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# Invasive pneumococcal and *Haemophilus influenzae* type b disease in the Autonomous Province of Vojvodina, Serbia (2003–2024): trends, vaccination impact, and serotype dynamics

## Invazivna oboljenja izazvana pneumokokom i hemofilusom influence tipa b u Autonomnoj Pokrajini Vojvodini, Srbija (2003–2024): trendovi, uticaj vakcinacije i dinamika serotipova pneumokoka

**Mioljub Ristić, Vladimir Petrović**

**Institute of Public Health, Novi Sad, Serbia; Faculty of Medicine, Department of Epidemiology, Novi Sad, Serbia**

**Abstract**

**Background/Aim.** Invasive pneumococcal disease (IPD) and invasive *Haemophilus influenzae* type b (Hib) disease remain associated with significant morbidity and mortality. The aim of the study was to analyze long-term trends, age-specific and seasonal disease patterns, clinical outcomes, IPD serotype distribution, and the impact of immunization programs on these diseases in the Autonomous Province (AP) of Vojvodina, Serbia, from 2003 to 2024. **Methods.** A descriptive population-based study was conducted using data from the regional communicable disease surveillance system coordinated by the Institute of Public Health of Vojvodina, Serbia. All reported cases of IPD and invasive Hib disease were included in the analysis. **Results.** The Hib immunization program introduced in 2006 led to a sustained reduction in invasive Hib disease, with only sporadic cases reported after 2009. IPD incidence fluctuated over the study period and has increased in recent years despite high coverage (≥ 90%) of the primary pneumococcal conjugate vaccine (PCV) series since 2019. PCV introduction markedly reduced the frequency of serotypes covered by PCV10. Serotype 3 and non-vaccine serotypes persisted, particularly among adults and infants aged < 1 year. Adults aged ≥ 40 years were predominantly affected by IPD, whereas invasive Hib disease mainly occurred in children aged 1–4 years. None of the patients had been previously vaccinated against IPD or invasive Hib disease. Case-fatality rates were significantly higher for IPD (9.6%) than for Hib disease (3.5%) ($p = 0.0361$). In the overall population, PCV10 serotypes declined sharply after vaccine introduction (from 55% to 22%), while PCV13-non-PCV10 serotypes remained stable (~40%), and non-vaccine serotypes increased (from 11% to 28%), with the additional emergence of PCV20-non-PCV15 serotypes. **Conclusion**. The Hib immunization program achieved sustained disease control in the AP of Vojvodina, while IPD remains a public health concern due to persistent serotype 3 and emerging non-vaccine serotypes. Continued surveillance and consideration of higher-valency pneumococcal vaccine (minimum PCV13) or adult-targeted vaccination strategies are crucial to further reduce disease burden.

**Key words:**
**epidemiology; haemophilus influenzae type b; incidence; pneumonia, pneumococcal; serbia; vaccination.**

**Apstrakt**

**Uvod/Cilj.** Invazivna pneumokokna bolest (*invasive pneumococcal disease* – IPD) i invazivna bolest izazvana bakterijom *Haemophilus influenzae* tipa b (Hib) i dalje su povezane sa značajnim morbiditetom i mortalitetom. Cilj rada bio je da se analiziraju dugoročni trendovi, obrasci specifični za uzrast i sezonski obrasci bolesti, klinički ishodi, distribucija serotipova IPD i uticaj programa imunizacije na ta oboljenja u Autonomnoj Pokrajini (AP) Vojvodini, Srbija, u periodu od 2003. do 2024. godine. **Metode.** Sprovedena je deskriptivna epidemiološka studija korišćenjem podataka iz regionalnog sistema nadzora nad zaraznim bolestima, kojim koordinira Institut za javno zdravlje Vojvodine. U analizu su uključeni svi prijavljeni slučajevi IPD i Hib-izazvane invazivne bolesti. **Rezultati.** Program imunizacije protiv infekcija izazvanih Hib, uveden 2006. godine, doveo je do trajnog sniženja učestalosti Hib-izazvane invazivne bolesti, sa sporadičnim slučajevima oboljenja prijavljenim posle 2009. godine. Incidencija IPD varirala je tokom posmatranog perioda i porasla je u poslednjim godinama, uprkos visokom obuhvatu (≥ 90%) primarnom serijom pneumokokne konjugovane vakcine (*pneumococcal conjugate vaccine* – PCV) od 2019. godine. Uvođenje PCV značajno je smanjilo učestalost serotipova obuhvaćenih PCV10. Serotip 3 i nevakcinalni serotipovi opstali su, naročito među odraslima i odojčadima starosti < 1

**Correspondence to:** Mioljub Ristić, University of Novi Sad, Faculty of Medicine, Institute of Public Health of Vojvodina, Center for Disease Control and Prevention, Futoška 121, 21 000 Novi Sad, Serbia. E-mail: mioljub.ristic@mf.uns.ac.rs

godine. Odrasle osobe starosti ≥ 40 godina pretežno su bile pogođene IPD, dok se Hib-izazvana invazivna bolest javljala uglavnom kod dece uzrasta 1–4 godine. Nijedan od obolelih nije prethodno bio vakcinisan protiv IPD ili Hib-izazvane invazivne bolesti. Stopa smrtnosti bila je značajno viša kod IPD (9,6%) nego kod Hib-izazvane bolesti (3,5%) ($p = 0{,}0361$). U ukupnoj populaciji, učestalost serotipova PCV10 naglo je opala posle uvođenja vakcine (sa 55% na 22%), dok su serotipovi PCV13-ne-PCV10 ostali stabilni (~40%), a prisustvo nevakcinalnih serotipova se povećalo (sa 11% na 28%), uz dodatnu pojavu serotipova PCV20-ne-PCV15. **Zaključak.** Program imunizacije protiv Hib-izazvanih oboljenja obezbedio je zadovoljavajuću kontrolu bolesti u AP Vojvodini, dok, zbog perzistentnog serotipa 3 i novih serotipova koji nisu obuhvaćeni vakcinom, IPD i dalje predstavlja značajan javnozdravstveni problem. Kontinuirani nadzor i razmatranje primene viševalentnih pneumokoknih vakcina (najmanje PCV13) ili strategije vakcinacije usmerene na odrasle osobe su od ključnog značaja za dalje smanjenje tereta bolesti.

**Ključne reči:**
**epidemiologija; hemofilus influence tip b; incidencija; pneumonija, pneumokokna; srbija; vakcinacija.**

## Introduction

Invasive infections caused by *Streptococcus* (*S.*) *pneumoniae* and *Haemophilus influenzae* type b (Hib) remain major global public health concerns, particularly among infants, young children, and older adults [1–3].

In 2022, 17,700 confirmed cases of invasive pneumococcal disease (IPD) were reported in the European Union/European Economic Area (EU/EEA) with a crude incidence of 5.1 *per* 100,000 population (hereafter expressed *per* 100,000). The highest incidence was recorded among infants < 1 year (13.4 *per* 100,000) and adults aged ≥ 65 years (12.6 *per* 100,000) [4]. In the United States (US), the overall IPD incidence is about 8.3 *per* 100,000, ranging from 10.8 in infants to 27.4 in the oldest adults [5]. Case fatality ratios (CFRs) remain high–around 13% in the EU/EEA and 10–12% in the US, depending on clinical presentation [4, 5]. In developing countries, CFRs may reach 20% for sepsis and up to 50% for meningitis [1].

Before Hib conjugate vaccines, invasive Hib disease was a leading cause of bacterial meningitis in young children, with incidence rates up to 50–60 *per* 100,000 in the US and about 23 *per* 100,000 in Europe among children aged 0–4 years [6, 7]. Following widespread vaccine implementation, Hib incidence in high-coverage regions, including Europe, has declined to about 1 *per* 100,000 or less among children under 5 years. In 2022, the EU/EEA reported a CFR of 9.2% for invasive Hib disease [8]. Before vaccine introduction, Hib meningitis in the US accounted for 50–65% of all cases, with a CFR of 3–6% [9].

Conjugate vaccines against pneumococcal and Hib diseases have markedly reduced incidence and mortality worldwide [1, 2, 10–12]. However, vaccine impact varies by serotype distribution, coverage, age, seasonality, and disruptions to routine immunization during public health crises [1–7, 13, 14].

In Serbia, surveillance of IPD and Hib disease is mandatory but largely passive, resulting in limited epidemiological data [15]. Routine immunization with pneumococcal conjugate vaccine (PCV) was introduced in 2018, with PCV10 administered according to a 3+1 schedule: the first dose at 2 months of age, the second at 4 months, the third at 6 months, and a booster dose one year after the third dose. In 2022, PCV13 replaced PCV10 using the same schedule, which shifted to a 2+1 program in 2023. In 2024, PCV10 was reintroduced using the 2+1 schedule, mainly due to economic rather than evidence-based considerations [16–18]. Mandatory Hib immunization with three doses of the monovalent vaccine during the first year of life (starting at two months) was introduced in Serbia in 2006. Since 2015, both primary and booster doses have been given as part of the combined pentavalent (5-in-1) vaccine that protects against diphtheria, tetanus, pertussis, inactivated polio vaccine, and Hib (DTaP-IPV-Hib) vaccine [16]. Pneumococcal and Hib vaccination is also mandatory for individuals at increased risk, particularly those with underlying conditions [17].

