

**BACKGROUND**

An infant 13-valent conjugate vaccine (PCV13) program was introduced in Ontario, Canada in December 2010 (Table 1). We assessed the epidemiology of invasive pneumococcal disease (IPD) among children in the period 2014-2022.

**Table 1:** Dates of authorization, public funding and recommended schedule for pediatric pneumococcal conjugate vaccines (PCV) in Ontario, Canada.

Month/Year	Authorization/Program funding
June 2001	PCV7 authorized – available on private market • By 6/2002: purchased doses 1 per child in birth cohort per year
January 2005	PCV7 publicly funded 4 dose infant vaccination program • Doses at 2,4,6,15-18 months
December 2008	PCV10 authorized
November 2009	PCV10 publicly funded 4 dose infant vaccination program • Doses at 2,4,6, 15-18 months • Children started on PCV7 to be continued on PCV7
December 2009	PCV13 authorized
November 2010	PCV13 publicly funded 3 dose vaccination program • Doses at 2,4,12 months • Children started on PCV7/10 should be switched to PCV13 • Catch-up for children aged 12-36 months: 1 dose PCV13 • High risk children should get 4 doses (2,4,6 and 12-15 months)

**METHODS**

TIBDN performs population-based surveillance for invasive pneumococcal disease (IPD) in Toronto and Peel Region (pop 4.5M) of Ontario. Microbiology laboratories serving area residents report sterile site isolates of *Streptococcus pneumoniae* to the study office; annual audits ensure completeness. Isolates are serotyped at the National Microbiology Laboratory. Population data is obtained from Statistics Canada, with estimates of prevalence of underlying conditions from ICES. Clinical and demographic information are collected by chart review and patient and physician interview. IPD incidence is adjusted for missing serotype results assuming that the distribution of serotypes is the same in missing isolates as in isolates with known serotypes.

Pneumococcal vaccination history is recorded based on immunization records provided by parents and/or physicians. Vaccination status is categorized as outlined in Table 2. A dose of vaccine is counted if it was received at least 14 days prior to positive culture date.

Cases of vaccine serotype disease were defined assessed by vaccine serotype group. Children were eligible for a vaccine based on their age and underlying illness relative to the introduction of particular vaccines. Among eligible children, IPD was categorized as vaccine failure (VF) if a child eligible for complete vaccination with an vaccine including the particular serotype was completely vaccinated, and as program failure (PF) if an eligible child was unvaccinated or incompletely vaccinated.

**Table 2:** Definitions of PCV vaccination schedule completion.

Category	Definition
Complete	• at least three PCV doses, with at least one dose received after 12 months of age, OR • two PCV doses with both received after 12 months of age
Up-to-date	• PCV doses were up to date for age but vaccination not complete
Incomplete	• at least 1 PCV dose received but not up-to-date for age.
Unvaccinated	• Eligible for PCV but no PCV dose received
Unknown	• Eligible for PCV but detailed vaccination history is not available

For analysis, serotypes (ST) were grouped as follows: PCV13 serotypes (1,3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F), PCV15 serotypes (additional serotypes 22F, 33F), PCV20 serotypes (additional 8, 10A, 11A, 12F, 15B), and non-PCV serotypes (those not included in any PCV vaccine). Serotypes 15B and 15C were grouped together as 15 B/C.

IPD incidence among populations with immunocompromising conditions, asthma, and chronic conditions without immunosuppression was estimated for children 5-17 years old (due to availability of prevalence estimates). Incidence rate ratios (IRR) for IPD among individuals with underlying conditions relative to healthy children was estimated (www.openepi.com).

**RESULTS**

In the nine years from 1/1/2014 to 31/12/2022, 373 IPD episodes were identified among children (<15 years), with 270 (70%) in children 0-4 years old. Clinical data were available for 349 (94%), and serotyping for 358 (96%).

