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Incidence of Invasive Pneumococcal Disease and Associated Factors in Latvian Population During 2012–2022

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Abbreviations used in the Thesis

APC	Annual Percent Change
ECDC	European Centre for Disease Prevention and Control
EUCAST	European Committee on Antimicrobial Susceptibility Testing
TPT	Total person-time at risk
NMRL	National Microbiology Reference Laboratory
OR	Odds ratio
PCV10	Pneumococcal 10-valent conjugate vaccine
PCV13	Pneumococcal 13-valent conjugate vaccine
PCV15	Pneumococcal 15-valent conjugate vaccine
PCV20	Pneumococcal 20-valent conjugate vaccine
PCV7	Pneumococcal 7-valent conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
WHO	World Health Organization
S. pneumoniae	*Streptococcus pneumoniae*
CDPC	Centre for Disease Prevention and Control of Latvia
ICD-10	International Classification of Diseases, 10-version
TESSy	European Surveillance System
CI	Confidence interval
VISUMS	Latvian State Surveillance and Monitoring System for Infectious Diseases

Introduction

Despite the availability of vaccines, invasive pneumococcal disease (IPD) remains a major public health challenge and continues to represent one of the leading causes of death among children and older adults worldwide (Scelfo et al., 2021). The causative agent of IPD is *Streptococcus pneumoniae*, a Gram-positive opportunistic pathogen that colonizes the mucosa of the upper respiratory tract and frequently constitutes part of the normal human microbiota. However, once it gains access to the bloodstream, cerebrospinal fluid, or other normally sterile sites, it may cause severe invasive manifestations of disease (Weiser et al., 2018; Rodgers et al., 2021). To date, more than 100 *S. pneumoniae* serotypes have been identified. These serotypes differ in their virulence, invasive potential, and geographical distribution, all of which contribute to variation in the IPD incidence (Rodgers et al., 2021).

IPD imposes a substantial burden on public health owing to its severe clinical course, frequent requirement for hospitalization, and unfavourable outcomes. The World Health Organization estimated that *S. pneumoniae* is responsible for approximately 1.6 million deaths annually (WHO, 2008). Notably, *S. pneumoniae* accounts for 5% of all deaths among children under five years of age globally (Grant et al., 2023). Older adults, particularly those aged 65 years and above, as well as individuals with chronic underlying conditions, are at elevated risk of IPD and are more likely to experience fatal outcomes. The clinical burden of IPD is further influenced by particular *S. pneumoniae* serotypes, as certain serotypes are associated with higher carriage prevalence and increased disease severity. In addition to its clinical impact, IPD is associated with a considerable economic burden, generating substantial healthcare expenditures related to hospitalization, management of complications, and long-term care. Beyond direct medical costs, the disease also gives rise to indirect costs, primarily through prolonged work incapacity and reduced economic productivity (Blasi et al., 2012; Drijkoningen, 2014; Mohanty et al., 2024).

Streptococcus pneumoniae has demonstrated increasing resistance to several classes of antimicrobial agents, including β-lactams, macrolides, and fluoroquinolones. Antimicrobial resistance complicates clinical management and may contribute to adverse disease outcomes (Scelfo et al., 2021). It is also important to note that, in 2017, WHO included *S. pneumoniae* in its list of priority pathogens established to guide and stimulate research and development of new antibiotics in response to the growing global threat of antimicrobial resistance. This list was updated in 2024, when *S. pneumoniae* was designated a macrolide-resistant priority pathogen and additional pathogens were incorporated (WHO, 2024).

The global introduction of pneumococcal conjugate vaccines began in 2007 and has resulted in substantial reductions in both the incidence of disease and the overall burden of

pneumococcal disease by reducing the circulation of vaccine-covered serotypes in countries where PCV have been incorporated into national immunization programmes. Nevertheless, millions of children remain unvaccinated, particularly in low- and middle-income countries, largely because of limited financial resources (Rodgers et al., 2021).

