National Immunisation Advisory Committee

UPDATED RECOMMENDATIONS FOR PNEUMOCOCCAL CONJUGATE VACCINATION IN CHILDHOOD

NIAC | 25.10.2024

About NIAC

NIAC membership includes nominees from the Royal College of Physicians in Ireland, its Faculties and Institutes, the Royal College of Surgeons in Ireland, the Irish College of General Practitioners, the National Immunisation Office, the Nursing and Midwifery Board of Ireland, the Infectious Diseases Society of Ireland, the Travel Medicine Society, the National Virus Reference Laboratory and lay members. Meetings are attended by representatives from the Department of Health and the HSE. Representatives of the Health Products Regulatory Agency attend to provide regulatory advice in relation to vaccines.

NIAC considers the evidence about vaccines and provides advice to the Chief Medical Officer and the Department of Health. The Department and the Minister for Health make policy decisions on vaccines which are implemented by the Health Service Executive.

UPDATED RECOMMENDATIONS FOR PNEUMOCOCCAL CONJUGATE VACCINATION IN CHILDHOOD

1. NIAC recommends PCV15 (Vaxneuvance, MSD) or PCV13 (Prevenar, Pfizer) for routine pneumococcal conjugate vaccination (PCV) in children.

2. PCV15 or PCV13 should be given according to the currently recommended three dose (2+1) PCV series.

3. The vaccine should be given as follows:
    - Dose one at 2 months of age.
    - Dose two at 6 months of age.
    - Dose three at 13 months of age.

4. If an infant commenced the PCV primary series with PCV13 further recommended doses of PCV may be given as PCV15 or PCV13.

5. Recommendations for additional PCV doses in high-risk children as laid out in Chapter 16 of the Immunisation Guidelines for Ireland are unchanged.

Recommendations may be updated when more information becomes available.

1. EXECUTIVE SUMMARY

- Invasive pneumococcal disease (IPD) is an illness characterised by the presence of *Streptococcus pneumoniae* in a normally sterile site leading to serious illness such as meningitis, sepsis and pneumonia. Invasive pneumococcal disease continues to be of public health importance in Ireland, predominantly affecting young children, older adults, and individuals with weakened immune systems.
- The incidence of IPD in children less than two years of age decreased considerably from approximately 35 per 100,000 per year to 10-15 per 100,000 per year following introduction of pneumococcal vaccination, PCV7, in 2008. Adults aged over 65 years are now the group with the highest incidence of IPD.
- With the introduction of PCV13 in 2010 there was a further but more modest reduction in IPD. Although, in Ireland, IPD remains lower than in the pre-vaccine era over time, serotype replacement has emerged, leading to an increase in IPD cases caused by non-vaccine serotypes.
- Two new pneumococcal vaccines have been licensed in children by the EMA. These are a 15-valent vaccine, Vaxneuvance, manufactured by MSD (PCV15) and a 20-valent vaccine, Prevenar20, manufactured by Pfizer (PCV20).
- Pneumococcal serotypes 3 and 19A continue to cause cases of IPD despite being covered by PCV13. Other serotypes responsible for considerable disease which are targeted in the new vaccines include serotype 22F which is covered by PCV15 and PCV20, and serotypes 10A, 12F and 15B/C which are covered by PCV20 but not PCV15.
- NIAC currently recommends PCV for infants without additional risk factors for IPD on a 3 dose (2+1) schedule at 2, 6 and 13 months of age.
- The Pneumococcal conjugate vaccine currently in use in Ireland is PCV13.
- Uptake of PCV in young children peaked in 2015 at 92.5% and has been on a general decline since. The uptake of three doses by 24 months of age was 83% nationally in 2024. This is below the WHO target of 95%.
- The tolerability and safety of PCV15 and PCV20 are generally comparable to PCV13 and no serious safety concerns have arisen from clinical trials reported to date.
- There are currently no efficacy or effectiveness data available for PCV15 or PCV20. The vaccines were approved by the EMA based on immunogenicity data in PCV15 on a 3 dose (2+1) or a 4 dose (3+1) schedule and in PCV20 on a 3+1 schedule only.
- With increasing valency of a vaccine, the immune response achieved per serotype can decrease. This effect has been observed for both PCV15 and PCV20.
- In clinical trials in which PCV13 was the comparator, non-inferiority criteria for PCV15 and PCV20 versus PCV13 were set at less than 1:1 for their 13 shared serotypes.
- In clinical trials the immune response generated by PCV15 is lower than that generated by PCV13 for 13 shared serotypes except for serotype 3 for which the response is significantly

higher. PCV15 generates an immune response for two additional serotypes. In a clinical trial comparing immunogenicity outcomes for PCV13 and PCV15 in infants on a 2+1 schedule, non-inferiority criteria were met for the majority of serotypes at dose two and all serotypes by dose three.

- In clinical trials the immune response generated by PCV20 is lower than that of PCV13 for 13 shared serotypes. PCV20 generates an immune response for five additional serotypes. In a clinical trial comparing immunogenicity outcomes for PCV13 and PCV20 in infants on a 2+1 schedule, non-inferiority criteria were not met for 11 serotypes after dose two, but were met for the majority of serotypes by dose three.
- Clinical trial results support the interchangeability of PCV15 with PCV13 in infants in terms of safety and immunogenicity for the 13 shared serotypes.
- PCV15 has been widely recommended internationally often interchangeably with PCV13. PCV20 is under review in many European countries including in Germany and in the UK and PCV20 has been recommended, along with PCV15, non-preferentially in the US in a 3+1 schedule and in Canada in either a 2+1 or a 3+1 schedule.

2. INTRODUCTION

Invasive pneumococcal disease (IPD) is a severe infection caused by *Streptococcus pneumoniae* (pneumococcus), which can lead to conditions such as meningitis, bacteraemia, and pneumonia. It primarily affects young children, older adults, and individuals with immunocompromising conditions, often resulting in high morbidity and mortality. The disease is transmitted through respiratory droplets, and its burden is influenced by the circulating serotypes of pneumococcus. Vaccination has proven to be an effective strategy in reducing the incidence of IPD.

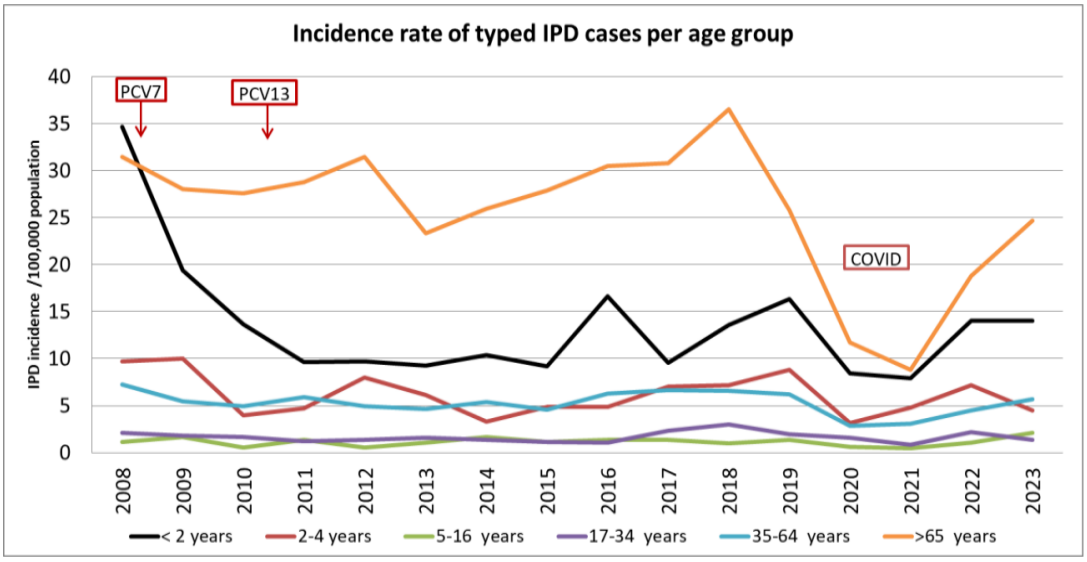
In 2008, the seven-valent pneumococcal conjugate vaccine (PCV7) was introduced into the Irish Primary Immunisation Schedule, with the thirteen-valent PCV (PCV13) replacing it in 2010. These vaccines have demonstrated safe and effective protection against IPD in young children. In addition to direct protection, herd immunity effects have been observed, with reductions in vaccine-type IPD among older adults. However, over time, serotype replacement has emerged, leading to an increase in IPD cases caused by non-vaccine serotypes. In response, higher-valency PCV vaccines have been developed to address this challenge.