These observations highlight the importance of continuous, comprehensive surveillance to monitor vaccine impact, detect potential serotype replacement, and guide immunization policy. Furthermore, insights into age-specific and seasonal patterns of invasive diseases are crucial for tailoring risk-targeted interventions and optimizing resource allocation [1–4, 8–10, 13, 14], which have not been well described in our territory.

The aim of this study was to analyze incidence trends, clinical outcomes, vaccination coverage, age and seasonal distribution, geographic clustering of IPD and Hib disease, as well as pneumococcal serotype changes before and after PCV introduction in the Autonomous Province (AP) of Vojvodina, Serbia. The findings aim to inform national vaccination strategies and address remaining challenges in controlling invasive bacterial diseases.

## Methods

### *Study design and data sources*

This descriptive study was conducted in the AP of Vojvodina, northern Serbia, which has a population of approximately 1.7 million inhabitants, accounting for about 25% of the total population of Serbia [19]. Data were retrieved from the regional communicable disease surveillance system, coordinated by the Institute of Public Health of Vojvodina (IPHV), Novi Sad, Serbia.

All cases (both clinically and laboratory confirmed) of IPD and invasive Hib disease reported between 2003 and 2024 were included in the comprehensive analysis. Hospitals across the AP of Vojvodina submitted notifications of these invasive cases through the national mandatory communicable disease reporting system, as previously described [20].

Case classification followed national surveillance standards and World Health Organization (WHO) guidelines [21, 22]. In addition, the case definition used for IPD was *S. pneumoniae* identified by culture from any normally sterile site (blood, cerebrospinal fluid – CSF, pleural fluid, joint fluid) in a symptomatic person, or *S. pneumoniae* identified in CSF or pleural fluid by antigen detection, immunochromatography, or polymerase chain reaction (PCR) [21]. Similarly, confirmed invasive Hib disease was defined as HiB identified by culture from any normally sterile site (e.g., blood, CSF, pleural fluid, joint fluid) in a symptomatic person, or detected in CSF or pleural fluid by antigen detection, immunochromatography, or PCR [22].

*Statistical analysis*

Demographic (gender, age, place of residence, district of the AP of Vojvodina), temporal (month, year), and clinical (case status, outcome) variables were analyzed. In order to assess specific characteristics (incidence rate, seasonal pattern, frequency of IPD and invasive Hib disease, and serotype distribution of IPD), patients were divided into six age groups: < 1, 1–4, 5–9, 10–19, 20–39, and ≥ 40 years. Annual and age-specific incidence rates *per* 100,000 were calculated using case counts and population estimates for the whole population and specific age groups in the AP of Vojvodina between 2003 and 2024 [19]. Vaccination coverage against diseases caused by *S. pneumoniae* and Hib was assessed using the administrative method [23], as previously described in detail [24]. Seasonal distribution was assessed by calendar month. Comparisons between the two clinical entities (IPD and invasive Hib disease) regarding gender, age, area of residence, district of the AP of Vojvodina, case status, and outcome were performed using Pearson's Chi-square test or Fisher's exact test, as appropriate. The value of $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using SPSS software, version 21 (IBM Corp., Armonk, NY, USA).

Based on officially reported IPD cases (from communicable disease notifications, excluding laboratory notifications) between 2009 and 2024, the serotype distribution was analyzed for the pre-vaccination and vaccination periods, vaccine and non-vaccine serotypes, and age groups.

All annual data, including official communicable disease notifications, were reported to the Center for Disease Control and Prevention at the IPHV as part of the routine communicable disease surveillance system in the province. As described previously [20, 24–26], these surveillance activities involved continuous collaboration between the IPHV and the district Institutes of Public Health located in the administrative centers of the seven districts of the AP of Vojvodina.

*Ethical considerations*

Similar to previously used methodology [20, 24–26], the data used in this retrospective study were derived from routine surveillance conducted between 2003 and 2024 at the Center for Disease Control and Prevention, IPHV, Novi Sad. Therefore, approval from an Ethics Committee was not required under Serbian regulations.

## Results

Annual incidence rates of IPD and invasive Hib disease from 2003 to 2024 are shown in Figure 1.

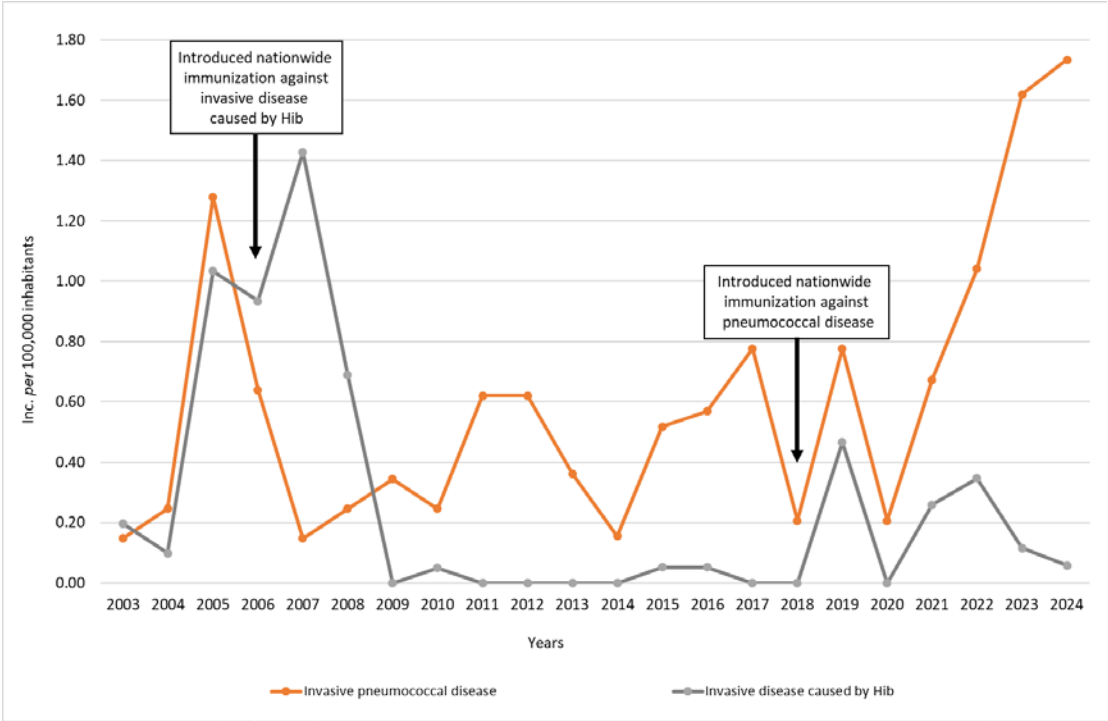


**Fig. 1 – Annual incidence rates of invasive pneumococcal disease and invasive *Haemophilus influenzae* type b (Hib) disease in relation to the introduction of nationwide immunization programs in the Autonomous Province of Vojvodina, Serbia (2003–2024).**

