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Report National Reference Centre invasive *Streptococcus pneumoniae* 2023

This is a report of the National Reference Centre (NRC) for invasive *Streptococcus pneumoniae* UZ Leuven with a main focus on invasive pneumococcal disease (IPD) isolates from 2023.

1. Characteristics of surveillance in 2023

Data of the NRC are based on a passive laboratory-based surveillance. We performed capsular typing (Quellung reaction, antisera SSI Diagnostica) to determine the pneumococcal serotype and assessed the antimicrobial susceptibility of all invasive *S. pneumoniae* strains sent to the NRC. This surveillance is not focused on non-invasive *S. pneumoniae* isolates (i.e. isolated from BAL, middle ear, sputum, …).

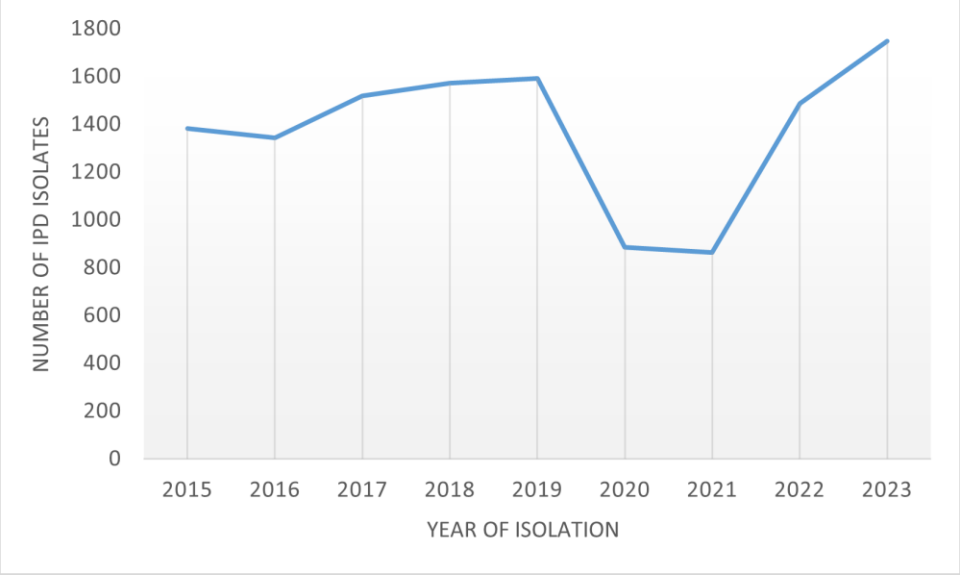


Figure 1: Evolution of the number of IPD isolates received at the NRC from 2015 to 2023.

For both years 2020 and 2021, the pneumococcal epidemiology was disturbed, characterized by a large reduction in the number of IPD isolates received at the NRC compared to pre-COVID years (Figure 1). While for the start of 2022, still a lower number of IPD isolates was analysed, for the year 2023, for all months, the number of isolates received at the NRC fluctuated around the mean number of pre-COVID years 2015-2019 (Figure 2), with for some months higher number of isolates observed (i.e. month of June 2023). The exceptional high number of IPD isolates received at the NRC for the month December 2022, continued early 2023, however less extensively pronounced. Despite the absence of exceptional outliers in the monthly number of IPD isolates received at the NRC, overall a high number of strains was analysed for the year 2023 (N=1748). It has been since the year 2012, characterized by 1776 IPD isolates, that the NRC was confronted with such a high number of IPD cases. It is hypothesized that the increase in number of infections is due to an anticipated post COVID-19 immunity decrease, although additional factors may play a role and warrant further investigation[1].

