0.9 (-2.2, -0.2)
6A	98.5 (531/539)	98.9 (529/535)	-0.4 (-1.9, 1.1)
6B	97.4 (525/539)	99.1 (530/535)	-1.7 (-3.5, -0.1)
7F	99.8 (538/539)	99.8 (535/536)	0.0 (-0.9, 0.9)
9V	98.9 (533/539)	100.0 (537/537)	-1.1 (-2.4, -0.4)
14	99.8 (538/539)	100.0 (537/537)	-0.2 (-1.0, 0.5)
18C	98.9 (533/539)	99.3 (532/536)	-0.4 (-1.8, 0.9)
19A	99.1 (534/539)	100.0 (535/535)	-0.9 (-2.2, -0.2)
19F	99.6 (537/539)	100.0 (537/537)	-0.4 (-1.3, 0.3)
23F	96.8 (521/538)	97.4 (521/535)	-0.5 (-2.7, 1.5)
2 Serotypes Unique to VAXNEUVANCE‡			
22F	99.6 (537/539)	5.8 (31/535)	93.8 (91.5, 95.6)
33F	99.1 (534/539)	4.2 (22/530)	94.9 (92.7, 96.5)

* Estimated difference and CI are based on the Miettinen & Nurminen method.
† A conclusion of non-inferiority for the 13 shared serotypes is based on the lower bound of the 95% CI for the difference in percentages (VAXNEUVANCE – Prevenar 13) being >-10 percentage points.
‡ A conclusion of superiority for the 2 unique serotypes is based on the lower bound of the 95% CI for the difference in percentages (VAXNEUVANCE – Prevenar 13) being >10 percentage points.
N=Number of participants randomised and vaccinated; n=Number of participants contributing to the analysis; m=Number of participants with the indicated response.
CI=confidence interval; IgG=immunoglobulin G.

Source: Australian product information for Vaxneuvance

PCV20 vs PCV13 immunogenicity trial data, proportions above IgG of ≥0.35 mcg/mL post dose 3 in a 2+1 schedule*

- For 8/13 common types PCV20 proportion similar/marginally higher
- PCV20 lower for 5, worst for ST3 & doesn't meet NI in this data, other meet NI criteria

Table 3. Percentages of Participants with Predefined Pneumococcal IgG Concentrations and Pneumococcal IgG GMCs (µg/mL) One Month after Dose 3 of a 3-Dose Series, Study 1012[a]

	Percentages of Participants with Predefined IgG Concentrations[b]		
	PREVENAR 20 N[c] = 493-495	Prevenar 13 N[c] = 501-502	PREVENAR 20 – Prevenar 13
	%	%	% (95% CI[d])
Serotypes			
1	97.2	98.2	-1.0 (-3.1, 0.9)
3	82.6	93.2	-10.6 (-14.7, -6.7)
4	99.2	99.2	0 (-1.4, 1.5)
5	98.4	98.0	0.4 (-1.4, 2.2)
6A	98.8	98.8	0 (-1.6, 1.5)
6B	98.4	97.6	0.8 (-1.1, 2.7)
7F	99.6	100.0	-0.4 (-1.5, 0.4)
9V	99.2	98.8	0.4 (-1.0, 1.9)
14	96.6	98.0	-1.5 (-3.7, 0.6)
18C	99.2	98.2	1.0 (-0.5, 2.7)
19A	99.6	99.6	0 (-1.1, 1.1)
19F	99.6	99.4	0.2 (-0.9, 1.4)
23F	96.4	97.2	-0.9 (-3.2, 1.4)
Additional Serotypes			
8	99.2	3.6	95.6 (93.4, 97.1)
10A	97.8	1.6	96.2 (94.1, 97.6)
11A	98.4	4.6	93.8 (91.3, 95.6)
12F	96.6	0.2	96.4 (94.3, 97.7)
15B	99.4	4.8	94.6 (92.3, 96.3)
22F	99.2	1.4	97.8 (96.1, 98.8)
33F	98.6	1.8	96.8 (94.8, 98.0)

Abbreviations: CI = confidence interval; GMC = geometric mean concentration; GMR = geometric mean ratio; IgG = immunoglobulin G; LLOQ = lower limit of quantitation.