Recently, two new pneumococcal conjugate vaccines, PCV15 (Vaxneuvance, MSD) and PCV20 (Prevenar20, Pfizer), have been approved for use in children in the European Union. NIAC has reviewed the clinical trial data for these vaccines, considering them alongside local IPD epidemiology to inform these updated recommendations. This review presents a summary of the evidence that guided these recommendations.

3. EPIDEMIOLOGY

Invasive pneumococcal disease, defined as isolation of *Streptococus pneumonie* or detection of *Streptococcus pneumoniae* nucleic acid or antigen from a normally sterile site is reportable to the HPSC. Laboratory isolates are sent for typing to the Irish Meningococcal and Sepsis Reference Laboratory (IMSRL). It is likely that the incidence of typed IPD underestimates the true burden of infection. The incidence of typed IPD in children less than two years of age decreased from approximately 35 per 100,000 per year to 10-15 per 100,000 per year in 2010 following introduction of pneumococcal vaccination in 2008. Adults aged over 65 years are now the group with the highest incidence of IPD. Both groups experienced a decrease in incidence during 2020 and 2021 likely secondary to the impact of the COVID-19 pandemic and related public health measures aimed at controlling infection. As shown in Figure 1 below, this decrease was greater in older adults. IPD is relatively uncommon in children over five years of age.

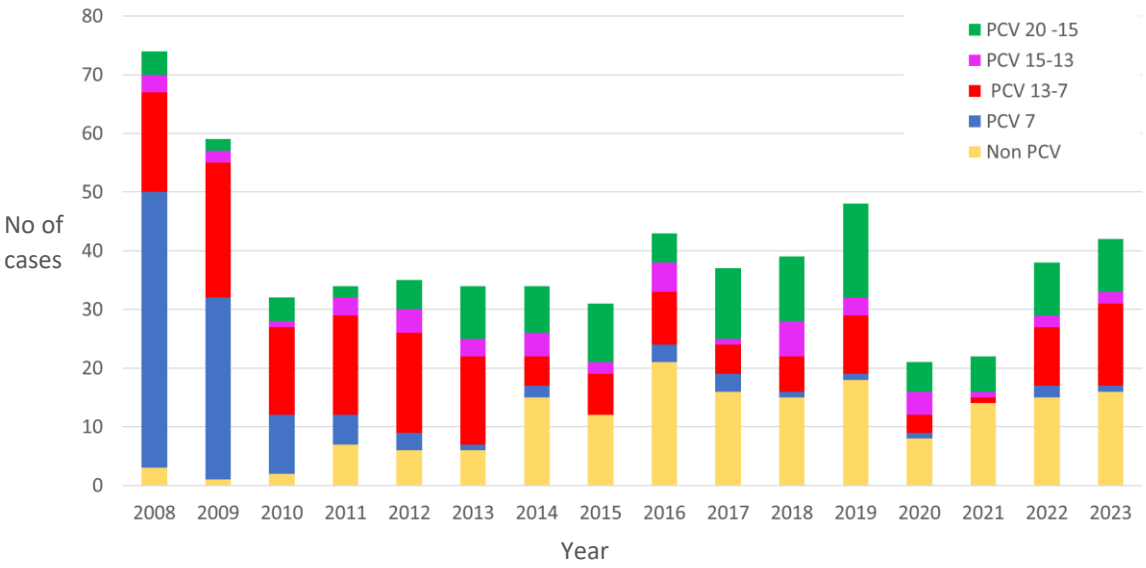
Figure 1. Incidence rate of typed IPD isolates based on patient age from 2008-2023. Source: IMSRL.[1]



Seroepidemiology

Following the introduction of PCV7 in 2008 there was a decrease in the number of PCV7 serotype cases. Following PCV13 introduction in 2010 there was also a decrease in PCV13 unique serotypes, although the decrease was smaller than that following PCV7 introduction. In addition, it should be noted that there was an increase in non-PCV serotypes. Figure 2 depicts paediatric IPD cases from 2003 to 2023 by vaccine serotype group. PCV15-13 serotypes (shown in pink) are also included in the PCV20 vaccine. In total during this time there were 623 cases of paediatric IPD. Of these, 7.4% (n=46) of cases were caused by the two additional serotypes included in PCV15, and 26% (n=163) were caused by the additional seven serotypes included in PCV20.[2]

Figure 2. Paediatric IPD cases in children aged <16 years from 2008 to 2023 grouped by specific vaccine and non-vaccine serotypes. Source: IMSRL.[2]

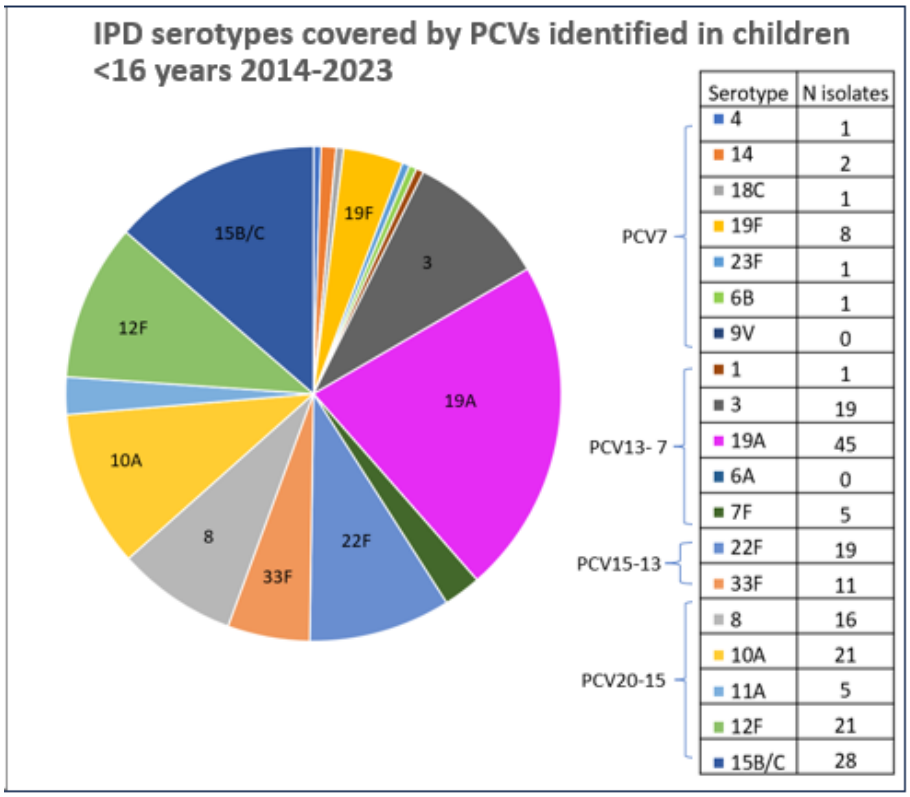


Serotypes covered by PCV7: 4, 6B, 9V, 14, 18C, 19F, 23F. Additional serotypes covered by PCV13: 1, 3, 5, 6A, 7F, 19A
Additional serotypes covered by PCV15: 22F, 33F. Additional serotypes covered by PCV20: 8, 10A, 11A, 12F, 15B

Of the serotypes covered by PCV13, the vaccine currently in use in Ireland, the two serotypes which have caused the most cases are 3 and 19A, (Figure 3). Between 2014 and 2023 there were 19 cases of serotype 3 and 45 cases of serotype 19A. The increase in 19A was thought at least in part to be due to a unique Irish clone identified on whole genome sequencing which was associated with vaccines failures.[3] Serotype 3 has been associated with lower vaccine responses and higher levels of antibiotic resistance in recent years.[4 5] In Ireland the number of serotype 3 cases in children has generally increased since 2015, similar to what has been observed internationally.[1]