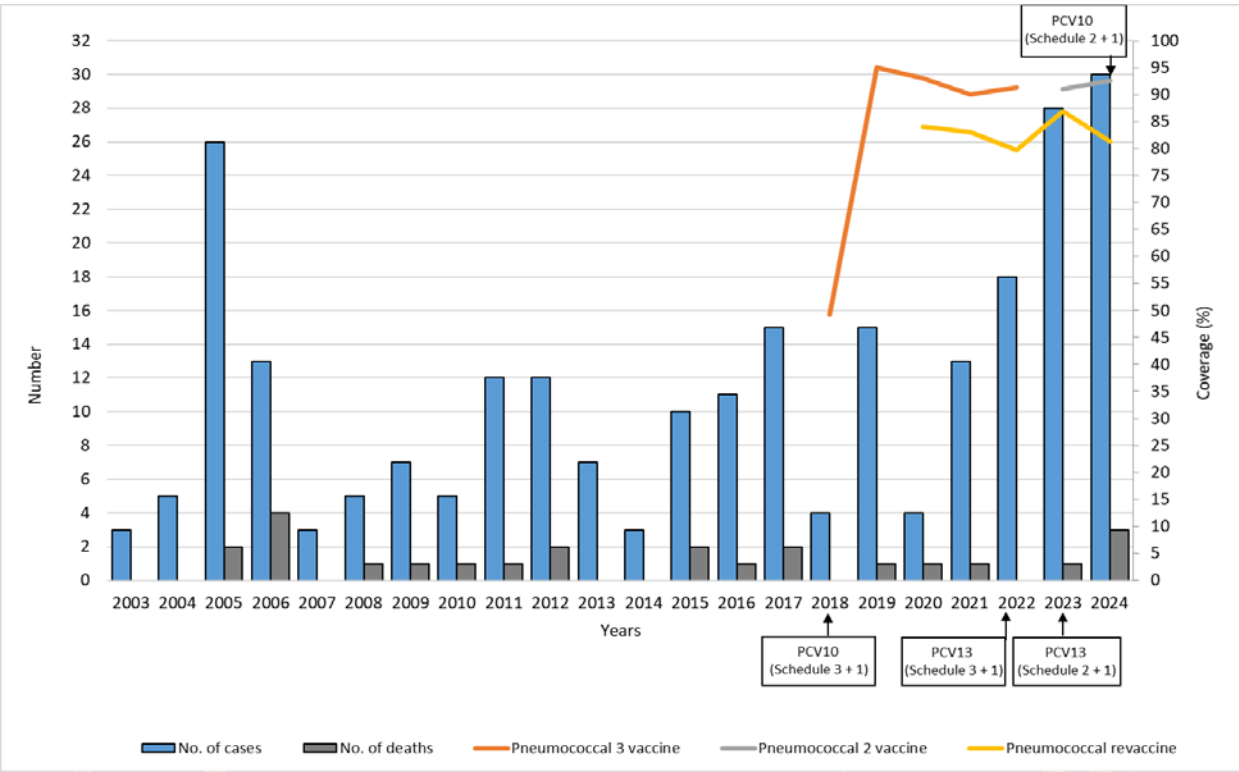


**Fig. 2 – Annual number of invasive pneumococcal disease cases and deaths, and vaccination coverage with primary series and booster doses in the Autonomous Province of Vojvodina, Serbia (2003–2024).**
**PCV – pneumococcal conjugate vaccine; No. – number.**
***Note:*** **numbers after PCV (meaning 'valent') refer to the number of specific strains (serotypes) of pneumococcal bacteria that the vaccine targets.**

IPD incidence fluctuated, ranging from 0.15 *per* 100,000 in 2003 and 2007 to a peak of 1.73 in 2024. Nationwide mandatory pneumococcal vaccination for infants began in 2018.

Invasive Hib disease showed a different trend, peaking in 2007 (1.43 *per* 100,000) and rapidly declining after the introduction of mandatory Hib vaccination in 2006. Between 2009 and 2018, incidence was negligible (≤ 0.05 *per* 100,000), with a brief resurgence in 2019 (0.47 *per* 100,000) and moderate levels in 2021–2022, followed by very low rates in 2023–2024.

IPD cases, fatal outcomes, and pneumococcal vaccination coverage in 2003–2024, including vaccine type, schedule, and timeline, are shown in Figure 2.

Reported IPD cases fluctuated, with lows in 2003, 2007, and 2014 (n = 3) and a peak in 2024 (n = 30).

Fatal outcomes ranged from 1 to 4 *per* year, with the highest number in 2006 (n = 4); most years had 1–2 deaths, and there were 3 deaths in 2024.

Mandatory infant pneumococcal vaccination was initiated in 2018, with coverage for the three-dose primary series increasing from 49.3% in 2018 to ≥ 90% from 2019 onwards. Booster coverage ranged from 79.8% to 86.9% between 2020 and 2023, and coverage for the two-dose primary series introduced in 2023 reached 92.6% in 2024.

Invasive Hib cases, fatal outcomes, and Hib vaccination coverage, including vaccine type, schedule, and timeline, from 2003 to 2024, are shown in Figure 3.

Reported cases peaked in 2005 (n = 21), 2006 (n = 19), and 2007 (n = 29). Fatal outcomes were rare, with only four recorded (2004, 2006, 2010, 2021).

Coverage with the three-dose primary Hib series rose steadily after introduction, exceeding 95% from 2008 to 2019, slightly declining to 94% in 2020 and ≤ 93% between 2021 and 2024. Revaccination began in 2015, with coverage ranging from 81.5% (2022) to 93.2% (2019), generally lower than the primary series.

Between 2003 and 2024, the age-specific incidence of IPD and invasive Hib disease in the AP of Vojvodina showed distinct patterns.

IPD incidence was highest in infants (< 1 year), with a peak especially in 2024 (12.69 *per* 100,000). In adults aged ≥ 40 years, incidence was low until the mid-2010s but increased post-PCV introduction, reaching 2.63 *per* 100,000 in 2024.

For invasive Hib disease, incidence was very high among children aged < 5 years before Hib vaccination, peaking between 2005 and 2007 (22.95 *per* 100,000 in infants; 27.95 *per* 100,000 in those aged 1–4 years). After 2006, incidence dropped sharply, with no cases reported in most years from 2009 onwards. Following the introduction of vaccination in 2018, only two peaks occurred–in 2019 (11.56 *per* 100,000) and 2023 (6.35 *per* 100,000)–both in unvaccinated infants aged < 1 year (Figure 4).

Between 2003 and 2024, IPD and invasive Hib disease in the AP of Vojvodina exhibited clear seasonal patterns. IPD peaked in December (n = 34) and October (n = 30),

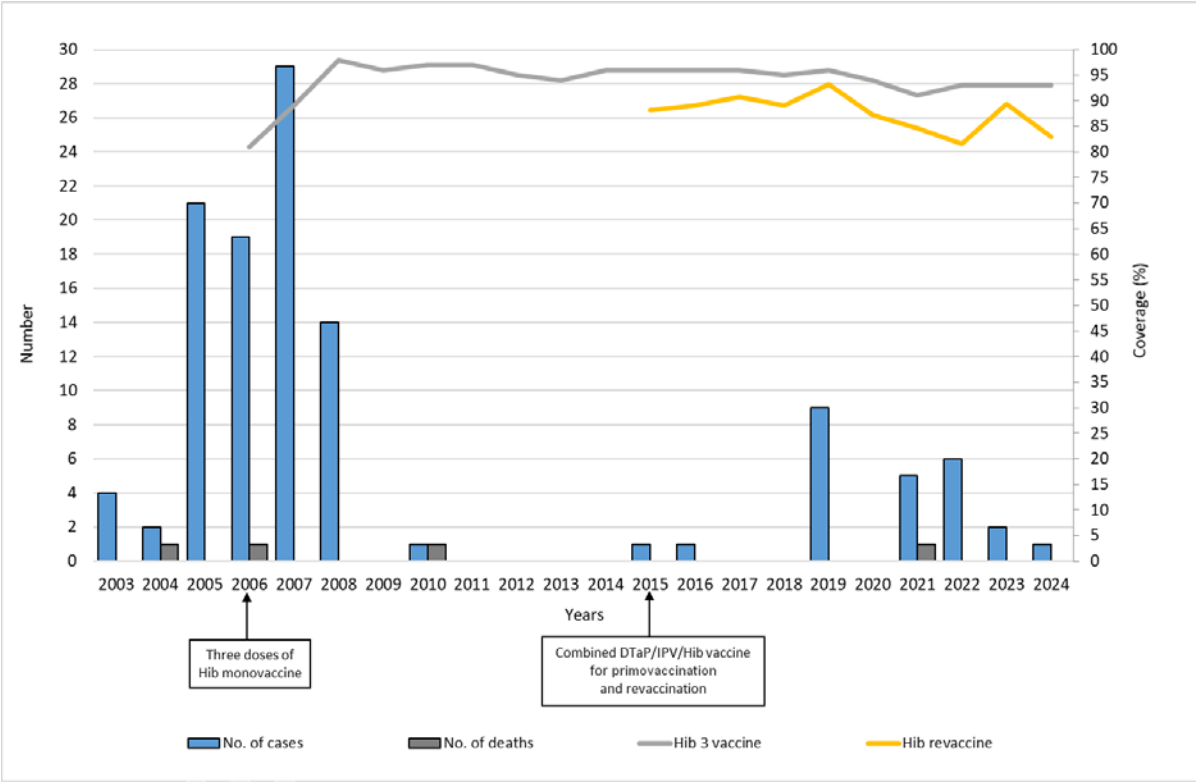


**Fig. 3 – Annual number of invasive *Haemophilus influenzae* type b disease cases and deaths, and vaccination coverage with primary series and booster doses in the Autonomous Province of Vojvodina, Serbia (2003–2024).**
**DTaP-IPV-Hib – vaccine that protects against diphtheria, tetanus, whooping cough, polio, and *Haemophilus influenzae* type B (Hib). No. – number.**

