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Report National Reference Centre *Streptococcus pneumoniae* 2022

This is a report of the National Reference Centre (NRC) for invasive *Streptococcus pneumoniae* UZ Leuven with a focus on invasive pneumococcal disease (IPD) isolates from 2022.

1. Characteristics of surveillance in 2022

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.

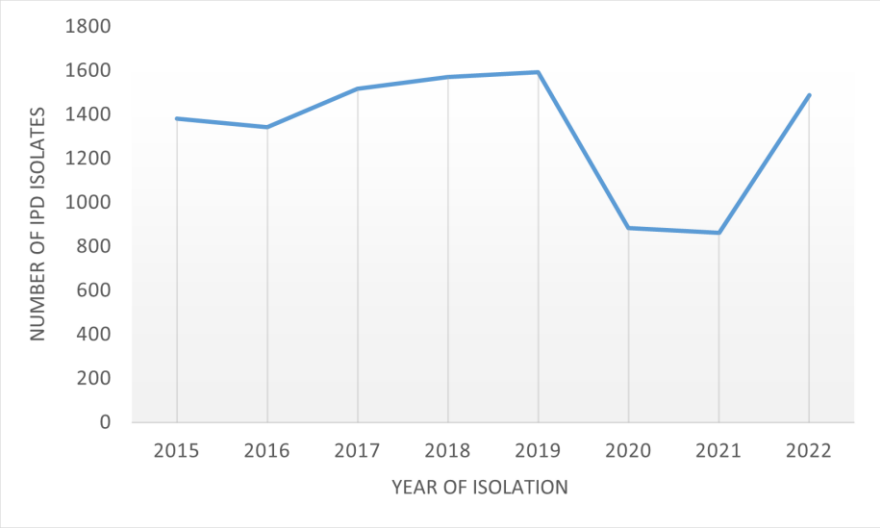


Figure 1: Evolution of the number of IPD (invasive pneumococcal disease) isolates received at the National Reference Centre from 2015 to 2022.

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 months January and February in 2022, still a lower number of IPD isolates was analysed, the amount of monthly isolates received at the NRC since March 2022 equalled or exceeded the mean number of isolates received between pre-COVID years 2015 to 2019 (Figure 2). For the month of December 2022, an exceptional high number of IPD isolates was received at the NRC.

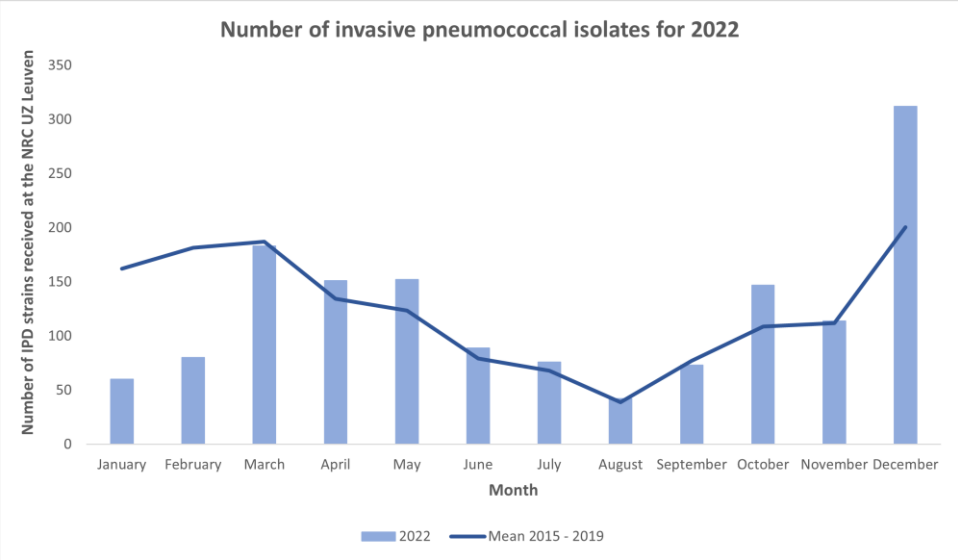


Figure 2: The number of IPD isolates received at the NRC per month for the year 2022, in comparison to the mean number of IPD isolates received between pre-COVID years 2015 to 2019.