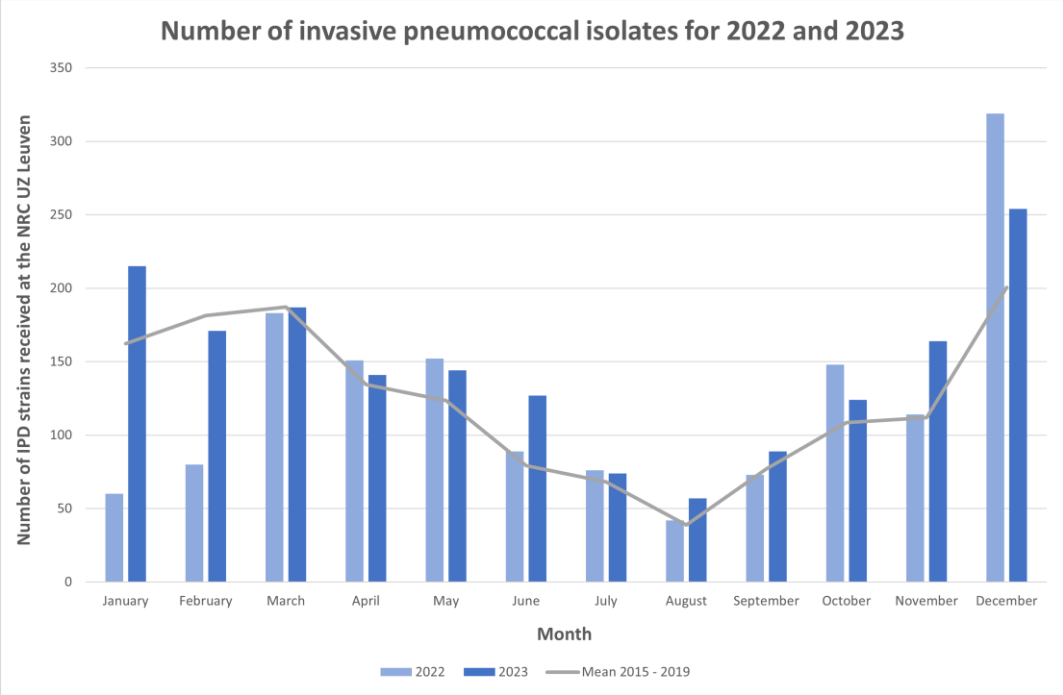


Figure 2: The number of IPD isolates received at the NRC per month for the years 2022 and 2023, in comparison to the mean number of IPD isolates received between pre-COVID years 2015 to 2019.

The decreasing trend for the years 2020 and 2021, followed by the years 2022 and 2023 with again an increasing number of infections (especially for the year 2023), in line with pre-COVID years; is also observed in other countries[2,3]. It is assumed that the surveillance itself remained stable for all these years, despite the disturbance by the COVID-19 epidemic. In 2023, the number of different participating laboratories (n=91, considering all strains received at the NRC, not specifically focused on IPD), as well as

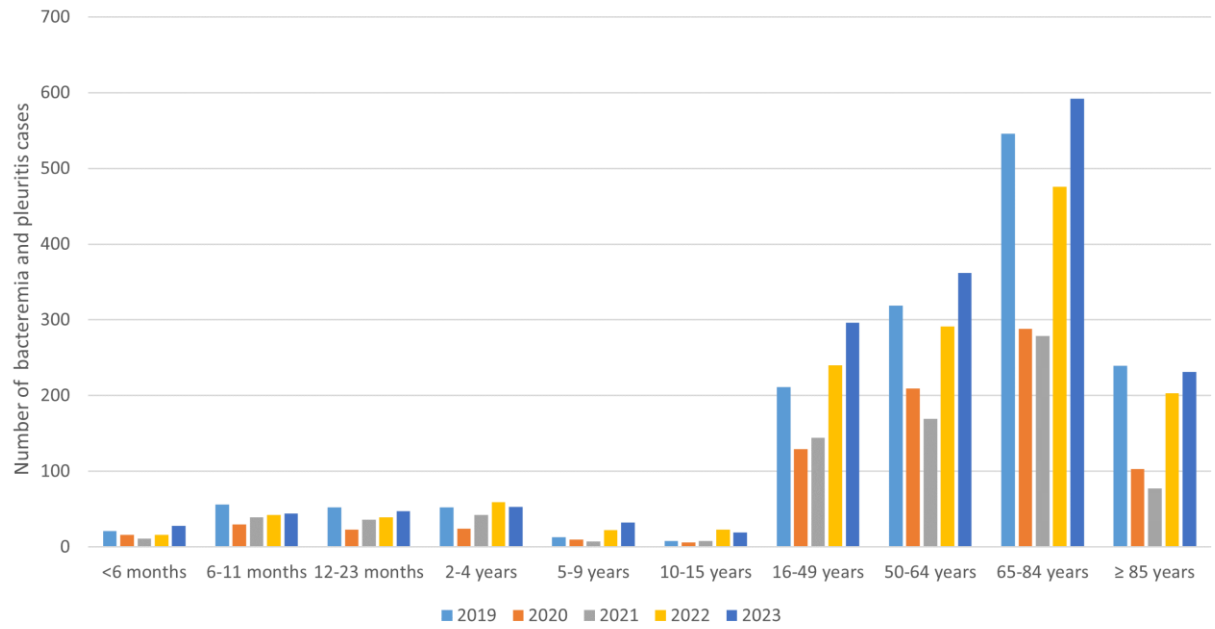
the number of hospitals sending more than 5 strains (n=74) to our NRC, normalized again compared to the pre-COVID year 2019 (Table 1).