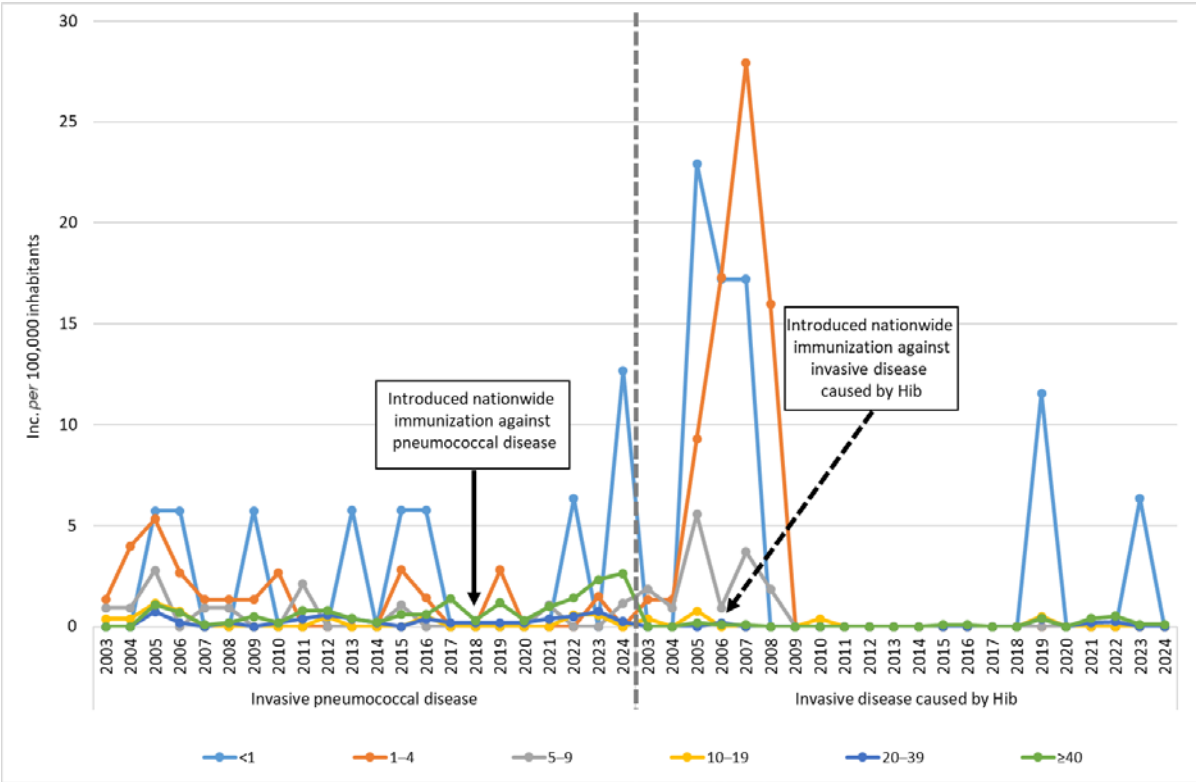


**Fig. 4 – Age-specific incidence rates of invasive pneumococcal disease and invasive disease caused by *Haemophilus influenzae* type b (Hib) in the Autonomous Province of Vojvodina, Serbia (2003–2024).**
***Note:* the grey dashed line represents the dividing line between the two clinical entities.**

accounting for 25.7% of cases. Invasive Hib disease showed pronounced winter predominance, with December (n = 17), October (n = 15), January (n = 14), and February (n = 15) comprising 53% of cases (Figure 5).

Between 2003 and 2024, IPD in the AP of Vojvodina occurred in all age groups, with the highest counts in adults aged ≥ 40 years, especially in winter. Peaks were in December (n = 27) and January (n = 21), accounting for 28.7% of cases in this group, while children aged < 5 years had few cases year-round. Invasive Hib disease primarily affected young children, particularly those aged 1–4 years, who accounted for most cases nearly every month. Between January and March, 24 cases (43.6% of cases in this age group) were recorded, showing strong winter predominance (Figure 6).

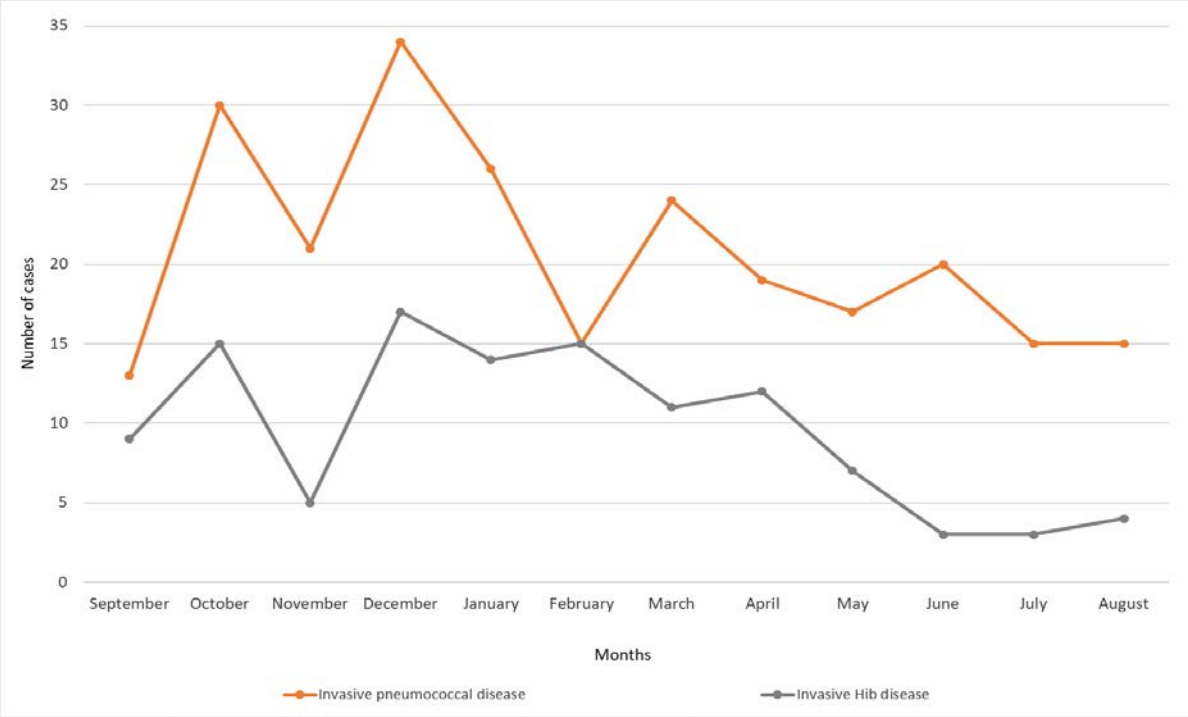


**Fig. 5 – Seasonal distribution of invasive pneumococcal disease and invasive disease caused by *Haemophilus influenzae* type b (Hib) cases in the Autonomous Province of Vojvodina, Serbia (2003–2024).**

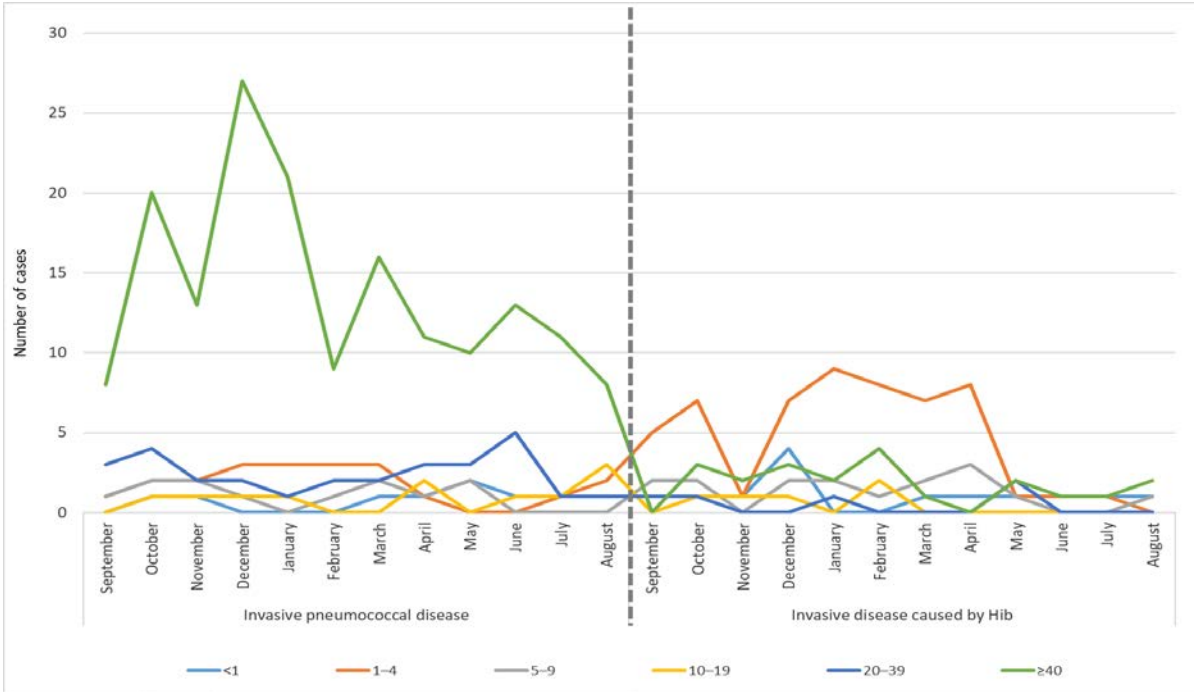


**Fig. 6 – Monthly distribution of invasive pneumococcal and invasive cases caused by *Haemophilus influenzae* type b (Hib) in the Autonomous Province of Vojvodina, Serbia, by age groups (2003–2024).**
***Note:* the grey dashed line represents the dividing line between the two clinical entities.**

None of the patients had received prior vaccination against IPD or invasive Hib disease. No significant gender differences were observed (IPD 62.65% vs. Hib 55.65% of males; $p = 0.2484$). However, age distribution differed markedly ($p < 0.0001$): IPD mainly affected adults aged ≥ 40 years (67.07%), whereas Hib disease predominated in children aged 1–4 years (47.83%). Both diseases were more common in urban residents (IPD 69.48% vs. Hib 74.78%), but this was not statistically significant ($p = 0.3605$). Pronounced geographic clustering was noted ($p < 0.0001$), with over half of IPD cases, i.e., 53.82%, and 85.22% of Hib cases reported from the South Bačka district. Most cases were laboratory-confirmed, with a higher proportion for IPD than Hib (94.38% vs. 86.09%; $p = 0.0135$). Clinical outcomes also differed ($p = 0.0361$): CFR was 9.64% for IPD (24/249) vs. 3.48% for Hib (4/115) (Table 1).