Regarding serotypes that could potentially be covered by newer PCVs, the serotypes which represented higher numbers of cases include serotype 22F which is covered by PCV15 and PCV20, but not PCV13, was identified in 19 paediatric cases between 2014 and 2023. In addition, serotypes 10A, 12F and 15B/C which are covered by PCV20 but not PCV15 accounted for 21, 21 and 28 cases of paediatric IPD respectively, over the same time period. (Figure 3)[6]

Figure 3. PCV serotypes causing IPD in Ireland in children <16 years of age from 2014 - 2023. Source: IMSRL.[6]

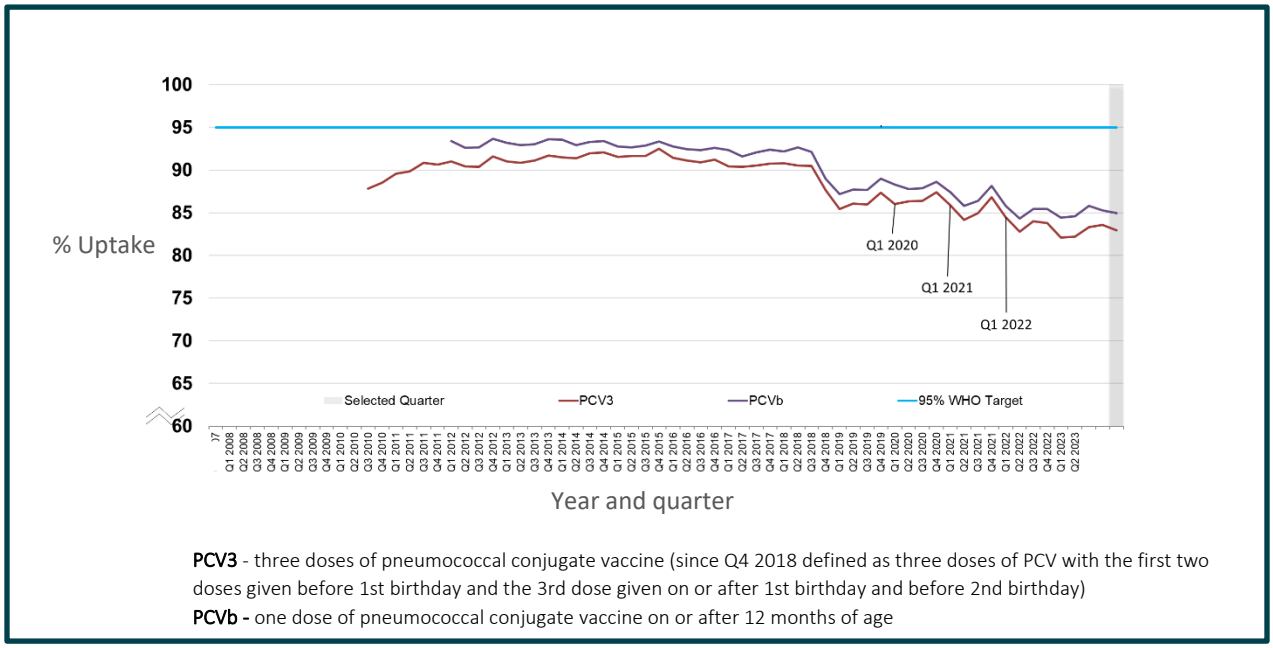


Serotype	N isolates
4	1
14	2
18C	1
19F	8
23F	1
6B	1
9V	0
1	1
3	19
19A	45
6A	0
7F	5
22F	19
33F	11
8	16
10A	21
11A	5
12F	21
15B/C	28

4. VACCINE UPTAKE

In quarter one 2024 the uptake rate for two doses of PCV by 12 months of age was 86.4% nationally. The uptake of three doses by 24 months of age was 83% nationally. Uptake of PCV peaked in 2015 at 92.5% and has been on a general decline since as shown in Figure 4.[7]

Figure 4. Uptake of PCV by 24 months in Ireland, 2008-2023. Source: Adapted from HPSC.[7]



PCV3 - three doses of pneumococcal conjugate vaccine (since Q4 2018 defined as three doses of PCV with the first two doses given before 1st birthday and the 3rd dose given on or after 1st birthday and before 2nd birthday)
PCVb - one dose of pneumococcal conjugate vaccine on or after 12 months of age

5. PNEUMOCOCCAL VACCINES

PCV15 contains the 13 serotypes already covered in PCV13 with an additional two serotypes; 22F and 33F. PCV20 contains the PCV15 serotypes with an additional 5 serotypes; 8, 10A, 11A, 12F and 15B. Figure 5 summarises the serotype coverage of available pneumococcal vaccines. Of note PPV23 is not used in children less than two years of age.

Figure 5. Pneumococcal vaccines by serotype coverage.

Vaccine	Serotype																							
	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F	33F	8	10A	11A	12F	15B	2	9N	17F	20
PCV13 Pfizer	■	■	■	■	■	■	■	■	■	■	■	■	■											
PCV15 Merck	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■									
PCV20 Pfizer	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■				
PPV23 Merck	■	■	■	■		■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■	■

For both PCV15 and PCV20, numerous clinical trials have been undertaken. Safety and immunogenicity were compared to that of PCV13. As the Primary Immunisation Schedule in Ireland includes PCV vaccination in a 2+1 schedule, i.e., two doses in infancy and one dose in the second year of life, this review focuses on summarising the trials for each vaccine in which a 2+1 schedule was implemented.

6. VACCINE SAFETY

The tolerability and safety of PCV15 and PCV20 was generally comparable to that of PCV13 with no clinically relevant differences or concerns from clinical trials reported to date.

PCV15

The safety of PCV15 in paediatric populations without underlying conditions compared to PCV13 has been assessed in seven clinical trials.[8-15] GRADE assessment of studies conducted by the Canadian National Advisory Committee on Immunization (NACI) concluded that in vaccine naive infants there was moderate to high certainty evidence of little to no difference between the PCV15 and PCV13 groups in terms of serious adverse events (SAEs). [16] A further integrated analysis of four of the trials which had a similar design, conducted by NACI, found that the proportions of participants with local and systemic AEs (solicited and unsolicited) after each dose in the primary series, after the booster dose, and after any dose were similar in both the PCV15 and PCV13 groups. In infants, the most frequently reported AEs after any dose of PCV15 were irritability (range: 47% to 55.1%), somnolence (22.8% to 40.7%), injection-site pain (19.1% to 27.1%), and decreased appetite and other injection site reactions (less than 20%). SAEs were reported for 10% (n=358) of PCV15 recipients and 10.5% (n=217) of PCV13 recipients. While the majority of SAEs were deemed to be non-vaccine related, there were three vaccine-related SAEs reported in two participants in the PCV15 group and one participant in the PCV13 group (all were pyrexia requiring hospitalisation). There were four deaths (2 in PCV13 and 2 in PCV15 recipients), of which none were considered to be related to either of the vaccines.[16]

One trial reported a significantly higher proportion of some solicited AEs in the PCV15 group versus the PCV13 group such as injection site pain (69% vs 61%), erythema (44% vs 36%), irritability (75% vs 69%) and decreased appetite (42% vs 36%), however the between group differences were small (<8%) and are not considered to be clinically significant. The majority of experienced AEs were of mild-to-moderate intensity and lasted ≤3 days.[17]

PCV20

The safety of PCV20 in paediatric populations without underlying conditions compared to PCV13 has been assessed in four clinical trials.[18-21] A GRADE assessment of PCV20 trials completed by NACI concluded that there was low to moderate certainty evidence of little to no difference between vaccines for solicited local and systemic AEs 1-7 days post-vaccination, AEs one month after each dose and SAEs up to six months following vaccination.[16] An integrated analysis, also conducted by NACI, of the four studies concluded the most commonly reported AEs in PCV20 recipients to be irritability (range 59.1% to 71.3%), somnolence (37.0% to 66.5%), injection site pain (33.5% to 46.3%), decreased appetite (22.7% to 26.0%), and other injection site reactions (15.1% to 24.7%).[16] There were no significant differences between PCV20 and PCV13 groups with respect to body temperature post vaccine dose.