Table 1: Characteristics of the surveillance of the Belgian National Reference Centre invasive *S. pneumoniae* during the period of 2019-2023. (IPD: invasive pneumococcal disease; *:taking into account mergers of laboratories)

		2019	2020	2021	2022	2023
number of unique IPD isolates sent to the NRC		1592	884	863	1487	1748
number of laboratories* involved in surveillance						
	all	92	93	85	88	91
	sending more than 5 isolates per year	70	55	57	71	74
	located in Flanders	54	55	50	52	49
	located in Wallonia	28	28	26	27	33
	located in Brussels	10	10	9	9	9
regional distribution of all isolates based on residence of patient (percentage)						
	Flanders	66,8%	64,3%	58,2%	57,9%	56,3%
	Wallonia	23,3%	25,4%	24,8%	26,6%	29,7%
	Brussels	9,3%	8,8%	13,9%	11,2%	11,2%
	other/unknown	0,5%	1,5%	3,1%	4,3%	2,9%

A total of 1861 bacterial strains, with 1748 unique IPD strains, were received in 2023. A majority of the strains were isolated from blood cultures (95.1%) and cerebrospinal fluid (3.3%). More IPD strains were identified from males (57%) compared to females (43%).

a



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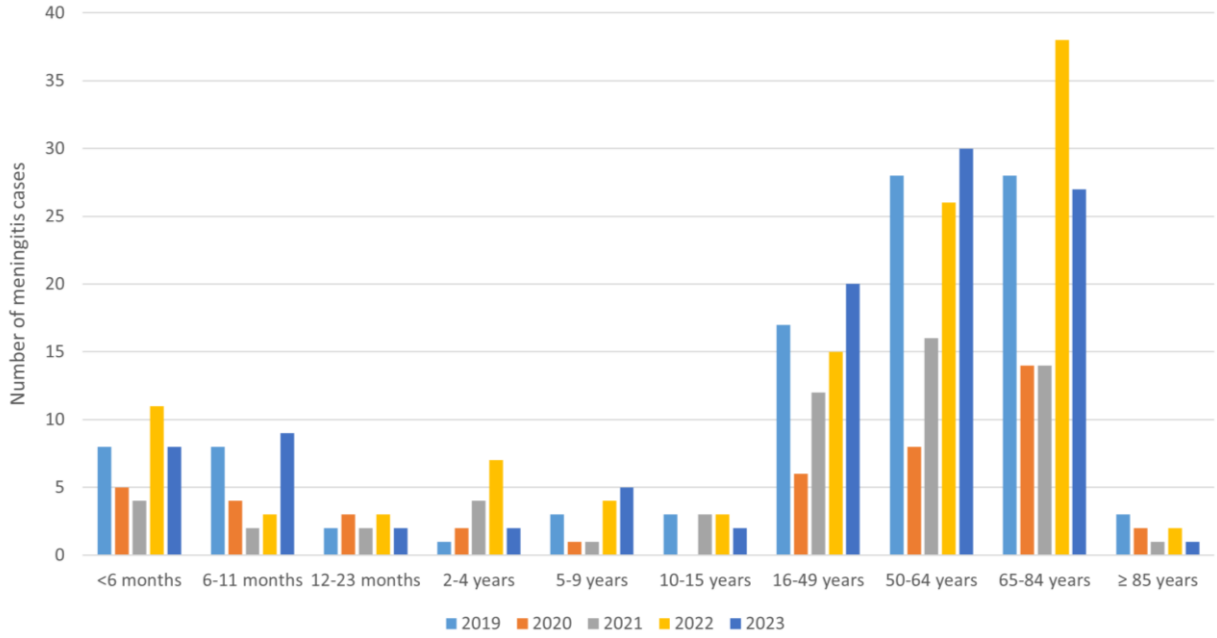


Figure 3: Evolution of the number of (a) bacteraemia/pleuritis based on origin of isolation and (b) meningitis cases based on clinical diagnosis of *S. pneumoniae* isolates sent to the NRC per age group, for the years 2019-2023. Bacteraemia/pleuritis: isolation of *S. pneumoniae* from blood culture and/or pleural fluid. Meningitis: clinical diagnosis; which are both cases with isolation of *S. pneumoniae* from cerebrospinal fluid and meningitis cases without a strain received from CSV but with indication of meningitis as clinical presentation.

