Pneumococcal disease and its prevention
PCV15,20,21 (24,30)

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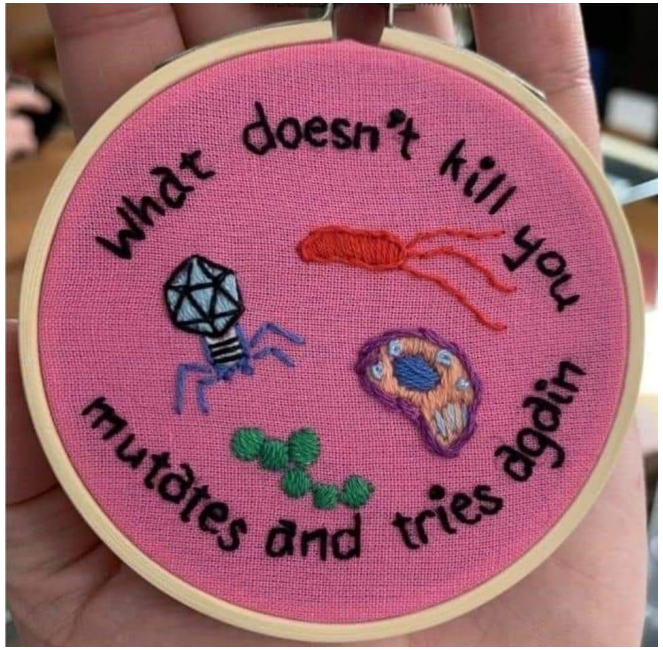


Disclosures

- At times, I have received funding support for travel, conduct of education sessions, research activity, and advisory board attendance from the following:
  - CSL Seqirus, Sanofi, Novartis, GSK, MSD, Moderna, Pfizer

- I am a member and past president of the Australian Immunisation Coalition, current member of the Australian Influenza Vaccination Committee, and the Asia Pacific Alliance for the Control of Influenza. I have been an expert member of NITAGs/subgroups in 3 continents.

- I have received input from both MSD and Pfizer

- **The views expressed are my own**

PP-PNA-AUS-0270, 12/2021.

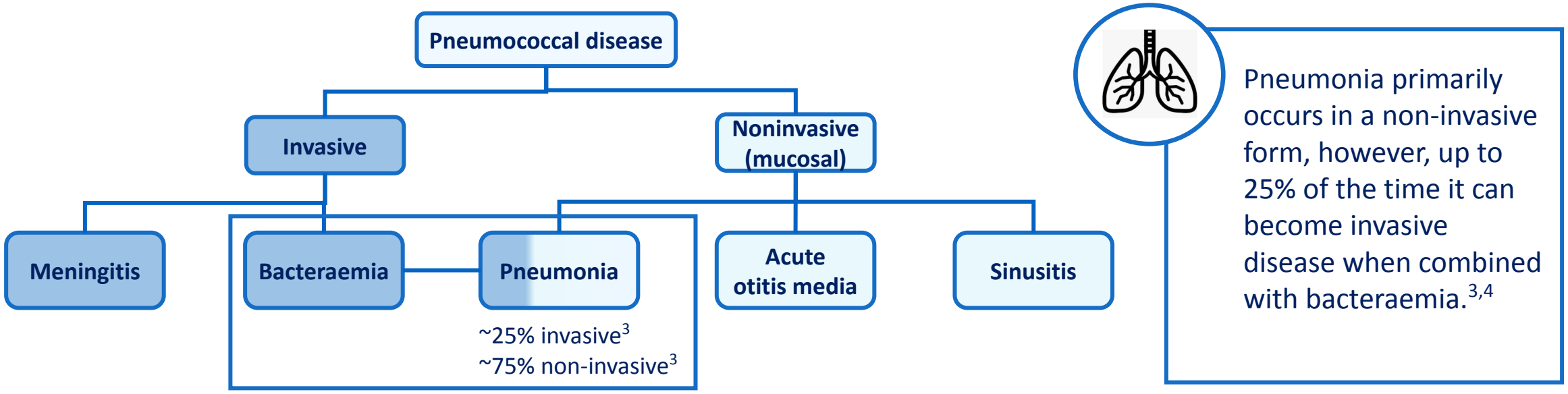
Learning outcomes

By the end of this talk, you will be able to:

- Be aware of ongoing pneumococcal disease and the impact of vaccination policy on both disease burden and serotype changes
- Identify the remaining challenges and the future prospects of pneumococcal vaccination to address this

Defining pneumococcal disease

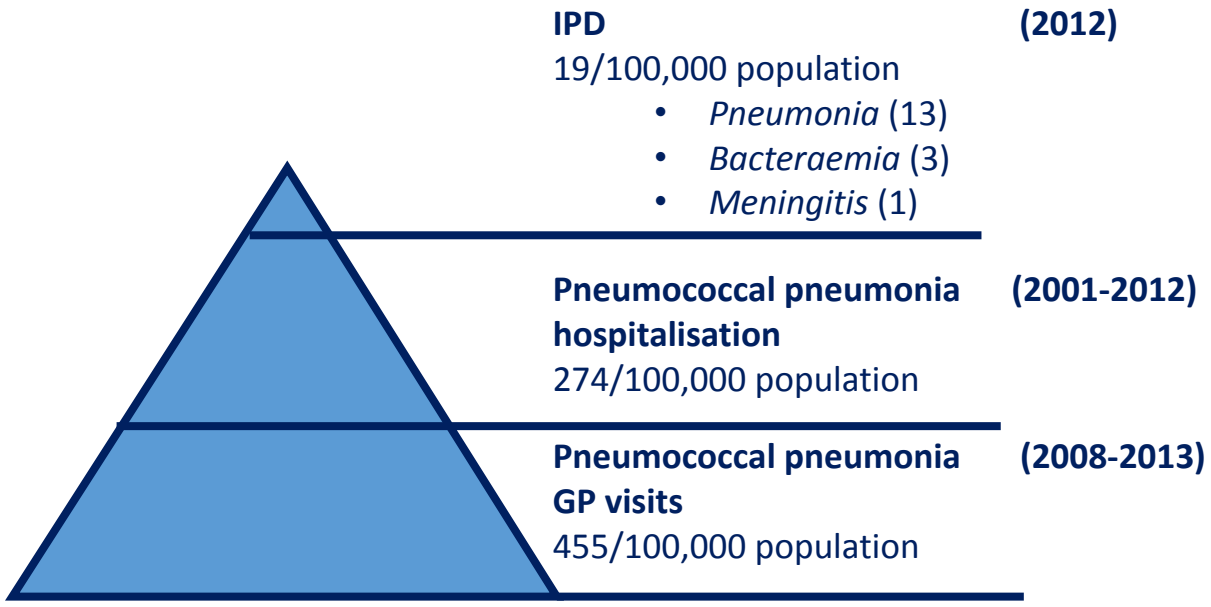
- Pneumococcal disease is a bacterial infection caused by *Streptococcus pneumoniae*[1]
- There are more than 95 known pneumococcal serotypes but most disease is caused by a small number of serotypes[2]
- Infection may be non-invasive or invasive[1]