We analyzed 44 serotypes (18% of all laboratory-confirmed IPD cases) reported between 2009 and 2024, including 26 serotypes pre-vaccination and 18 during the vaccination period.

In the AP of Vojvodina, PCV10 serotype cases declined markedly after vaccine introduction. Serotypes 14 and 19F were the most common PCV10 serotypes in the pre-vaccination period (five and four cases, respectively), while single cases of 4, 6B, 18C, and 23F serotypes were also observed. After vaccination, no cases of 4, 9V, 19F, or 23F were detected. Among additional PCV10 serotypes, 7F persisted with one case in each period; serotypes 1 and 5 were absent. For PCV13 serotypes, serotype 3 remained the most frequent (five cases in the pre-vaccine, and six in the post-vaccine period), 6A disappeared after vaccination, and 19A appeared once during the vaccination period.

Extended PCV15 coverage included one 22F case in the pre-vaccination period; 33F was not detected. PCV20-related serotypes were rare, with single cases of serotype 8 in the pre-vaccine period and 11A and 15B during vaccination. No cases were caused by pneumococcal polysaccharide vaccine (PPV)23-exclusive serotypes (2, 9N, 17F, 20). Non-vaccine serotypes represented a small but notable fraction: 23A (two cases in the pre-vaccine period and one in the post-vaccine period), 15A (one case in the pre-vaccine period), and several others detected only during the vaccination period (15C, 28A, 6C, 7C; one case each) (Figure7).

**Table 1**

**Demographic and clinical characteristics of patients with invasive pneumococcal disease and invasive *Haemophilus influenzae* type b (Hib) disease in the Autonomous Province (AP) of Vojvodina, Serbia (2003–2024).**

| Variable | Invasive pneumococcal disease (n = 249) | Invasive Hib disease (n = 115) | *p*-value |
|---|---|---|---|
| Gender | | | |
| male | 156 (62.65) | 64 (55.65) | 0.2484 |
| female | 93 (37.35) | 51 (44.35) | |
| Age group (years) | | | |
| < 1 | 9 (3.61) | 13 (11.30) | < 0.0001 |
| 1–4 | 21 (8.43) | 55 (47.83) | |
| 5–9 | 12 (4.82) | 16 (13.91) | |
| 10–19 | 11 (4.42) | 5 (4.35) | |
| 20–39 | 29 (11.65) | 5 (4.35) | |
| ≥ 40 | 167 (67.07) | 21 (18.26) | |
| Area of residence | | | |
| urban | 173 (69.48) | 86 (74.78) | 0.3605 |
| rural | 76 (30.52) | 29 (25.22) | |
| District of AP of Vojvodina | | | |
| North Bačka | 20 (8.03) | 4 (3.48) | < 0.0001 |
| West Bačka | 17 (6.83) | 2 (1.74) | |
| South Bačka | 134 (53.82) | 98 (85.22) | |
| North Banat | 13 (5.22) | 6 (5.22) | |
| Central Banat | 18 (7.23) | 2 (1.74) | |
| South Banat | 28 (11.24) | 1 (0.87) | |
| Srem | 19 (7.63) | 2 (1.74) | |
| Case status | | | |
| laboratory-confirmed | 235 (94.38) | 99 (86.09) | 0.0135 |
| clinically-confirmed | 14 (5.62) | 16 (13.91) | |
| Outcome | | | |
| survived | 225 (90.36) | 111 (96.52) | 0.0361 |
| fatal cases | 24 (9.64) | 4 (3.48) | |

**All values are given as numbers (percentages).**

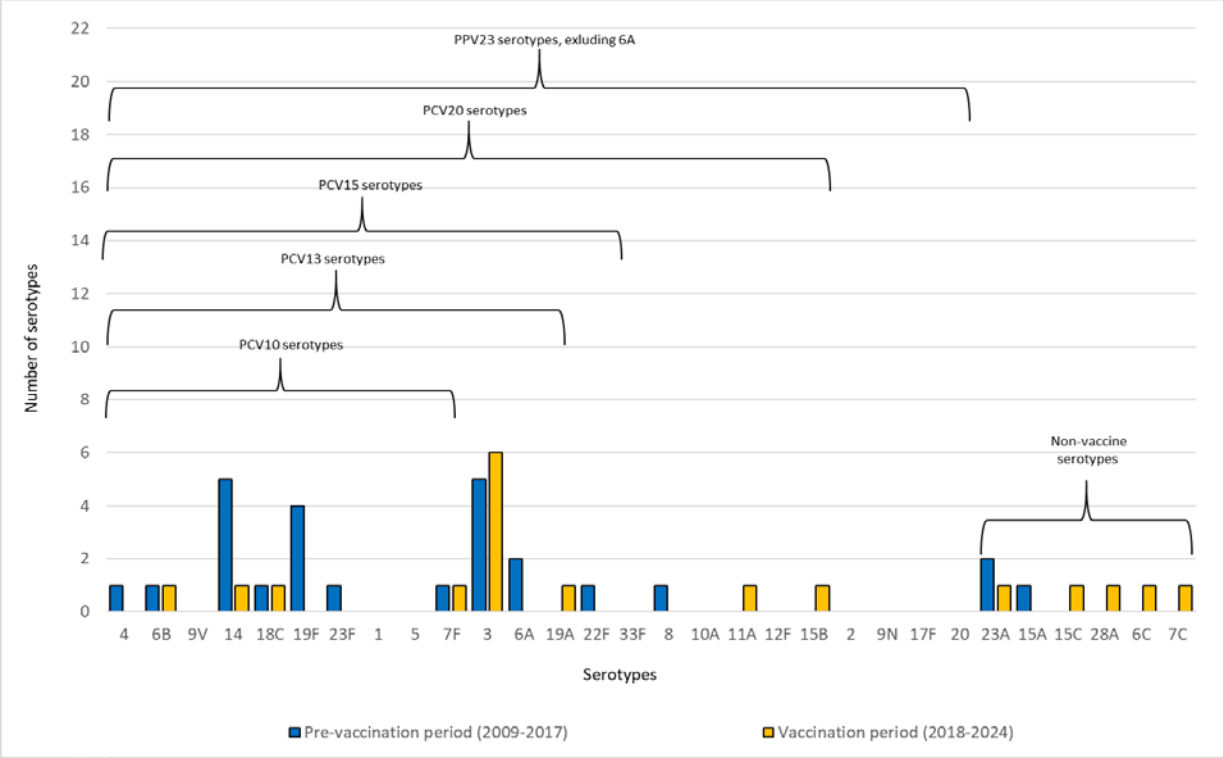


**Fig. 7 – Serotype distribution of invasive pneumococcal disease in the Autonomous Province of Vojvodina, Serbia, before and after vaccine introduction (2009–2024).**
**PCV – pneumococcal conjugate vaccine; PPV– pneumococcal polysaccharide vaccine.**
***Note*: numbers after PCV and PPV (meaning 'valent') refer to the number of specific strains (serotypes) of pneumococcal bacteria that the vaccines target.**

In the overall population, prior to vaccine introduction, PCV10 serotypes accounted for about 55% of cases, PCV13-non-PCV10 serotypes for approximately 25%, and non-vaccine serotypes for 11% of cases, with only a minor proportion (around 4%) attributable to PCV20-non-PCV15 and PCV15-non-PCV13 serotypes. During the vaccination period, the proportion of PCV10 serotypes decreased to 22%, while PCV13-non-PCV10 serotypes remained stable at around 40%. Non-vaccine serotypes increased to 28%, with PCV20-non-PCV15 serotypes contributing 11%.

Among children aged ≤ 5 years, PCV10 serotypes dominated in the pre-vaccination period, accounting for approximately 80% of IPD cases, with the remaining 20% caused by non-vaccine serotypes. In the vaccination period, only one 6B serotype from PCV10 was detected in this age group, while PCV13-non-PCV10, PCV20-non-PCV15, and non-vaccine serotypes each accounted for about 20% of cases.

