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Report National Reference Centre *Streptococcus pneumoniae* 2021

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 2021.

1. Characteristics of surveillance in 2021

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.

During the last 10 years, 121 laboratories were involved in this surveillance, with a yearly mean of 92 laboratories sending isolates to the NRC. Likewise in 2020, also in 2021 the pneumococcal epidemiology was disturbed. We observed a steep reduction (-47%) in the number of IPD isolates received at the NRC compared to 2019 (pre-COVID year). (Figure 1)

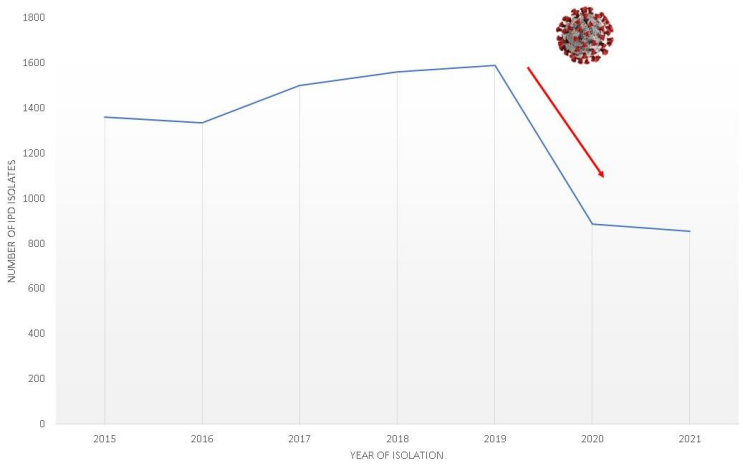


Figure 1: Evolution of the number of IPD (invasive pneumococcal disease) isolates received at the National Reference Centre from 2015 to 2021. Arrow indicates the decrease in cases due to the COVID-19 pandemic and its containment measures.

This trend is also observed in other countries. It is assumed that the surveillance itself remained stable. While the number of hospitals sending more than 5 strains (n=57) remained stable compared to 2020, a lower number of different laboratories (n = 85) sent pneumococcal strains to our NRC (Table 1). Supported by the results of the published international study to which the NRC contributed (Brueggemann *et al*. Lancet Digital Health 2021), 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.

Table 1: Characteristics of the surveillance of the Belgian National Reference Centre invasive *S. pneumoniae* during the period of 2017-2021. (IPD: invasive pneumococcal disease; *:taking into account mergers of laboratories)

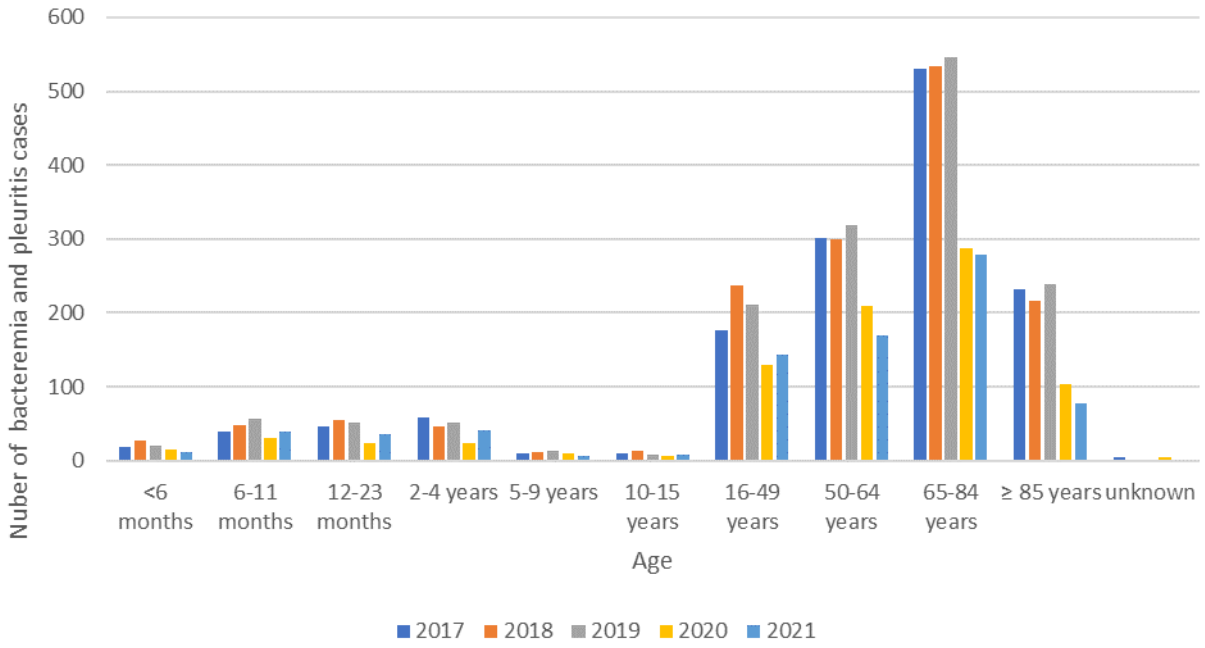
		2017	2018	2019	2020	2021
number of unique IPD isolates sent to the NRC		1518	1571	1592	884	863
number of laboratories* involved in surveillance						
	all	91	91	92	93	85
	sending more than 5 isolates per year	76	75	70	55	57
	located in Flanders	53	53	54	55	50
	located in Wallonia	28	29	28	28	26
	located in Brussels	10	9	10	10	9
regional distribution of all isolates based on residence of patient (percentage)						
	Flanders	63.0%	63.8%	66.8%	64.3%	58.2%
	Wallonia	25.5%	26.1%	23.3%	25.4%	24.8%
	Brussels	11.4%	9.9%	9.3%	8.8%	13.9%
	other/unknown	0.1%	0.2%	0.5%	1.5%	3.1%