SAEs were reported for 4.8% of PCV20 recipients and 4.5% of PCV13 recipients. While the majority of SAEs were assessed as non-vaccine related, one SAE with onset seven days after the first vaccine dose was assessed as possibly related to either PCV20 or one of the concomitant vaccines received. The study participant was hospitalised with fever, painful swelling in the right groin and a right inguinal hernia. Laboratory tests revealed elevated inflammatory markers (C-reactive protein and procalcitonin) and a negative blood culture. The study participant was treated with antibiotics in hospital and the event resolved. No deaths were reported in any of the PCV20 paediatric trials.[16]

7. VACCINE IMMUNOGENICITY

The immunogenicity PCV20 have been assessed in infants without underlying conditions using a 2+1 schedule in one clinical trial.[19] The immunogenicity of PCV15 has been assessed in infants without underlying conditions using a 2+1 schedule in two clinical trials with very similar results.[8] [15]

PCV15

The immunogenicity induced by PCV15 in infants on a 2+1 schedule was studied in a phase 3 randomised double blinded study, conducted in Europe and Australia including 1,207 participants, who were 42-90 days old at dose one. In the study healthy infants were randomised 1:1 to receive PCV15 or PCV13 administered at 2, 4, and 11-15 months of age.[8]

Serotype specific IgG concentrations were measured one month after dose two and one month after dose three. Opsonophagocytic activity (OPA) was also assessed in a subset of participants. The primary study objective was to assess non-inferiority of PCV15 to PCV13 for geometric mean concentrations (GMC) of IgG and response rates, which is the percentage of participants with predefined serotype specific concentrations by 30 days post dose. The serotype specific immune response of 13 matched serotypes and two additional serotypes were directly compared. Predefined target IgG concentrations were ≥0.35 µg/mL, for all serotypes.

At one month after the second dose, non-inferiority was not met for two of the 13 shared serotypes (6A,9V) regarding the percentage of participants with predefined IgG concentrations. Following dose three, non-inferiority regarding the percentage of participants with predefined IgG concentrations was met for all serotypes. Regarding IgG geometric mean concentration ratios (GMR)s, after dose two, non-inferiority was not met for two of the shared serotypes (6A, 9V). Following the third dose this non-inferiority criterion was met for all serotypes. IgG GMCs achieved with PCV15 were lower than those achieved with PCV13 for all shared serotypes except serotype 3. Also, a higher proportion of infants in the PCV15 group reached the predefined target IgG concentrations for serotype 3 than in the PCV13 group, after both dose two and dose three. This difference was more pronounced post dose two than dose three. For the two additional

serotypes covered in PCV15 and not in PCV13, the immune response achieved for serotype 33F was low post dose two and while the percentage of infants meeting the target IgG threshold of ≥0.35 µg/mL for serotype 22F was 96%, it was 49% for 33F. By dose 3 the IgG GMC for 33F was more comparable to that of other targeted serotypes and the response rate had increased to 100% for 22F and 99% for 33F. See Appendix 1, figure A1 and A2 for a graphical representation of immunogenicity results.

At both 30 days post dose two and post dose three, serotype-specific OPA GMTs were generally comparable for the 13 shared serotypes between the vaccination groups and were higher for the two additional serotypes (22F and 33F) in the PCV15 group compared with the PCV13 group.

PCV20

PCV20 immunogenicity was studied in a phase 3 randomised double blinded study, conducted at 58 centres in 9 countries including 1,184 participants, with a mean age of 68 (43–112) days at dose one. Healthy infants were randomised 1:1 to receive PCV20 or PCV13 in a 2+1 schedule, dose one was administered at enrolment, with a second dose eight weeks later and a third dose at 11-12 months of age.[19]

Serotype specific IgG concentrations were measured one month after dose two and, before and one month after dose three. OPA was also assessed in a selected subset. The primary objective was to assess non-inferiority of PCV20 to PCV13 for GMC of IgG and for percentage of participants with predefined serotype specific concentrations. The 13 matched serotypes were compared to PCV13 responses, the seven unique serotypes were compared with the lowest result among the 13 matched serotypes. Predefined IgG target concentration was ≥0.35 µg/mL for all serotypes, except for serotypes 5 (≥0.23 µg/mL), 6B (≥0.10 µg/mL) and 19A (≥0.12 µg/mL).

At one month after the second dose, PCV20 met non-inferiority for nine of the twenty serotypes regarding the percentage of participants with predefined IgG concentrations; five of these were serotypes unique to PCV20, and four were shared serotypes. Non-inferiority was not met for serotypes 1, 3 ,4, 5, 6A, 6B, 9V, 18C, 23F, 10A and 12F. Following dose three non-inferiority was met for 19 out of the 20 serotypes. Non-inferiority was not met for serotype 3.

Regarding IgG concentration GMRs, after dose two non-inferiority was met for 16 of the 20 serotypes. Non-inferiority was not met for serotypes 6A, 6B, 9V and 23F. Following the third dose non-inferiority was met for 19 out of the 20 serotypes. Non-inferiority was not met for serotype 6B. See Appendix 1 Figure A3 for a graphical representation of vaccine performance to non-inferiority criteria.

OPA titres were assessed in a smaller number of participants with the number of valid assay results for specified serotypes ranging between 72-116 for PCV20 and 92-118 for the PCV13 group. The OPA geometric mean titres for the 13 matched serotypes one month after dose two

and dose three were similar in both vaccine groups. For the additional seven serotypes that are unique to PCV20, the OPAs were substantially higher in the PCV20 group.

Direct comparisons between PCV15 and PCV20 are difficult to make due to differences in study designs. However, a 2024 Canadian study computed and compared functional OPA titres, measured in the same and different randomised trials, for PCV20 and PCV15, following the third dose in a 2+1 schedule. The ratio of mean geometric OPA titres one month after the toddler dose for PCV15/PCV13 was 0.75, and for PCV20/PCV13 which was 0.72. This suggests that in terms of functional capacity of antibodies PCV15 and PCV20 may be comparable following the toddler dose of a three dose (2+1) schedule.[22]

8. INTERCHANGEABILITY

The interchangeability of PCV13 with PCV15 has been studied in a phase 3, controlled trial of 900 healthy infants in a 3+1 schedule randomised to five different intervention groups as per Table 1. Vaccines were also administered concomitantly with other routine childhood immunisations.[14]

Table 1. Dosing schedule of different intervention groups in PCV15 (V114) and PCV13 interchangeability trial. Source: Bili et al.[14]

	Dose 1	Dose 2	Dose 3	Dose 4
Group 1	PCV13	PCV13	PCV13	PCV13
Group 2	PCV13	PCV13	PCV13	V114
Group 3	PCV13	PCV13	V114	V114
Group 4	PCV13	V114	V114	V114
Group 5	V114	V114	V114	V114

Frequencies of injection-site and systemic AEs were generally comparable across all intervention groups. At 30 days post dose 4, IgG GMCs for the 13 shared serotypes were generally comparable between mixed PCV15/PCV13 and 4-dose regimens of PCV13 or PCV15. In mixed regimens at 30 days post dose 4, a toddler dose of PCV was sufficient to achieve IgG GMCs comparable to a 4-dose regimen of PCV15 for serotype 22F, while at least one infant dose was needed in addition to the toddler dose to achieve IgG GMCs comparable to a 4-dose regimen of PCV15 for serotype 33F.

9. VACCINE EFFECTIVENESS

At the time of consideration, no efficacy or effectiveness studies on PCV15 or PCV20 have been published. NIAC will endeavour to review efficacy and effectiveness data when they become available.

10. MODELLING

There are no independent modelling studies using a 2+1 schedule. In the UK the use of PCV15 or PCV20 in a 1+1 schedule was modelled. The study found that the introduction of PCV15 to the childhood schedule could lead to an increase of IPD in the population overall and that the introduction of PCV20 could decrease overall IPD rates in the population. This was due to the modelled impact of reduced efficacy against carriage and emergence of non-vaccine serotypes. The model had several limitations. The model was dependent on assumptions about the efficacy of both vaccines which are limited as correlates between immunogenicity and efficacy are not clearly defined. The model only addressed a 1+1 schedule and assumed that adult recommendations remained unchanged.[23]

11. INTERNATIONAL POSITIONS

Table 2: International Positions.