According to data from the European Centre for Disease Prevention and Control, the incidence of IPD in Europe remained relatively stable between 2010 and 2022, at 4–5 cases per 100 000 population annually, with the exception of the COVID-19 pandemic period in 2020 and 2021, when the incidence declined to an average of three cases per 100 000 population per year (ECDC, 2025). Current immunization strategies against pneumococcal disease recommend completion of the primary vaccination series within the first year of life, followed by a booster dose at the age of one year or later (Scelfo et al., 2021). In Latvia, vaccination against pneumococcal disease was introduced in 2010, when the PCV7 vaccine was incorporated into the national childhood immunization schedule. In 2012, PCV7 was replaced by PCV10, which remained in use until the end of 2023. The vaccination schedule consisted of three doses: two primary doses administered at two and four months of age, followed by a booster dose at 12–15 months of age. Since 2024, PCV15 has been included in the national immunization programme, while maintaining the same vaccination schedule (Regulation, 2000).

A number of risk factors have been identified that increase susceptibility to IPD. Age constitutes one of the most important determinants, as children younger than two years and adults aged 65 years and older are particularly vulnerable because of immature or declining immune function and the higher prevalence of comorbidities. Several medical conditions are also associated with an increased risk of IPD, including HIV infection, sickle cell anaemia, congenital or acquired asplenia, complement deficiencies, and other immunodeficiency states, as well as diabetes mellitus and chronic cardiac or renal disease. Previous viral respiratory tract infection, especially influenza, may impair host immune defences and thereby increase susceptibility to bacterial superinfection, including IPD. Additional risk factors include attendance at preschool educational institutions, recent antibiotic use, exposure to tobacco smoke, and residence in overcrowded living conditions. A marked seasonal increase in IPD incidence has been observed during colder months, possibly reflecting increased indoor exposure and prolonged interpersonal contact. Higher incidence rates have also been reported among African Americans, American Indians, Alaska Natives, Micronesians, and Aboriginal populations in Australia and New Zealand, potentially due to a combination of genetic susceptibility, reduced access to healthcare, and delayed vaccination. Taken together, these risk factors interact in a manner that renders certain population groups particularly vulnerable to

IPD and highlights the importance of targeted preventive strategies for high-risk populations (Mohanty et al., 2023).

Aim of the Study

To characterise the incidence of invasive pneumococcal disease in the Latvian population, the dynamics of circulating *Streptococcus pneumoniae* serotypes, and their susceptibility to antimicrobial agents during the period from 2012 to 2022, and to determine the association between demographic and disease-related characteristics of patients with IPD and fatal disease outcome.

Objectives of the Study

1 To investigate changes in the incidence of invasive pneumococcal disease in Latvia from 2012 to 2022, with assessment of differences across regions, age groups, and sex.
2 To characterise the *S. pneumoniae* serotypes isolated from patients with IPD, their temporal dynamics, and their susceptibility to antimicrobial agents during the study period, and to determine their association with fatal outcome.
3 To describe the clinical manifestations of IPD and to determine their association with fatal outcome.
4 To determine the association between comorbidities in patients with IPD, including HIV/AIDS, any oncological diagnosis, hepatitis C virus infection, diabetes mellitus, and tuberculosis, and fatal outcome.
5 To determine the association between demographic characteristics of patients with IPD, including age and sex, and fatal outcome.