Due to the remarkable lower number of strains received in 2020 and 2021, comparison of this year's data with the data from previous years is complicated. Changes between 2021 and previous years need to be interpreted with caution.

A total of 916 pneumococcal strains, with 863 unique IPD strains, were received in 2021. A majority of the strains were isolated from blood cultures (89%) and cerebrospinal fluid (4%). More IPD strains were identified from males (59%) compared to females (40%).

Figure 2 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 decrease in the number of isolates received compared to pre-COVID years. Compared to 2020, we observe in 2021 a slightly higher number of bacteremia and pleuritis cases in children aged 6 months - 4 years, and a lower number of cases in adults aged 50-64 years and >= 85 years. The numbers of meningitis cases per age group are too low to draw a meaningful conclusion regarding the comparison between data of 2021 and 2020.

a



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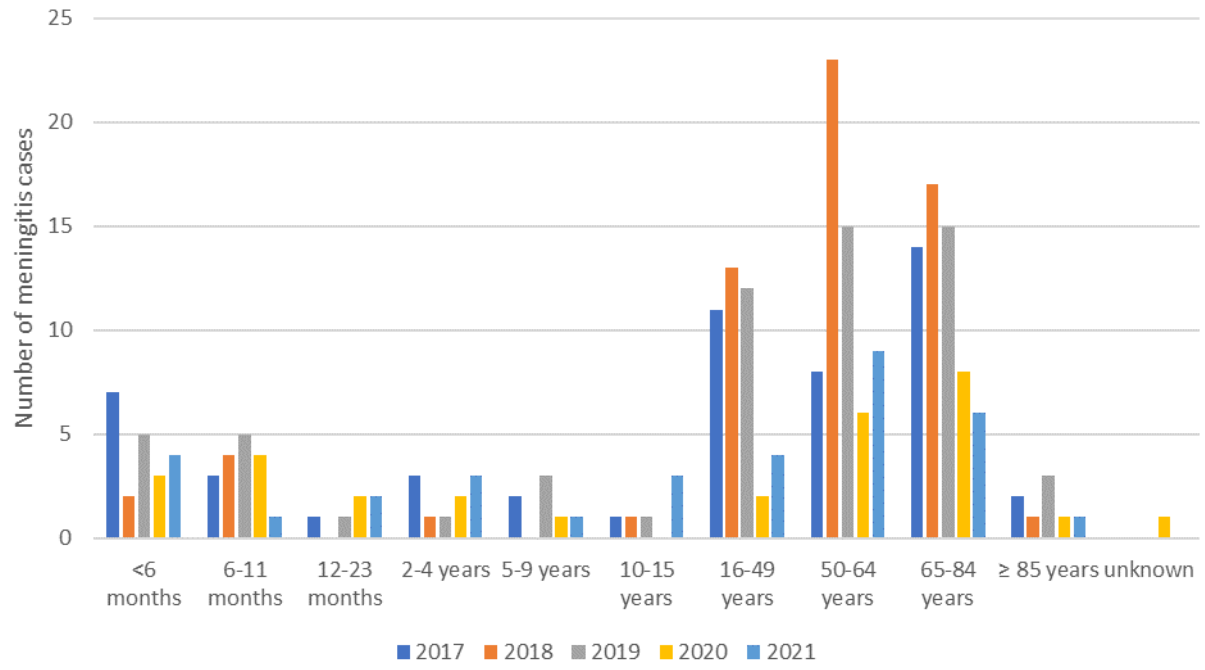