Country	Vaccine	Recommended schedule	Notes
Germany[24]	PCV13 or PCV15	2+1 schedule for term infants 3+1 schedule for preterm infants	Currently reviewing PCV20
France[25]	PCV13 or PCV15	2+1 schedule 2, 4 and 11 months Catch up 12-23 months 2 doses 3+1 for preterm	
Belgium[26]	PCV13 or PCV15 - non preferential	2+1 schedule at 2, 4 and 12 months	
UK[27]	PCV13 or PCV15	1+1 schedule 0.5ml at 12 weeks, booster 0.5ml at 1 year	PCV20 under consideration by JCVI
Australia[28]	PCV13 or PCV15 - non preferential	2+1 schedule	Currently reviewing PCV20
Netherlands[29]	PCV13 or PCV15	2+1 schedule	PCV20 has not yet been considered
Europe[30]	No country in Europe has published a recommendation for paediatric PCV20 to date		
Canada[31]	PCV15 or PCV20 Preferential recommendation for PCV20 for high risk	2+1 schedule 2, 4 and 12 months or **3+1 schedule** 2, 4, 6 months and 12-15 months	Strong recommendation, March 2024 Analysis includes SR of modelling
USA[32]	PCV15 or PCV20	**3+1 schedule**	

12. DISCUSSION

Invasive pneumococcal disease continues to be an important cause of morbidity in children in Ireland and throughout the world. With the introduction of the first pneumococcal conjugate vaccine (PCV7) to Ireland in 2008 a significant decline in IPD was seen, this decline continued, although more modest, with the expansion of coverage provided by PCV13. Despite the progress made through vaccination, IPD continues to be a problem for children in Ireland. This is due to both serotype replacement with pathogenic non-vaccine serotypes and poor efficacy of PCV13 against certain virulent vaccine serotypes, such as 19a and 3.

To be licensed for use in Europe, new PCVs must demonstrate non-inferiority to the current PCV in use. As valency of PCV vaccines increase, immunogenicity appears to decrease. PCVs are licensed based on immunogenicity data and to date there are no available efficacy or effectiveness data for either PCV15 or PCV20. Correlates of protection against IPD are not clearly established, thus caution must be taken when issuing recommendations for these newer extended valent PCVs in the absence of efficacy and effectiveness data.

While PCV20 has the potential to offer broader serotype protection, the decreased immunogenicity demonstrated in clinical trials particularly after dose 2 is of concern. PCV20 did not meet non-inferiority criteria after dose 2 for 11 serotypes and thus the EMA licensed PCV20 only for use in a 3+1 schedule, meaning three doses given before 6 months of age followed by a booster dose given at least six months after the last primary dose. On the other hand, PCV15 was licensed for use in either a 3+1 or 2+1 schedule. Invasive pneumococcal disease under 12 months of age causes significant morbidity and thus the potential for an increase in cases due to decreased immunogenicity of PCV20 is considered an important potential risk. In the absence of effectiveness data, there is currently insufficient evidence to support recommending PCV20 for use in a 2+1 schedule. There is also insufficient evidence to consider a switch to a 3+1 schedule at present. Adding an additional dose of a vaccine to the childhood schedule has major cost and implementation implications and should not be considered in the absence of efficacy and effectiveness data if there is not an urgent public health need. PCV15 provides coverage for two additional serotypes and PCV15 demonstrated an increased immunogenicity to serotype 3 compared with PCV13. However, it is not yet clear if this will lead to increased efficacy as the immune correlate of protection for serotype 3 is unknown. On the other hand, while PCV15 met non-inferiority criteria for all other shared PCV13 serotypes after dose 3, immune responses were lower than PCV13. For these reasons, at present there is insufficient evidence to give a preferential recommendation for PCV15 above PCV13.

As highlighted in previous NIAC recommendations, the decline in uptake of the primary childhood schedule is a concern, and good uptake particularly of the 13-month PCV dose is critical to its impact. It is also important that accurate and timely data on PCV uptake is available so that

changes in seroepidemiology can be interpreted in the correct context. As per prior NIAC recommendations, NIAC again highlights the urgent need for a single, unique, integrated vaccination database in Ireland. NIAC strongly supports the work that has already commenced to develop such a database.

The uncertainties around the effectiveness of extended valent PCVs, are occurring against a backdrop of changes in pneumococcal epidemiology following the effects of the pandemic, that may not yet be stable. Pneumococcal epidemiology can be difficult to predict, and it is uncertain how decreased immunogenicity of extended valent vaccines may impact carriage and emergence of both vaccine and non-vaccine type serotypes. PCV20 and PCV15 are also licensed in adults, and it is anticipated that a new 21 valent vaccine may be licensed for adults in Europe towards the beginning of next year. The vaccines used in children will indirectly impact rates of IPD in adults and serotype distribution. Pneumococcal vaccines with lower immunogenicity are likely to be less effective against carriage and thus will offer less indirect protection to older adults than earlier lower valent PCVs. Continued pneumococcal serotype surveillance will be critical in the coming years as changes are made to both childhood and adult pneumococcal vaccine schedules.

Based on the current available evidence, NIAC recommends the use of either PCV13 or PCV15 for pneumococcal conjugate vaccination according to the 2+1 routine childhood schedule. This recommendation may change once effectiveness data are available for PCV15 and PCV20. NIAC will continue to review emerging evidence on PCVs in children and adults and will update recommendations accordingly.

ACKNOWLEDGEMENTS

NIAC would like to thank all the individuals and organisations who provided data, time, advice and information in support of this work.

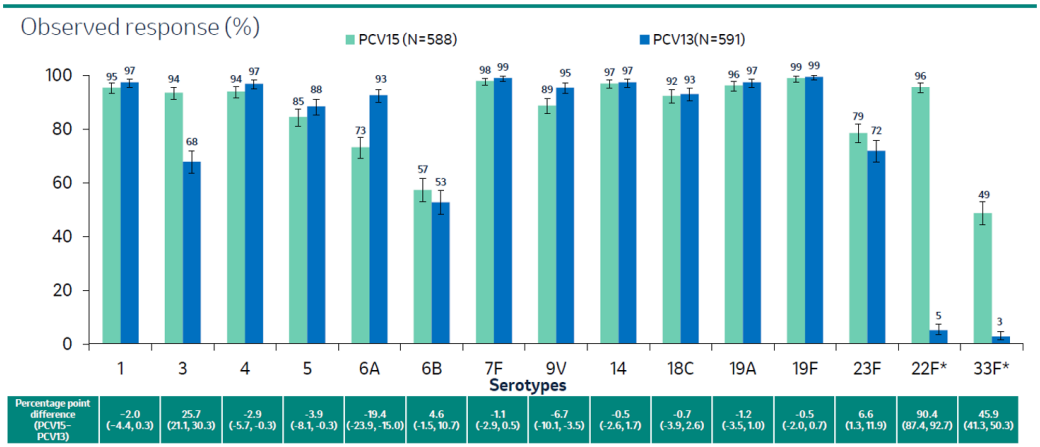
APPENDICES

Appendix 1: Immunogenicity results' figures

1. PCV15 phase III clinical trial with 2+1 vaccination schedule

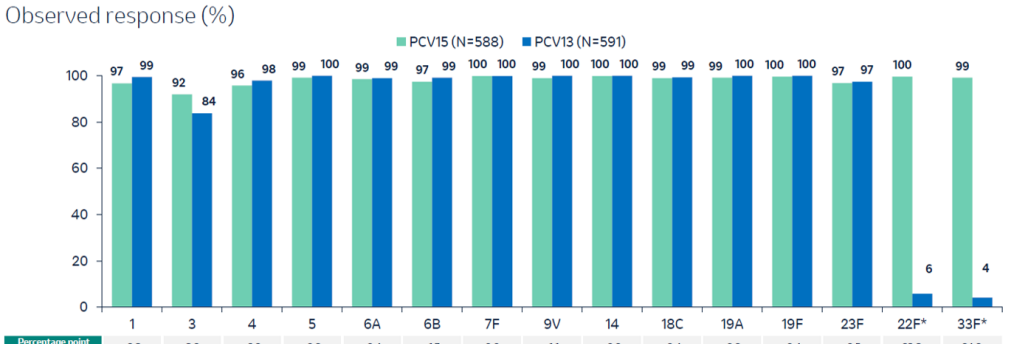
Figure A1 (A-D). Immunogenicity results from PCV15 phase II clinical trial using a 2+1 vaccination schedule. **A** Percentage of infants meeting target IgG threshold (≥ 0.35) ug/mL) one month post dose 2, **B** Percentage of infants meeting target IgG threshold (≥ 0.35) ug/mL) one month post dose 3, **D** Serotype specific IgG geometric mean concentrations (GMC)s post dose 2. Source: MSD.[33]

