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Rapid increase in serotype 4 invasive pneumococcal disease among vulnerable young male adults in Belgium (2020-2024)

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ABSTRACT

Objectives: Invasive pneumococcal disease (IPD) remains a significant global health threat. Although pneumococcal conjugate vaccines have considerably reduced the burden of IPD after their implementation, changes in serotype distribution do occur. This study examines the epidemiology of serotype 4 IPD in Belgium from 2007 to 2024, focusing on a recent and pronounced increase in cases. The aim is to identify and characterize high-risk populations.

Methods: Epidemiologic data from the passive laboratory-based IPD surveillance, as conducted by the national reference center for invasive pneumococci at UZ Leuven, were used to study the evolution of serotype 4 IPD over time. Because clinical and behavioral data are lacking in the nationwide surveillance, this was complemented with a multicenter sub-analysis for 248 serotype 4 cases (2020 to mid-2024), which represented 61% of all serotype 4 IPD cases within that period. Patient records were retrospectively consulted, and information was captured in REDCap.

Results: A notable resurgence of serotype 4 IPD cases was noticed, beginning in 2020 and peaked in 2023 as the third most common serotype causing IPD in Belgium. This increase was primarily seen among young adult males (18-49 years old) residing in large urban areas (Brussels Capital Region, Antwerp, Liège, Namur, and Hainaut). The sub-analysis revealed that a high proportion of these patients were unemployed (60.9%), experienced homelessness or unstable housing (30.2%), and reported substance use (72.6%). Tobacco (63.3%) and heavy alcohol consumption (35.1%) were the most reported, whereas a subgroup used hard drugs (26.6%).

Conclusion: This study identifies a specific population of vulnerable adults at risk for serotype 4 IPD, emphasizing the need for a specific prevention strategy. Vaccination of this risk group with a pneumococcal

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vaccine targeting serotype 4 is needed to reduce the increasing burden of invasive disease caused by this vaccine serotype.

Introduction

Invasive pneumococcal disease (IPD) is a common cause of mortality, mainly affecting young children (<5 years) and older adults (>65 years). Over 100 capsular serotypes are described [1], of which a limited number can be prevented using pneumococcal conjugated vaccines (PCVs), helping to reduce the IPD burden [2]. Pneumococcal vaccination has been part of Belgium's childhood immunization program since 2007, achieving a high and stable uptake of >95% for the youngest children [3], in contrast to adult risk groups at <30% [4]. At first, PCV7 (Prevnar) was implemented, followed by periods of use of PCV13 (Prevnar 13, 2011-2015 and 2019-current) and a period of PCV10 use (Synflorix, 2015/2016-2018). For adults, depending on age, risk factors, and co-morbidities, polysaccharide vaccine PPV23 (Pneumovax 23) was advised, with or without PCV13, until 2022. Currently, PCV20 (Prevnar 20) is preferred [5] but only partially reimbursed in specific older adult populations at risk.

After PCV implementation, IPD infections caused by vaccine serotypes dropped significantly, with dynamic changes in serotype distributions observed after vaccine switches in Belgium [6,7]. For over 25 years, the National Reference Centre (NRC) for invasive pneumococci performs IPD epidemiologic surveillance in Belgium covering >90% of Belgian IPD cases [6].

Despite a drastic decline in IPD incidence rates since 2020 (to nearly half pre–COVID-19 level [8,9]), an increase in vaccine-preventable serotype 4 was noted. After lifting containment measures, the overall IPD incidence rose again, accompanied by a continued rapid rise in serotype 4 cases [10,11]. Serotype 4 is a PCV7 serotype, included in all pneumococcal vaccines used and/or licensed since 2007 in Belgium (PCV7, PCV10, PCV13, PCV15, PCV20, and PPV23). Over past decades, increased incidence of serotype 4 IPD has been reported in some countries [12–21], including in outbreaks. Associations with homelessness and/or substance use have been identified [12,14,16]. In the United States and Canada (2010-2018), specific increases of serotype 4 IPD in adults were reported in densely populated cities, whereas a study from Finland, Norway, and Ireland (2015-2019) identified an outbreak of serotype 4 in shipyard workers [13]. Recently, in spring 2025, a third outbreak of serotype 4 was reported in a Finish shipyard, showing close relatedness to the isolates of the two earlier outbreaks [21]. People experiencing homelessness are considered at risk of acquiring IPD [22], raising the question of including them as a risk population for targeted pneumococcal vaccination [22,23].

Epidemiologic data collected at the NRC were used to describe the evolution of serotype 4 IPD from 2007 to 2024 in Belgium. More patient characteristics were collected for a subset of recent serotype 4 cases to understand drivers of the increase and better define groups that would benefit most from preventive measures aiming to halt the further increase in invasive disease.

Materials and methods

Data collection at the NRC for invasive pneumococci

S. pneumoniae isolates were obtained from patients with IPD between 2007 and 2024 and sent from laboratories across Belgium to the NRC for invasive pneumococci at UZ Leuven. Throughout this period, 80 or more laboratories participated in this voluntary surveillance, estimating the coverage of IPD surveillance to be stable around 90% [6]. Surveillance coverage estimates were used to correct incidence rates per 100,000 individuals over time, considering national population data [24]. Capsular typing by Quellung and antimicrobial susceptibility testing were performed for all IPD isolates, as described in previous studies [6,7,25]. Between 2007 and 2024, the NRC received 28,195 unique isolates, of which 727 were typed as serotype 4. To evaluate the clones circulating during the period of serotype 4 increase, all isolates from 2021 and 2022 (n = 140) and a selection from 2023 (73 of 168) were characterized by whole-genome sequencing, as described elsewhere [25], and processed with the GPS pipeline [26] to determine the multi-locus sequence type.