The decreasing trend for the years 2020 and 2021, followed by the year 2022 with again an increasing number of infections, in line with pre-COVID years; is also observed in other countries. It is assumed that the surveillance itself remained stable for the years 2020 and 2021. In 2022, still a lower number of different laboratories (n=88) sent pneumococcal strains to our NRC, while the number of hospitals sending more than 5 strains (n=71) normalized again compared to the pre-COVID year 2019 (Table 1). Supported by the results of the published international study to which the NRC contributed[1], we assume that the decrease in IPD cases is a result of the COVID-19 pandemic and the related containment measures that were taken from March 2020 on. Further analysis in the framework of the IRIS (Invasive Respiratory Infection Surveillance) network is ongoing to elucidate the impact of COVID-19 and its containment measures on the epidemiology of invasive pneumococcal disease in more detail[2].

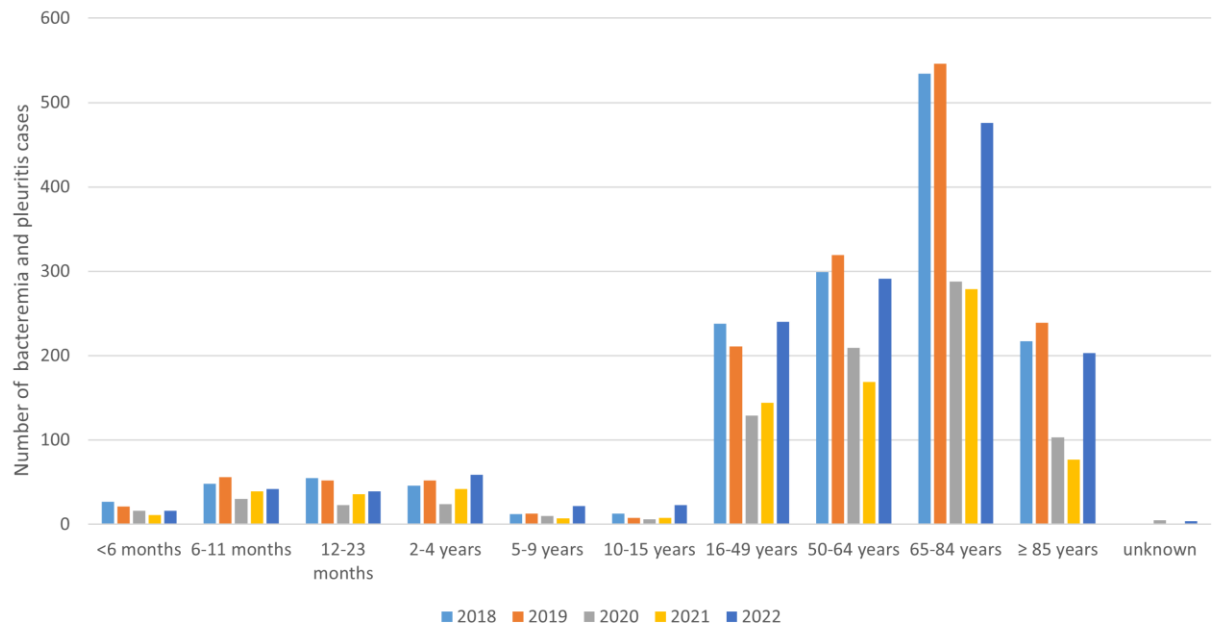
For the month of December 2022, over 300 IPD isolates were received at the NRC, this being the highest number of strains ever received during the time period of one month since the start of the surveillance. The same trend is observed for other countries in Europe with a strong and stable IPD surveillance, such as Germany, the Netherlands and Denmark. Possibly the intense co-circulation of different respiratory pathogens (e.g. Influenza and RSV), after lifting the restrictive measures in the context of the SARS-CoV-2 pandemic, may have resulted in the high incidence of invasive (super)infections with pneumococci.