Hypotheses of the Study

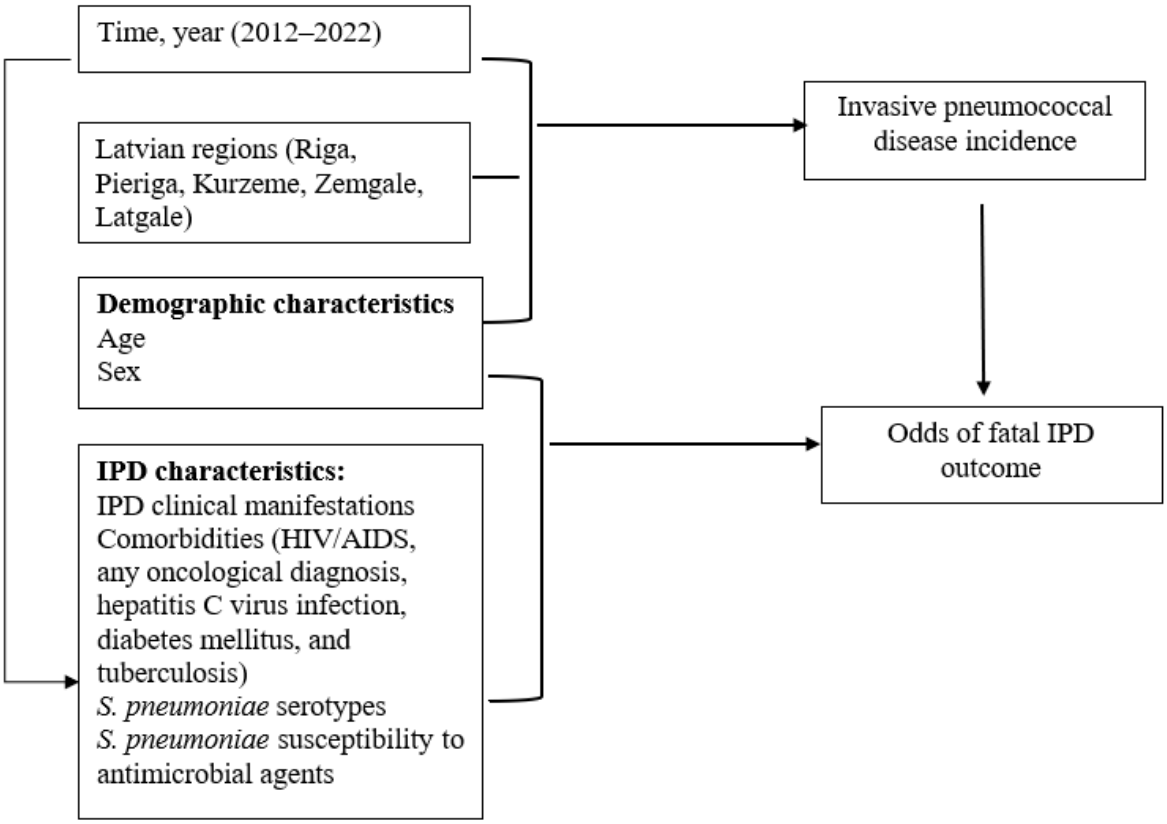
1 The incidence of invasive pneumococcal disease in Latvia shows an increasing trend.
2 Fatal IPD outcome among patients with invasive pneumococcal disease is associated with demographic characteristics and disease course-related factors, including both chronic comorbidities and the clinical manifestations of IPD.
3 Fatal IPD outcome among patients with invasive pneumococcal disease is associated with infection caused by S. pneumoniae serotypes not included in vaccine formulations and by serotypes resistant to antimicrobial agents.

Novelty of the Study

This Doctoral Thesis makes an important contribution to the investigation of invasive pneumococcal disease in Latvia by providing a detailed epidemiological analysis of IPD incidence and trends over time, as well as a long-term characterisation of *S. pneumoniae* serotypes and antimicrobial resistance patterns during the period 2012–2022. For the first time, changes in IPD incidence in Latvia were comprehensively analysed at the national level, across regions, and by age group and sex. The thesis also provides an in-depth evaluation of the dynamics of *S. pneumoniae* serotypes following the introduction of the PCV10 vaccine in Latvia. Furthermore, the study characterises trends in antimicrobial resistance of *S. pneumoniae* to the principal antibiotic classes, including penicillin, erythromycin, and cefotaxime/ceftriaxone.

Within the framework of this doctoral research, the association between fatal outcomes of IPD and several patient-related factors was identified for the first time in Latvia. These included demographic factors (age and sex), disease-related factors (clinical manifestations of IPD), and selected comorbidities (HIV/AIDS, oncology, diabetes mellitus, tuberculosis, and hepatitis C virus infection). This study provides an evidence base for public health decision-making and offers strong scientific justification for Latvia's recent decision to transition to a broader spectrum pneumococcal conjugate vaccine in the childhood immunisation programme, while also reinforcing the importance of pneumococcal vaccination for risk groups.