Sub-analysis for recent serotype 4 IPD infections

Additional data were collected for serotype 4 IPD isolates obtained between January 1, 2020 and June 30, 2024 (Figure 1). The NRC received 6153 unique isolates, of which 409 were typed as serotype 4. Of the 62 laboratories that sent serotype 4 isolates, only 13 hospital (group)s with minimal 10 cases between 2020 and mid-2024 were invited to participate to a sub-analysis to collect additional information. Together, they covered 60.6% (248 of 409) of all serotype 4 cases for that period. After approval by the central ethical committee for research of UZ/KU Leuven (S69457) and local ethical committees if needed, study data were collected and managed using REDCap electronic data capture tools [27]. Retrospective data collection was conducted between mid-December 2024 and mid-March 2025 by consulting the respective patient records, without contacting the patient to ask for additional or more detailed information. The variables that were collected, included demographic, clinical, behavioral, and vaccination information, and are listed in detail in the Supplementary Methods. Stable housing was defined when reported specifically or assumed when unstable housing was not reported. Unstable housing was defined as having no fixed address (i.e. under-housing, couch surfing, living in tents or shelter). Individuals recorded to be homeless or living in unstable housing were grouped as persons living in frailty. Migrants were defined as residents in Belgium holding a different nationality [28].

Statistical analysis

Descriptive statistics summarized demographic, clinical, and microbiological variables for the subset of 248 serotype 4 IPD cases. Categorical data were expressed as frequencies, rates, or proportions. Chi-square tests were used to evaluate differences between serotype 4 IPD cases of subgroups for profession, social status, substance use, country of birth, and nationality for all cases and on the provincial level. P <0.05 were considered to be significant, using Bonferroni correction to account for multiple comparisons. Comparison with non-serotype 4 IPD cases was not possible due to data constraints. All analyses were performed in RStudio (v12.1).

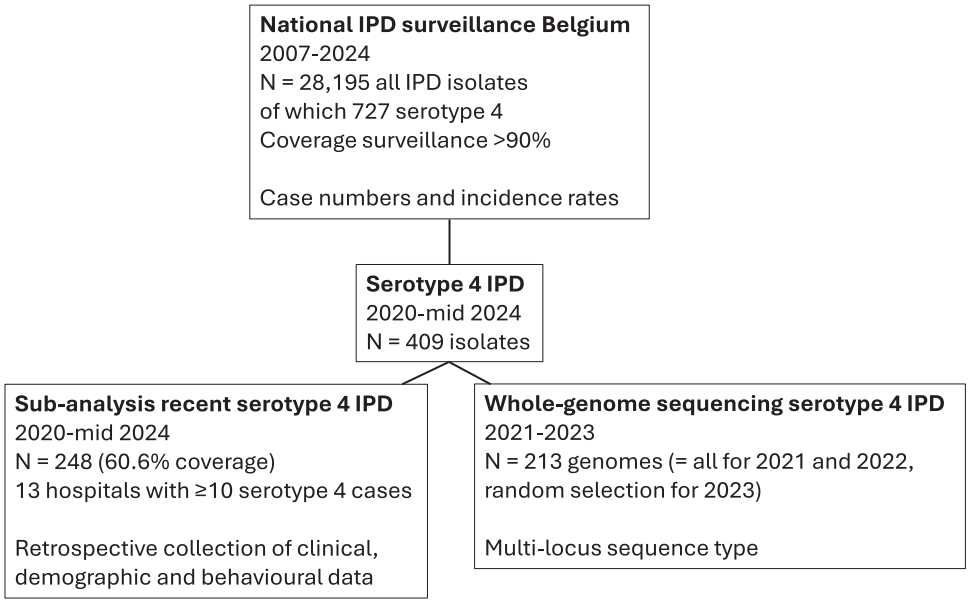

Figure 1. Flowchart of IPD data collection. Flowchart of data collected within the national surveillance of invasive pneumococci in Belgium, hosted at the national reference center at UZ Leuven, followed by downstream analyses (i.e. whole-genome sequencing and sub-analysis of recent serotype 4 IPD cases) and use of additional data sources (i.e. national population data from Statbel [24] for calculation of incidence rates) throughout the manuscript.
IPD, invasive pneumococcal disease.

Results

Rapid increase of serotype 4 IPD in Belgium from 2020 onwards

After PCV7 introduction, the number of serotype 4 IPD cases decreased from 55 in 2007 to 17 in 2011 (incidence rates of 0.6 to 0.2 per 100,000 individuals). Serotype 4 cases continued to decrease to low or rare levels until 2019, with incidence rates fluctuating between 0.03 and 0.1 cases per 100,000 individuals (or between three and nine cases), except for 2013 with 0.2 per 100,000 individuals (n = 15). In parallel, the overall IPD fluctuated between 1225 and 1945 cases per year for 2007-2019 (incidence rates between 13.1 and 22.0 per 100,000 individuals). Despite the important reduction in overall IPD during COVID (2020-2021), there has been a marked increase in serotype 4 infections since early 2020, with cases doubling between 2019 and 2020 (from six to 13 cases), for the latter, to an incidence rate of 0.1 per 100,000 individuals. In 2021, cases rose further to 38 and reaching 102 infections in 2022, with respective incidence rates of 0.3 and 0.9 per 100,000 individuals. The number of serotype 4 cases peaked in 2023, ranking it as the third most frequent IPD serotype in Belgium, accounting for 168 cases (9.6% or incidence rate of 1.5 per 100,000 individuals), following serotypes 8 (13.6%) and 3 (12.8%), which were ranked first and second, respectively. In parallel, the number of overall IPD cases increased again to pre–COVID-19 levels in 2022, followed by an exceedance in 2024 (Figures 2a and b).