Table 1: Characteristics of the surveillance of the Belgian National Reference Centre invasive *S. pneumoniae* during the period of 2018-2022. (IPD: invasive pneumococcal disease; *:taking into account mergers of laboratories)

		2018	2019	2020	2021	2022
number of unique IPD isolates sent to the NRC		1571	1592	884	863	1487
number of laboratories* involved in surveillance						
	all	91	92	93	85	88
	sending more than 5 isolates per year	75	70	55	57	71
	located in Flanders	53	54	55	50	52
	located in Wallonia	29	28	28	26	27
	located in Brussels	9	10	10	9	9
regional distribution of all isolates based on residence of patient (percentage)						
	Flanders	63,8%	66,8%	64,3%	58,2%	57,9%
	Wallonia	26,1%	23,3%	25,4%	24,8%	26,6%
	Brussels	9,9%	9,3%	8,8%	13,9%	11,2%
	other/unknown	0,2%	0,5%	1,5%	3,1%	4,3%

A total of 1554 pneumococcal strains, with 1487 unique IPD strains, were received in 2022. A majority of the strains were isolated from blood cultures (91%) and cerebrospinal fluid (4%). More IPD strains were identified from males (56%) compared to females (43%).

a



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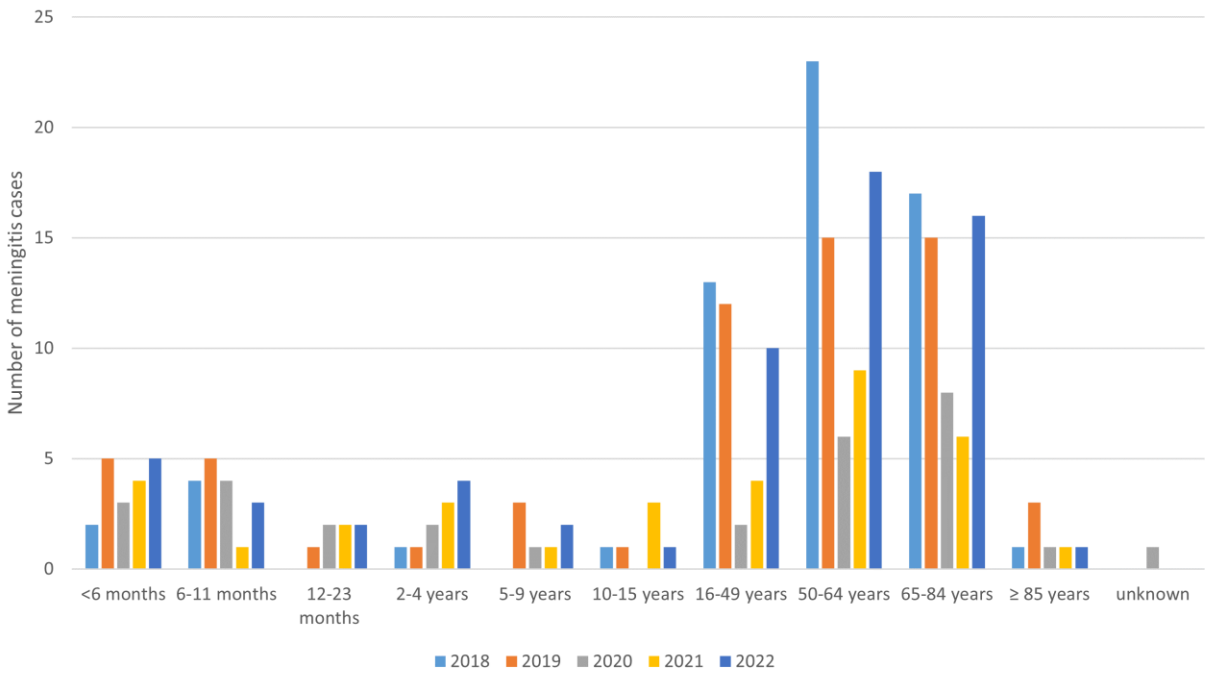


Figure 3: Evolution of the number of (a) bacteraemia/pleuritis and (b) meningitis cases based on origin of isolation of *S. pneumoniae* isolates sent to the NRC per age group. Bacteraemia/pleuritis: isolation of *S. pneumoniae* from blood culture and/or pleural fluid. Meningitis: isolation of *S. pneumoniae* from cerebrospinal fluid with or without isolation of *S. pneumoniae* from blood culture.