124/349 (36%) children had an underlying illness predisposing to IPD, and 65 (19%) were immunocompromised (Table 3). Underlying conditions were more common among 5-14 year-olds than 0-4 year-olds: any condition 48% vs 31%,  $P=.002$ , immunocompromising illness 37% vs 12%,  $P<.0001$ . The most common underlying conditions were: leukemia (7.4%), asthma (6.9%), congenital cardiac disease (4.6%), organ transplantation (4.6%), and conditions that impair ability to clear respiratory secretions (4.3%).

Overall, 38 (11%) children required ICU admission, 25 (7%) had meningitis, 7 (2%) died. There were no statistically significant differences in clinical presentation and outcomes by age group (Table 3).

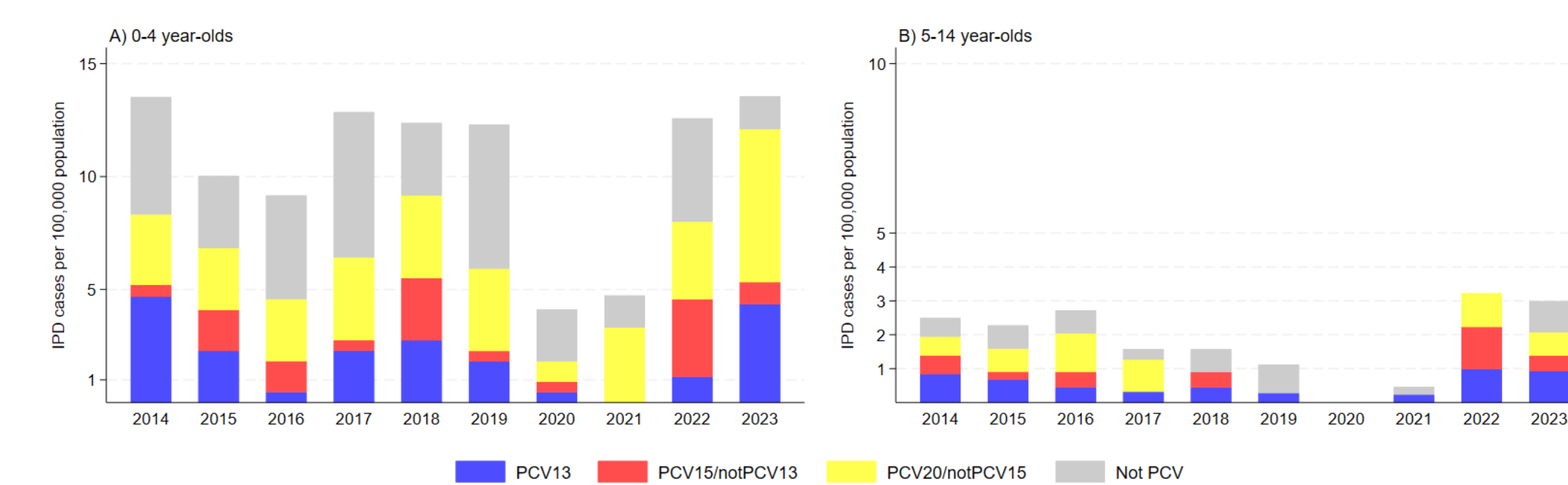
**Table 3:** Characteristics of children with IPD episodes, 2014-2022.

	0-4 years N=252	5-14 years N=97	All N=349
Sex at birth, female	101 (40%)	36 (37%)	137 (39%)
Clinical presentation			
Bacteremic pneumonia	95 (38%)	41 (42%)	136 (39%)
Primary bacteremia	118 (47%)	38 (39%)	156 (45%)
Meningitis	17 (6.7%)	8 (8.2%)	25 (7.2%)
Other	22 (8.7%)	10 (10%)	32 (9.2%)
At least one underlying illness <sup>1</sup>	77 (31%)	47 (48%)	124 (36%)
Immunocompromised <sup>2</sup>	29 (12%)	36 (37%)	65 (19%)
Hospitalized	224 (89%)	93 (96%)	317 (91%)
Required ICU admission	25 (9.9%)	13 (13%)	38 (11%)
Died	4 (1.6%)	3 (3.1%)	7 (2%)

<sup>1</sup> Underlying illness predisposing to IPD includes conditions per NACI recommendations, as well conditions such as prematurity, metabolic diseases.