Recent increase mainly pronounced in young men living in large cities

Only 1.5% of serotype 4 cases (11 of 727) were diagnosed in children (aged <18 years) between 2007 and 2024, whereas 16.8% of overall IPD cases were diagnosed in children. For 2020-2024, marked by the increase in serotype 4, the mean age was 51.3 years, ranging between 0 and 97 years. Considering all IPD cases for 2020-2024, the mean age was 64 years (0-105 years). Most serotype 4 IPD cases (74.8%, 362 of 484) were identified as younger adults (aged 18-64 years), specifically, aged 18-49 years, accounting for nearly half of all serotype 4 cases between 2020 and 2024 (45.7%). Considering all IPD cases of 2023 in those aged 18-49 years, one (25.6%) in four infections was caused by serotype 4. The difference in age distribution for serotype 4 and non-serotype 4 IPD cases is detailed for 2019-2024 in Table 1. Although 59.3% of serotype 4 infections between 2007 and 2019 were observed in males, from 2020 onward, this further increased to 76.7%. For 2020-2024, the highest proportions of serotype 4 were found in five provinces: Brussels Capital Region (29.8%), Hainaut (16.5%), Antwerp (15.3%), Liège (14.5%), and Namur (5.8%). This geographical spread differs from non-serotype 4 IPD, with their top 5 provinces being Antwerp (17.6%), East-Flanders (13.8%), West-Flanders (11.3%), Flemish Brabant (11.0%), and Hainaut (10.7%). On a more refined scale, recent serotype 4 cases (2020 to mid-2024) are mainly concentrated in five large cities within these provinces: Antwerp city, Brussels Capital Region, Charleroi, Liège city, and Namur City (Figure 3), whereas in other larger cities where overall IPD is also high, no disproportional increase of serotype 4 was observed. Most IPD cases (96.1%) were diagnosed with bacteremia (with or without pneumonia), followed by meningitis (3.5%) and other clinical diagnoses (0.4%).

Two predominant serotype 4 clones in Belgium

All serotype 4 isolates from 2007-2024 were determined to be susceptible to penicillin and cefotaxime. For the increase in serotype 4 cases of 2020 onward, resistance rates of 4.8% were identified for tetracycline, 2.3% for erythromycin, and 0.2% for cotrimoxazole. An analysis of 213 serotype 4 genomes, sampled in 2021-2023, showed the predominance of two circulating clones (95.3%), specifically, ST801 (71.8%) and ST15063 (23.5%). Six additional multi-locus sequence types were identified, all representing one case, except for ST205, with four cases and ST800 with two cases. Nearly all serotype 4 cases from the province of Antwerp were assigned to ST15063 (92.7%), whereas ST801 dominated all other cities.

Demographics and clinical characteristics of serotype 4 sub-analysis

The 13 hospitals participating in the sub-analysis are located in one of the five large cities with higher serotype 4 proportions