In adults aged ≥ 40 years, PCV10 serotypes accounted for 47% of IPD cases in the pre-vaccination period, with PCV13-non-PCV10 serotypes representing about 35% and non-vaccine serotypes 6%. During the vaccination period, the share of PCV10 serotypes declined to below 20%, while PCV13-non-PCV10 serotypes increased to about 45%, and non-vaccine serotypes rose to 27%. The proportion of PCV15-non-PCV13 and PCV20-non-PCV15 serotypes remained small in both periods (Figure 8).

During the pre-vaccination period (2009–2017), IPD in children aged < 5 years was most frequently associated with PCV10 serotypes, including serotype 6B (one case in a child aged < 1 year) and serotype 14 (two cases in children aged 1–4 years). Serotype 19F was identified in four cases across age groups (1–4 years, 20–39 years, and ≥ 40 years). Serotype 3 predominated among adults, with five cases recorded (one in the 20–39-year age group and four in those aged ≥ 40 years). Additional cases were attributed to non-vaccine serotypes 15A and 23A, each detected only once or twice, among children aged 1–4 years and adults (Figure 9a).

In the vaccination period (2018–2024), the age distribution shifted. Only sporadic cases of PCV10 serotypes persisted: serotype 6B (one case in a child aged 1–4 years), serotype 14 (one case in an adult aged ≥ 40 years), and serotype 18C (one case in a patient aged 20–39 years). Serotype 3 continued to dominate, with six cases in adults (one in the 20–39-year group and five in those ≥ 40 years). Sporadic cases were also attributed to serotypes 7F, 19A, 11A, and 15B, while several non-vaccine serotypes (23A, 15C, 28A, 6C, and 7C) were recorded, predominantly among adults, and sporadically in children aged 5–9 years. Overall, serotypes 14 and 19F were the leading causes of IPD in adults in the pre-vaccination period, whereas serotype 3 predominated in the same age groups in both periods (Figure 9b).

For the six patients with fatal outcomes for whom serotype characterization was available, the majority were male (5/6), with ages ranging from 3 to 77 years. Four cases originated from urban areas, and meningitis was the leading clinical manifestation, identified in four of the fatal

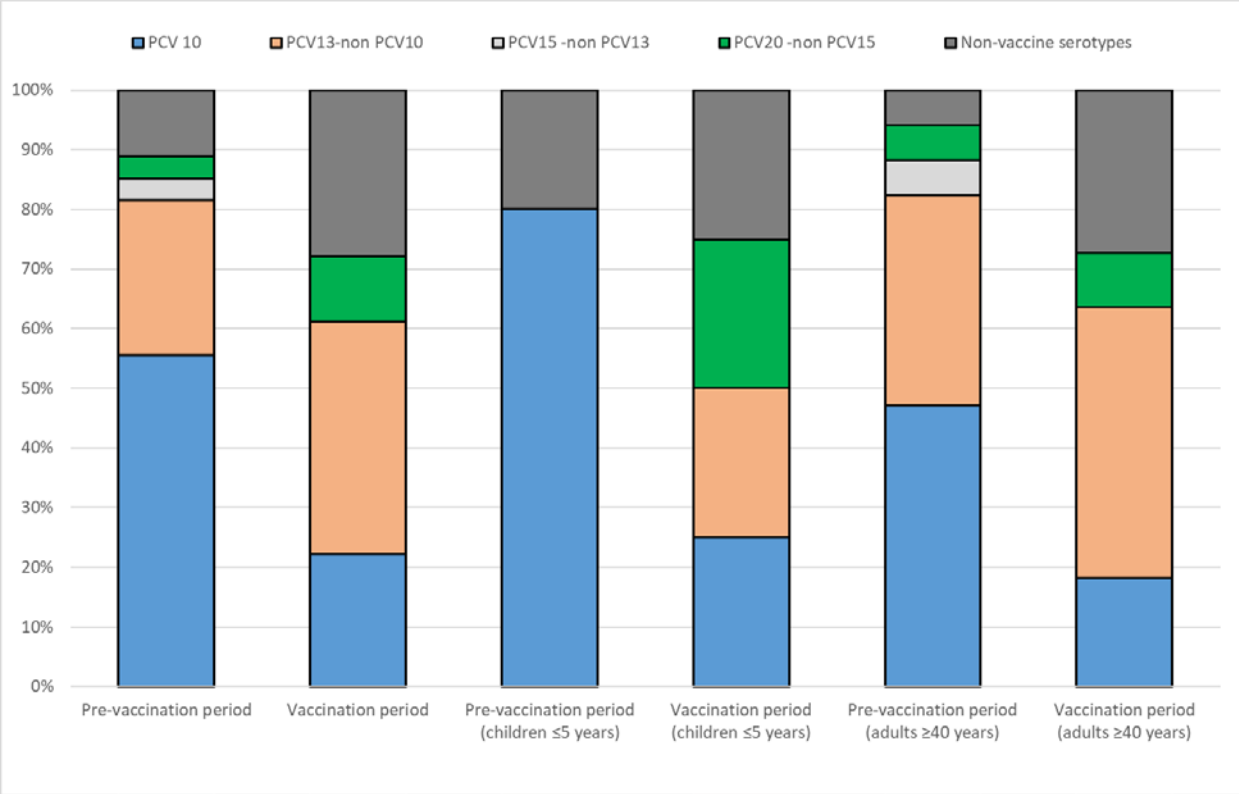


**Fig. 8 – Distribution of invasive pneumococcal disease serotypes by pneumococcal conjugate vaccine (PCV) serotypes coverage in children under 5 years and adults ≥ 40 years, during the pre-vaccination (2009–2017) and vaccination (2018–2024) periods.**

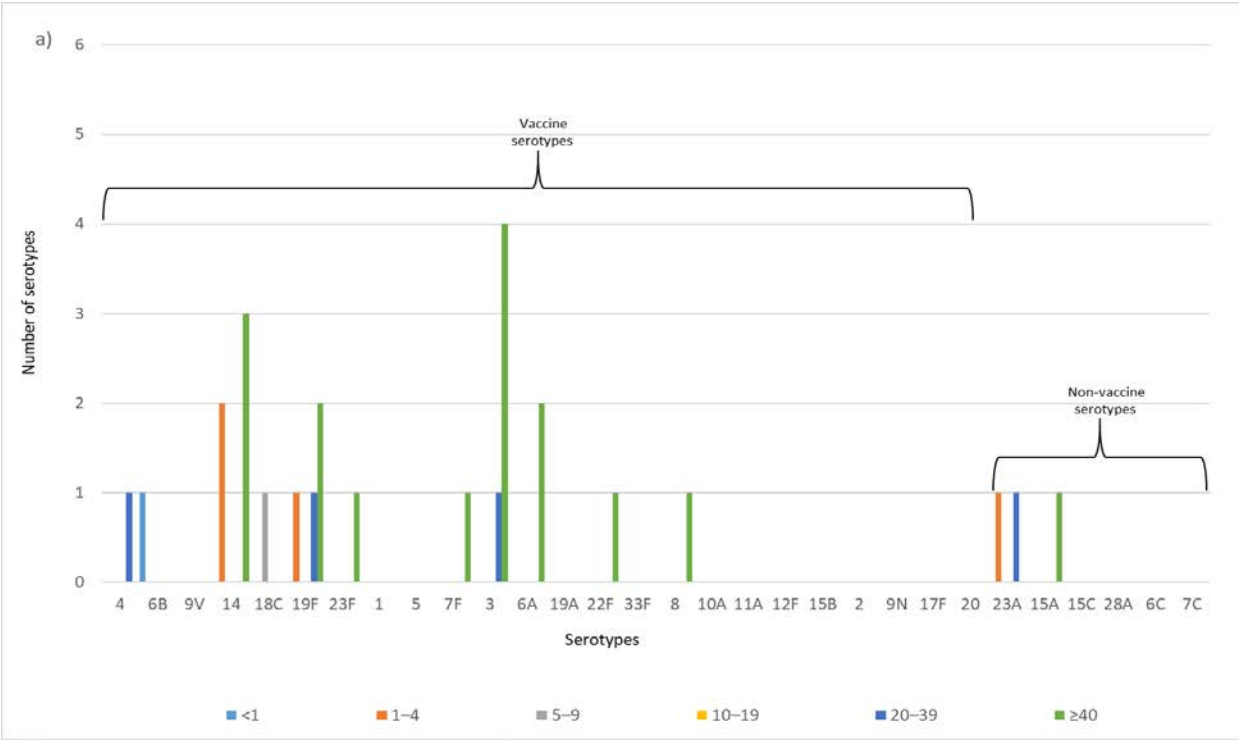


**Fig. 9 – Distribution of invasive pneumococcal disease serotypes in the Autonomous Province of Vojvodina, Serbia, by age groups: a) pre-vaccination period (2009–2017) and b) vaccination period (2018–2024).**