Note: Noninferiority for a matched serotype was concluded if the lower bound of the 2-sided 95% CI for the percentage difference (PREVENAR 20 - Prevenar 13) was > -10% or the lower bound of the 2-sided 95% CI for the GMR (PREVENAR 20 to Prevenar 13) was >0.5 for that serotype.

Note: Assay results below the LLOQ were set to 0.5 × LLOQ in the analysis.

a. Study 1012 was conducted in Europe and Australia.

b. The predefined IgG concentration was ≥0.35 µg/mL for all serotypes except for serotypes 5, 6B and 19A which were ≥0.23 µg/mL, ≥0.10 µg/mL and ≥0.12 µg/mL respectively.

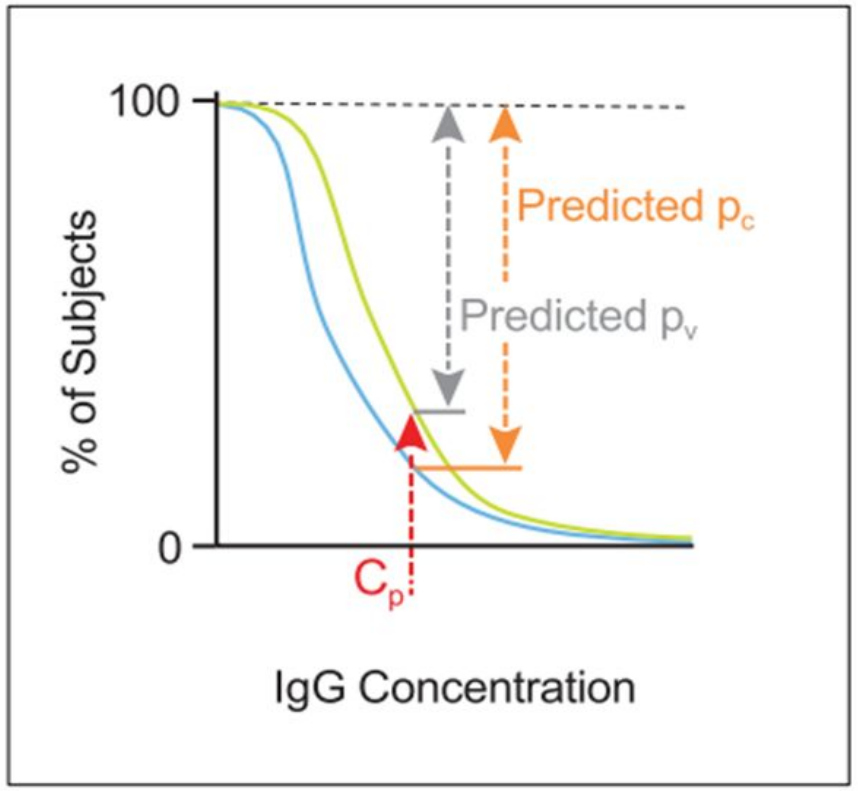
c. N = Number of participants with valid IgG concentrations.

d. Two-sided CI based on the Miettinen and Nurminen method.