A. Post Dose 2: Percentage of participants with IgG≥0.35µg/mL by serotype



Serotype	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F*	33F*
Percentage point difference (PCV15–PCV13)	-2.0 (-4.4, 0.3)	25.7 (21.1, 30.3)	-2.9 (-5.7, -0.3)	-3.9 (-8.1, -0.3)	-19.4 (-23.9, -15.0)	4.6 (-1.5, 10.7)	-1.1 (-2.9, 0.5)	-6.7 (-10.1, -3.5)	-0.5 (-2.6, 1.7)	-0.7 (-3.9, 2.6)	-1.2 (-3.5, 1.0)	-0.5 (-2.0, 0.7)	6.6 (1.3, 11.9)	90.4 (87.4, 92.7)	45.9 (41.3, 50.3)

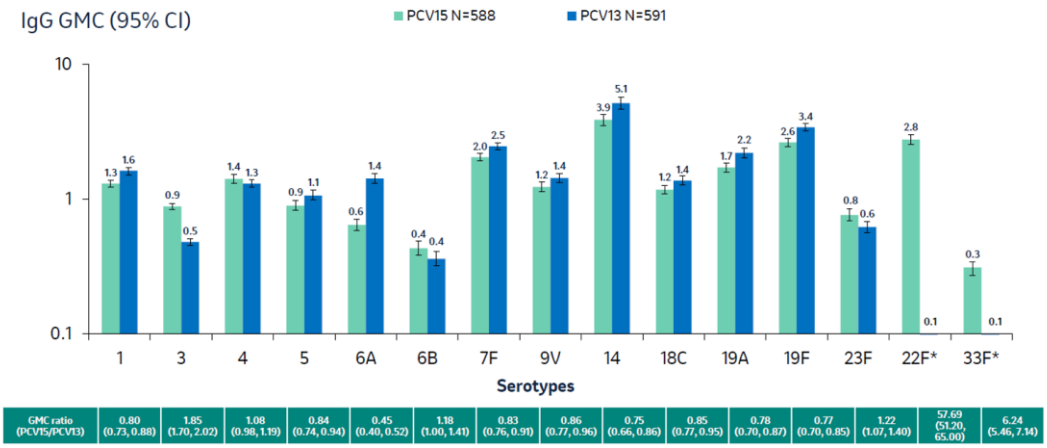
B. Post Dose 3: Percentage of participants with IgG≥0.35µg/mL by serotype



Serotype	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F	22F*	33F*
Percentage point difference (PCV15 –PCV13)	-2.8 (-4.7, -1.3)	8.2 (4.4, 12.2)	-2.2 (-4.5, -0.1)	-0.9 (-2.2, -0.2)	-0.4 (-1.9, 1.1)	-1.7 (-3.5, -0.1)	0.0 (-0.9, 0.9)	-1.1 (-2.4, -0.4)	-0.2 (-1.0, 0.5)	-0.4 (-1.8, 0.9)	-0.9 (-2.2, -0.2)	-0.4 (-1.3, 0.3)	-0.5 (-2.7, 1.5)	93.8 (91.5, 95.6)	94.9 (92.7, 96.5)
P-value (1-sided)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Error bars indicate 95% CIs; CI=confidence interval; *Serotypes not included in Prevnar* 13 ; IgG=immunoglobulin G; PD3 = post dose 3; PTD = post toddler dose.

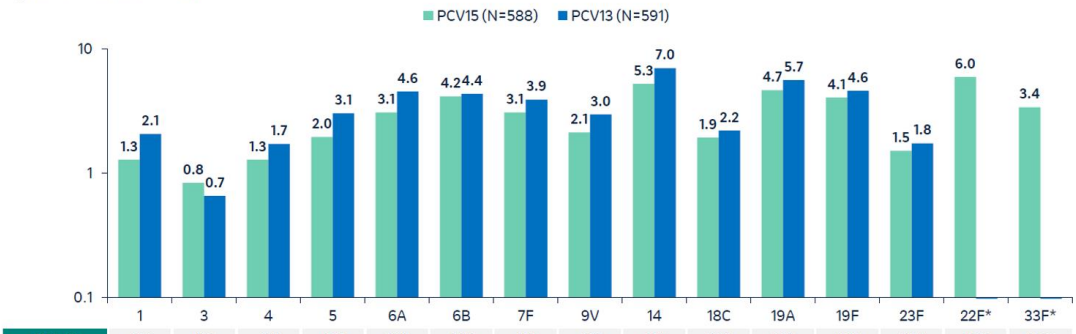
C. Post Dose 2: IgG geometric mean concentrations (GMC) by serotype



GMC ratio (PCV15/PCV13)	0.80 (0.73, 0.88)	1.85 (1.70, 2.02)	1.08 (0.98, 1.19)	0.84 (0.74, 0.94)	0.45 (0.40, 0.52)	1.18 (1.00, 1.41)	0.83 (0.76, 0.91)	0.86 (0.77, 0.96)	0.75 (0.66, 0.86)	0.85 (0.77, 0.95)	0.78 (0.70, 0.87)	0.77 (0.70, 0.85)	1.22 (1.07, 1.40)	57.69 (51.20, 65.00)	6.24 (5.46, 7.14)

GMC = geometric mean concentration (µg/mL). *Serotypes not included in Prevnar 13™; PD2 = post dose 2; PPS = post primary series

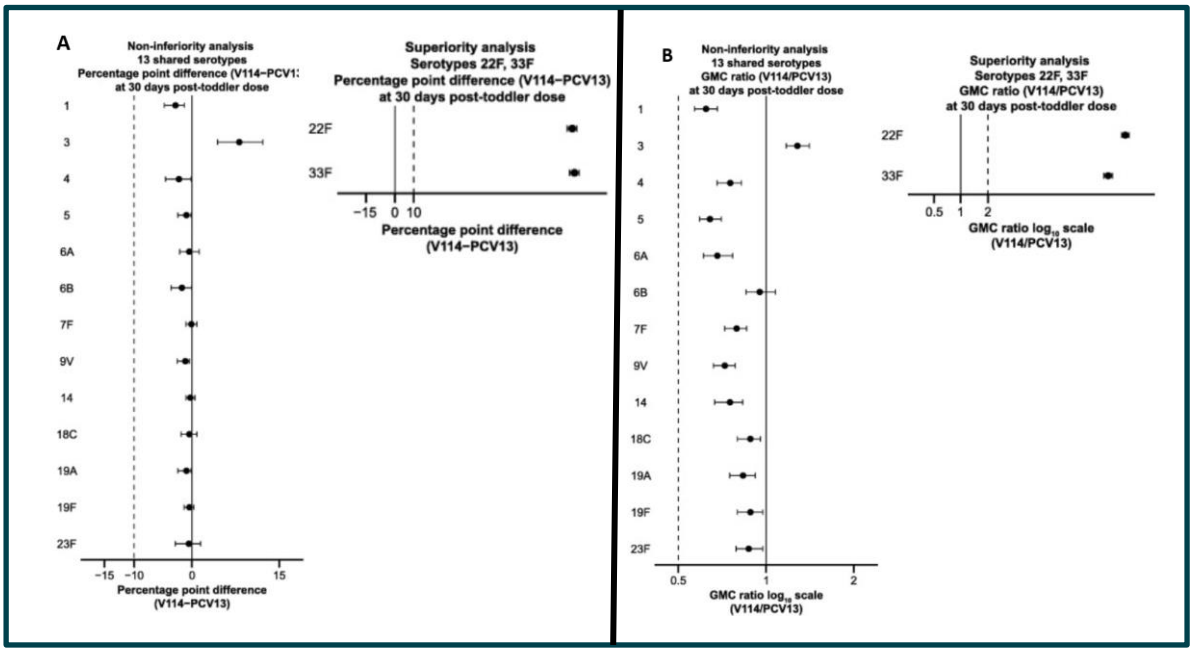
D. Post Dose 3: IgG geometric mean concentrations (GMC) by serotype