Research model



Ethical Considerations

Approval for the study was obtained from the Ethics Committee of Rīga Stradiņš University (No. 1/28.06.2018), as well as from the Ethics Committee of the Centre for Disease Prevention and Control of Latvia (No. 6.1-1/2024/3).

1 Materials and Methods

1.1 Data sources and data collection

The Doctoral Thesis was based on data obtained and requested from multiple sources:

- the National Infectious Disease Surveillance and Monitoring System (VISUMS);
- the HIV/AIDS Patient Register (Cabinet, 2008b);
- the Hepatitis C Patient Register (Cabinet, 2008a);
- the database maintained by the Centre for Disease Prevention and Control of Latvia on causes of death in the Latvian population – *Medical Certificate of Cause of Death* (Cabinet, 2006b);
- the Diabetes Mellitus Patient Register (Cabinet, 2014a);
- the Tuberculosis Patient Register (Cabinet, 2014b);
- the Cancer Patient Register (Cabinet, 2014);
- the database of the Central Statistical Bureau, IRD041: *Population by Sex and Age in Regions, State Cities, and Municipalities at the Beginning of the Year, 2012–2024*.

The selection of IPD cases included in the study was performed using a multistage approach based on data from the CDPC VISUMS database. First, cases of invasive pneumococcal disease with a corresponding diagnosis and an acceptance date between 1 January 2012 and 31 December 2022 were extracted from VISUMS. Final diagnoses corresponding to IPD were selected in accordance with ICD-10, as follows:

- **B95.3** – *Streptococcus pneumoniae* as the cause of diseases classified elsewhere;
- **A40.3** – sepsis due to *Streptococcus pneumoniae*;
- **G00.1** – pneumococcal meningitis;
- **J13** – pneumonia due to *Streptococcus pneumoniae*.

1.2 Principles for constructing the dataset at the Centre for Disease Prevention and Control of Latvia

For the construction of the dataset on patients with invasive pneumococcal disease for the period 2012–2022, the following variables were extracted from the patient case records available in the VISUMS system:

- **Age** – recorded in months for children under two years of age and in years for all other patients with IPD;
- **Sex** – male or female;
- **Personal identification number** – an 11-digit identifier required to verify the presence of patients with IPD in other disease registers (diabetes mellitus, tuberculosis, oncological diseases, HIV/AIDS, and hepatitis C patient registers), as well as in the database on causes of death of the Latvian population;

- **Territory** – the statistical region of residence of the patient with IPD, in accordance with the Classifier of Administrative Territories and Territorial Units;
- **Date of case acceptance** – the date on which the epidemiologist completed the epidemiological investigation and accepted the IPD case in VISUMS, after which the case was included in the epidemiological surveillance statistics (dd.mm.yyyy);
- **Date of disease onset** – the date on which, according to the medical practitioner, the symptoms of illness began (dd.mm.yyyy);
- **Date of hospital admission** – the date on which, according to the medical practitioner, the patient with IPD was admitted to hospital (dd.mm.yyyy);
- **Date of hospital discharge** – the date on which, according to the medical practitioner, the patient with IPD was discharged from inpatient care (dd.mm.yyyy);
- **Type of specimen** – the specimen from the patient with IPD that was submitted for laboratory investigation. Responses were categorised into four groups: "Blood", "Cerebrospinal fluid", "Blood and cerebrospinal fluid", and "Pleural fluid";
- ***S. pneumoniae* serotype** – the serotype of *S. pneumoniae* identified in the clinical specimen of the patient with IPD. The recorded responses included the identified serotype designation (for example, 3, 14, 19A, etc.), "unknown" (if no information on *S. pneumoniae* serotyping was available in the VISUMS patient case record), "not typed" (if the VISUMS patient case record indicated that the identified *S. pneumoniae* had not been serotyped), or "non-typeable" (if the VISUMS patient case record indicated that the identified *S. pneumoniae* could not be serotyped);
- **Antimicrobial susceptibility to penicillin** – information from the VISUMS patient case record was categorised into four groups: susceptible, intermediate, resistant, and no data (if the laboratory had not submitted data or had indicated that susceptibility testing had not been performed);
- **Antimicrobial susceptibility to erythromycin** – information from the VISUMS patient case record was categorised into four groups: susceptible, intermediate, resistant, and no data (if the laboratory had not submitted data or had indicated that susceptibility testing had not been performed);
- **Antimicrobial susceptibility to ceftriaxone/cefotaxime** – information from the VISUMS patient case record was categorised into four groups: susceptible, intermediate, resistant, and no data (if the laboratory had not submitted data or had indicated that susceptibility testing had not been performed).