Figure 3 indicates the age distribution of patients from whom pneumococci were isolated from one of the three major infection sites (blood, pleural fluid and cerebrospinal fluid) and/or clinically diagnosed with meningitis. In line with the results of 2022, the number of isolates has stabilized for all age groups compared to the level of pre-COVID year 2019, with the number of bacteraemia/pleuritis cases being the highest since the year 2011.

A total number of 58 meningitis cases, based on isolation of *S. pneumoniae* from cerebrospinal fluid, was observed for the year 2023. When considering meningitis based on clinical diagnosis, and therefore not limiting the definition to isolation from cerebrospinal fluid, the number of cases nearly doubles (+45.3%), with 106 cases indicated as meningitis (Figure 3b). The same phenomenon of an increase of approximately 40% was observed for the last five years when comparing the number of meningitis cases based on isolation from cerebrospinal fluid, to meningitis cases defined based on clinical diagnosis.

2. Serotype distribution of invasive pneumococcal isolates

2.1. All ages

Table 2 describes in descending order of frequency the serotypes of IPD isolates detected in 2023. The serotype distribution is determined per age group. Overall, serotype 8 is the most prevalent serotype responsible for 13.6% of the IPD isolates in 2023. Serotypes 3 (12.8%), 4 (9.6%), 22F (8.2%) and 19A (7.9%) complete the top 5 of most frequently detected serotypes. Focusing solely on the 106 meningitis cases clinically diagnosed among all age groups, the top 5 of most frequently detected serotypes is somewhat different: serotype 3 (11.3%), 10A (7.5%), and serotypes 12F, 19A and 22F (each 5.7%).

Table 2: Distribution of serotypes of IPD isolates from 2023 (n=1748) per age group. (colour code: orange/red: highest proportion, yellow: intermediate proportion, dark green: lowest proportion; PCV7: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F); PCV10: PCV10 non-PCV7 serotype: 1, 5, 7F; PCV13: PCV13 non-PCV10 serotype: 3, 6A, 19A; PCV15: PCV15 non-PCV13 serotypes: 22F, 33F; PCV20: PCV20 non-PCV15 serotypes: 8, 10A, 11A, 12F, 15B; PPV23: PPV23 only serotypes: 2,9N, 17F, 20, NVT: non-vaccine serotype)

serotype		<16 years (n=233)	16-49 years (n=311)	50-64 years (n=368)	65-84 years (n=603)	>85 years (n=232)	all ages (n=1748)
8	PCV20	6,4%	16,7%	17,6%	15,2%	6,5%	13,6%
3	PCV13	3,8%	12,8%	13,3%	15,4%	13,8%	12,8%
4	PCV7	0,4%	25,3%	13,0%	6,0%	1,3%	9,6%
22F	PCV15	3,4%	5,1%	7,9%	10,2%	12,9%	8,2%
19A	PCV13	9,8%	5,4%	8,9%	7,0%	9,9%	7,9%
12F	PCV20	12,4%	10,3%	8,1%	5,3%	2,2%	7,3%
10A	PCV20	6,4%	2,2%	3,3%	1,7%	4,3%	3,1%
9N	PPV23	1,3%	4,5%	3,3%	3,0%	3,0%	3,1%
24F	NVT	9,8%	1,0%	0,8%	2,8%	2,2%	2,9%
33F	PCV15	6,4%	1,3%	1,6%	2,5%	4,3%	2,9%
23B	NVT	5,6%	1,9%	2,2%	2,3%	0,9%	2,5%
23A	NVT	3,0%	0,6%	1,6%	2,7%	4,3%	2,3%
6C	NVT	1,3%	1,0%	1,9%	2,8%	4,7%	2,3%
14	PCV7	3,4%	1,9%	0,3%	3,3%	1,7%	2,2%
15A	NVT	0,9%	1,6%	1,6%	2,7%	3,9%	2,2%
11A	PCV20	1,7%	0,6%	2,7%	2,8%	1,7%	2,1%
16F	NVT	0,9%	1,3%	1,4%	1,7%	3,4%	1,7%
38	NVT	4,3%	0,0%	0,0%	1,7%	3,4%	1,6%
15B	PCV20	3,4%	1,6%	0,8%	1,2%	1,3%	1,5%
35B	NVT	1,3%	0,3%	0,5%	1,3%	3,0%	1,2%
7B	NVT	0,4%	0,3%	1,6%	1,3%	1,3%	1,1%
31	NVT	0,4%	0,0%	1,4%	1,2%	1,7%	1,0%
35F	NVT	2,1%	0,0%	0,5%	0,7%	1,3%	0,8%
19F	PCV7	0,4%	0,0%	0,3%	1,5%	0,4%	0,7%
7C	NVT	0,9%	0,3%	0,3%	0,3%	2,2%	0,6%
20	PPV23	0,0%	0,3%	0,5%	0,5%	1,3%	0,5%
15C	NVT	2,1%	0,3%	0,3%	0,3%	0,0%	0,5%