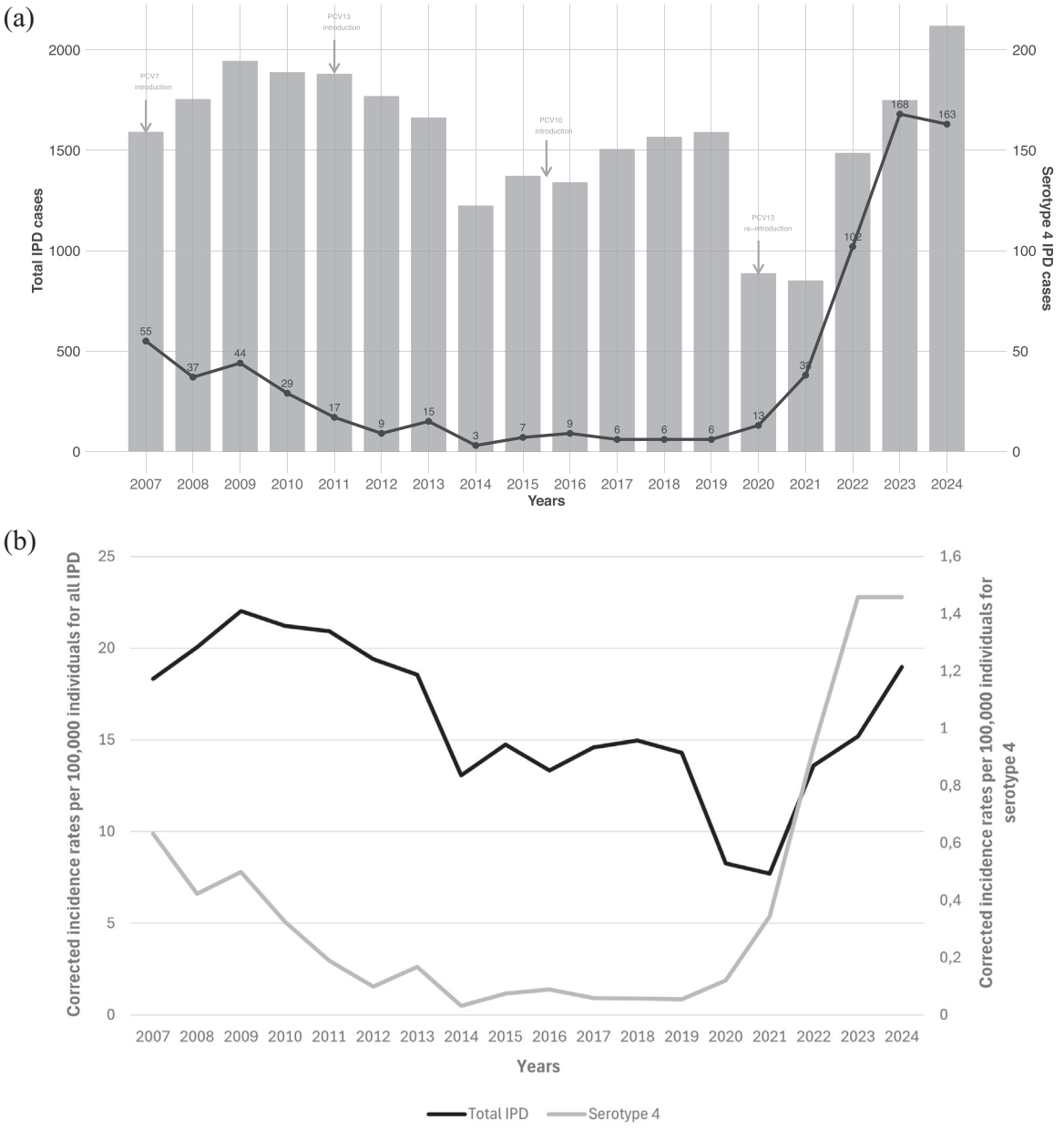

Figure 2. Evolution of case numbers and incidence rates of IPD serotype 4 in Belgium (2007-2024). (a) Number of IPD cases in Belgium between 2007 and 2024: on the main y-axis, the total IPD cases (grey bars) are shown, with serotype 4 case numbers on the secondary y-axis (black line). The introduction of the different PCVs within the national childhood vaccination program is indicated above the downward pointing arrows. (b) Incidence rates per 100,000 individuals (corrected by the coverage estimates of the national IPD surveillance) for total IPD cases (in grey) and serotype 4 cases (black) between 2007 and 2024 in Belgium.
IPD, invasive pneumococcal disease; PCV, pneumococcal conjugate vaccine.

Table 1
Age distribution of serotype 4 IPD cases and non-serotype 4 IPD cases for the years 2019-2024. The total number of IPD infections in both categories is listed, with the number and respective percentage for the following age categories: <5 years, 5-17, 18-49, 50-64, 65-84 years, ≥85 years, and unknown.

Age group (years)	2019		2020		2021		2022		2023		2024	
	Serotype 4	Non-serotype 4	Serotype 4	Non-serotype 4	Serotype 4	Non-serotype 4	Serotype 4	Non-serotype 4	Serotype 4	Non-serotype 4	Serotype 4	Non-serotype 4
<5	0 (0.0%)	197 (12.4%)	0 (0.0%)	113 (12.9%)	0 (0.0%)	141 (17.3%)	1 (1.0%)	170 (12.3%)	1 (0.6%)	181 (11.4%)	0 (0.0%)	205 (10.5%)
5-17	0 (0.0%)	30 (1.9%)	0 (0.0%)	17 (1.9%)	0 (0.0%)	16 (2.0%)	2 (2.0%)	54 (3.9%)	1 (0.6%)	54 (3.4%)	1 (0.6%)	72 (3.7%)
18-49	1 (16.7%)	219 (13.8%)	7 (53.8%)	124 (4.2%)	17 (44.7%)	129 (15.8%)	47 (46.1%)	199 (14.4%)	79 (47.0%)	230 (14.5%)	71 (43.6%)	264 (13.5%)
50-64	1 (16.7%)	336 (21.2%)	3 (23.1%)	217 (24.8%)	16 (42.1%)	166 (20.4%)	27 (26.5%)	283 (20.4%)	48 (28.6%)	320 (20.2%)	47 (28.8%)	379 (19.4%)
65-84	2 (33.3%)	562 (35.5%)	3 (23.1%)	297 (33.9%)	4 (10.5%)	282 (34.6%)	24 (23.5%)	471 (34.0%)	36 (21.4%)	567 (35.8%)	38 (23.3%)	767 (39.2%)
≥85	2 (33.3%)	241 (15.2%)	0 (0.0%)	105 (12.0%)	1 (2.6%)	79 (9.7%)	1 (1.0%)	207 (14.9%)	3 (1.8%)	228 (14.4%)	5 (3.1%)	268 (13.7%)
Unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	2 (0.1%)	1 (0.6%)	2 (0.1%)
Total	**6**	**1585**	**13**	**875**	**38**	**814**	**102**	**1385**	**168**	**1582**	**163**	**1957**

IPD, invasive pneumococcal disease.