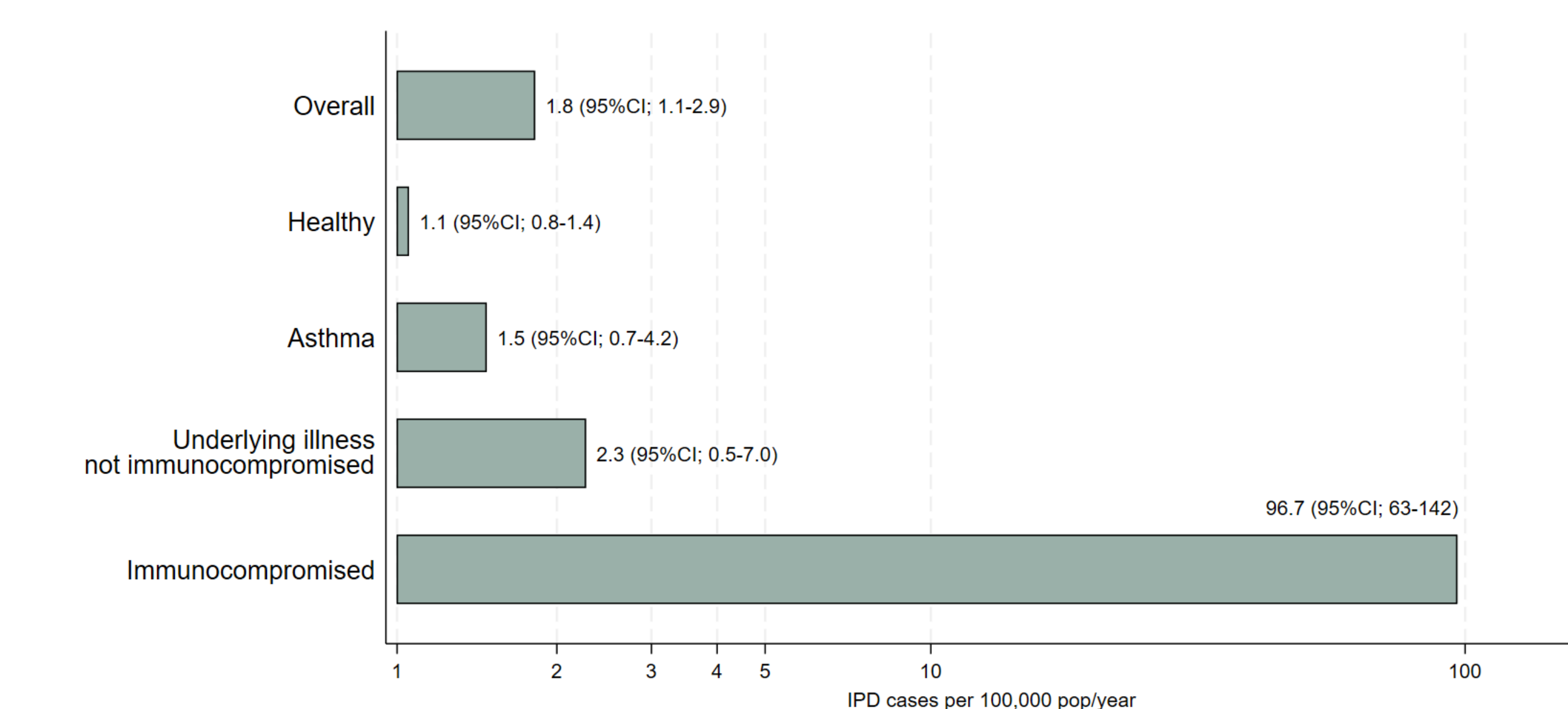
<sup>2</sup> Immunocompromising conditions are defined as: HIV infection, previous solid organ or bone marrow/stem cell transplantation, asplenia, sickle cell disease or other hematologic disorders, hematologic malignancy, solid organ cancers receiving chemotherapy, systemic lupus erythematosus, nephrotic syndrome, chronic renal failure, primary immunodeficiency or chronic receipt of immunosuppressive medications.