17F	PPV23	0,9%	0,0%	0,3%	0,3%	1,3%	0,5%
other serotypes (< 0.5% all ages)		6,8%	3,2%	4,1%	2,2%	1,7%	3,3%

Compared to 2022, the only decrease in serotype proportion larger than 2% was observed for serotype 8, while the proportion of serotypes 3, 19A and 6C remained relatively stable. The largest increase in serotype distribution was observed for serotype 22F (proportion doubled compared to 2022, +4.1%) and 12F (+3.5%). Both serotypes are covered by PCV20, with 22F also included in PCV15. The proportion of serotype 4, a PCV7 vaccine serotype, continued to increase (+8.1% since 2020), more specifically +2.7% compared to 2022, ranking this serotype third. Especially a high proportion of serotype 4 infections was observed among individuals aged 16-49 years old (proportion of 25.3% compared to 0.4% for children <16 years old). Whole-genome sequencing of the serotype 4 isolates of the year 2022 revealed the predominance of sequence types 801 (71.6%) and 15063 (21.6%). In-depth analyses of the different clones as well as the epidemiology of serotype 4 is currently ongoing to understand the advantage this serotype seems to currently have[4].

Differences in serotype distribution are observed among the different age groups. The largest difference in serotype proportion between children (<16 years old) and older adults (65-84 years old) was noted for serotype 3 (3.8% in children versus 15.4% in older adults), serotype 8 (6.4% versus 15.2%), serotype 4 (0.4% versus 6.0%), serotype 22F (3.4% versus 10.2%), serotype 12F (12.4% versus 5.3%), serotype 10A (6.4% versus 1.7%) and serotype 24F (9.8% versus 2.8%).

In 2022, two new pneumococcal conjugate vaccines (PCVs) were authorized in the European Union by the European Medicines Agency (EMA):

- 15-valent pneumococcal conjugate vaccine (Vaxneuvance, Merck Sharp & Dohme B.V.) (PCV15) containing the same serotypes as PCV13 with additionally serotypes 22F and 33F.
- 20-valent pneumococcal conjugate vaccine (Prevenar 20 (previously Apexxnar), Pfizer) containing the same serotypes as PCV15 with additionally serotypes 8, 10A, 11A, 12F and 15B.

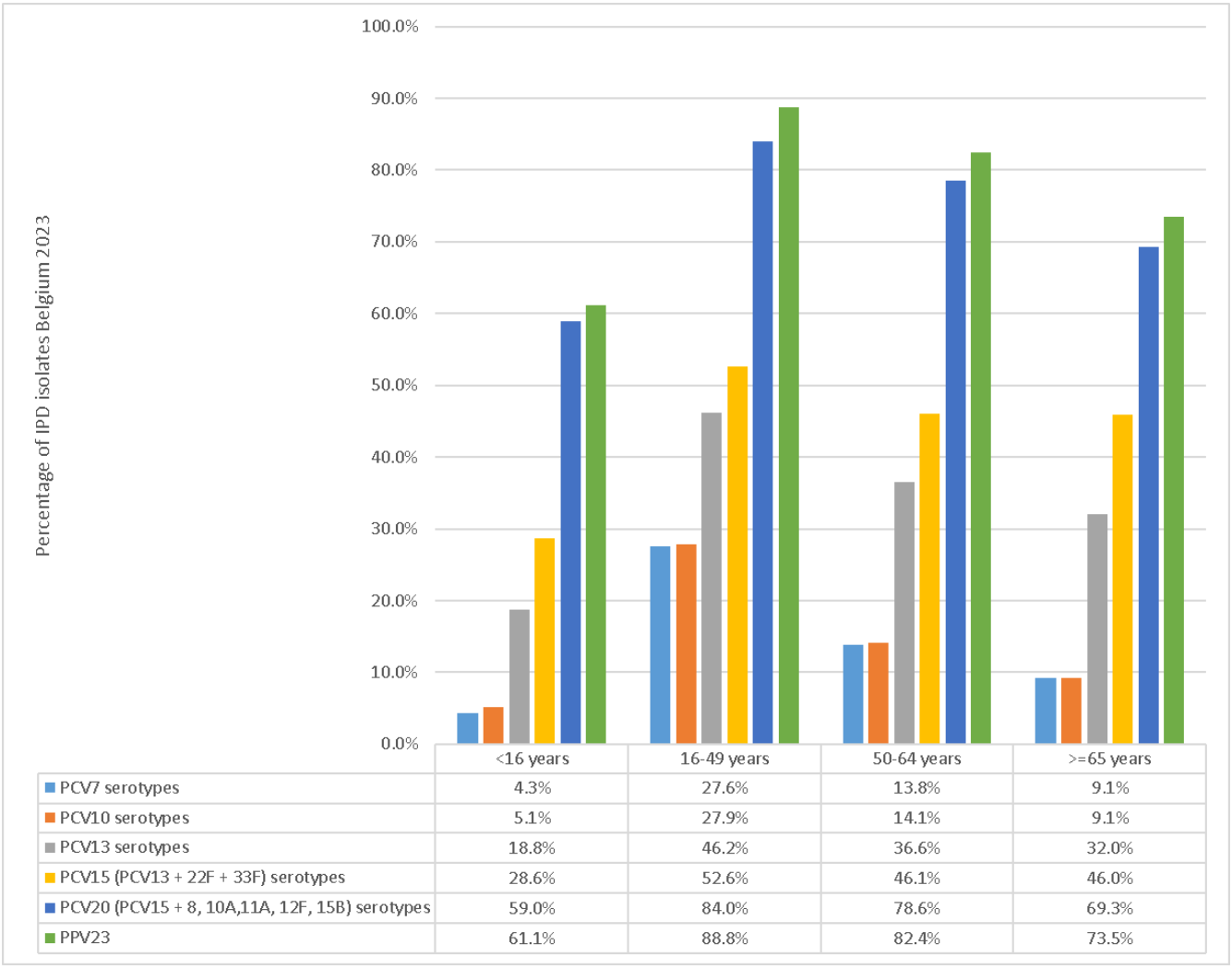
PCV15 and PCV20 are both approved for use in adults. PCV15 has also approval for use in children since 2022, and very recently PCV20 received also EMA approval for use in children.[1] The most recent advices of the Superior Health council regarding pneumococcal immunisation for adults[2] and children[3] can be found at the website of the Superior Health Council.