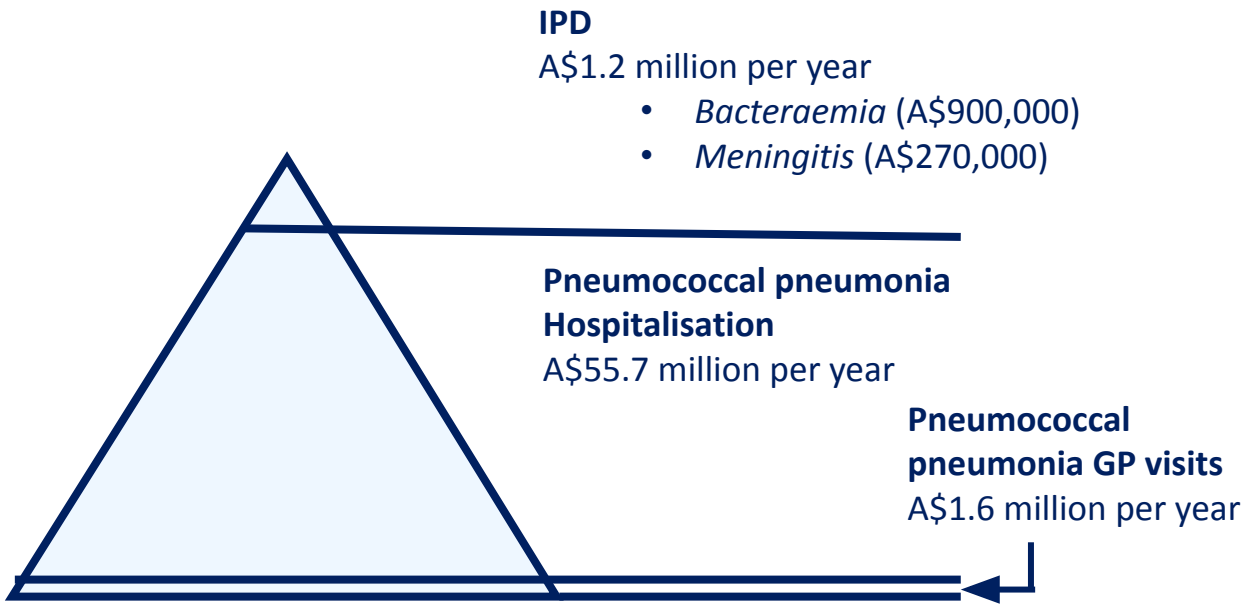
1. Toms C and Kluyver R. *Commun Dis Intell Q Rep.* 2016;40(2):E267-84. 2. Australian Technical Advisory Group on Immunisation (ATAGI). Australian Immunisation Handbook – Pneumococcal Disease. Australian Government Department of Health, Canberra, 2018. Available at: https://immunisationhandbook.health.gov.au. Accessed May 2021. 3. Said M et al. *PloS One.* 2013;8(4):e60273. 4. World Health Organisation. Pneumococcal vaccines WHO position paper – 2012. Weekly Epidemiological Record. 2012;87(14):129–144.

Burden of pneumococcal disease in Australia

Distribution of incidence[1]



Distribution of cost[1]

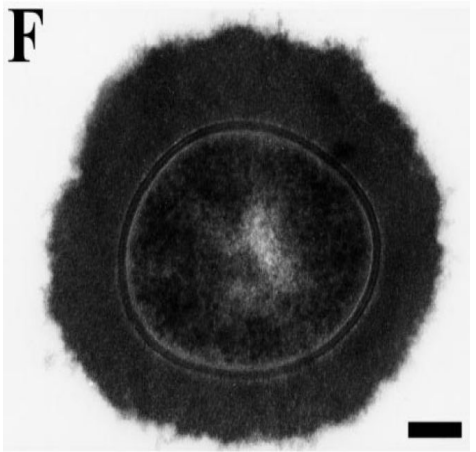


Retrospective cross-sectional study using administrative data from four national databases (Australian Institute of Health and Welfare (AIHW), Bettering Evaluation and Care of Health (BEACH), Australian Bureau of Statistics (ABS), National Hospital Data Collection for public hospitals [Australian Refined Diagnosis Related Groups; AR-DRG]) and published literature, to estimate burden of pneumococcal disease.
GP, general practitioner, IPD, invasive pneumococcal disease.

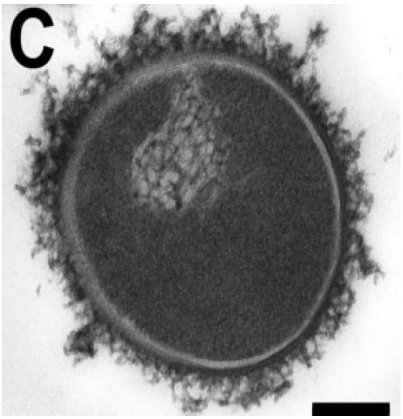
1. Earle K and William S. *Pneumonia.* 2016:27;8:9.

Pneumococcal capsules are highly variable giving rise to multiple **serotypes**

- Pneumococci are grouped into many serotypes, on the basis of their chemically and serologically distinct capsular polysaccharides
- Pneumococci infectivity is enhanced by its **polysaccharide capsule**
- There are **more than 95 serotypes** identified and grouped into 46 serogroups based on immunological similarities



Serotype **3**



Serotype 19F

1 Principi N, Di Cara G, Bizzarri I, Isidori C, Borgia P, Mignini C, et al. Prevention of invasive pneumococcal disease: Problems emerged after some years of the 13- valent pneumococcal conjugate vaccine use. Curr Infect Dis Rep 2018;20(1):1. https://doi.org/10.1007/s11908-018-0607-z.
2 Namkoong H, Ishii M, Funatsu Y, Kimizuka Y, Yagi K, Asami T, et al. Theory and strategy for pneumococcal vaccines in the elderly. Hum Vaccin Immunother 2016;12(2):336–43. https://doi.org/10.1080/21645515.2015.1075678
https://www.nfid.org/infectious-diseases/pneumococcal/
3. CDC. 2021. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pneumo.pdf. Accessed July 01, 2021.

IPD, Invasive Pneumococcal Disease

Sugar Coated Killer. Serotype 3 Disease

- The capsular polysaccharide prevents entrapment in mucus during colonization, traps water to protect against desiccation, can serve as an energy reserve, and protects the bacterium against complement-mediated opsonization and immune cell phagocytosis.
- Most significantly, Serotype 3 infections are characterized as having severe clinical manifestations including empyema, bacteremia, cardiotoxicity, and meningitis; consequently, with a fatality rate of 30%–47%.
- Serotype 3 resists antibody-mediated clearance despite its inclusion in the current vaccines formulation.
- Serotype 3 capsule synthesis and presentation on the bacterial surface is distinct from other serotypes

Luck, J et al, Front Cell Infect Microbiol 2020 10: 613287

Multiple chronic conditions increase the risk for developing invasive pneumococcal disease (IPD) and for poorer outcomes[1,2]

IPD risk in at-risk adults 18 to 64 years versus healthy adults[a]

Chronic liver disease
~7-9X the average risk[3,4]

Asthma
~4X the average risk[3,4]

Chronic lung disease
~10-11X the average risk[3,4]
During 2007 to 2010, among adults older than 65 years of age, **19% suffered from chronic lung disease**[3]

Chronic heart disease
~4-6X the average risk[3,4]
During 2007 to 2010, among adults older than 65 years of age, **52% had chronic heart disease**[3]

Diabetes
~4-5X the average risk[3,4]
During 2007 to 2010, among adults older than 65 years of age, **50% had diabetes**[3]

Adults with

3+

at-risk conditions[4]

~13X

the average risk.[2,a]

- [a]Data for proportion of the population with each condition is from the United States.
- IPD, invasive pneumococcal disease.

1. Ludwig E et al. *Eur Respir Rev*. 2012;21(123):57-65. **2.** Shea KM et al. Published online April 18, 2014. *Open Forum Infect Dis.* 2014;1(1):24. DOI:10.1093/ofid/ofu024. **3.** Weycker D et al. Published online May 13, 2016. *BMC Health Sci Res.* 2016;16:182. DOI:10.1186/s12913-016-1432-4. **4.** Zhang D et al. Published online August 29, 2018. *BMC Infect Dis*. 2018;18(436):1-4. DOI:10.1186/s12879-018-3326-z.