GMC ratio (PCV15/PCV13)	0.62 (0.57, 0.68)	1.28 (1.17, 1.39)	0.75 (0.68, 0.82)	0.64 (0.59, 0.70)	0.68 (0.61, 0.76)	0.95 (0.85, 1.07)	0.79 (0.72, 0.85)	0.72 (0.66, 0.78)	0.75 (0.67, 0.83)	0.88 (0.80, 0.95)	0.83 (0.75, 0.91)	0.88 (0.80, 0.97)	0.87 (0.79, 0.97)	71.97 (65.16, 79.10)	46.58 (42.19, 51.42)
P-value (1-sided)	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

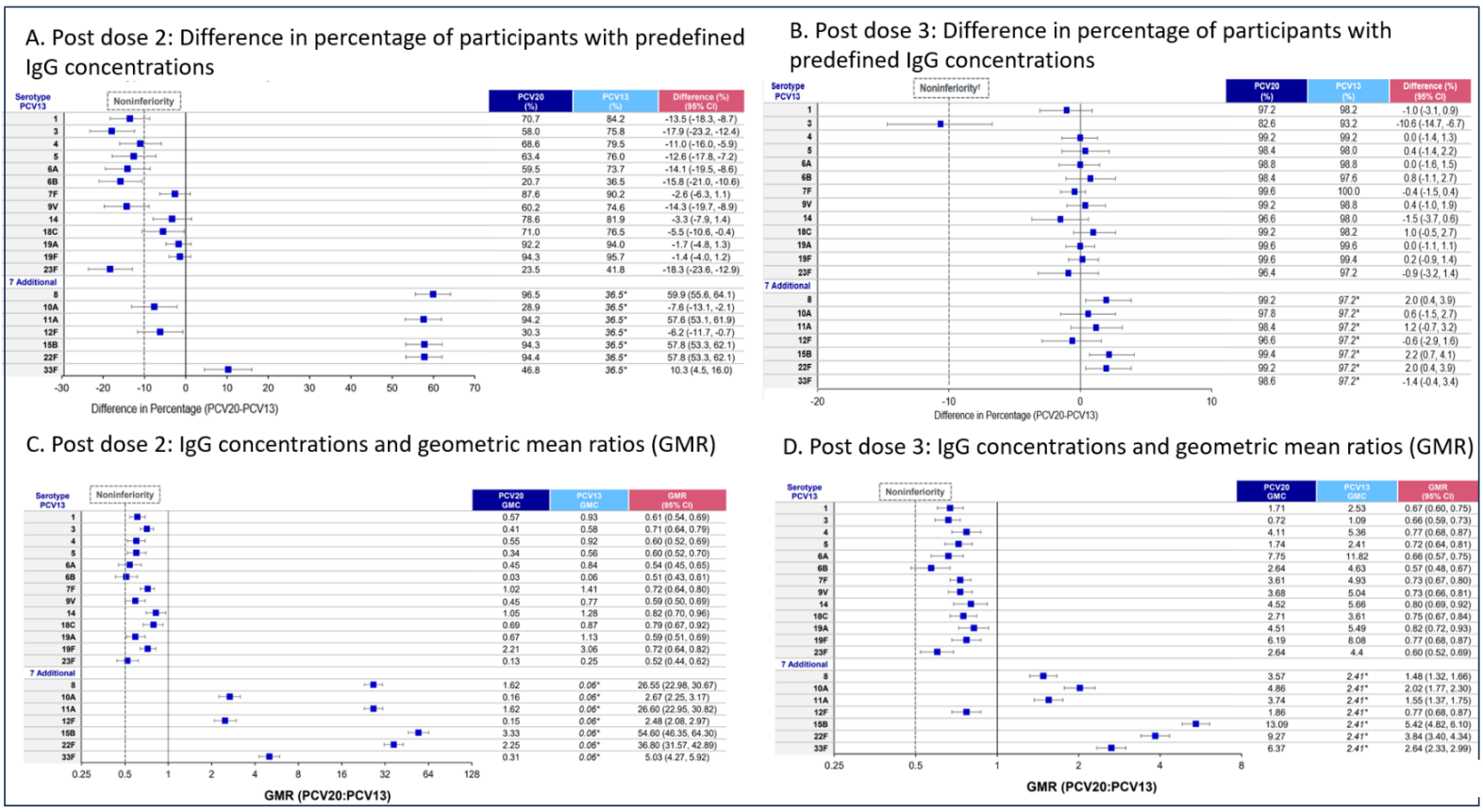
Error bars indicate 95% CIs; CI=confidence interval; *Serotypes not included in Prevnar* 13; GMC = geometric mean concentration (µg/mL); IgG=immunoglobulin G; PD3 = post dose 3; PTD = post toddler dose.

Figure A2. A; Forest plot of the proportions of participants with serotype-specific anti-PnP IgG response rates at 30 days PTD. B; Forest plot of the proportions of participants with serotype-specific anti-PnP IgG GMCs at 30 days post toddler dose. V114 = 15-valent pneumococcal conjugate vaccine. Source: Martinon-Torres, Vaccine 2024.[8]



2. PCV20 phase III clinical trial with 2+1 vaccination schedule

Figure A3. Difference in percentage of participants with predefined IgG concentrations after dose 2 (A) and after dose 3 (B). IgG concentrations and geometric mean ratios after does 2 (C) and after does 3 (D). Source: Pfizer.[34]



REFERENCES

1. Health Protection Surveillance Centre (HPSC); Irish Meningitis & Sepsis Reference Laboratory (IMSRL); Children's Health Ireland at Temple Street, Typing & Antimicrobial Susceptibilities of isolates causing Invasive Pneumococcal Disease (IPD) in Ireland – Results from 2022-2023: biennial report 2024 [Available from: https://www.lenus.ie/bitstream/handle/10147/642689/Irish%20IPD%20Report%202022-2023.%20July%202024.pdf?sequence=1&isAllowed=y.

2. Irish Meningitis & Sepsis Reference Laboratory. Data provided directly from IMSRL to NIAC. , 2024.

3. Corcoran M, Mereckiene J, Cotter S, et al. Using genomics to examine the persistence of Streptococcus pneumoniae serotype 19A in Ireland and the emergence of a sub-clade associated with vaccine failures. *Vaccine* 2021;39(35):5064-73. doi: https://doi.org/10.1016/j.vaccine.2021.06.017

4. Groves N, Sheppard CL, Litt D, et al. Evolution of Streptococcus pneumoniae Serotype 3 in England and Wales: A Major Vaccine Evader. *Genes* 2019;10(11):845. doi: doi:10.3390/genes10110845

5. Azarian T, Mitchell P, K, Georgieva M, et al. Global emergence and population dynamics of divergent serotype 3 CC180 pneumococci. *PLOS Pathogens* 2018 doi: https://doi.org/10.1371/journal.ppat.1007438

6. ISMRL. PCV serotypes causing IPD in Ireland in children less than <16 years of age from 2014 - 2023. Data provided directly to NIAC 2024 [

7. HPSC. Immunisation uptake statistics at 12 and 24 months of age 2024 [Available from: https://www.hpsc.ie/a-z/vaccinepreventable/vaccination/immunisationuptakestatistics/immunisationuptakestatisticsat12and24monthsofage/ accessed June 2024.