[1] https://www.ema.europa.eu/en/medicines/human/EPAR/prevenar-20-previously-apexxnar

[2] https://www.health.belgium.be/nl/advies-9674-vaccinatie-tegen-pneumokokken-volwassenen

[3] https://www.health.belgium.be/nl/advies-9746-vaccinatie-van-kinderen-en-adolescenten-tegen-pneumokokken

In Figure 4, we analysed the theoretical serotype coverage of the five currently available vaccines (PCV10, PCV13, PCV15, PCV20 and the 23-valent polysaccharide vaccine (PPV23)) based on the serotype distribution of the invasive pneumococcal strains per age group in 2023. The proportion of PCV15 non-PCV13 serotype and PCV20 non-PCV13 serotype IPD ranges respectively from 6.4 to 16.6% and 37.8 to 44.3% depending on the age group. It has to be taken into account that serotype 3 is a serotype included in PCV13 and the newer PCVs available on the market, but the effectiveness of the vaccines to protect against the important serotype 3 is low or not yet known (for the new vaccines).



	<16 years	16-49 years	50-64 years	>=65 years
PCV7 serotypes	4.3%	27.6%	13.8%	9.1%
PCV10 serotypes	5.1%	27.9%	14.1%	9.1%
PCV13 serotypes	18.8%	46.2%	36.6%	32.0%
PCV15 (PCV13 + 22F + 33F) serotypes	28.6%	52.6%	46.1%	46.0%
PCV20 (PCV15 + 8, 10A,11A, 12F, 15B) serotypes	59.0%	84.0%	78.6%	69.3%
PPV23	61.1%	88.8%	82.4%	73.5%

Figure 4: Serotype coverage of the current authorized pneumococcal vaccines per age group based on the invasive pneumococcal disease isolates received at the National Reference Centre in 2023.

2.2. Children < 2 years old

In 2023, 128 invasive pneumococcal isolates from children <2 years old were received at the NRC. This number is lower compared to the pre-COVID year 2019 (n=142) (end of PCV10 period), but indicates an increase by 16% compared to 2022 (n=107).

Table 3 indicates the serotype distribution of invasive isolates (isolated only from blood, cerebrospinal fluid, pleural fluid and joint fluid) in children during the first two years of life by capsular type in 2023. The predominant serotypes in 2023 (with a proportion >5%) are serotypes 33F (10.9%), 10A (10.9%), 24F (10.9%), 19A (10.2%), 12F (9.4%), and 15B (5.5%). When focusing on the 19 meningitis cases clinically diagnosed in these youngest children, serotype 10A was detected in three cases, and serotypes 15B and 24F both in two cases each, while for the other 12 cases unique serotypes were found (serotypes 8, 14, 12F, 17F, 19A, 22F, 23A, 24, 28, 33F, 35F and 38).