The compiled dataset of IPD cases from VISUMS was then forwarded to the Register Supervision Department of the Centre for Disease Prevention and Control of Latvia (CDPC),

where, on the basis of the personal identification number of each patient with IPD, the dataset was supplemented with information from the HIV/AIDS and hepatitis C patient registers, as well as with data from medical certificates of cause of death. Thereafter, personal data were coded, and the dataset was transferred to the National Health Service, where it was further supplemented with information on patients' comorbidities from the relevant national medical registers (patient records for diabetes mellitus, tuberculosis, and oncological diseases).
Following completion of the data linkage process, the Register Supervision Department of the CDPC carried out pseudonymisation of the data by assigning a code to the identifying information of patients with IPD and subsequently provided the dataset to the author of the Doctoral Thesis.

Permission to use anonymised patient data recorded in medical documents for the purposes of the study was obtained from the Centre for Disease Prevention and Control of Latvia (No. 6.1-1/2024/3, Riga, Latvia).

1.3 Study variables and their grouping

1.3.1 Dependent Variable

In the Doctoral Thesis, the following were analysed as dependent variables:

- the frequency of new IPD cases – incidence;
- an unfavourable IPD outcome – a fatal case.

A fatal IPD outcome was defined as the death of a patient with IPD that was recorded both in the VISUMS system and in the Latvian database on causes of death and that occurred within 30 days after disease onset, in a patient from whom *S. pneumoniae* had been isolated from a sterile biological specimen (blood, cerebrospinal fluid, pleural fluid, or another normally sterile specimen), and for whom the cause of death included at least one of the following diagnoses: A40.3, A40.9, A41.9, J10.0, J11.0, J13, J15.4, J15.9, J18.0, J18.1, J18.8, J18.9, J44.0, J85.1, G00.1, G00.2, G00.9, G03.9, G04.2, or G04.9. The date of disease onset was determined on the basis of the disease onset date recorded in the urgent notification form (dd.mm.yyyy). The dependent variable fatal IPD outcome was created as a new variable and dichotomised as yes/no.

1.3.2 Independent Variables

Demographic Factors

Age (years) was initially analysed as a continuous variable in order to describe the age distribution of patients with IPD. To visualise the age distribution, a histogram was constructed (see Figure 2.1), which enabled identification of potential irregularities and provided the basis

for the formation of age groups. For the purposes of analysis, age was transformed into a categorical variable by creating three age groups.

Age group. This variable was created by grouping the continuous variable of patient age into categories. Three age groups were established in the Doctoral Thesis:

- 0–17 years (children) – all patients with IPD aged 0 to 17 years inclusive;
- 18–64 years (adults) – all patients with IPD aged 18 to 64 years inclusive;
- 65 years and older (older adults) – all patients with IPD aged 65 years and above.

Sex – female or male.