Key Points

Conjugation

CAPiTA trial in Netherlands

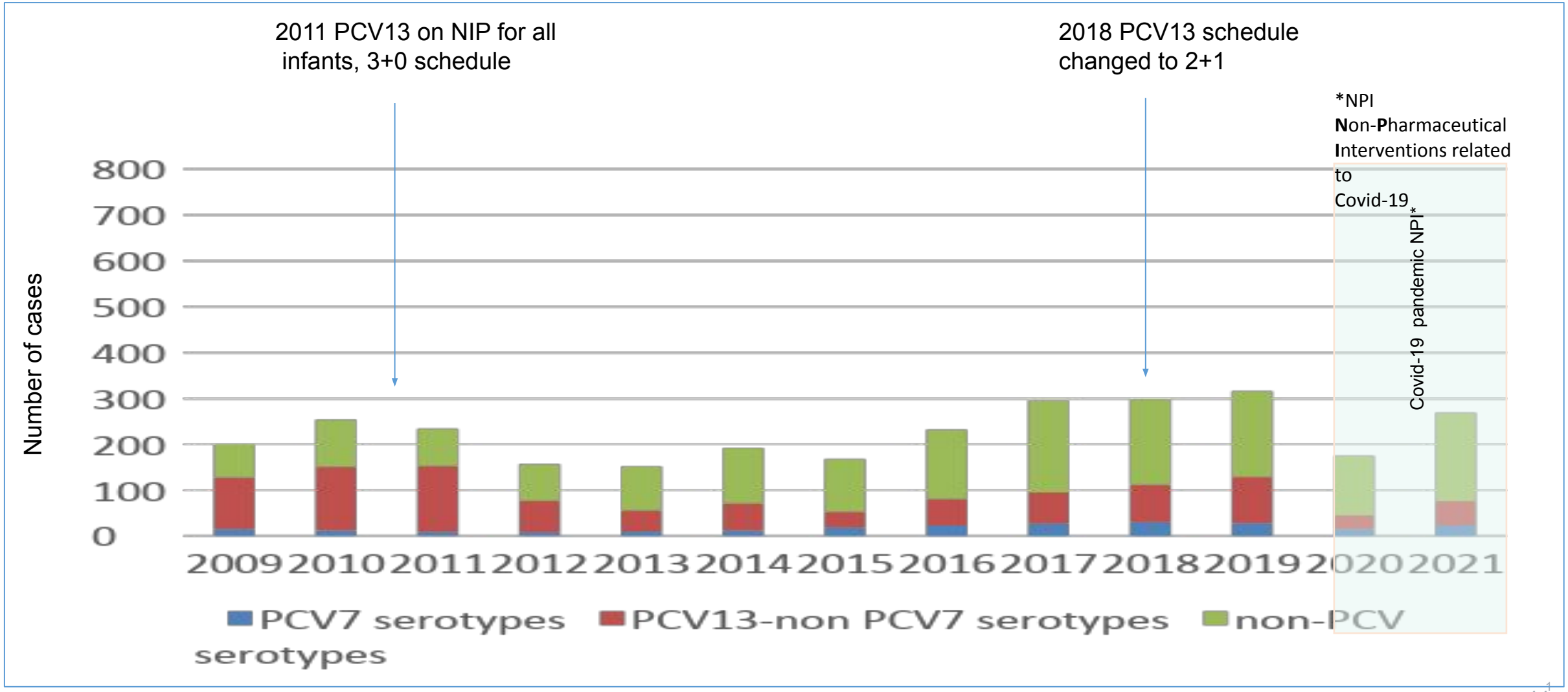
Need	A clear medical need exists among adults for an effective vaccine to prevent pneumococcal disease, including pneumococcal community-acquired pneumonia (CAP)
Purpose	The primary outcome of CAPiTA is to establish in adults aged 65 years and older the efficacy of **PCV13** to prevent a first episode of confirmed vaccine-serotype pneumococcal CAP (VT-CAP)
Design	CAPiTA is a randomized, placebo-controlled clinical trial that is one of the largest prospective vaccine efficacy trials ever conducted in adults

Hak E, Grobbee DE, Sanders EAM, et al. *Netherlands J Med.* 2008;66:378-383.

Epidemiology in Australia

Children
Older Adults

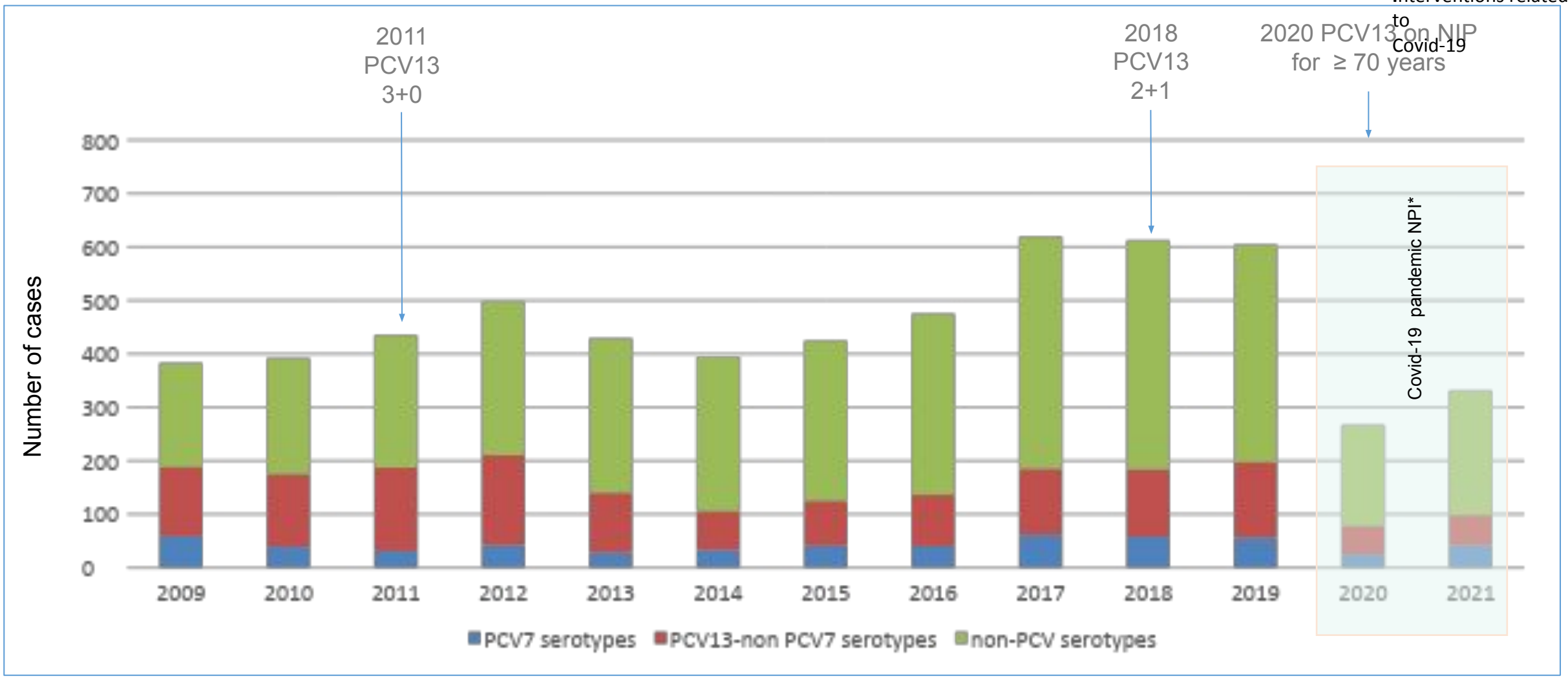
The number of IPD cases and epidemiology in Australian children <5 years



Data source: 1. NNDSS Public data set: https://www.health.gov.au/resources/publications/national-notifiable-diseases-surveillance-system-nndss-public-dataset-pneumococcal-disease-invasive?language=en
2. Prevenar 13 Australian Approved Product Information, 13 August 2020. 3. Vaccine History Registration timeline: https://www.health.vic.gov.au/immunisation/vaccine-history-timeline