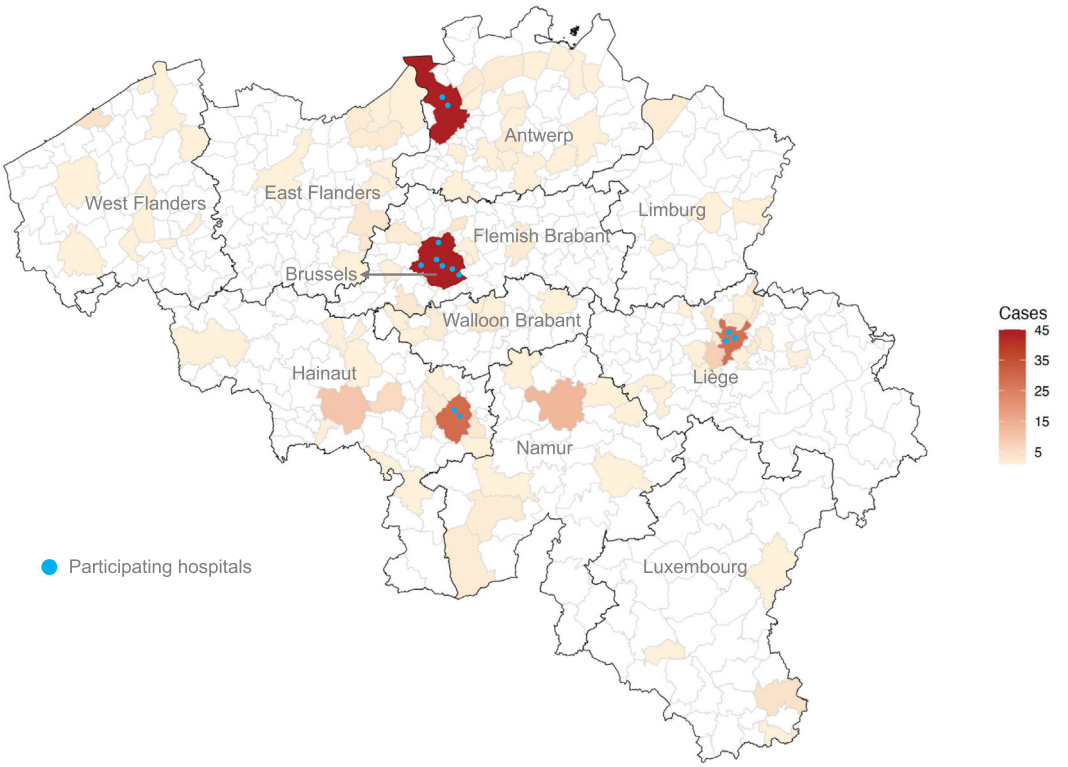

Figure 3. Geographical distribution of IPD serotype 4 cases in Belgium. Heat map illustrating the distribution of serotype 4 cases in Belgium from January 2020 to June 2024 (N = 409). Number of patients are grouped by municipality and visualized using a red color scale on the map. Data for Brussels include the 19 municipalities within the Brussels Capital region. The blue points indicate the locations of hospitals participating in the sub-analysis study, showing that these hospitals are located in the cities with the highest proportion of serotype 4 cases.
IPD, invasive pneumococcal disease.

(Figure 3). The coverage of serotype 4 cases included in the sub-analysis (n = 248) of the total serotype 4 cases diagnosed for 2020 to mid-2024 (n = 409) was highest for Liège (98.1%) and Brussels Capital Region (97.4%) and lower for Antwerp (58.5%) and Hainaut (41.8%). The mean age of the 248 included patients was 52 years (range 2-97 years), with 79.8% being male. The main proportion of serotype 4 cases was diagnosed in those aged 18-49 years (44.0%), followed by those aged 50-64 years (31.1%) and 65-84 years (19.0%) (Table 2). Although for Brussels Capital Region, Hainaut, and Liège, around 70% and more of cases were among those between 18 and 64 years old; for Antwerp, this was 63.1%, with slightly more patients being aged ≥65 years. Most isolates were collected from blood (98.4%), and bacteremia with pneumoniae was the main clinical presentation. Nine cases were diagnosed with meningitis. Overall, 23.8% of patients were admitted to the intensive care unit (ICU), of which 79.7% were aged <65 years. Nine patients died within 7 days after IPD diagnosis, of which seven were admitted to the ICU, characterized with a mortality rate of 11.9% at the ICU (seven of 59 patients). Only five patients were declared to be vaccinated, of which the vaccination type was known for four cases (PCV13, PCV13+PPV23, PPV23, and PCV20).

Most patients were Belgian (69.4%), which is a significantly higher proportion than non-Belgians (24.6%, P <0.001). The top 3 non-Belgian nationalities were Moroccan (6.9%), Polish (2.8%), and Portuguese (2.0%). Interestingly, of all patients with Belgian nationality, 12.8% were born outside Belgium: seven in Morocco, two in Poland, six in other European countries, five in Africa, and two in Asia. In comparison, overall, around 22% of persons with Belgian nationality have an origin outside Belgium [24]. Nearly 61% of all cases were unemployed, significantly more than those being retired or employed (both P <0.00001). Although significantly more patients were unemployed than employed for Brussels Capital Region (P <0.00001), Hainaut (P = 0.0041), and Liège (P <0.00001), this was not true for Antwerp (P = 0.0903). In Antwerp, less than 40% of individuals were unemployed (Table 2).