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). Among all age groups we see a re-increase in the number of isolates received compared to the COVID years 2020 and 2021 for which all numbers were decreased. Numbers increased to the level of pre-COVID years 2018 and 2019, for all age groups. The latter demonstrates that the exceptional high number of isolates received for December 2022 was not associated with an increase in infections in a particular age group.

A total number of 62 meningitis cases, based on isolation of *S. pneumoniae* from cerebrospinal fluid, was observed for the year 2022. When considering meningitis based on clinical diagnosis, and therefore not limiting the definition to isolation from cerebrospinal fluid, the number of cases nearly doubles (+46.6%), with 116 cases indicated as meningitis. 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 2022. The serotype distribution is determined per age group. Overall, serotype 8 is the most prevalent serotype responsible for 15.7% of the IPD isolates in 2022. Serotypes 3 (14.5%), 19A (9.2%), 4 (6.9%) and 22F (4.1%) complete the top 5 of most frequently detected serotypes, with serotype 6C sharing the fifth place with serotype 22F.

Table 2: Distribution of serotypes of IPD isolates from 2022 (n=1487) per age group. (colour code: orange: 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=222)	16-49 years (n=251)	50-64 years (n=311)	65-84 years (n=493)	>85 years (n=206)	all ages (n=1487)
8	PCV20	4,1%	30,7%	20,6%	14,0%	6,8%	15,7%
3	PCV13	5,0%	13,1%	14,8%	18,1%	18,0%	14,5%
19A	PCV13	13,1%	5,2%	10,0%	7,9%	12,1%	9,2%
4	PCV7	0,9%	19,5%	8,7%	4,7%	0,5%	6,9%
22F	PCV15	2,7%	2,8%	6,1%	5,1%	1,9%	4,1%
6C	NVT	3,2%	0,4%	2,9%	6,5%	5,8%	4,1%
12F	PCV20	7,2%	5,6%	3,5%	2,6%	1,0%	3,8%
9N	PPV23	1,4%	3,2%	1,6%	4,5%	4,4%	3,2%
23B	NVT	9,5%	1,6%	2,6%	1,8%	1,5%	3,0%
10A	PCV20	7,2%	0,8%	2,9%	2,0%	3,4%	3,0%
33F	PCV15	5,9%	0,8%	2,9%	2,8%	2,4%	2,9%
11A	PCV20	5,4%	1,2%	2,3%	2,2%	4,4%	2,8%
15A	NVT	1,8%	0,8%	2,3%	3,9%	4,9%	2,8%
23A	NVT	2,3%	1,2%	1,9%	2,0%	5,3%	2,4%
24F	NVT	5,9%	0,4%	1,3%	2,2%	1,5%	2,2%
38	NVT	3,2%	0,8%	1,0%	1,6%	2,9%	1,7%
14	PCV7	3,2%	2,0%	1,3%	0,8%	2,4%	1,7%
35B	NVT	1,8%	1,2%	1,0%	1,6%	2,9%	1,6%
16F	NVT	0,9%	0,8%	0,6%	2,2%	2,4%	1,5%
15B	PCV20	2,3%	0,4%	1,3%	1,2%	1,5%	1,3%
7B	NVT	1,8%	0,0%	1,3%	1,4%	1,5%	1,2%
31	NVT	0,5%	0,8%	1,0%	1,4%	1,9%	1,1%
35F	NVT	1,4%	0,0%	1,0%	1,4%	1,5%	1,1%
17F	PPV23	0,5%	1,2%	0,6%	1,0%	1,9%	1,0%
20	PPV23	0,5%	0,4%	1,0%	1,0%	0,5%	0,7%
19F	PCV7	0,5%	0,4%	0,3%	0,6%	1,5%	0,6%