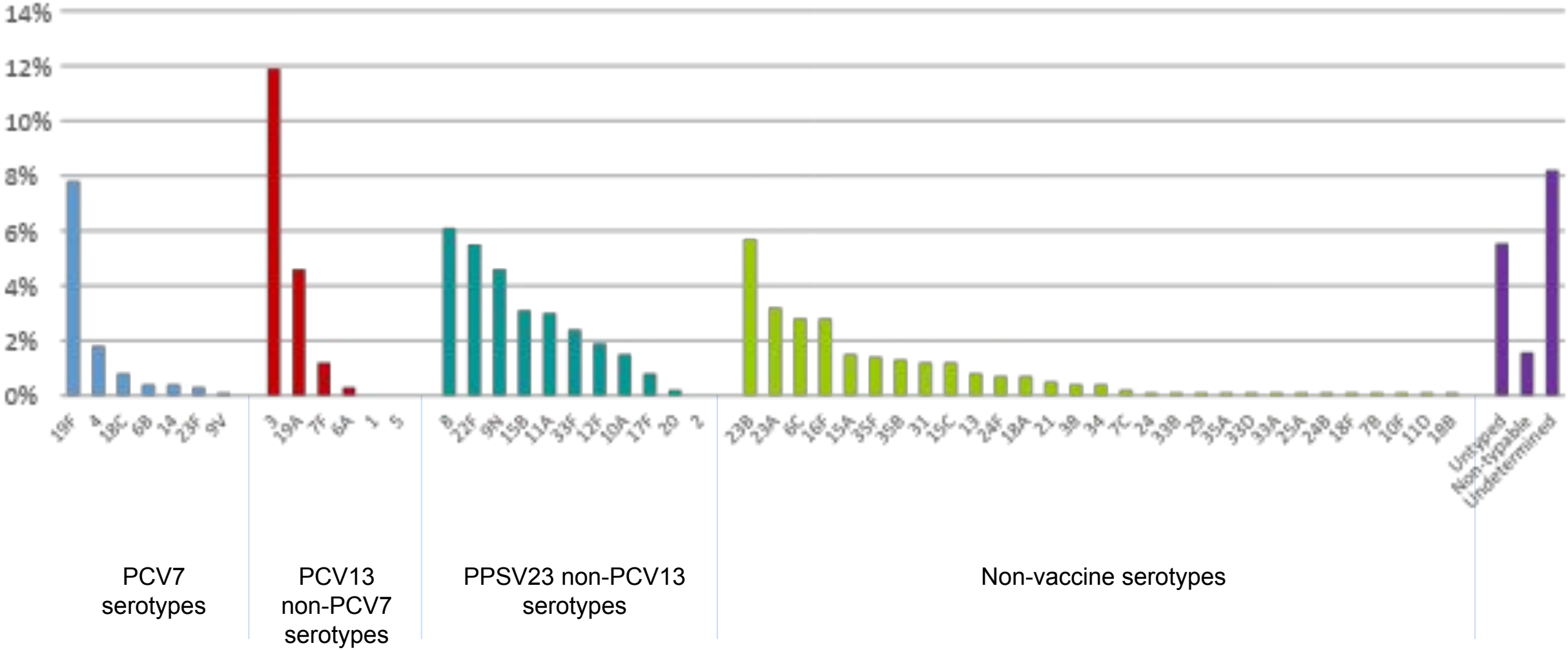
The number of IPD cases and epidemiology in Australian adults ≥70 years

*NPI
Non-**P**harmaceutical
Interventions related to Covid-19



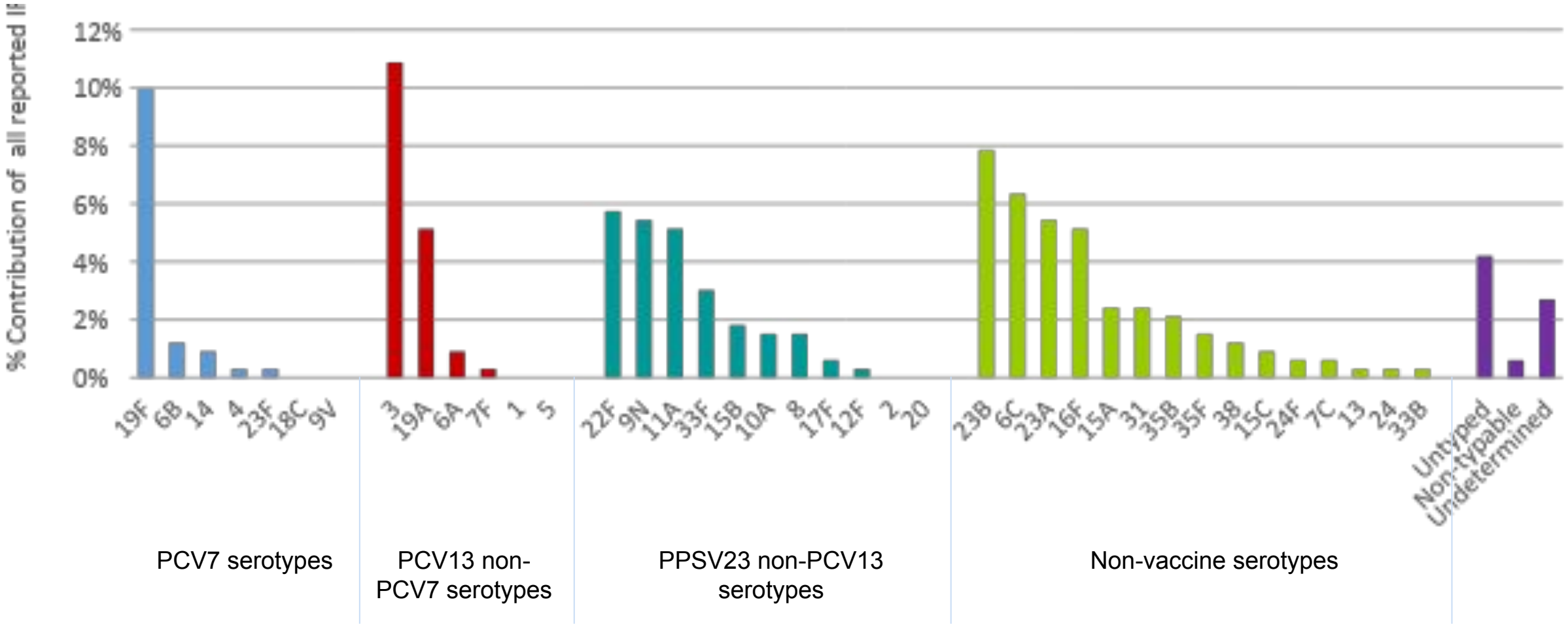
Data source: 1. NNDSS Public data set: https://www.health.gov.au/resources/publications/national-notifiable-diseases-surveillance-system-nndss-public-dataset-pneumococcal-disease-invasive?language=en
2. Prevenar 13 Australian Approved Product Information, 13 August 2020. 3. Vaccine History Registration timeline: https://www.health.vic.gov.au/immunisation/vaccine-history-timeline

Serotype distribution of total Australian IPD cases across all ages by vaccine type, 2021



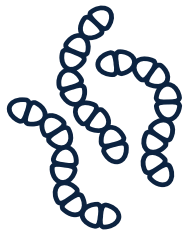
Data source: 1. NNDSS Public data set: https://www.health.gov.au/resources/publications/national-notifiable-diseases-surveillance-system-nndss-public-dataset-pneumococcal-disease-invasive?language=en 2. Prevenar 13 Australian Approved Product Information, 13 August 2020. 3. Vaccine History Registration timeline: https://www.health.vic.gov.au/immunisation/vaccine-history-timeline PNEUMOVAX23 Australian Approved Product Information, 2 November 2020.

Serotype distribution of IPD cases in Australian adults ≥70 years by vaccine type, 2021



Data source: 1. NNDSS Public data set: https://www.health.gov.au/resources/publications/national-notifiable-diseases-surveillance-system-nndss-public-dataset-pneumococcal-disease-invasive?language=en 2. Prevenar 13 Australian Approved Product Information, 13 August 2020. 3. Vaccine History Registration timeline: https://www.health.vic.gov.au/immunisation/vaccine-history-timeline PNEUMOVAX23 Australian Approved Product Information, 2 November 2020.