Socioeconomic Factors

Region of residence – this variable was created by grouping the response categories of the existing variable *Territory* into six categories:

- Riga – comprising residents from the entire territory of Riga;
- Pierīga region – comprising the following response categories: Salaspils, Ķekava Parish, Ropaži Municipality, Aloja, Sigulda, More Parish;
- Kurzeme region – comprising the following response categories: Liepāja, Pāvilosta, Talsi, Vērgale Parish, Nīgrande Parish, Zaņa Parish;
- Zemgale region – comprising the following response categories: Jēkabpils, Jelgava, Aizkraukle;
- Vidzeme region – comprising the following response categories: Plāņi Parish, Grundzāle Parish, Valka, Burtnieki Parish, Zilaiskalns Parish, Kauguri Parish, Gulbene, Kocēni Parish, Vecate Parish, Ērģeme Parish, Smiltene, Rencēni Parish, Dikļi Parish, Ķoņi Parish, Liepna Parish;
- Latgale region – comprising the following response categories: Daugavpils, Viļaka, Audriņi Parish, Dubna Parish, Biķernieki Parish, Ilūkste Municipality.

Disease-Related Factors

1. *Clinical manifestations of IPD*

To determine the clinical manifestations of IPD, information on the detection of *S. pneumoniae* in clinical specimens was used, and four dichotomous variables (yes/no) were created:

- Sepsis, which included the response category: tested biological specimen "blood";
- Meningitis, which included the response category: tested biological specimen "cerebrospinal fluid";
- Meningitis with sepsis, which included the response category: tested biological specimen "blood and cerebrospinal fluid";

- Pneumonia, which included the response category: tested biological specimen "pleural fluid".

2. *Comorbidities*

Information from the National Health Service and CDPC registers was used in relation to the date of disease onset. For data analysis, five dichotomous variables were created:

- Diabetes mellitus (yes/no), including patients with IPD for whom the variable "Year of diabetes diagnosis" was less than or equal to the variable "Date of IPD onset";
- Tuberculosis (yes/no), including patients with IPD for whom the variable "Date the patient was entered into the register" was less than or equal to the variable "Date of IPD onset";
- Any oncological disease (yes/no), including patients with IPD for whom the variable "Date of diagnosis" was less than or equal to the variable "Date of IPD onset";
- Human immunodeficiency virus (yes/no), including patients with IPD for whom the variable "Date of confirmation of HIV infection at the National Microbiology Reference Laboratory" was less than or equal to the variable "Date of IPD onset";
- Hepatitis C virus infection (yes/no), including patients with IPD for whom the variable "Year of hepatitis C diagnosis" was less than or equal to the variable "Date of IPD onset".

3. *S. pneumoniae serotype*

The distribution of serotypes was characterised by calculating the absolute number and proportion of identified serotypes among all serotyped invasive isolates, both overall and by year and within selected subgroups.

4. *S. pneumoniae serotype: "PCV serotype"*

A new variable was created in which the response categories from the existing variable *S. pneumoniae* serotype were grouped according to PCV vaccine type. The response categories were combined into seven categories:

- PCV10 – comprising *S. pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F;
- PCV13 but not PCV10 – comprising *S. pneumoniae* serotypes 3, 19A, and 6A;
- PCV15 but not PCV13 – comprising *S. pneumoniae* serotypes 22F and 33F;
- PCV20 but not PCV15 – comprising *S. pneumoniae* serotypes 8, 10A, 11A, 12F, and 15B;
- PPSV23 – comprising *S. pneumoniae* serotypes 20, 17F, and 9N;

- Non-vaccine serotypes – comprising all other response categories, namely serotypes not included in PCV10, PCV13, PCV15, PCV20, or PPSV23;
- Serotype not determined – comprising the response categories "Unknown", "Not typed", and "Non-typeable".

5. ***Antimicrobial susceptibility***

Three variables were used to characterise antimicrobial susceptibility:

- antimicrobial susceptibility to penicillin;
- antimicrobial susceptibility to erythromycin;
- antimicrobial susceptibility to ceftriaxone/cefotaxime.

The response categories were dichotomised as follows: "**resistant**", combining the laboratory response categories "intermediate susceptibility" and "resistant", and "**not resistant**", corresponding to the response category "susceptible".

1.4 Study Design

The Doctoral Thesis consisted of two parts with different study designs. A **cross-sectional study** was conducted to determine the annual incidence of invasive pneumococcal disease and its trends during the period from 2012 to 2022, as well as to characterise annual incidence rate according to demographic characteristics, disease-related factors, comorbidities, and case fatality. In addition, a **case–control study** design was applied to characterise fatal IPD cases in comparison with non-fatal cases and to determine the extent to which the presence of various factors associated with case fatality increased the odds of a fatal outcome.