Table 3: Serotypes causing IPD in children <2 years old in 2023 categorized based on their inclusion in pneumococcal conjugate vaccines (based on isolations of *S. pneumoniae* from blood, cerebrospinal fluid, pleural fluid and joint fluid) *non-PCV20 serotypes only detected in one strain (<1%)

serotype	number	%
PCV7	**1**	**0,8%**
4	0	0,0%
14	1	0,8%
PCV10 non-PCV7	**1**	**0,8%**
7F	1	0,8%
PCV13 non-PCV10	**16**	**12,5%**
3	3	2,3%
19A	13	10,2%
PCV15 non-PCV13	**20**	**15,6%**
22F	6	4,7%
33F	14	10,9%
PCV20 non-PCV15	**37**	**28,9%**
8	1	0,8%
10A	14	10,9%
11A	3	2,3%
12F	12	9,4%
15B	7	5,5%
non-PCV20 serotypes	**53**	**41,4%**
24F	14	10,9%
23B	6	4,7%
38	6	4,7%
15C	4	3,1%
23A	3	2,3%

35B	3	2,3%
35F	3	2,3%
24B	2	1,6%
17F	2	1,6%
21	2	1,6%
non-typable	2	1,6%
other*	6	4,7%
TOTAL	**128**	**100,0%**

The proportion of serotype 19A infections continued to slightly decrease in 2023 (-3.8% compared to 2022), following re-introduction of PCV13 in 2019. Increasing proportions were observed for serotypes 24F (+5.3%), 12F (+3.8%) and 15B (+3.6%) compared to 2022, while a decreasing trend was seen for serotype 11A (-6.1%). Of note, serotype 11A was observed to have increased substantially from 2021 to 2022 (+5.2%) as reported last year, in 2023 the opposite trend was observed. Despite the important decrease in serotype 11A, both serotypes 12F and 15B increased, slightly increasing the proportion of PCV20 non-PCV15 serotypes from 26.2% to 28.9%; while due to a more modest increase of serotype 22F (+2.8%) the proportion of PCV15 non-PCV13 serotypes increased from 12.1% to 15.6%. In 2023, still 14.1% of cases were caused by serotypes included in PCV13.

3. Antimicrobial susceptibility of pneumococcal isolates

Table 4 illustrates the evolution of resistance of pneumococcal isolates to the 4 antibiotics (penicillin, tetracycline, erythromycin and levofloxacin) that are systematically tested on submitted strains. From the start of the surveillance, the paper disk-diffusion technique on Mueller Hinton agar with 5% horse blood has been used. After incubation for 18 hours at 36°C with 5% CO_2, the inhibition zones are measured and interpreted according to EUCAST guidelines. For the detection of resistance to penicillin, oxacillin disks with a charge of 1 µg are used as screening method. In case of a positive oxacillin screen (oxacillin diameter <20 mm), MICs are determined for penicillin, amoxicillin and cefotaxime. Until July 2020, MICs were determined by using Etest (BioMérieux, France). From the first of August 2020 on, MICs were determined by using broth microdilution (Sensititre, ThermoScientific, USA). This change in method is situated in the context of a warning of EUCAST against the use of gradient tests to determine MICs of penicillin (November 2019). In their study, gradient tests (Etest and MTS) frequently underestimated penicillin MIC values by one or more doubling dilutions. This underestimation is detrimental in the important area close to the R breakpoint (R> 0.06 mg/L) used in our report and the R clinical breakpoint for non-meningitis (MIC > 2 mg/L). In accordance with the new definition of 'I' of EUCAST, the strains categorized as I were counted together with the S categorized strains.

Table 4: Antibiotic resistance rates of all unique invasive pneumococcal strains received at the NRC from 2018-2023. *change of method mid 2020 (cells coloured in grey for the years 2018-2020).

antibiotic	**2018**	**2019**	**2020***	**2021**	**2022**	**2023**
	n=1571	**n=1592**	**n=884**	**n=863**	**n=1487**	**n=1747**