In 2022 and 2023 IPD incidence was 13 per 100000/year among children aged 0-4 years, and 3.1 cases per 100000/year among 5-14 year-olds, similar to 2014-2019 (Figure 1). Although PCV13 IPD appeared to be decreasing before the pandemic, the declines were not statistically significant, and PCV13 IPD persists in both age groups in 2022 and 2023.



**Figure 1:** Annual IPD incidence by PCV serotype groups, 2014-2023. A) 0-4 year-olds, B) 5-14 year-olds.

In children 5-17 years of age, IPD incidence was 80-fold higher among those with immunocompromising conditions relative to those without ( $P<.0001$ ) (Figure 2). IPD incidence was also statistically significantly increased in children with renal/liver conditions (IRR 9.7, 95%CI 2.0-28) and in children with non-asthma lung conditions (IRR 14, 95%CI 1.7-51).

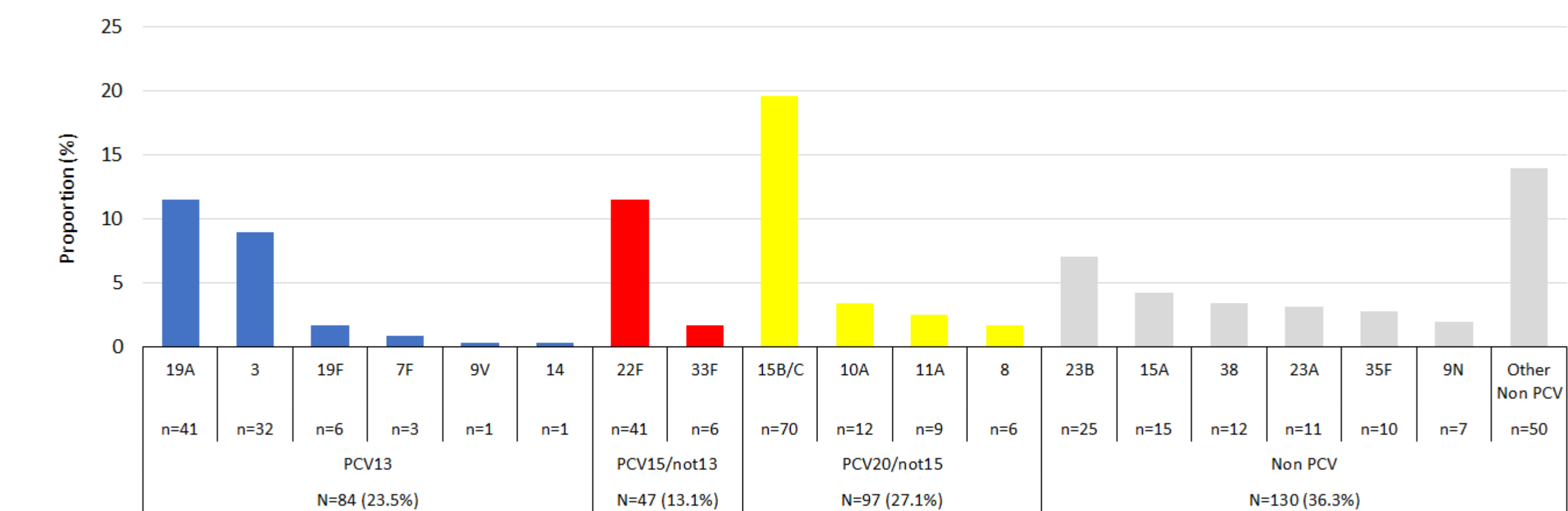


**Figure 2:** Average annual IPD incidence rate among 5-17 year-olds with underlying conditions in 2014-2019, and 2022<sup>1</sup>.