1.5 Statistical Analysis

1.5.1 Cross-sectional Study Component

To characterise invasive pneumococcal disease (IPD) over the study period, the annual incidence rate was calculated by study year and on average for the entire period, stratified by age group and sex, using the following formula:

- ***Annual incidence rate = (b / c) × 100 000****, where:*

  a *– annual incidence rate;*

  b *– number of new cases in a given year and population;*

  c *– total person-time at risk (TPT) in the given year.*

$$TPT = \left(\frac{\text{population at the beginning of the year} + \text{population at the beginning of the following year}}{2}\right) \times 1$$

Overall incidence during the study period was also calculated by region of Latvia and stratified by age group and sex, using the following formula:

- ***Overall incidence rate = (b / c) × 100 000****, where:*

  a *– overall incidence rate;*

  b *– number of new IPD cases in a given population during the 11-year study period;*

  c *– total person-time at risk (TPT), calculated according to the following formula:*

$$TPT = \left(\frac{\text{population at the beginning of the period} + \text{population at the end of the period}}{2}\right) \times 11$$

  where 11 represents the total number of years included in the study period.

- To assess the statistical significance of differences in IPD incidence rates between groups, the online software OpenEpi, *Comparing 2 Person-Time Rates*, was used.
- To identify the direction of trends and possible change-points in IPD incidence, *Joinpoint* regression analysis was performed. This method was used to model annual changes in incidence over time by calculating the annual percentage change (APC) and determining whether the observed trend was statistically significant.
- In addition, to describe overall temporal trends within subgroups, linear regression analysis was performed, presenting the regression equation and coefficient of determination (R^2), which was calculated using the Poisson method.
- In the descriptive component of the analysis, cross-tabulations were used. Categorical variables were described by absolute numbers and proportions, with 95% confidence intervals calculated. For comparison of subgroups of new IPD cases according to demographic characteristics, disease-related factors, comorbidities, and other categorical variables, the chi-square (χ^2) test was applied, with corresponding p-values determined.

1.5.2 Case–Control Study Component

A case was defined as a fatal outcome associated with IPD, whereas controls were defined as patients with IPD who survived, or who died later than 30 days after disease onset and whose cause of death was not related to invasive pneumococcal disease.

- To characterise factors associated with case fatality in the study sample, descriptive statistical methods were used, including the determination of the proportion of characteristics within the study groups and the chi-square (χ^2) test for comparison of groups in cross-tabulations.
- Confidence intervals for proportions were calculated using the online software Sample Size-Net: Confidence Interval for a Proportion.

- In addition, p-values were determined for the comparison of subgroup differences in cross-tabulations.
- To assess the association between the studied factors and fatal IPD outcome, odds ratio (OR) were calculated. Logistic regression models were developed to analyse the association between each studied factor and fatal outcome, estimating:
  - crude odds ratios for fatal outcome in relation to the studied factor (Model 1);
  - odds ratios adjusted for sex and age for fatal outcome in relation to the studied factor (Model 2).

For all statistical tests, the selected level of significance was $p < 0.05$. Data analysis was performed using Microsoft Excel, IBM SPSS Statistics (29.0.0.0), Jamovi (2.3.28), and *Joinpoint* (5.4.0.0).

2 Results

2.1 Characteristics of the Study Population

According to data from the Centre for Disease Prevention and Control of Latvia, a total of 811 cases of invasive pneumococcal disease were notified in Latvia during the period from 2012 to 2022. This corresponds to an average of 74 cases annually, or 3.8 cases per 100 000 population. All 811 IPD cases were included in the present Doctoral Thesis for analysis (see Table 2.1).