***Note*: Fig.9 continued on next page.**

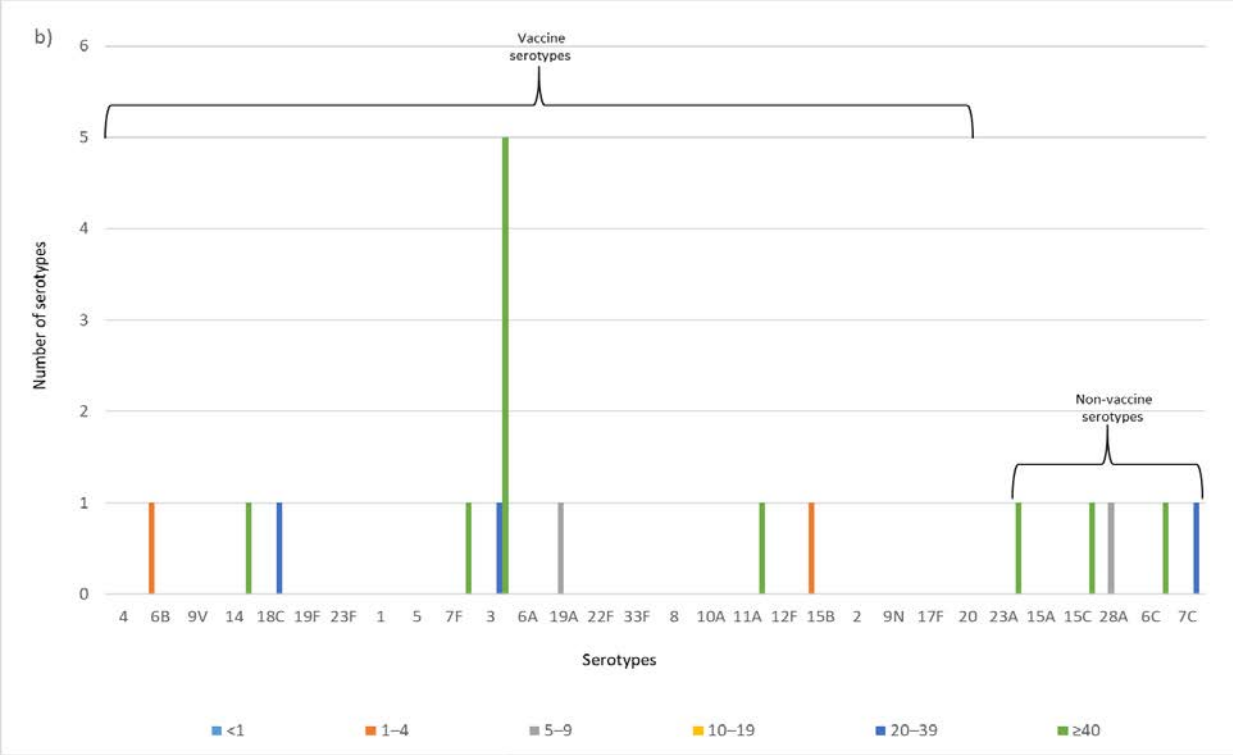


**Fig. 9 (Continued) – Distribution of invasive pneumococcal disease serotypes in the Autonomous Province of Vojvodina, Serbia, by age groups: a) pre-vaccination period (2009–2017) and b) vaccination period (2018–2024).**

**Table 2**

**Characteristics of patients with total outcomes due to invasive pneumococcal disease in the Autonomous Province of Vojvodina, Serbia (2009–2024).**

| Gender | Year of death | Age (years) | Area of residence | Diagnosis | Month of death | Serotype |
|---|---|---|---|---|---|---|
| Male | 2009 | 52 | Urban | pneumococcal meningitis | March | 3 |
| Female | 2010 | 77 | Rural | streptococcal pneumonia | June | 3 |
| Male | 2017 | 69 | Rural | pneumococcal meningitis | March | 14 |
| Male | 2020 | 38 | Urban | pneumococcal meningitis | November | 3 |
| Male | 2021 | 33 | Urban | streptococcal pneumonia | February | 7C* |
| Male | 2023 | 3 | Urban | pneumococcal meningitis | January | 6B |

*** Non-vaccine serotype**.

cases. Regarding seasonality, deaths occurred mainly during winter and spring months. Half of the fatal cases were caused by serotype 3. Additional serotypes associated with fatal outcomes included 14, 6B, and 7C, the latter being a non-vaccine serotype recorded during the vaccine period (Table 2). None of the patients with fatal outcomes had a history of vaccination against IPD.

## Discussion

To our knowledge, this is the first long-term analysis of IPD and invasive Hib disease in the AP of Vojvodina, Serbia, spanning from 2003 to 2024 and covering pre- and post-vaccination periods. The study demonstrates the sustained success of Hib vaccination and the impact of childhood PCV immunization in reducing vaccine-type IPD, while highlighting persistent disease burden, age-specific vulnerabilities, seasonal patterns, and emerging non-vaccine serotypes. These findings underscore the importance of ongoing surveillance and adaptation of immunization programs [1–4, 18, 27].

According to the most recent Annual Epidemiological Report by the European Center for Disease Prevention and Control (ECDC), IPD incidence in 30 EU/EEA countries declined from 5.6 to 2.7 *per* 100,000 between 2018 and 2021, increasing to 5.1 in 2022 [28]. In the US, where IPD surveillance began in 1998, incidence fell sharply after PCV intro-

duction in 2000, reaching ~5 *per* 100,000 in 2020–2021 and ~8 *per* 100,000 in 2022 [29].

In the EU/EEA, confirmed Hib incidence remained ≤ 0.8 *per* 100,000 between 2018 and 2021, increasing slightly to 0.9 in 2022 [8]. In the US, widespread Hib vaccination in the 1990s reduced incidence in children < 5 years by 99%, to 0.08 *per* 100,000 by 2018 [30]. Globally, WHO reports substantial declines in Hib-related morbidity and mortality [2, 11].

In the AP of Vojvodina, the nationwide Hib immunization program introduced in 2006 led to a sustained decline in invasive Hib disease, with only sporadic cases after 2009. In contrast, pneumococcal vaccination, introduced in 2018, has not yet produced a similar decline in IPD, which has risen over the past five years, peaking in 2023–2024. This difference reflects high coverage and herd immunity for Hib, whereas pneumococcal vaccination is recent, with effects still evolving. The greater diversity of pneumococcal serotypes, including non-vaccine types, variable coverage–especially for revaccination–and improved surveillance likely contributed to the recent increase in IPD cases.

Consistent with the EU/EEA and US data [4, 8, 28–30], our results demonstrate that IPD mainly affected infants aged < 1 year and adults aged ≥ 40 years, while invasive Hib disease was most common in children aged 1–4 years. After Hib vaccination, cases shifted to unvaccinated infants aged < 1 year, demonstrating strong vaccine protection. In contrast, despite PCV introduction in 2018, IPD incidence has not declined consistently. The ongoing burden and recent rise in older adults highlight that high-risk groups remain vulnerable and need targeted prevention.

Both IPD and Hib showed clear seasonality, peaking in the colder months (October–February) and declining in summer. This likely reflects school and preschool attendance among children and increased indoor contact during family gatherings and holiday celebrations among adults, which are particularly frequent during these months in Serbia. Similar seasonal patterns are observed across the EU/EEA, with the lowest incidence in summer and rises in autumn and winter [8, 28]. In Europe, the incidence of both IPD and Hib declined sharply during the COVID-19 pandemic (2020–2021), likely due to public health measures such as physical distancing, mask use, and lockdowns [8]. Following the relaxation of these measures, IPD incidence increased during the winter of 2021–2022, with an unusual rise observed in spring 2022 [28]. Influenza is known to elevate invasive pneumococcal pneumonia incidence and influence seasonal case fatality in the elderly [31]. These observations align with local influenza and acute respiratory infection surveillance, which documented recent influenza resurgence concurrent with rising IPD in this study [32].

Biological differences between Hib and pneumococcus likely contribute to their distinct epidemiology. Although exact basic reproduction ratio ($R_0$) estimates are unclear, studies suggest Hib has lower transmission potential. Hib carriage is shorter and less likely to spread, consistent with rapid declines after widespread Hib vaccination [33]. In contrast, pneumococcus sustains transmission through prolonged, serotype-dependent carriage and diverse circulating serotypes. Longitudinal and genomic studies show serotype-specific differences in carriage duration and fitness, supporting pneumococcus's higher transmission potential and capacity for serotype replacement under vaccine pressure [34]. Finally, vaccine impact further highlights these differences: Hib conjugate vaccines rapidly and durably reduced carriage and invasive disease, whereas PCVs substantially decreased vaccine-type disease but were followed by variable overall trends due to serotype replacement and heterogeneous herd effects [1, 11, 12]. These findings suggest that Hib has a lower effective reproductive potential than pneumococcus, which explains its faster and more sustained decline compared with IPD after vaccination.