	(%)	(%)	(%)	(%)	(%)	(%)
penicillin R						
penicilline MIC > 0.06 mg/L	10.2%	9.9%	15.0%	18.4%	14.3%	13.3%
penicilline MIC > 2 mg/L	0.0%	0.0%	1.2%	3.6%	2.0%	1.8%
cefotaxime R						
cefotaxime MIC > 0.5 mg/L	0.2%	0.6%	2.1%	4.9%	3.5%	3.4%
cefotaxime MIC > 2 mg/L	0.0%	0.1%	0.2%	0.7%	0.2%	0.1%
tetracycline R	14.0%	14.4%	18.8%	15.1%	14.1%	18.1%
levofloxacin R	0.1%	0.1%	0.1%	0.1%	0.1%	0.1%
erythromycin R	15.3%	15.8%	19.8%	16.5%	14.7%	14.9%

Two hundred thirty-three (13.3%) of the 1747 IPD strains showed a reduced susceptibility to penicillin (MIC > 0.06 mg/L= EUCAST epidemiological cut-off and meningitis R breakpoint), which is lower than the three last years. Thirty-one of these 233 strains had a penicillin MIC above 2 mg/L (non-meningitis R breakpoint). For cefotaxime, the resistance rates are stable compared to last year. Fifty-nine strains (3.4%) had a cefotaxime MIC > 0.5 mg/L (EUCAST meningitis R breakpoint). Only one strain had a MIC above 2 mg/L and was categorized as resistant making use of the EUCAST non-meningitis breakpoint.

When only focussing on strains isolated form patients with meningitis (n=106): 21 strains were penicillin resistant (19.8%), 6 strains (5.6%) were amoxicillin resistant and 5 strains (4.7%) were cefotaxime resistant according to EUCAST clinical breakpoints for meningitis. All 5 cefotaxime resistant isolates had a cefotaxime MIC of 1 mg/L which is close to the breakpoint (R>0.5 mg/L). We observe an evolution of cefotaxime resistance with two cases in 2021 (2/59 or 3.4%) to five cases in 2023 (5/106 or 4.7%), while for the other years (2018-2020 and 2022) no such cases were identified possibly due to the different AST method before mid-2020). For 2021, both cases with cefotaxime resistant strains were older than 60 years while for 2023, three out of five cases were younger than 60 years (two cases between 50-60 years and one case between 20-30 years old). Four of the five cases with cefotaxime resistant strains in 2023 were diagnosed in the months October and November.

The erythromycin (14.9%) resistance rate in 2023 is in line with the rate observed in 2022, while for tetracycline (18.1%) the resistance rate is higher compared to the years 2021 and 2022 but in the same range as for the year 2020. Levofloxacin resistance remains rare, with 0.1% (2/1746) of the strains interpreted as resistant in 2023.

Among the isolates with reduced susceptibility to penicillin in 2023, five serotypes accounted each for 10% or more of the isolates, more specifically serotypes 24F, 23B, 11A, 19A and 6C.

4. Pneumococcal vaccines

During ast 10 years, different changes in the childhood immunization programmes were made. In 2015 (in the Flemish region) and in 2016 (Walloon region) PCV13 was replaced by PCV10. In summer of 2019, PCV10 was again replaced by PCV13. The number of vaccines sold for immunization of children remained overall stable (see Table 5).

Table 5: Evolution of the number of blood culture isolates received at the NRC and the number of the different vaccines sold in Belgium for period 2015-2023. (source: personal communication with Pfizer Belgium and MSD Belgium). (*ex-factory doses PCV13 in 2023: paediatric: 345613; adult: 6673, not taking into account parallel import)

Year	2015	2016	2017	2018	2019	2020	2021	2022	2023
Number of blood culture isolates	1280	1257	1421	1477	1503	837	817	1401	1692
Pneumovax (PPV23)	63494	75768	110992	105029	122604	152950	185991	76445	55728
Synflorix (PCV10)	103661	326545	368288	359056	209962				
Prevenar 13 (PCV13)	304768	68775	88036	93888	126420	518016	406278	364844	352286*
Vaxneuvance (PCV15)								873	514
Apexxnar (PCV20)								33111	89895

For adult pneumococcal immunisation in Belgium in 2023, four different vaccines could be used: PPV23, PCV13, PCV15 and PCV20. The number of PPV23 vaccine doses sold in 2023 further decreased by about 27% compared to 2022. Despite the fact that the number of administered doses of PCV13 to adults is not exactly known due to the significant parallel import of PCV13 from other countries (and based on the known numbers would be about half of the doses compared to 2022), it is estimated that, due to the higher uptake of the newly introduced higher-valent vaccine PCV20 (+271% compared to 2022), the immunisation of patients at risk seems to have increased in 2023. This is certainly hopeful, as the overall vaccination rate in adult risk groups is historically below 35%[5-8], despite the high vaccination grade in the youngest children (> 95%).

5. References

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