Behavioral features of serotype 4 sub-analysis

Significantly more persons were living in a stable housing situation than those living in frailty (P <0.0001), although 21.8% experienced homelessness. The proportion of patients with stable housing was significantly higher in provinces Antwerp and Hainaut than in Brussels Capital Region (P <0.005), with especially few persons living in frailty in Antwerp (15.8%) (Table 3). For nearly 73% of the study population, substance use was reported. Among them, all but three used soft drugs, with the most prevalent drugs being tobacco (88.7%), heavy alcohol (49.2%), and cannabis (22.0%). Hard drug use was reported by over 36% of substance users, with cocaine most frequently reported (66.7%), followed by opioids (57.6%) and injection drug use without specification of the used substance (24.2%). Nearly 24% were classified as users of soft and hard drugs. No significant differences were observed between the provinces in the proportion of persons who used soft drugs, hard drugs, or a combination (P <0.05).

Discussion

Our findings reveal a rapid increase in serotype 4 IPD cases in Belgium beginning in 2020, despite the drastic reduction in overall IPD incidence, and peaking in 2023 as the third most frequent IPD serotype. This resurgence is predominantly observed in young men (aged 18-49 years) residing in large urban centers. A sub-analysis of recent serotype 4 cases identified many patients as unemployed and tobacco smokers, whereas an important proportion is living in

Table 2
Demographic and clinical variables IPD serotype 4 sub-analysis. Descriptive table of the demographic and clinical variables evaluated for the 248 patients with serotype 4 IPD included in the sub-analysis study.

Demographic and clinical characteristics		Belgium total n (%)	Antwerp n (%)	Brussels n (%)	Hainaut n (%)	Liège n (%)	Other provinces n (%)
Total		248	38	114	28	53	15
Age range (years)							
	<5	1 (0.4)			1 (3.6)		
	5-17	4 (1.6)		3 (2.6)		1 (1.9)	
	18-49	109 (44.0)	15 (39.5)	52 (45.6)	15 (53.6)	17 (32.1)	10 (66.7)
	50-64	77 (31.0)	9 (23.6)	37 (32.5)	7 (25.0)	20 (37.7)	4 (26.7)
	65-84	47 (19.0)	11 (29.0)	18 (15.8)	5 (17.9)	12 (22.6)	1 (6.7)
	≥85	10 (4.0)	3 (7.9)	4 (3.5)		3 (5.7)	
Gender							
	Male	198 (79.8)	27 (71.1)	97 (85.1)	20 (71.4)	41 (77.4)	13 (86.7)
	Female	50 (20.2)	11 (28.9)	17 (14.9)	8 (28.6)	12 (22.6)	2 (13.3)
Source of isolate							
	Blood	244 (98.4)	36 (94.7)	113 (99.1)	28 (100)	53 (100)	14 (93.3)
	Cerebrospinal fluid	3 (1.2)	2 (5.3)	1 (0.9)			
	Punction fluid	1 (0.4)					1 (6.7)
Hospital admission ward							
	Intensive care unit	59 (23.8)	12 (31.6)	26 (22.8)	4 (14.3)	12 (22.6)	5 (33.3)
	Non-intensive care unit	189 (76.2)	26 (68.4)	88 (77.2)	24 (85.7)	41 (77.4)	10 (66.7)
Clinical presentation							
	Bacteremia with pneumonia	195 (78.6)	34 (89.5)	90 (79.0)	23 (82.1)	36 (67.9)	12 (80.0)
	Sepsis (with pneumonia)	35 (14.1)		18 (15.7)	3 (10.7)	13 (24.5)	1 (6.7)
	Meningitis	9 (3.6)	1 (2.7)	4 (3.5)		3 (5.6)	1 (6.7)
	Bacteremia without focus	6 (2.4)	2(5.3)	2 (1.8)	2 (7.1)		
	Other IPD	3 (1.2)	1 (2.7)			1 (1.9)	1 (6.7)
Mortality							
	Alive	237 (95.6)	37 (97.4)	108 (94.7)	25 (89.3)	52 (98.1)	15 (100)
	Death	9 (3.6)	1 (2.6)	5 (4.4)	2 (7.1)	1 (1.9)	
	Unknown	2 (0.8)		1 (0.9)	1 (3.6)		
Nationality							
	Belgium	172 (69.4)	25 (65.8)	63 (55.3)	27 (96.4)	45 (84.9)	12 (80.0)
	Non-Belgium	61 (24.6)	13 (34.2)	39 (34.2)	1 (3.6)	6 (11.3)	2 (13.3)
	Morocco	17 (6.9)	1 (2.6)	14 (12.3)		1 (1.9)	1 (6.7)
	Other Europe[a]	15 (6.1)	2 (5.3)	9 (7.9)	1 (3.6)	3 (5.7)	
	Africa[a]	12 (4.8)	3 (7.9)	9 (7.9)			
	Poland	7 (2.8)	5 (13.2)	1 (0.9)			1 (6.7)
	Portugal	5 (2.0)		3 (2.6)		2 (3.8)	
	Brazil	3 (1.2)		3 (2.6)			
	Asia[a]	2 (0.8)	2 (5.3)				
	Unknown	15 (6.1)		12 (10.5)		2 (3.8)	1 (6.7)
Country of birth							
	Belgium	84 (33.9)	20 (52.6)	27 (23.7)	9 (32.1)	24 (45.3)	4 (26.7)
	Non-Belgium	69 (27.8)	18 (47.4)	36 (31.6)	1 (3.6)	10 (18.9)	4 (26.7)
	Morocco	22 (8.9)	4 (10.5)	16 (14.0)		1 (1.9)	1 (6.7)
	Other Europe[a]	13 (5.2)	1 (2.6)	7 (6.1)	1 (3.6)	3 (5.7)	1 (6.7)
	Africa[a]	16 (6.5)	4 (10.5)	9 (7.9)		2 (3.8)	1 (6.7)
	Poland	9 (3.6)	5 (13.2)	2 (1.7)		1 (1.9)	1 (6.7)
	Portugal	3 (1.2)		1 (0.9)		2 (3.8)	
	Brazil	1 (0.4)		1 (0.9)			
	Asia[a]	5 (2.0)	4 (10.5)			1 (1.9)	
	Unknown	95 (38.3)		51 (44.7)	18 (64.3)	19 (35.9)	7 (46.7)
Profession							
	Unemployed	151 (60.9)	15 (39.5)	77 (67.5)	18 (64.3)	32 (60.4)	9 (60.0)
	Retired[b]/Medical leave	56 (22.6)	15 (39.5)	21 (18.4)	5 (17.9)	14 (26.4)	1 (6.7)
	Employed	41 (16.5)	8 (21.1)	16 (14.0)	5 (17.9)	7 (13.2)	5 (33.3)
	Manual labor/construction	16 (6.5)	2 (5.3)	5 (4.4)	4 (14.3)	3 (5.7)	2 (13.3)
	Service industry/hospitality	13 (5.2)	4 (10.5)	6 (5.3)		1 (1.9)	2 (13.3)
	Other	12 (4.8)	2 (5.3)	5 (4.4)	1 (3.6)	3 (5.7)	1 (6.7)