<sup>1</sup> Estimates exclude the 2020 and 2021 pandemic years. Immunocompromised is defined in Table 1. Underlying illness not immunocompromised includes children with underlying illness but without immunosuppression, excluding those with asthma.

**RESULTS**

Of the 358 cases with serotype available, 84 (23%) were due to isolates of PCV13 STs, 47 (13%) PCV15/not13 STs, 97 (27%) PCV20/not15 STs and 130 (36%) due to STs not included in any PCV. The most common serotypes causing IPD are shown in Figure 3.



**Figure 3:** Distribution of serotypes causing IPD by vaccine covered groups 2014-2022.

Of 358 cases with STs, 318 had complete vaccination data available. Of these, 84 and 78 respectively had disease due to PCV13 STs. Vaccination history for these children is shown in Table 4. There were 33 cases representing PCV13 vaccine failure (10.4% of all IPD cases), 16 representing program failure (9 unvaccinated, 7 with missed doses).

Among 33 children with PCV13 VF, 11 (33%) had underlying conditions, and 3 (9%) were immunocompromised. Most (30, 91%) presented with bacteremic pneumonia, all were hospitalized 5 (15%) required ICU, 1 died.

**Table 4:** Vaccination history in children with IPD due to PCV13 serotypes (N=78)

	Serotype (N)	Median age at IPD onset	# with Chronic condition
<b>PCV13 Vaccine Failure (N=33)</b>			
•28 children with 3 PCV13 doses (4,6,12-15m)	19A (11), 3 (12), 19F (5)	53m	9 (2 IC)
•5 children with 4 PCV13 doses (2,4,6,12-15m)	19A (4), 9V (1)	46m	2
<b>Program failure (N=16)</b>			
•7 children with missed doses <sup>a</sup>	19A (3), 3 (2), 7F (1), 14 (1)	57m	1 IC
•9 unvaccinated children	19A (5), 3 (4)	35m	0
<b>Vaccination up-to-date but incomplete (N=4)</b>			
•4 children with PCV13 doses but IPD at <12m	19A (1), 3 (3)	8.3m	0
<b>Not eligible for relevant PCV (N=25)</b>			
•18 too old to be eligible for PCV13	19A (11), 3 (7)	78m	5 (1 IC)
•2 too old to be eligible for PCV10	7F (2)	146m	0
•5 too young to be vaccinated; IPD at <2m	19F (1), 3 (4)	0.4m	0

<sup>a</sup>6 children with ≥2 PCV13 doses at <12 mos who had missed their 12-15 month dose, and one child with PCV13 doses at 9 and 13 mos.

Of 19 children who received either PCV7 or PCV10, none had IPD due to STs included in the respective vaccine.

Among children with known vaccination history infected with isolates of STs not included in PCV13, who were born after 11/2009 and ≥18 mos old at IPD onset 106 (79%) were completely vaccinated, 22 (16%) had ≥1 missed dose and 7 (5%) were unvaccinated. 13 of 22 (59%) cases with missed doses had missed only their 12 month dose.

**CONCLUSION**

Post PCV13 implementation, IPD has stabilized, with increased disease due to PCV15 and PCV20 STs; some PCV13 disease persists. Disease in 2022/3 may reflect either rebound from the pandemic, or the new normal for IPD.

Persisting PCV13 disease is a mix of vaccine and program failures, and disease in children ineligible for complete vaccination. The largest gap in vaccination is missed 12 month doses.

Higher-valency vaccines should significantly reduce IPD in younger children. A catch-up dose of PCV20 should be considered for older children with underlying chronic conditions associated with significantly elevated IPD risk.

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