* For 5,6B and 19A a lower Ab threshold was used

Source: Australian product information for Prevenar 20

Estimating predicted benefits for new PCVs - alternative approach

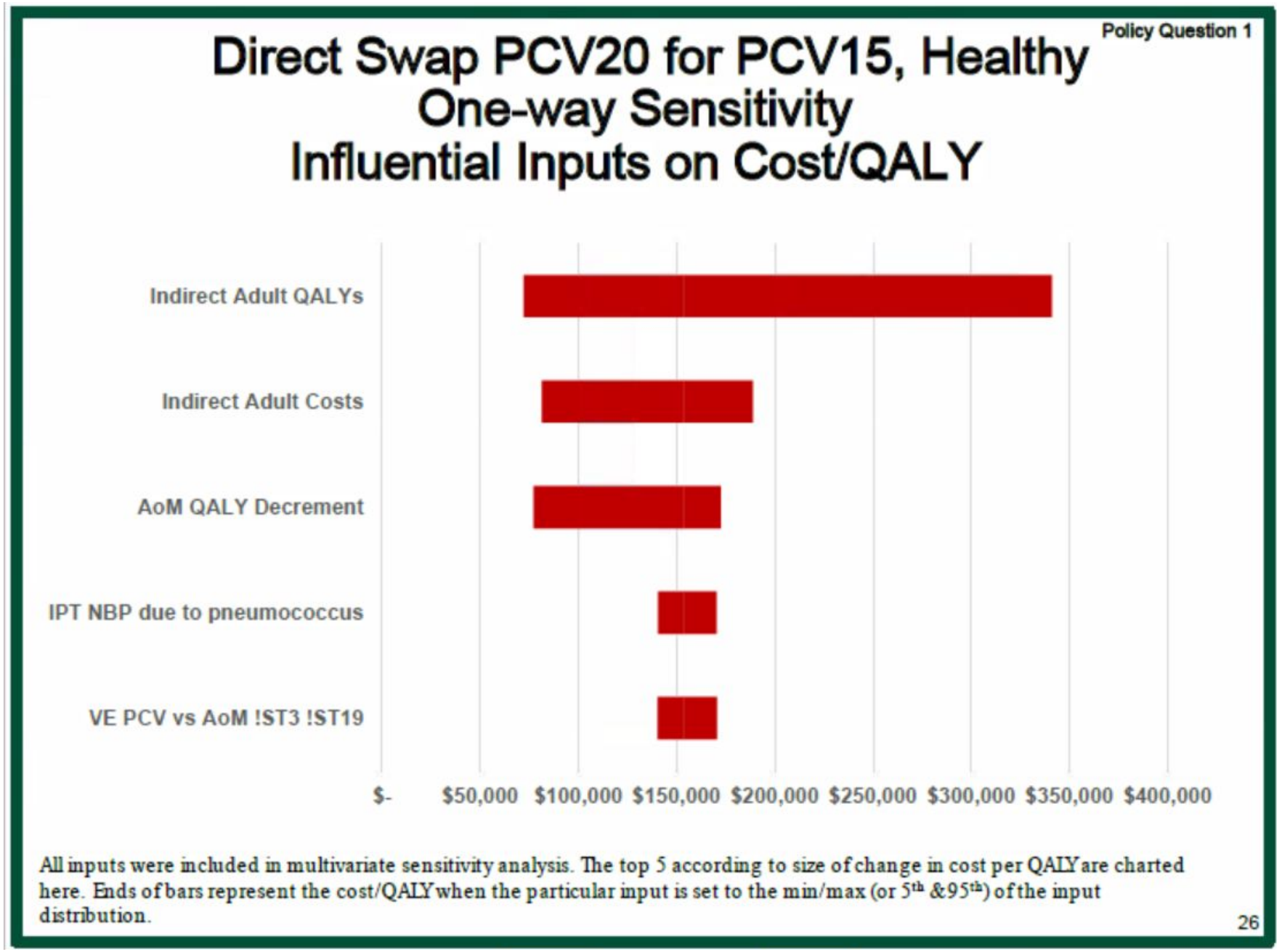


Clinical benefit inferences for PCV15& PCV20 from Ab data needs to factor in, both
- variation of their Ab level by ST
- variation of Cp for each ST

Apply Siber method 'in reverse'
- create RCDC using Ab responses data from PCV15 & PCV20 for individuals STs
- combine with ST specific Cp (from Andrews et al) to predict VE by ST for PCV15 & PCV20
- then use those ST specific VE estimates to calculate reductions in disease weighted by relative burden of vaccine STs to estimate expected clinical benefits

Fig source: Ryman J et al. Predicted serotype-specific effectiveness of pneumococcal conjugate vaccines V114 and PCV20 against invasive pneumococcal disease in children, Expert Review of Vaccines 2024; 23:1, 60-68, DOI: 10.1080/14760584.2023.2292773