IPD, invasive pneumococcal disease.
[a] A total of <3 cases per country
[b] persons aged ≥65 years unless stated otherwise or at a younger age when specifically reported.

frailty (e.g. homeless), uses hard drugs, and has a migration background. Nearly one in four patients required intensive care, stressing the need to implement preventive measures for this at-risk population.

The suggested risk factors driving this serotype 4 increase in Belgium are consistent with international observations [12–21]; associations with homelessness, unstable housing, and substance use among young adult males in urban settings have been previously reported [12,14,16,29]. Recent Belgian reports indicate an increase in the number of people experiencing homelessness, particularly, in Brussels, Charleroi, and Namur [30,31]. Homeless populations are well known to be at high risk of invasive bacterial infections and respiratory infections due to poorer health status, higher frequency of co-morbidities, and crowding situations [30,32,33], making them potentially more vulnerable to severe diseases. A recent shift in substance use (from heroin to crack) and associated in-

Table 3
Behavioral characteristics invasive pneumococcal disease serotype 4 sub-analysis. Descriptive table of the behavioral features evaluated for the 248 patients with serotype 4 invasive pneumococcal disease included in the sub-analysis study.

Behavioral characteristics			Belgium total n (%)	Antwerp n (%)	Brussels n (%)	Hainaut n (%)	Liège n (%)	Other provinces n (%)
Total			248	38	114	28	53	15
Housing								
	Stable		133 (53.6)	31 (81.6)	46 (40.4)	20 (71.4)	28 (52.8)	8 (53.3)
	Frailty							
		Homeless	54 (21.8)	3 (7.9)	30 (26.3)	5 (17.9)	13 (24.5)	3 (20.0)
		Unstable	21 (8.5)	3 (7.9)	9 (7.9)	2 (7.1)	6 (11.3)	1 (6.7)
	Institutionalized	7 (2.8)		3 (2.6)		4 (7.6)		
	Unknown		33 (13.3)	1 (2.6)	26 (22.8)	1 (3.6)	2 (3.8)	3 (20.0)
Substance use	(current and/or former)							
	No		48 (19.4)	5 (13.2)	19 (16.7)	11 (39.3)	12 (22.6)	1 (6.7)
	Unknown		20 (8.1)	4 (10.5)	10 (8.8)		2 (3.8)	4 (26.7)
	Yes		180 (72.6)	29 (76.3)	85 (74.6)	17 (60.7)	39 (73.6)	10 (66.7)
	Soft drugs		177 (71.4)	28 (73.7)	84 (73.7)	17 (60.7)	39 (73.6)	9 (60.0)
		Tobacco	157 (63.3)	26 (68.4)	76 (66.7)	15 (53.6)	32 (60.4)	8 (53.3)
	Heavy alcohol use	87 (35.1)	12 (31.6)	40 (35.1)	9 (32.1)	23 (43.4)	3 (20.0)	
		Cannabis	39 (15.7)	3 (7.9)	15 (13.2)	8 (28.6)	9 (17.0)	4 (26.7)
	Benzodiazepines/ antipsychotics	6 (2.4)		1 (1.8)		5 (9.4)		
	Hard drugs		66 (26.6)	8 (21.1)	24 (21.1)	10 (35.7)	21 (39.6)	3 (20)
		Cocaine	44 (17.7)	5 (13.2)	21 (18.4)	8 (28.6)	9 (17)	1 (6.7)
	Opioids (including heroin)	38 (15.3)	3 (7.9)	9 (7.9)	8 (28.6)	18 (33.9)		
	Injection drug use (without specification of used substance)	16 (6.5)	3 (7.9)	6 (5.3)	1 (3.6)	6 (11.3)		
	Methamphetamine	5 (2)	4 (10.5)			1 (6.7)		
	Soft and hard drugs	59 (23.8)	7 (18.4)	23 (20.2)	10 (35.7)	17 (32.0)	2 (13.3)	

creased exposure to toxic smoke might have contributed to the increasing number of serotype 4 cases in Belgium. The identified high prevalence of unemployment highlights the socio-economic vulnerabilities of the affected group. Although earlier studies suggested a link between serotype 4 and outbreaks in specific occupations [13,21], our data reveal a concomitant increase in specific larger Belgian cities (although not all) across Belgium without a clear link to a specific profession. Our findings highlight a critical gap in current vaccination strategies because this (younger) adult risk group is not specifically addressed by the current pneumococcal vaccine recommendations.