Key points to consider



Despite the success of PCVs, there is **a need to address residual disease in adult and pediatric populations**[1]

Older adults and **adults with chronic or immunosuppressive conditions** are at **increased risk for pneumococcal disease**[2,3]

IPD caused by both **vaccine serotypes and non-vaccine serotypes persist** in **older adults**[6-9]

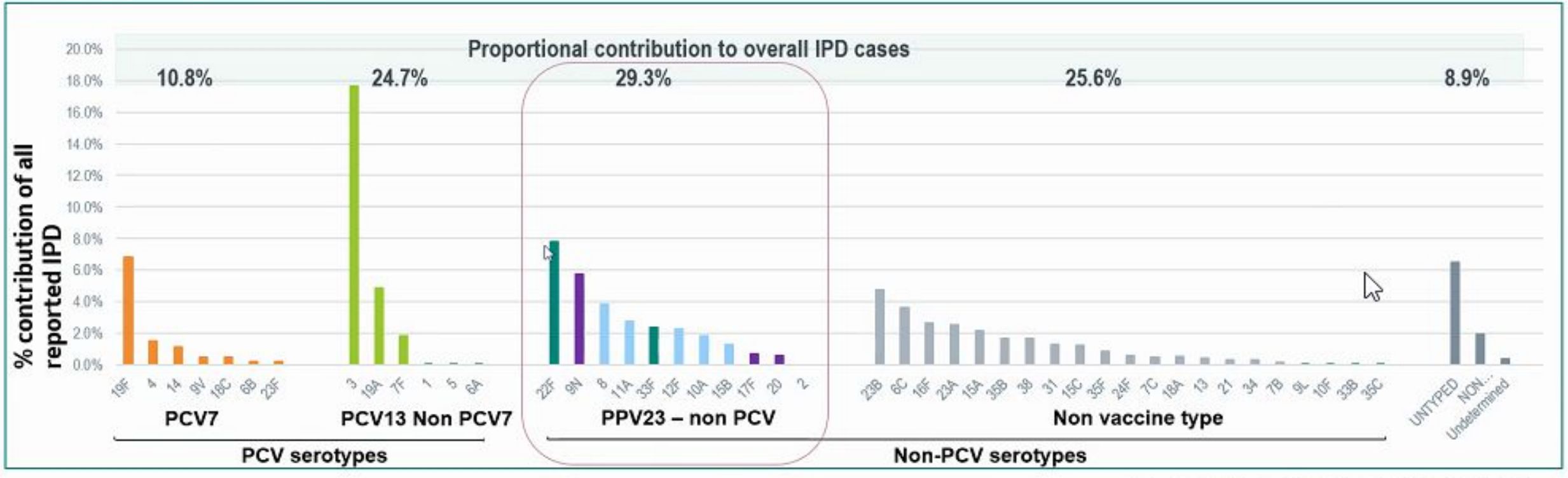
The **increase** of **common non-vaccine serotypes**, and **other non-vaccine serotypes** seen across countries highlight the **need for continued surveillance** on **serotype distribution** and **serotype-specific invasiveness.** [10]

PCV, pneumococcal conjugate vaccine. **1.** Klugman KP, Rodgers, GL. *Lancet Infect Dis*. 2021;21(1):14-16. **2.** CDC. 2021. http://www.cdc.gov/vaccines/pubs/pinkbook/downloads/pneumo.pdf. Accessed July 01, 2021. **3.** Ludwig E et al. *Eur Respir Rev*. 2012;21(123):57-65. **4.** Institute of Environmental Science and Research Limited**.** Invasive pneumococcal disease quarterly report October–December 2018**.** Accessed July 1, 2021. https://surv.esr.cri.nz/PDF_surveillance/IPD/2018/IPDQuarterlyReportOct-Dec2018.pdf. **5.** Severiche-Bueno DF, et al. *Int J Infect Dis*. 2021;105:32-39. . **6.** Naucler P, et al. *Clin Infect Dis*. 2017;65:1780-1789. **4.** Navarro-Torné A, Mendéz C. ISPPD 2020. Abstract 470.7**.** Navarro-Torné A, et al. ISPPD 2020. Abstract 1184. **8.** Desai S, et al. *CMAJ Open*. 2016;4:E545-E550. Desmet S et al. *Lancet.* 2018:18(8):830-831. **10** Qian-qian Du et al. 2021. Hum Vaccin Immunother. 2021; 17(12): 5628–5637. Published online 2021 Nov 2. doi: 10.1080/21645515.2021.1985353 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8903918/. Accessed June 2023.

To reduce pneumococcal disease we need vaccines with good effectiveness against prevailing serotypes

and we need to use them!

Serotype distribution of IPD cases, by associated vaccine type, Australia 2019



Non-typable: ST reported by reference lab at non-typable strain
Untyped: may be due to no isolate/isolate not referred for typing/isolate not vi

Common PCV15 and PCV20 additional serotypes

Unique PCV20 additional serotypes

Serotypes not covered by new PCV

*PCV15 and PCV20 are approved in Australia, US and EU.

IPD Annual Reports. https://www1.health.gov.au/internet/main/publishing.nsf/Content/cda-surveil-nndss-ipd-reports.htm

Pneumococcal vaccine serotype overview

Previously/currently registered pneumococcal vaccines																						
PCV7*	4	6B	9V	14	18C	19F	23F															
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A									
PPV23	4	6B	9V	14	18C	19F	23F	1	3	5		7F	19A	22F	33F	2	8	9N	10A	11A	12F	15B	17F	20
V114 PCV15	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F									
PCV20	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F		8		10A	11A	12F	15B		

*Prevenar 7 is no longer available Australia

VAXNEUVANCE Australian Approved Product Information, 27 March 2023, PNEUMOVAX23 Australian Approved Product Information, 2 November 2020
PREVENAR 13 Australian Approved Product Information, 13 August 2020, PREVENAR 13 Australian Approved Product Information, 2 December 2022,
PREVENAR 7 is no longer available Australia.

So ? Which one?

Is more better?

Proprietary

GRADE review by NCIRS

- 15vPCV likely results in little difference in OPA GMT ratios for shared STs. 15vPCV likely increases OPA GMTs for STs unique to 15vPCV Note: OPA GMT ratios all met a non-inferiority margin of LCI>0.33. Across all studies 15vPCV is statistically significantly higher than 13vPCV for ST 3, 22F, 33F.[1]
- A statistically significantly higher proportion of participants in 15vPCV group had ≥4-fold rise of GMC pre to 30 days post vaccination compared with 13vPCV participants across all studies for ST 3 (shared with 15vPCV and 13vPCV), 22F and 33F (vaccine serotypes for PCV15 but not PCV13)[1]
- Adult: PBAC recommendation November 2021[2]
- Added to the Aust Immunisation Handbook for use in adult groups in January 2023[3]
- Paediatric: PBAC recommendation March 2023[4]

1. NCIRS. Pneumococcal vaccines GRADE assessments. https://ncirs.org.au/pneumococcal-vaccines-grade-assessments Accessed May 2023
2. PBAC. Public Summary Document – November 2021 PBAC Meeting
3. Australian Immunisation Handbook. Pneumococcal disease. https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/pneumococcal-disease. Accessed May 2023
4. PBAC. Pharmaceutical Benefits Advisory Committee (PBAC) Meeting Outcomes March 2023 PBAC meeting

Summary of evidence:
Benefits, children <2 years

- **Informed by 2 randomized controlled trials (Phase II and III)[1,2]**
  - Healthy children randomized to either PCV13 or PCV20
  - PCVs given using 3+1 schedule
- **Summary of findings**
  - PCV20 had numerically **lower** immune responses* vs. PCV13 for most of the 13 shared serotypes
  - **Post dose 3**:
    - PCV20 did **not** meet noninferiority criteria vs. PCV13 for some serotypes
  - **Post dose 4**:
    - PCV20 **noninferior** to PCV13 for all 13 shared serotypes
    - PCV20 **noninferior** to PCV13** for all 7 additional serotypes

*measured as IgG GMCs and GMRs

**Compared with the serotype with lowest immune response among PCV13 serotypes except for serotype 3

1. Senders et al. PIDJ 2021
2. Pfizer unpublished data from B7471011

Matching-adjusted indirect comparison of pneumococcal vaccines V114 and PCV20

Shahrul Mt-Isa, Lauren A. Abderhalden, Luwy Musey & Thomas Weiss

https://doi.org/10.1080/14760584.2021.1994858

PUBLISHED ONLINE:
27 October 2021

Figure 1 of 2

Figure 1. Indirect treatment comparison network.