Figure 2: Evolution of the number of (a) bacteremia/pleuritis and (b) meningitis cases based on origin of isolation of *S. pneumoniae* isolates sent to the NRC per age group. Bacteremia/pleuritis: isolation of *S. pneumoniae* from blood culture and/or pleural fluid. Meningitis: isolation of *S. pneumoniae* from cerebrospinal fluid with or without isolation of *S. pneumoniae* from blood culture.

2. Serotype distribution of invasive pneumococcal isolates

2.1. All ages

Table 2 describes in descending order of frequency the serotypes detected in 2021. The serotype distribution is determined per age group. Overall, serotype 8 is the most prevalent serotype responsible for 14.7% of the IPD isolates in 2021. Serotypes 19A (13.6%), 3 (10.7%), 23B (5.4%) and 6C (4.5%) complete the top 5 of most frequently detected serotypes. Compared to 2020, a decrease of the proportion of serotype 19A (-5.7%) and serotype 12F (-3.5%) was observed, while the proportion of serotypes 8, 3 and 23B remained mainly stable. Interestingly, the proportion of serotype 4 (4.4%), a vaccine serotype, increased compared to previous years. The increase in serotype 4 was mainly observed in patients aged 16-64 years old. 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 8 (3.1% in children versus 16.1% in older adults), serotype 23B (12.4% versus 2.8%), serotype 19A (18.6% versus 13.3%) and serotype 6C (1.9% versus 7.3%).

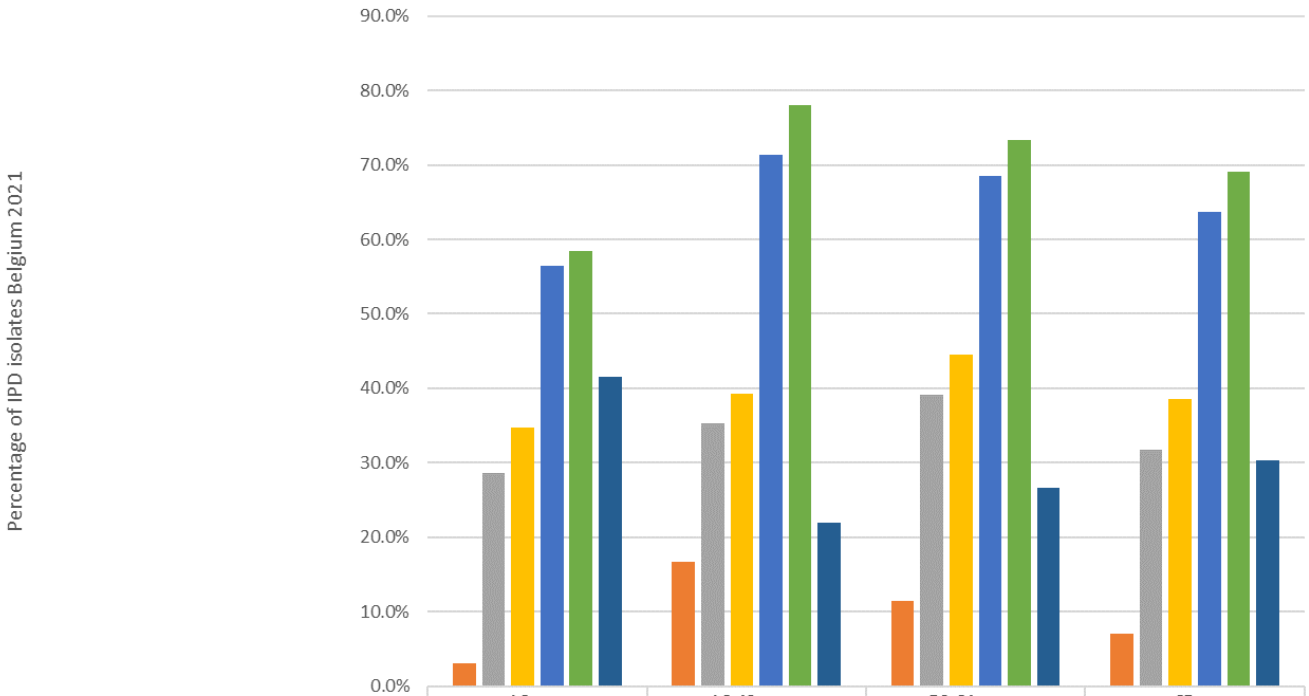
Two new pneumococcal conjugate vaccines (PCVs) were authorized in the European Union by the European Medicines Agency (EMA) in 2021-2021:

- 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.