Although the overall trend of increasing serotype 4 IPD and its association with vulnerable populations holds, some notable provincial differences were observed. Patients from Antwerp exhibited a higher proportion of stable housing and a lower unemployment rate than other provinces, potentially due to the higher share of older patients. Genomic characterization of 2021-2023 isolates revealed recent circulation of two distinct clones, specifically, STs 801 and 15063 [10]. Remarkably, ST15063 has been mainly identified in Antwerp, whereas ST801 was found across Belgium, alluding to not solely a demographic difference but also behaviorwise. Due to incomplete genomic information for all serotype 4 cases of the sub-analysis, a more detailed comparison of STs was not included in this study. Refined phylogenetic reconstruction and downstream analyses focusing on genetic divergence and virulence factor genes, including serotype 4 genomes from countries outside of Belgium, will help to understand whether the recent increase of serotype 4 IPD is caused by local transmission and close contact between the cases or due to specific advantages of these two serotype 4 clones that make them prone to rapid and increased circulation. Despite some observed provincial disparities in social and behavioral factors, our results underscore the necessity for a national tailored public health intervention. Providing targeted support and care for these vulnerable groups is not only crucial for public health but also a smart way to make the most of health care resources.

One of the main strengths of this study is the more than 25 years of experience of the NRC to perform nationwide IPD surveillance. Furthermore, for a substantial share of recent serotype 4 cases, detailed information was collected, which is essential for identifying risk groups and informing targeted public health interventions. However, the laboratory-based nature of the surveillance necessitated retrospective data collection, relying on existing patient records, potentially being incomplete. Second is the lack of direct comparison of serotype 4 and other IPD serotypes, unfeasible due to data constraints but essential to determine whether risk factors are uniquely linked to serotype 4 or pose a general IPD risk. Furthermore, excluding hospitals with few serotype 4 cases, together resembling a substantial share, could potentially have introduced a selection bias, particularly, whether serotype 4 infections in smaller hospitals would differ with respect to demographics and/or behavior. Finally, our study did not explore all risk factors and co-morbidities known to be associated with IPD, although this could have provided valuable insights into disease severity, patient outcomes, and overall burden on healthcare resources.

Despite limitations, our findings provide a strong basis for understanding the shifting landscape of serotype 4 IPD in Belgium and support identification of a new crucial at-risk population. In new recommendations for adult pneumococcal vaccination, vulnerable groups of tobacco smoking adult males living in certain urban regions, experiencing homelessness, and using hard drugs and/or heavy alcohol (latter for persons aged <50 years) should be identified as at risk for serotype 4 IPD. Moreover, the use of a serotype 4 containing PCV (e.g. PCV15 or PCV20) in favor of a vaccine not including serotype 4 (e.g., PCV21) should be advised for these people, in line with recent American Advisory Committee on Immunization Practices guidelines [34].

Declaration of competing interest

Lize Cuypers reports support for attending meetings and/or travel from MSD. Stefanie Desmet reports consulting fees and pay-

ment or honoraria for lectures, presentations, speakers bureaus, manuscript writing, or educational events, both from MSD. Nicolas Dauby reports consulting or advisory and funding grants from MSD; speaking and lecture fees from AstraZeneca; and support for travel from MSD, Gilead, and ViiV Healthcare. Maya Hites reports support for travel from Pfizer, MSD, and Gilead; consulting or advisory from MSD and Gilead; and board membership from Société Belge d'Infectiologie et Microbiologie Clinique. Katrien Lagrou received consultancy fees from Mundipharma; speaker fees from Pfizer, Gilead, Mundipharma, and FUJIFILM Wako chemicals Europe GmbH; a service fee from TECOmedical; a fee for advisory board participation from Pfizer and travel support from Pfizer, Gilead, MSD, and AstraZeneca. Gerardo J. Sanchez, Juan Paula Herra Avila, Sandra Koenig, Gilles Darcis, Sophie Herens, Thomas Antoine-Moussiaux, Henry Paridaens, Reinout Naesens, Fabrizio Buttafuoco, Brice Layeux, Laetitia Brassine, and Philippe Clevenbergh report no conflicts of interest.

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Ethical statement

UZ Leuven is appointed as a national reference center for invasive pneumococci, for which the role to perform epidemiologic surveillance is described in the Royal Decree of September 2, 2011.

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Author contributions

Lize Cuypers was responsible for conceptualization, data curation, formal analysis, investigation, and writing of the original draft. Gerardo J. Sanchez was responsible for data curation, formal analysis, investigation, visualization, and writing the original draft. Stefanie Desmet was responsible for conceptualization, formal analysis, investigation, supervision, and writing of the original draft. Nicolas Dauby was responsible for conceptualization, data curation, and revising the original draft. Katrien Lagrou was responsible for conceptualization and revising the original draft. All other co-authors were responsible for data curation and revising the original draft.

Access to data

Not applicable.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2025.108216.

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