Abbreviations: MAIC, matching-adjusted indirect comparison; PCV13, 13-valent pneumococcal conjugate vaccine; PCV20, 20-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine. [a]Weighting is only applicable to MAIC.

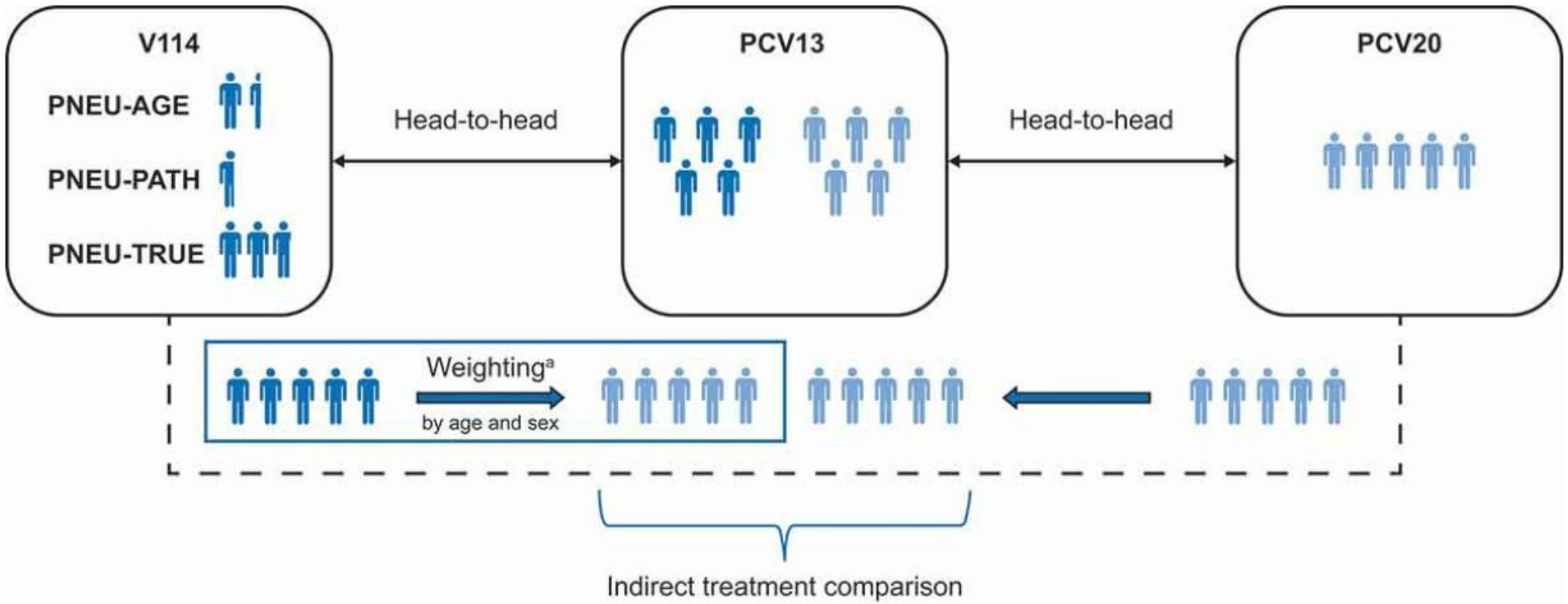
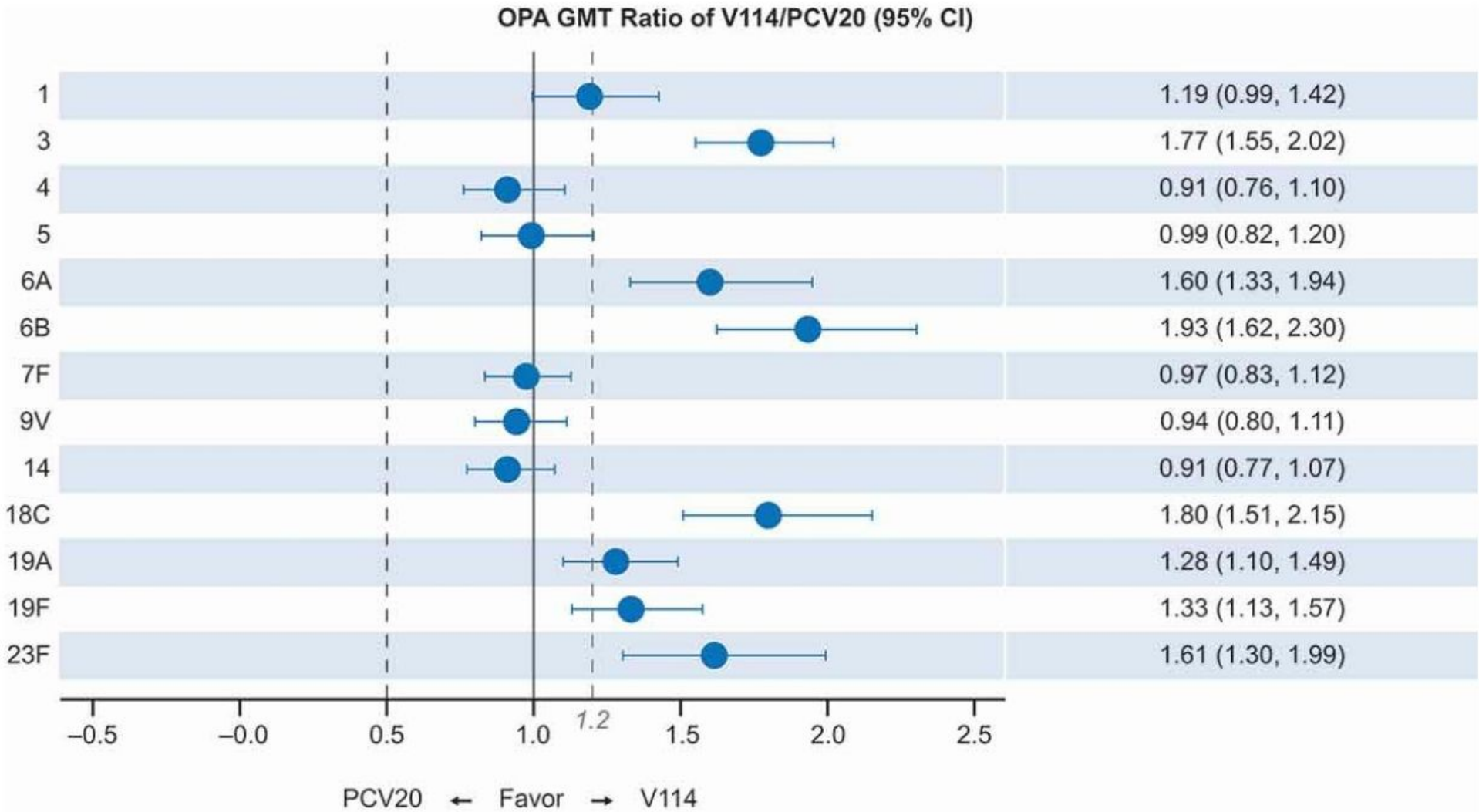


Figure 2 of 2

Figure 2. MAIC analysis of GMT ratio for V114 versus PCV20.

Abbreviations: CI, confidence interval; GMT, geometric mean titer; MAIC, matching-adjusted indirect comparison; OPA, opsonophagocytic activity; PCV20, 20-valent pneumococcal conjugate vaccine; V114, 15-valent pneumococcal conjugate vaccine. Non-inferiority margin was defined as a lower bound of the 95% CI of >0.50. Superiority margin was defined as a lower bound of the 95% CI of >1.2.