At the moment of writing of this report, both PCV15 and PCV20 are authorized by EMA for active immunisation to prevent invasive disease and pneumoniae caused by *S. pneumoniae* in adults ≥ 18 years old. In Figure 3 we analyzed 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 the invasive pneumococcal strains per age group in 2021.

Table 2: Distribution of serotypes of IPD isolates from 2022 (n=863) per age group. (colour code: orang: 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=161)	16-49 years (n=150)	50-64 years (n=184)	65-84 years (n=286)	>85 years (n=80)	all ages (n=863)
8	PCV20	3.1%	24.7%	17.4%	16.1%	7.5%	14.7%
19A	PCV13	18.6%	8.0%	12.5%	13.3%	17.5%	13.6%
3	PCV13	6.8%	10.7%	15.2%	9.8%	10.0%	10.7%
23B	NVT	12.4%	4.0%	5.4%	2.8%	3.8%	5.4%
6C	NVT	1.9%	1.3%	3.3%	7.3%	8.8%	4.5%
4	PCV7	0.6%	11.3%	8.2%	1.4%	1.3%	4.4%
9N	PPV23	0.6%	4.0%	3.8%	4.9%	2.5%	3.5%
15A	NVT	5.0%	2.7%	3.3%	2.8%	5.0%	3.5%
10A	PCV20	6.2%	0.0%	2.2%	3.8%	5.0%	3.4%
22F	PCV15	2.5%	1.3%	2.7%	4.5%	3.8%	3.1%
12F	PCV20	6.2%	3.3%	1.6%	2.8%	1.3%	3.1%
11A	PCV20	2.5%	2.7%	2.2%	2.8%	5.0%	2.8%
33F	PCV15	3.7%	2.7%	2.7%	2.1%	3.8%	2.8%
16F	NVT	1.9%	2.7%	4.3%	2.4%	1.3%	2.7%
23A	NVT	1.2%	4.0%	2.2%	2.4%	1.3%	2.3%
14	PCV7	1.9%	1.3%	1.6%	3.1%	3.8%	2.3%
35B	NVT	2.5%	0.7%	0.5%	2.1%	5.0%	1.9%
15B	PCV20	3.7%	1.3%	0.5%	1.0%	1.3%	1.5%
31	NVT	0.6%	0.7%	1.1%	2.1%	1.3%	1.3%
19F	PCV7	0.6%	2.0%	0.0%	1.7%	0.0%	1.0%
35F	NVT	1.9%	0.7%	0.5%	1.0%	1.3%	1.0%
7B	NVT	0.0%	0.7%	0.5%	1.7%	1.3%	0.9%
24F	NVT	3.1%	0.7%	0.5%	0.0%	1.3%	0.9%
10B	NVT	1.2%	0.7%	0.0%	1.4%	0.0%	0.8%
24A	NVT	1.9%	1.3%	1.1%	0.0%	0.0%	0.8%
20	PPV23	0.0%	1.3%	0.5%	1.0%	0.0%	0.7%
17F	PPV23	0.6%	1.3%	0.5%	0.3%	1.3%	0.7%
15C	NVT	1.9%	0.7%	0.0%	0.3%	1.3%	0.7%
7F	PCV10	0.0%	1.3%	0.5%	0.3%	0.0%	0.5%
non-typable	NVT	0.0%	0.7%	0.5%	0.3%	1.3%	0.5%
21	NVT	2.5%	0.0%	0.0%	0.0%	0.0%	0.5%
other serotypes (< 0.5% all ages)		4.3%	1.3%	4.3%	3.8%	3.8%	3.6%



	<16 years	16-49 years	50-64 years	>= 65 years
PCV10 serotypes	3.1%	16.7%	11.4%	7.1%
PCV13 serotypes	28.6%	35.3%	39.1%	31.7%
PCV15 (PCV13 + 22F + 33F) serotypes	34.8%	39.3%	44.6%	38.5%
PCV20 (PCV15 + 8, 10A,11A, 12F, 15B) serotypes	56.5%	71.3%	68.5%	63.7%
PPV23	58.4%	78.0%	73.4%	69.1%
non-vaccine serotypes (NVT)	41.6%	22.0%	26.6%	30.3%

Figure 3: 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 2021.