21	NVT	1,4%	0,4%	0,0%	0,4%	0,5%	0,5%
15C	NVT	0,5%	0,0%	1,0%	0,4%	0,5%	0,5%
7C	NVT	1,4%	0,4%	0,3%	0,2%	0,5%	0,5%
other serotypes (< 0.5% all ages)		5,4%	4,0%	4,2%	4,3%	3,9%	4,3%

Compared to 2021, a decrease in the proportion of serotype 19A (-4.4%) and serotype 23B (-2.4%) was observed, while the proportion of serotypes 8, 12F, 6C and 22F remained mainly stable. The proportion of serotype 3 increased by over 4%, ranking this serotype higher than serotype 19A for the first time since 2019. Interestingly, the proportion of serotype 4 (6.9%), a vaccine serotype, increased compared to previous years (+2.5% since 2021 and +5.4% since 2020). The increase in serotype 4 was mainly observed in patients aged 16-64 years old (proportion of 19.5% compared to 0.9% for children <16 years old). All serotype 4 isolates of the year 2022 have been prepared for whole-genome sequencing to evaluate if this increase in serotype 4 is due to an increase of infections due to a single clone, or due to an increase of different clones.

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 (5.0% in children versus 18.1% in older adults), serotype 8 (4.1% versus 14.0%), serotype 23B (9.5% versus 1.8%), serotype 19A (13.1% versus 7.9%) and serotype 10A (7.2% versus 2.0%).

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

- 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 (Apexxnar, Pfizer) containing the same serotypes as PCV15 with additionally serotypes 8, 10A, 11A, 12F and 15B.

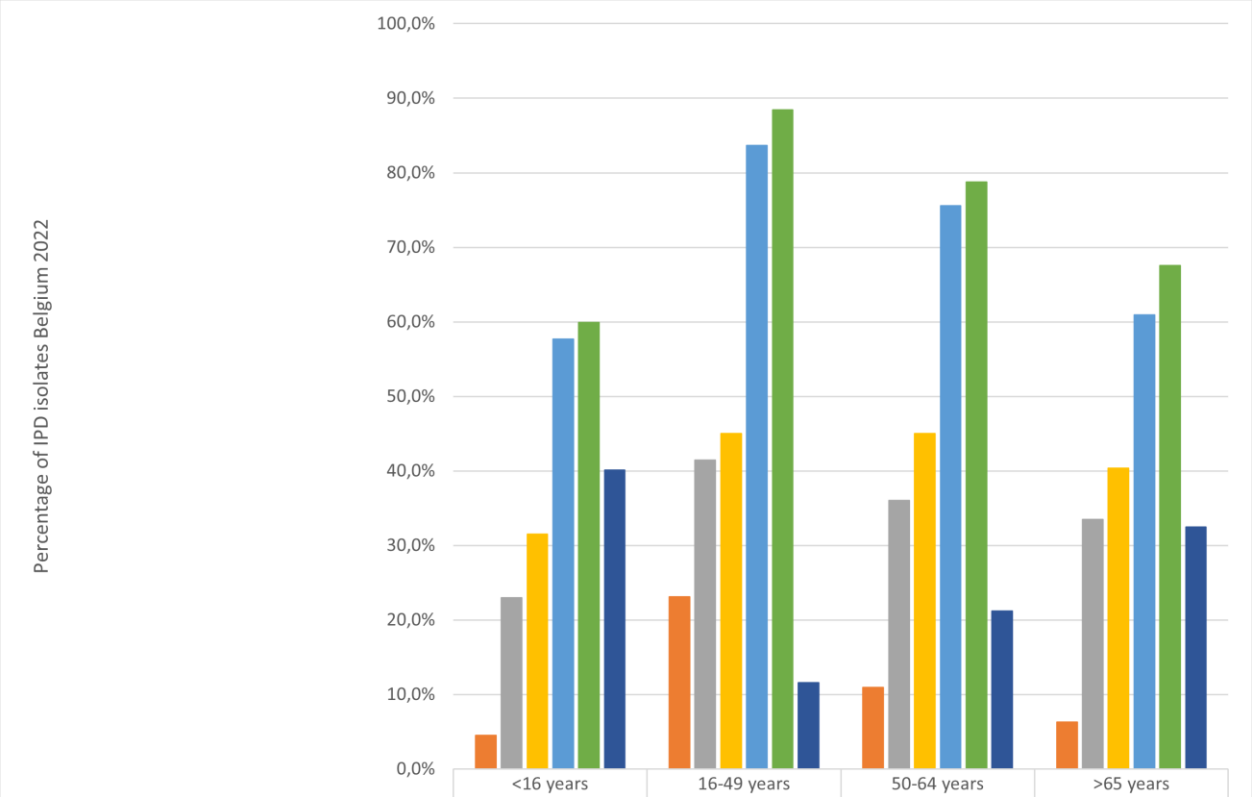
PCV15 and PCV20 are both approved for use in adults, but only PCV15 has also approval for use in children since 2022. The most recent advices of the Superior Health council regarding pneumococcal immunisation for adults[1] and children[2] can be found at the website of the Superior Health Council.