All children and adults with newly identified risk conditions are recommended to receive:

- 1 dose of 13vPCV or 15vPCV (for people aged ≥18 years) at diagnosis (at least 2 months after any previous doses of 13vPCV or 15vPCV)
- 1 dose of 23vPPV 12 months after 13vPCV or 15vPCV (2–12 months later is acceptable) or at 4 years of age whichever is later
- a 2nd dose of 23vPPV at least 5 years later

NCIRS National Centre for Immunisation Research and Surveillance

ATAGI recommendation for using 15vPCV+23vPPV vaccine versus 13vPCV+23vPPV vaccine in adults aged ≥18 years with specific risk conditions.

15vPCV+23vPPV vaccine is recommended as an alternative to 13vPCV+23vPPV vaccine in adults aged ≥18 years with specific risk conditions. It should be noted that 15vPCV provides additional anticipated protection against two more serotypes.

Aboriginal and Torres Strait Islander adults without risk conditions receive:

- a dose of 13vPCV or 15vPCV at age ≥50 years
- a dose of 23vPPV 12 months later
- a 2nd dose of 23vPPV at least 5 years later

AND NOW .. PCV 15 for children also

Summary Vaxneuvance Recommendations

- Vaxneuvance is now indicated in adults and children from six weeks of age for the active immunisation for the prevention of pneumococcal disease caused by 15 Streptococcus pneumoniae serotypes.[1,2]
- Vaxneuvance is now available on private script for all medically at-risk patients aged 18 – 69 years for which it is recommended but not funded.[3]
- Added to the Australian Immunisation Handbook for use in specified adult and at-risk adults in January 2023
- Pharmaceutical Benefits Advisory Committee (PBAC) has recommended Vaxneuvance to be a designated vaccine for the prevention of pneumococcal disease in all infants from 2 months of age, specified at-risk paediatric populations and in certain at-risk adults

1. Australian Government Department of Health and Aged Care. Therapeutic Goods Administration. Public Summary. Vaxneuvance. Available at https://www.ebs.tga.gov.au/servlet/xmlmillr6?dbid=ebs/PublicHTML/pdfStore.nsf&docid=350791&agid=%28PrintDetailsPublic%29&actionid=1. Last accessed April 2023.
2. Vaxneuvance Product Information. 27 March 2023.
3. Australian Government Department of Health and Aged Care. Australian Immunisation Handbook. Pneumococcal Disease. Recommendations. Available at https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/pneumococcal-disease#recommendations. Last accessed May 2023.
4. Pharmaceutical Benefits Advisory Committee (PBAC). PBAC Meeting Outcomes November 2021. Available at: https://www.pbs.gov.au/industry/listing/elements/pbac-meetings/pbac-outcomes/2021-11/pbac-web-outcomes-11-2021-v2.pdf.
5. Pharmaceutical Benefits Advisory Committee (PBAC). Recommendations made by the PBAC - March 2023. Available at: https://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/pbac-outcomes/recommendations-made-by-the-pbac-march-2023. Last accessed April 2023.

2021 ACIP Recommendations

- October 20, 2021: Advisory Committee on Immunizations Practices (ACIP) recommended the following:
- For adults ≥ 65 years
- Adults 19-64 y with certain underlying medical conditions or risk factors who have not previously received PC vaccine
  - PCV20 alone OR
  - PCV15 in series with PPSV23

Summary of WG Considerations: PCV20 Use Alone OR PCV15+PPSV23

Advantages of PCV20 Use Alone	Disadvantages of PCV20 Use Alone
• Acceptable and feasible to implement a single vaccine option • Cost-saving* in cost-effectiveness analyses • Expected to provide better protection for the serotypes covered by PPSV23 alone	• Clinical significance of lower immunogenicity vs. PCV13 unknown • No data in immunocompromised adults • Losing protection against PPSV23, non-PCV20 serotypes
Advantages of PCV15+PPSV23	**Disadvantages of PCV15+PPSV23**
• Provides broad serotype coverage • Age-based use at age 65 was cost-saving* according to CDC's cost-effectiveness analysis	• Logistically more challenging to administer PCV15-PPSV23 vaccine series • Need to know vaccination history to correctly complete series • Can result in lower serotype coverage if series not completed

*lower cost and better health outcome compared to current recommendations

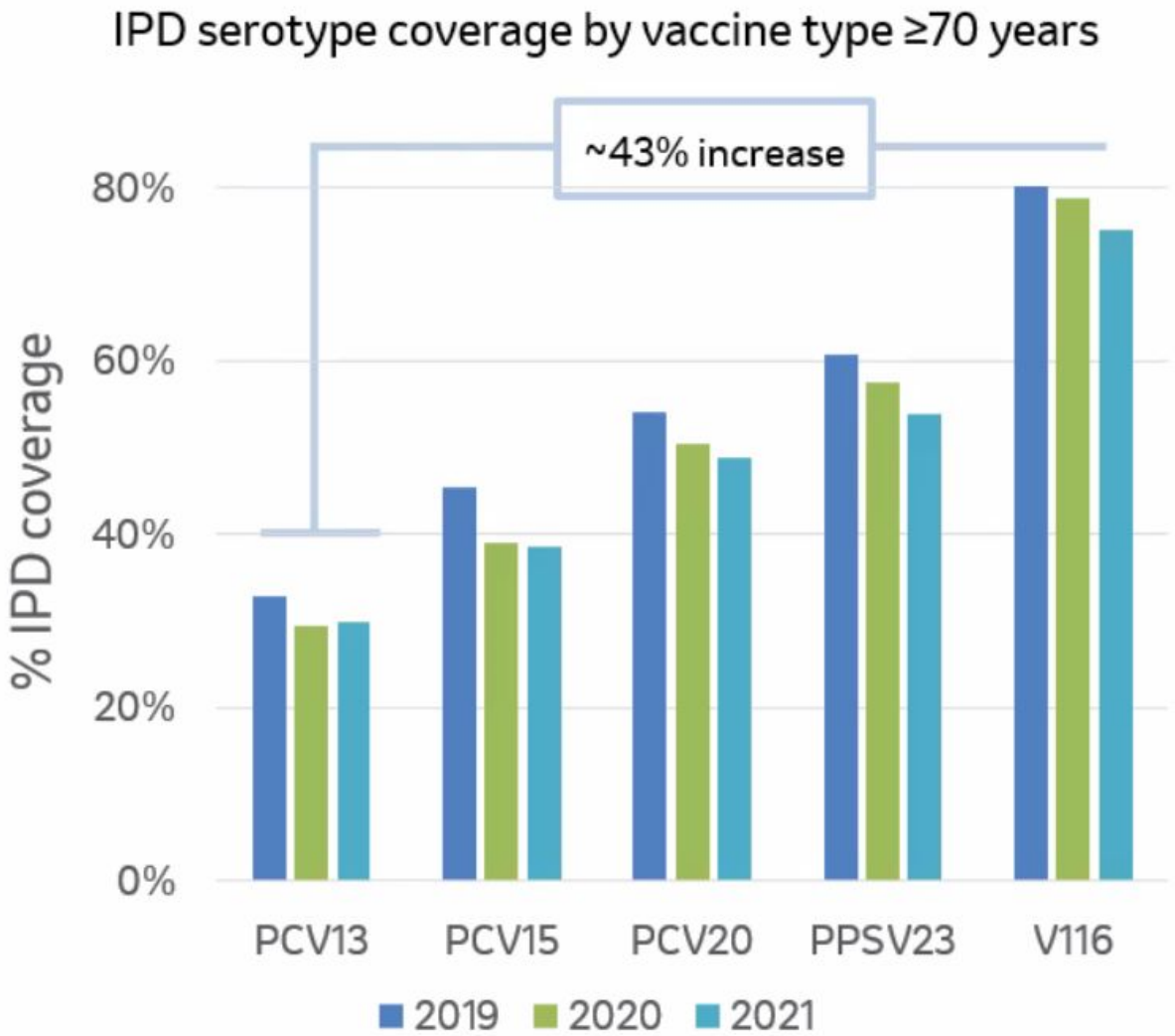
V116 covers important current and new PCV serotypes, broadening coverage to 8 additional non-vaccine serotypes[1,2]