2.2. Children < 2 years old

In 2021, 93 invasive pneumococcal isolates from children < 2 years old were received at the NRC. This is a decrease by 35% compared to the number of isolates received in the pre-COVID-19 year 2019 (n=142), and a slight increase compared to 2020 (n=80). Due to the lower number of cases in the COVID-19 years, changes in serotype distribution need to be interpreted with caution in this youngest age group.

Table 3 indicates the serotype distribution of invasive isolates (blood, cerebrospinal fluid, pleural fluid and joint fluid) in children during the first two years of life by capsular type in 2021. The predominant serotypes in 2021 are serotypes 19A (14.0%), 10A (7.5%), 12F (6.5%), 15A (6.5%) and 23B (6.5%). Serotypes 10A and 15A were in previous years never observed in the top 5 of most prevalent serotypes. Interestingly is the decrease in serotype 19A (-29.8%) and serotype 12F (-3.5%) proportions and the increase of serotype 10A (+3.7%) and serotype 15A (+6.5%) proportions compared to 2020. The decrease in serotype 19A results in a decrease in the proportion of PCV13 non-PCV10 serotypes from 47.5% in 2020, to 19.4% in 2021. In 2021, 23.7% of cases were caused by serotypes included in PCV13.

Table 3: Serotypes causing IPD in children <2 years old in 2021 categorized based on there 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 (<2%)

serotype	number	%
PCV7	**4**	**4.3%**
4	1	1.1%
14	2	2.2%
19F	1	1.1%
PCV13 non-PCV10	**18**	**19.4%**
3	5	5.4%
19A	13	14.0%
PCV15 non-PCV13	**7**	**7.5%**
22F	3	3.2%
33F	4	4.3%
PCV20 non-PCV15	**22**	**23.7%**
8	2	2.2%
10A	7	7.5%
11A	3	3.2%
12F	6	6.5%
15B	4	4.3%
non-PCV20 serotypes	**42**	**45.2%**
15A	6	6.5%
23B	6	6.5%
35B	4	4.3%
21	3	3.2%
24F	3	3.2%
35F	3	3.2%
24	2	2.2%
10B	2	2.2%
15C	2	2.2%
24A	2	2.2%
other*	9	9.7%

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 contrast to previous reports from the NRC and 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 2018-2021. *change of method mid 2020

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

One hundred and fifty-nine (18.4%) of the 863 strains showed a reduced susceptibility to penicillin (MIC > 0.06 mg/L= EUCAST epidemiological cut-off and meningitis R breakpoint), which is higher than in previous years (2018 (10.2%); 2019 (9.9%); 2020 (15.0%)). Thirty-one of these 159 strains had a penicillin MIC above 2 mg/L (non-meningitis R breakpoint)). We assume that the change in method to determine the MIC is the main reason for the higher resistance rate. Also for cefotaxime the resistance rates are higher than in previous years, which may also be related to the change in method. Forty-two strains (4.9%) had a cefotaxime MIC > 0.5 mg/L (EUCAST meningitis R breakpoint). Six strains had a MIC above 2 mg/L and were categorized as resistant making use of the EUCAST non-meningitis breakpoint. Tetracycline (15.1%) and erythromycin (16.5%) resistance rates in 2021 are again in line with the rates observed in 2018 and 2019. Levofloxacine resistance remains rare, with 0.1% (1/863) of the strains interpreted as resistant in 2021.

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 2014-2021. (*ex-factory doses PCV13 in 2021: pediatric: 353089; adult: 53189)

year	2014	2015	2016	2017	2018	2019	2020	2021
number of blood culture isolates	1153	1280	1257	1421	1477	1503	837	817
Pneumovax (PPV23)	72154	63494	75768	110992	105029	122604	152950	185991
Prevenar 7 (PCV7)								
Prevenar 13 (PCV13)	394637	304768	68775	88036	93888	126420	518016	406278*
Synflorix (PCV10)		103661	326545	368288	359056	209962		

Both PPV23 and PCV13 are used for adult pneumococcal immunization in Belgium. Despite an increase in ex-factory doses of PPV23 in 2021 compared to previous years, a decrease by 67 % in PCV13 doses for adults was observed in 2021 (53.189 doses) compared to 2020 (157.022 doses) (source: personal communication with Pfizer Belgium and MSD Belgium). This decrease in total doses for adults is 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%[1-4].

5. References

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6. Acknowledgements

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