In Figure 4, we analysed the serotype coverage of the 5 currently available vaccines (PCV10, PCV13, PCV15, PCV20 and the 23-valent polysaccharide vaccine (PPV23)) based on the serotype distribution of

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

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

the invasive pneumococcal strains per age group in 2022. The proportion of PCV15 non-PCV13 serotype and PCV20 non-PCV13 serotype IPD ranges respectively from 3.6 to 9.0% and 27.5 to 42.2% depending on the age group.



	<16 years	16-49 years	50-64 years	>65 years
PCV10 serotypes	4,5%	23,1%	10,9%	6,3%
PCV13 serotypes	23,0%	41,4%	36,0%	33,5%
PCV15 (PCV13 + 22F + 33F) serotypes	31,5%	45,0%	45,0%	40,3%
PCV20 (PCV15 + 8, 10A, 11A, 12F, 15B) serotypes	57,7%	83,7%	75,6%	60,9%
PPV23	59,9%	88,4%	78,8%	67,5%
non-vaccine serotypes (NVT)	40,1%	11,6%	21,2%	32,5%

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 2022.

2.2. Children < 2 years old

In 2022, 107 invasive pneumococcal isolates from children <2 years old were received at the NRC. This is still a decrease by 25% compared to the number of isolates received in the pre-COVID-19 year 2019 (n=142), but an important increase compared to COVID years 2020 (n=80) and 2021 (n=93).

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 2022. The predominant serotypes in 2022 (with a proportion >5%) are serotypes 19A (14.0%), 33F (10.3%), 10A (9.3%), 11A (8.4%), 23B (7.5%), 12F (5.6%) and 24F (5.6%). Serotypes 11A, 24F and 33F were in the last 5 years not observed among the list of most prevalent serotypes, but serotype 24F and 33F were during the first PCV13 period (2012-2016) already detected as important non-PCV13 serotypes.

Table 3: Serotypes causing IPD in children <2 years old in 2022 categorized based on their inclusion in pneumococcal conjugate vaccines (based on isolations of *S. pneumoniae* from blood, cerebrospinal fluid, pleural fluid and joint fluid) *serotypes only detected in one strain (<1%)

serotype	number	%
PCV7	**2**	**1,9%**
4	1	0,9%
14	1	0,9%
PCV13 non-PCV10	**19**	**17,8%**
3	4	3,7%
19A	15	14,0%
PCV15 non-PCV13	**13**	**12,1%**
22F	2	1,9%
33F	11	10,3%
PCV20 non-PCV15	**28**	**26,2%**
8	1	0,9%
10A	10	9,3%
11A	9	8,4%
12F	6	5,6%
15B	2	1,9%
non-PCV20 serotypes	**45**	**42,1%**
23B	8	7,5%
24F	6	5,6%
38	5	4,7%
7B	4	3,7%
15A	3	2,8%
24B	3	2,8%
6C	2	1,9%
9N	2	1,9%
23A	2	1,9%
24	2	1,9%
35F	2	1,9%
other*	6	5,6%
TOTAL	**107**	**100%**