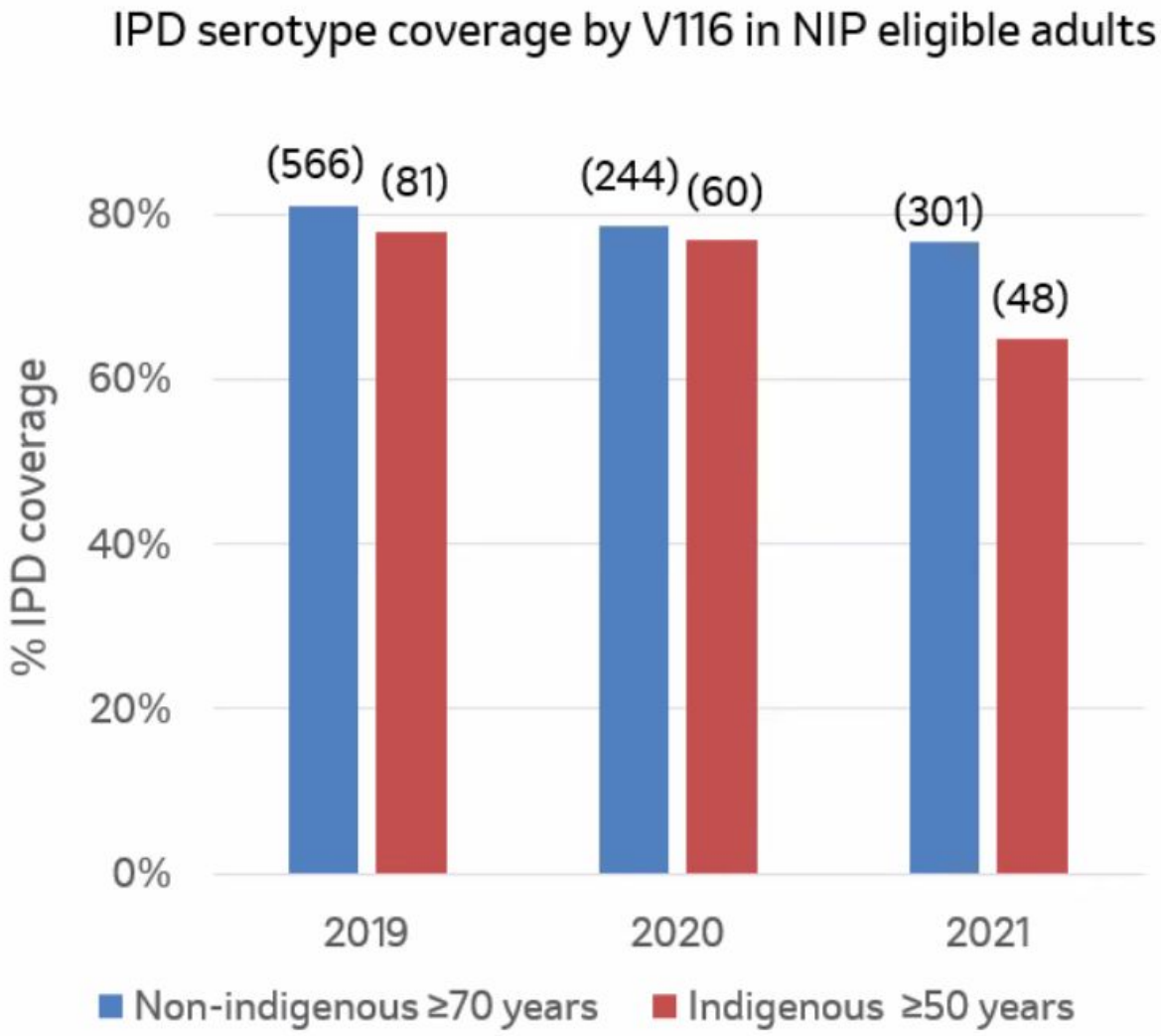
- Serotypes were selected, in part, based on analysis of the available global epidemiology data in older adults following introduction of PCVs into both paediatric and adult NIP.

Serotypes 15A, 15C*, 16F, 23A, 23B, 24F, 31 and 35B are not in any currently licensed pneumococcal vaccine but are found to significantly contribute to current adult IPD burden, in Australia accounting for 20% of IPD[3].

	Serotype Composition																													
PCV7	4	6B	9V	14	18C	19F	23F																							
PCV13	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A																	
PCV15	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F															
PPSV23	4	6B	9V	14	18C	19F	23F	1	3	5		7F	19A	22F	33F	2	8	9N	10A	11A	12F	15B	17F	20						
PCV20	4	6B	9V	14	18C	19F	23F	1	3	5	6A	7F	19A	22F	33F		8		10A	11A	12F	15B								
V116									3		6A	7F	19A	22F	33F		8	9N	10A	11A	12F		17F	20	15A	15C	16F	23A	23B	24F	31	35B

V116 expands serotype coverage beyond current and new pneumococcal vaccines in both non-indigenous and indigenous adult populations





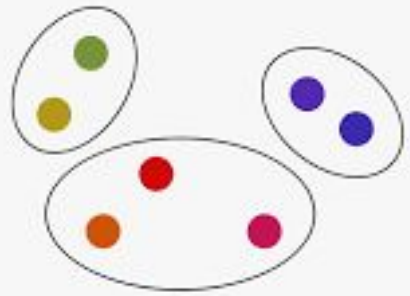
Summary

- Pneumococcal disease, both invasive and community acquired pneumonia, remains a significant cause of morbidity, frailty and death in children and adults, especially in older adults.
- Improving the situation will require
  1. Vaccines against emerging serotypes
  2. Vaccines which work effectively against serotypes of concern especially serotype 3.
  3. Recommendations from primary care physicians for these vaccines

List 1: Risk factors associated with an increased risk of pneumococcal disease and their eligibility for funding under the NIP

Risk condition	Eligibility for NIP funding	
	<5 years of age	≥5 years of age
Previous episode of invasive pneumococcal disease	✓	✓
Functional or anatomical asplenia, including		
– sickle cell disease or other haemoglobinopathies	✓	✓
– congenital or acquired asplenia (for example, splenectomy) or hyposplenia	✓	✓
Immunocompromising conditions, including		
– congenital or acquired immune deficiency, including symptomatic IgG subclass or isolated IgA deficiency	✓	✓
– haematological malignancies	✓	✓
– solid organ transplant	✓	✓
– haematopoietic stem cell transplant	✓	✓
– HIV infection	✓	✓
– immunosuppressive therapy, where sufficient immune reconstitution for vaccine response is expected; this includes those with underlying conditions requiring but not yet receiving immunosuppressive therapy		
– non-haematological malignancies receiving chemotherapy or radiotherapy (currently or anticipated)		
Proven or presumptive cerebrospinal fluid (CSF) leak, including		
– cochlear implants	✓	✓
– intracranial shunts	✓	✓
Chronic respiratory disease, including*		
– suppurative lung disease, bronchiectasis and cystic fibrosis	✓	✓
– chronic lung disease in preterm infants	✓	✓
– chronic obstructive pulmonary disease (COPD) and chronic emphysema		
– severe asthma (defined as requiring frequent hospital visits or the use of multiple medications)		
– interstitial and fibrotic lung disease		
Chronic renal disease		
– relapsing or persistent nephrotic syndrome	✓	✓
– chronic renal impairment – eGFR <30 mL/min (stage 4 or 5 disease)	✓*	✓*
Cardiac disease, including*		
– congenital heart disease	✓	
– coronary artery disease	✓	
– heart failure	✓	
Children born less than 28 weeks gestation	✓	
Trisomy 21	✓	
Chronic liver disease, including*		
– chronic hepatitis		
– cirrhosis		
– biliary atresia		
Diabetes		
Smoking (current or in the immediate past)		
Harmful use of alcohol (Defined as consuming on average ≥60 g of alcohol (6 Australian standard drinks) per day for males and ≥40 g of alcohol (4 Australian standard drinks) per day for females)		

* Funded under the NIP for eGFR <15 mL/min only (including patients on dialysis)



https://immunisationhandbook.health.gov.au/resources/tables/list-risk-conditions-for-pneumococcal-disease