Our results showed no significant gender differences for IPD and invasive Hib disease, consistent with previous surveillance data, although a slightly higher number of male cases was generally observed [4, 5, 8, 9, 28]. In addition, our analysis showed that IPD mainly affected adults aged ≥ 40 years, while invasive Hib disease occurred primarily in children aged 1–4 years. All invasive cases in this study occurred in unvaccinated individuals. These patterns reflect the known epidemiology: Hib historically caused severe disease in young children before vaccination, whereas pneumococcal disease displays a bimodal distribution, affecting both young children and older adults [1–11, 21, 22, 28–30, 35].

Both diseases were more common in urban areas. However, differences from rural areas were not statistically significant, which suggests that population density influences transmission but is not the sole determinant. Case numbers were highest in the South Bačka District, likely reflecting local differences in healthcare access, surveillance, and population susceptibility. As previously noted for invasive meningococcal disease [20], this district hosts the University Clinical Center of Vojvodina–the region's only tertiary care facility–receiving the most severe cases, and it is also the most populous district in the AP of Vojvodina [19]. Laboratory confirmation was more frequent for IPD than Hib, reflecting better diagnostic capabilities for pneumococcus and potential underreporting of Hib due to prior antibiotics or less sensitive methods. Blood cultures are less sensitive for Hib than pneumococcus; for instance, one study found real-time PCR detected Hib DNA in 11 samples, while blood cultures were all negative, highlighting culture limitations for Hib detection [36]. Clinical outcomes differed significantly, with higher case-fatality for IPD (9.6%) than for invasive Hib disease (3.5%). This aligns with previous reports showing that IPD, especially in older adults, carries a greater mortality risk than Hib disease in the post-vaccine era [4, 5, 8, 9].

In a previous study of IPD isolates in the AP of Vojvodina (2009–2016), the most frequent serotypes were 3, 19F, and 14 [37]. A broader Serbian study (2010–2018) also found serotypes 3, 19F, and 14 most common, followed by 6B, 6A, 19A, and 23F [27].

Although not the primary aim, our 2009–2024 analysis in the AP of Vojvodina showed significant shifts in serotype distribution after PCV introduction. PCV10-related serotypes, especially 14 and 19F, declined markedly, consistent with European and global data showing rapid reduction or

near-elimination of vaccine serotypes *via* direct and herd protection [38–41]. Despite routine pneumococcal immunization starting only in 2018, early reductions in specific IPD serotypes are already evident [18].

Serotype 3 persisted across both study periods (pre-vaccination and vaccination), a pattern reported globally [42–44]. In our study, it caused the highest number of adult cases, including half of all fatal outcomes, highlighting its clinical significance and challenges for current vaccines [45, 46]. In the post-PCV period, serotype 3 showed the largest increase, including a sharp rise in children aged < 5 years. The immune response to serotype 3 polysaccharide is known to be suboptimal compared with other vaccine serotypes [18, 47]. Evidence indicates that countries using PCV10 have experienced a linear increase in serotype 3 disease across all ages, whereas PCV13 users saw only a modest decline during the first 3–4 years post-introduction [18, 48]. Given that PCV13 was used in Serbia only from 2022 to 2023, the lack of decline in serotype 3 incidence is expected.

The emergence of non-vaccine serotypes (e.g., 15C, 28A, 6C, 7C) during the vaccine era, though few in number, reflects local [18] and global trends of serotype replacement after PCV introduction [49–51]. Serotype 6C is notable for its high antibiotic resistance [18, 50, 51]. While the overall rise in non-vaccine serotypes was not statistically significant–likely due to the short duration of continuous vaccination–continued surveillance is warranted.

After vaccine introduction, IPD caused by PCV10 serotypes declined from 55% to 22% in the overall population, PCV13-non-PCV10 remained stable (~40%), and non-vaccine serotypes increased from 11% to 28%, with additional PCV20-non-PCV15 emergence. In children aged < 5 years, IPD caused by PCV10 serotypes (80% pre-vaccine) decreased to 20% in the vaccination period, while PCV13-non-PCV10, PCV20-non-PCV15, and non-vaccine serotypes each accounted for ~33%. In adults aged ≥ 40 years, IPD caused by PCV10 fell from 47% to < 20%, PCV13-non-PCV10 rose to ~45%, non-vaccine serotypes to 27%, and PCV15-non-PCV13/PCV20-non-PCV15 remained minor contributors. These findings clearly indicate that the PCV10 immunization program affected not only children but also provided indirect protection to adults.

A previous study from the AP of Vojvodina covering isolates from the pre-vaccine era showed that IPD in children aged < 5 years was dominated by serotypes 19F (44%) and 14 (16%), while serotype 3 predominated in adults aged ≥ 50 years [37]. A broader Serbian study confirmed a higher prevalence of serotype 3 in adults and 19F/14 in young children [27]. In the post-vaccine period (2018–2023), serotype 3 accounted for 33% of IPD cases, followed by 19A, 14, and 6B [18], consistent with our findings showing increased non-vaccine serotypes in adults. Adult fatalities were largely linked to serotype 3, with one death due to a non-vaccine serotype (7C), highlighting the need for continued molecular surveillance. The 2022 ECDC report lists the five most common serotypes as 3, 8, 19A, 22F, and 6C [28].

All 30 EU/EEA countries have introduced pneumococcal vaccination, with childhood immunization mandatory in seven (Bulgaria, Croatia, France, Hungary, Latvia, Poland, Slovakia), similar to Serbia. While schedules vary, Serbia's revaccination – given one year after the second primary PCV10 dose – may benefit from a shorter interval, ideally at 11–12 months based on the EU/EEA schedules [52].

This study has several notable strengths. First, it is based on a comprehensive 22-year dataset (2003–2024), providing one of the longest continuous epidemiological assessments of IPD and invasive Hib disease in the region. Such a long observation period enabled the identification of secular trends, vaccination impact (particularly for Hib invasive disease), and temporal variations, including seasonal patterns. Second, the analysis integrates multiple dimensions of disease dynamics–incidence rates, age-specific distribution, seasonal variation, demographic and clinical characteristics, and serotype distribution–allowing for a holistic evaluation of disease epidemiology and immunization program performance. Third, the assessment of vaccine coverage data alongside incidence trends provides valuable insight into the relationship between immunization program implementation, coverage levels, and disease dynamics, highlighting both the successes of Hib immunization and the ongoing challenges related to IPD. However, due to the relatively short period since the introduction of pneumococcal vaccination, the reintroduction of PCV10 under the 2+1 schedule–driven mainly by economic considerations and persistently low booster-dose coverage (in the second year of life)–the number of IPD cases has not declined during the vaccination period in our setting.

Finally, despite the limited number of cases, by examining serotype distribution in the pre- and post-vaccine periods, this study provides important evidence on serotype replacement and persistence–particularly of serotype 3–and on the emergence of non-vaccine serotypes, which is highly relevant for evaluating the potential need for higher-valency vaccines in the future.

Nevertheless, several limitations should be acknowledged. First, the study relied on passive surveillance data, which may underestimate the true burden of disease due to underreporting or misclassification. Second, although case definitions followed national and WHO standards, diagnostic practices and reporting completeness may have varied across hospitals and over time, potentially affecting case ascertainment. Third, serotype data were available for only 18% of all laboratory-confirmed IPD cases, limiting the representativeness of the serotype distribution analysis. For comparison, among the EU/EEA countries that reported serotyping data in 2022, serotype information was available for 52.3% of cases [28]. However, our dataset included only officially notified communicable diseases (IPD or invasive Hib disease). Moreover, serotyping at the National Reference Center for Streptococci in Serbia is also passive, based on voluntary submission, and covers a limited number of isolates, particularly among children [18]. Fourth, vaccination coverage was assessed using the administrative method, which may overestimate or underestimate true coverage levels. Fifth, potential disruptions of routine immunization and healthcare-seeking behavior during the COVID-19 pandemic could have influ-

enced both disease incidence and vaccine uptake. Finally, as this was a descriptive study, causal inferences between vaccination and observed epidemiological trends cannot be firmly established.

## Conclusion

Our study confirms the sustained success of the *Haemophilus influenzae* type b immunization program in substantially reducing disease incidence. Introduction of pneumococcal conjugate vaccines in the Autonomous Province of Vojvodina, Serbia, markedly decreased the circulation of pneumococcal conjugate vaccines10 serotypes; however, serotype 3 and emerging non-vaccine serotypes continue to challenge disease control. Given that none of the patients in this study had received prior vaccination against diseases caused by *Streptococcus pneumoniae* or *Haemophilus influenzae* type b, enhancing physician awareness and education at all levels of healthcare is a critical priority for improving vaccine uptake and disease prevention. Our findings emphasize the need for ongoing surveillance, enhanced laboratory-based serotyping, and regular evaluation of immunization coverage to inform vaccine policy, including the potential use of higher-valency pneumococcal conjugate vaccines (minimum pneumococcal conjugate vaccines 13) or targeted adult vaccination strategies. Maintaining high vaccine uptake, alongside continuous monitoring of vaccine impact, remains essential to further reduce the burden of invasive bacterial diseases in Serbia.

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