After the important decrease in serotype 19A proportion in 2021 compared to 2020 (from 43.8% to 14.0%), a stabilisation of serotype 19A proportion at 14.0% was observed in 2022. Increasing proportions were observed for serotypes 33F (+6.0%) and 11A (+5.2%) compared to 2021, while a decreasing trend was seen for serotypes 15A (-3.7%) and 35B (-3.4%). Due to the increase in serotypes 11A and 33F for 2022, the proportion of PCV20 non-PCV15 and PCV15 non-PCV13 serotypes, respectively increased from 23.7 to 26.2% and 7.5% to 12.1%. In 2022, 17.8% 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, MICs are determined for penicillin 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 2018-2022. *change of method mid 2020

antibiotic	2018 n=1571 (%)	2019 n=1592 (%)	2020 n=884 (%)	2021 n=863 (%)	2022 n=1487 (%)
penicillin R					
penicilline MIC > 0.06 mg/L	10.2%	9.9%	15.0%	18.4%	14.3%
penicilline MIC > 2 mg/L	0.0%	0.0%	1.2%	3.6%	2.0%
cefotaxime R					
cefotaxime MIC > 0.5 mg/L	0.2%	0.6%	2.1%	4.9%	3.5%
cefotaxime MIC > 2 mg/L	0.0%	0.1%	0.2%	0.7%	0.2%
tetracycline R	14.0%	14.4%	18.8%	15.1%	14.1%
levofloxacin R	0.1%	0.1%	0.1%	0.1%	0.1%
erythromycin R	15.3%	15.8%	19.8%	16.5%	14.7%

Two hundred and eleven (14.3%) of the 1487 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 two last years (2020 (15.0%) and 2021 (18.4%)). Twenty-nine of these 211 strains had a penicillin MIC above 2 mg/L (non-meningitis R breakpoint). Also for cefotaxime the resistance rates are lower than last year. Fifty-two strains (3.5%) had a cefotaxime MIC > 0.5 mg/L (EUCAST meningitis R breakpoint). Three strains had a MIC above 2 mg/L and were categorized as resistant making use of the EUCAST non-meningitis breakpoint. Tetracycline (14.1%) and erythromycin (14.7%) resistance rates in 2022 are in line with the rates observed in the previous years, with the exception of the year 2020. Levofloxacin resistance remains rare, with 0.1% (2/1487) of the strains interpreted as resistant in 2022. Among the isolates with reduced susceptibility to penicillin in 2022, four serotypes accounted each for >14% of the isolates, more specifically serotypes 24F, 11A, 23B and 6C.

4. Pneumococcal vaccines

Last 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 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 2015-2022. (source: personal communication with Pfizer Belgium and MSD Belgium). (*ex-factory doses PCV13 in 2022: paediatric: 351948; adult: 12896, not taking into account significant parallel import of PCV13)

Year	2014	2015	2016	2017	2018	2019	2020	2021	2022
Number of blood culture isolates	1153	1280	1257	1421	1477	1503	837	817	1401
Pneumovax (PPV23)	72154	63494	75768	110992	105029	122604	152950	185991	76445
Synflorix (PCV10)		103661	326545	368288	359056	209962			
Prevenar 13 (PCV13)	394637	304768	68775	88036	93888	126420	518016	406278	364844*
Vaxneuvance (PCV15)									873
Apexxnar (PCV20)									33111

For adult pneumococcal immunisation in Belgium in 2022, four different vaccines could be used: PPV23, PCV13, PCV15 and PCV20. The number of PPV23 vaccine doses sold in 2022 decreased by about 60% compared to 2021. 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, it is estimated that, even with the introduction of new higher-valent vaccines, the immunisation of patients at risk decreased in 2022. This is very worrisome and needs further attention. Despite the high vaccination grade in the youngest children (> 95%), the vaccination rate in adult risk groups remains below 35%[3-6].

5. References

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