Economic Assessment of Routine PCV20 for Children



Source: ACIP June 2023 meeting presentation

PCV15 & PCV20 for paediatric use in Australia

	PCV15 (Vaxneuvance)	PCV20 (Prevenar-20)
TGA	**Jan 2022;** 2+1 or 3+1 schedule with first dose from age 6/52 Private market price: ~$110/dose	**Dec 2023;** 2+1 or 3+1 schedule with first dose from age 6/52 Private market price: ~$150/dose
AIH (ATAGI)	**Non preferential alternative** to PCV13 using the same schedule **'Interim recommendation only awaiting the comprehensive review of optimal pneumococcal vaccination program currently underway'**	TBC
PBAC	**March 2023 meeting:** Recommended for NIP listing for paediatric populations based on, among other matters, its assessment that the cost-effectiveness of 15vPCV would be acceptable if it were **cost-minimised against the nominated comparator PCV13.**	Nov 2023 meeting: Recommendation for NIP listing based on, among other matters, its assessment that the cost-effectiveness of 20vPCV would be acceptable if it were **cost-minimised against the nominated comparators, 13vPCV and 15vPCV.**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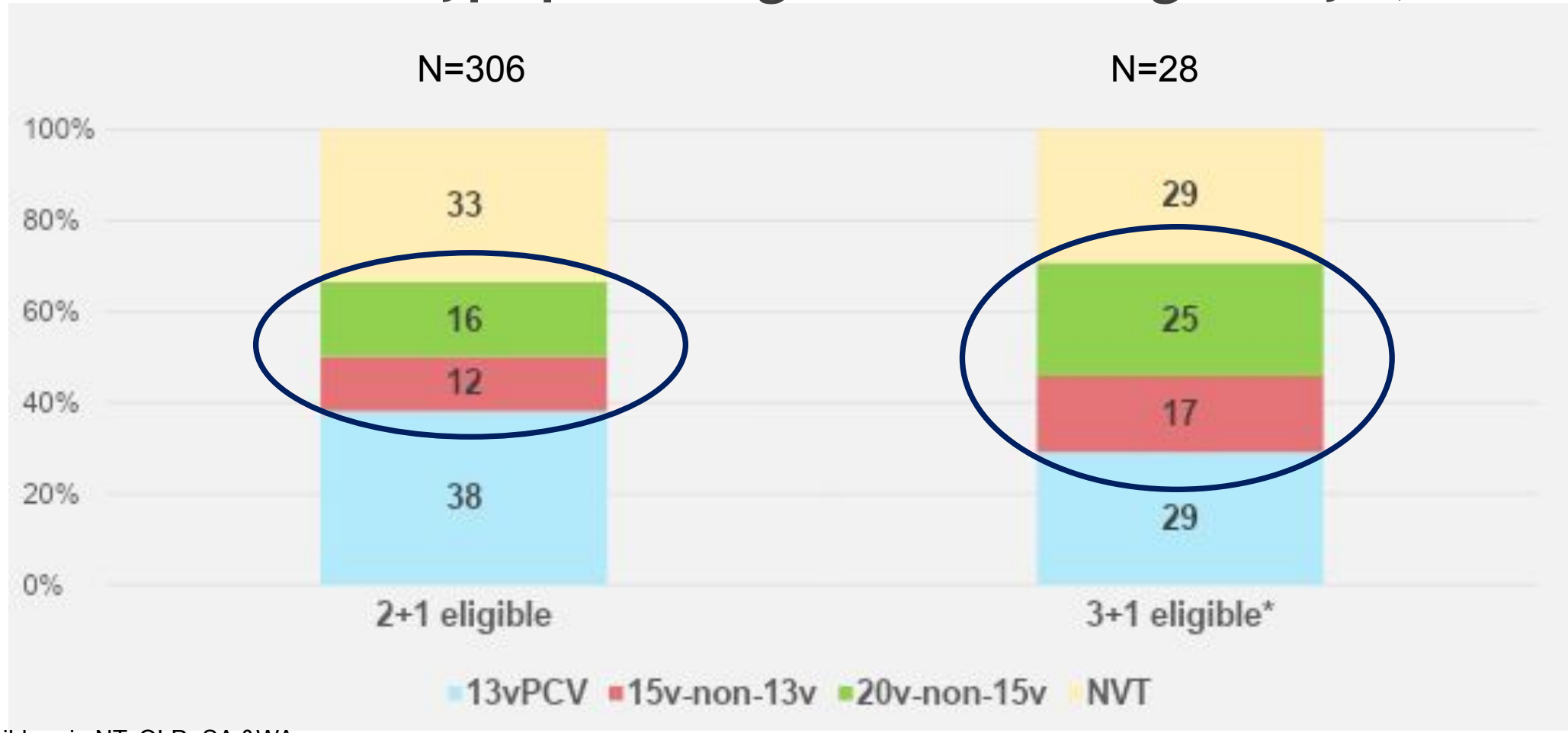
How much disease among Australian children is caused by the extra ST in new PCVs

IPD vaccine serotype percentages in children aged < 5yrs, 2022



* Indigenous children in NT, QLD, SA &WA

Based on national enhanced IPD surveillance data in NNDSS, data access approval #547(Nov)/2022 (May 2023 extract)