8. Martinon-Torres F, Wysocki J, Szenborn L, et al. A Phase III, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of V114 compared with PCV13 in healthy infants (PNEU-PED-EU-1). *Vaccine* 2023;41(21) doi: 10.1016/j.vaccine.2023.04.036

9. Banniettis N, Wysocki J, Szenborn L, et al. A phase III, multicenter, randomized, double-blind, active comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of catch-up vaccination regimens of V114, a 15-valent pneumococcal conjugate vaccine, in healthy infants, children, and adolescents (PNEU-PLAN). 2022;40(44) doi: 10.1016/j.vaccine.2022.09.003

10. Greenberg D, Hoover PA, Vesikari T, et al. Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV15) in healthy infants. *Vaccine* 2018;36(45) doi: 10.1016/j.vaccine.2018.02.113

11. Ishihara Y, Kuroki H, Hidaka H, et al. Safety and immunogenicity of a 15-valent pneumococcal conjugate vaccine in Japanese healthy infants: a Phase I study (V114-028). 2023;19(1) doi: 10.1080/21645515.2023.2180973

12. Lupinacci R, Rupp R, Wittawatmongkol O, et al. A phase 3, multicenter, randomized, double-blind, active-comparator-controlled study to evaluate the safety, tolerability, and immunogenicity of a 4-dose regimen of V114, a 15-valent pneumococcal conjugate vaccine, in healthy infants (PNEU-PED). *Vaccine* 2023;41(5) doi: 10.1016/j.vaccine.2022.12.054

13. Platt HL, Greenberg D, Tapiero B, et al. A Phase II Trial of Safety, Tolerability and Immunogenicity of V114, a 15-Valent Pneumococcal Conjugate Vaccine, Compared With 13-Valent Pneumococcal Conjugate Vaccine in Healthy Infants. 2020(1532-0987 (Electronic)) doi: 10.1097/INF.0000000000002765

14. Bili A, Dobson S, Quinones J, et al. A phase 3, multicenter, randomized, double-blind study to evaluate the interchangeability of V114, a 15-valent pneumococcal conjugate vaccine, and PCV13 with respect to safety, tolerability, and immunogenicity in healthy infants (PNEU-DIRECTION). 2023;41(3) doi: 10.1016/j.vaccine.2022.10.072

15. Benfield T, Rämet M, Valentini P, et al. Safety, tolerability, and immunogenicity of V114 pneumococcal vaccine compared with PCV13 in a 2+1 regimen in healthy infants: A phase III study (PNEU-PED-EU-2). *Vaccine* 2023;41(15):2456-65. doi: https://doi.org/10.1016/j.vaccine.2023.02.041

16. National Advisory Committee on Immunization (NACI). Recommendations for public health programs on the use of pneumococcal vaccines in children, including the use of 15-valent and 20-valent conjugate vaccines 2024 [Available from: https://www.canada.ca/en/public-health/services/publications/vaccines-immunization/national-advisory-committee-immunization-recommendations-public-health-programs-use-pneumococcal-vaccines-children-including-use-15-valent-20-valent-conjugate-vaccines.html accessed June 2024.

17. Banniettis N, Horn M, Sadarangani M, et al. Safety and Tolerability of V114 Pneumococcal Vaccine in Infants: A Phase 3 Study. *Pediatrics* 2023;152(1) doi: 10.1542/peds.2022-060428

18. Senders S, Klein NP, Lamberth E, et al. Safety and Immunogenicity of a 20-valent Pneumococcal Conjugate Vaccine in Healthy Infants in the United States. *Pediatric Infectious Disease Journal* 2021;40(10) doi: 10.1097/inf.0000000000003277

19. Korbal P, Wysocki J, Jackowska T, et al. Phase 3 Safety and Immunogenicity Study of a Three-dose Series of Twenty-valent Pneumococcal Conjugate Vaccine in Healthy Infants and Toddlers. *Pediatr Infect Dis J* 2024;43(6):587-95. doi: 10.1097/inf.0000000000004300

20. Pfizer. 20-valent Pneumococcal Conjugate Vaccine Safety and Immunogenicity Study of a 4-Dose Series in Healthy Infants 2022 [Available from: https://clinicaltrials.gov/study/NCT04382326 accessed June 2024.

21. Pfizer. 20-valent Pneumococcal Conjugate Vaccine Safety Study in Healthy Infants 2020 [Available from: https://clinicaltrials.gov/study/NCT04379713 accessed June 2024.

22. De Wals P. PCV13, PCV15 or PCV20: Which vaccine is best for children in terms of immunogenicity? *Can Commun Dis Rep* 2024;50(1-2):35-39. doi: 10.14745/ccdr.v50i12a04 [published Online First: 2024/04/24]

23. Choi YH, Bertran M, Litt DJ, et al. Potential impact of replacing the 13-valent pneumococcal conjugate vaccine with 15-valent or 20-valent pneumococcal conjugate vaccine in the 1 + 1 infant schedule in England: a modelling study. *The Lancet Public Health* 2024;9(9):e654-e63. doi: 10.1016/S2468-2667(24)00161-0

24. Robert Koch Institut (STIKO). Epidemiologisches Bulletin 4, 26 Jan 2023 2023 [Available from: https://www.rki.de/EN/Content/infections/Vaccination/recommandations/04_23_englisch.pdf?__blob=publicationFile accessed 22 Oct 2024.

25. Haute Autorite de Sante (France). Stratégie de vaccination contre les infections à pneumocoque - Place du vaccin VAXNEUVANCE chez l'enfant de 6 semaines à 18 ans. Vaccine recommendation. 2023 [Available from: https://www.has-sante.fr/jcms/p_3457417/en/strategie-de-vaccination-contre-les-infections-a-pneumocoque-place-du-vaccin-vaxneuvance-chez-l-enfant-de-6-semaines-a-18-ans accessed 22 Oct 2024.

26. Conseil Supérieur de la Santé (CSS). Pneumococcal vaccination in children and adolescents in Belgium 2023 [Available from: https://www.hgr-css.be/en/report/9746/pneumococcal-vaccination-in-children-and-adolescents accessed 15 Sept 2024.

27. Joint Committee on Vaccination and Immunisation (JCVI). Green Book Chapter 25: Pneumococcal 2023 [Available from: https://assets.publishing.service.gov.uk/media/64d68d6edd15ff000d278019/Green_Book_Chapter_25_Pneumococcal_27_7_23.pdf accessed 22 Oct 2024.

28. Australian Government Department of Health and Aged Care. Australian Immunisation Handbook, Pneumococcal Disease 2024 [Available from: https://immunisationhandbook.health.gov.au/contents/vaccine-preventable-diseases/pneumococcal-disease accessed 22 Oct 2024.

29. Health Council of the Netherlands. Pneumococcal vaccination of children (2023) 2023 [Available from: https://www.healthcouncil.nl/documents/advisory-reports/2023/06/20/pneumococcal-vaccination-of-children-2023 accessed 22 Oct 2024.

30. European Centre for Disease Prevention and Control. Pneumococcal Disease: Recommended vaccinations 2024 [Available from: https://vaccine-schedule.ecdc.europa.eu/Scheduler/ByDisease?SelectedDiseaseId=25&SelectedCountryIdByDisease=-1 accessed 22 Oct 2024.

31. National Advisory Committee on Immunisation (NACI). Recommendations for public health programs on the use of pneumococcal vaccines in children, including the use of 15-valent and 20-valent conjugate vaccines 2024 [Available from: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/vaccines-immunization/national-advisory-committee-immunization-recommendations-public-health-programs-use-pneumococcal-vaccines-children-including-use-15-valent-20-valent-conjugate-vaccines/naci-statement-2024-03-11.pdf accessed 22 Oct 2024.

32. Advisory Committee on Immunisation Practices (ACIP). ACIP Updates: Recommendations for the Use of 20-Valent Pneumococcal Conjugate Vaccine in Children — United States, 2023 2023 [Available from: https://stacks.cdc.gov/view/cdc/133252 accessed 10 Oct 2024.

33. MSD. Pneumococcal Polysaccharide 15-Valent Conjugate Vaccine (PCV15) Paediatric Clinical Development Programme presentation to NIAC, October 2023. 2023

34. Additional data provided to NIAC directly from Pfizer, April 2024; 2024.