Table 2.1

Distribution of the IPD cases by sex and age groups

Year	Number of cases	Incidence per 100 000 population	Sex		Age groups		
			Male	Female	0–17	18–64	65+
2012.	56	2.7	17	39	2	35	19
2013.	56	2.8	20	36	3	36	17
2014.	51	2.5	20	31	3	38	10
2015.	87	4.4	32	55	8	52	27
2016	65	3.3	28	37	3	36	26
2017.	75	3.8	31	44	4	43	28
2018.	76	3.9	34	42	1	40	35
2019.	83	4.3	33	50	4	45	34
2020.	67	3.5	27	40	3	38	26
2021.	70	3.7	32	38	5	33	32
2022.	125	6.7	49	76	5	55	65
Total	811	–	323	488	41	451	319

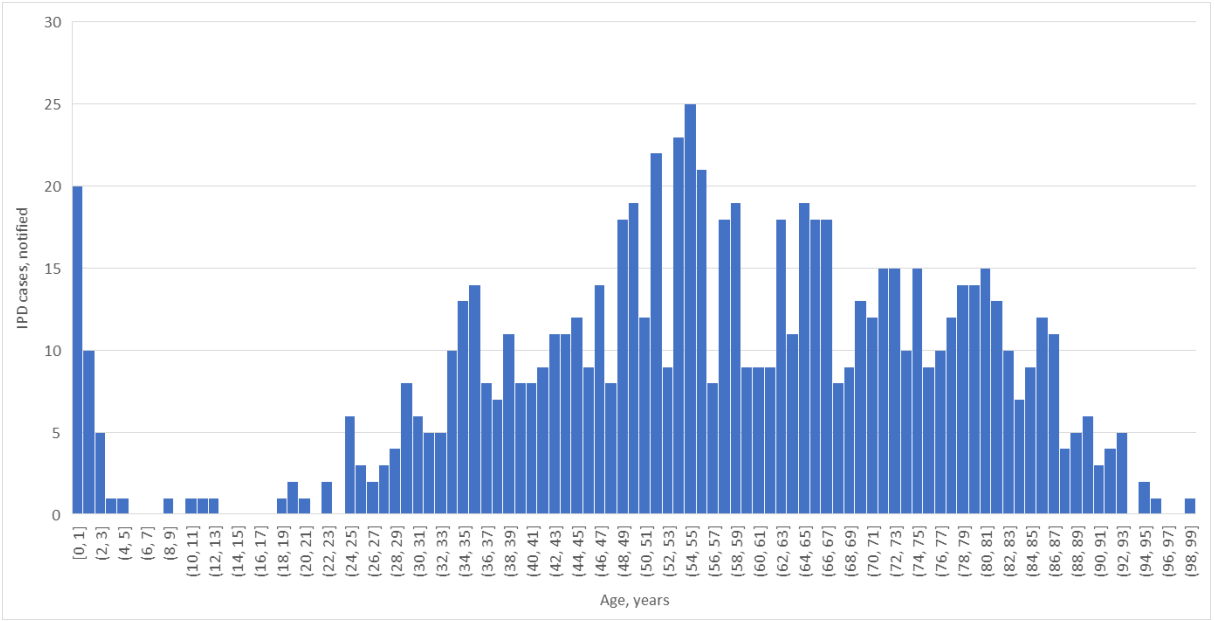


Figure 2.1 **Invasive pneumococcal disease cases by age**

2.2 Incidence of invasive pneumococcal disease in Latvia from 2012 to 2022

2.2.1 Number of cases and incidence of invasive pneumococcal disease: Incidence trends

Overall, 811 cases of invasive pneumococcal disease were reported in Latvia during the study period from 2012 to 2022, corresponding to an average of 74 IPD cases per year and an overall incidence rate of 3.8 cases per 100 000 population (95% CI: 3.51–4.02).

Based on the linear regression equation ($y = 0.2432x + 2.3323$, where y denotes the incidence rate per 100 000 population and x denotes year (time period)), it was determined that the average annual increase in IPD incidence was approximately 0.2432 cases per 100 000 population. The coefficient of determination, $R^2 = 0.5031$, indicates a moderate correlation between calendar year and the increase in incidence (see Figure 2.2.a).

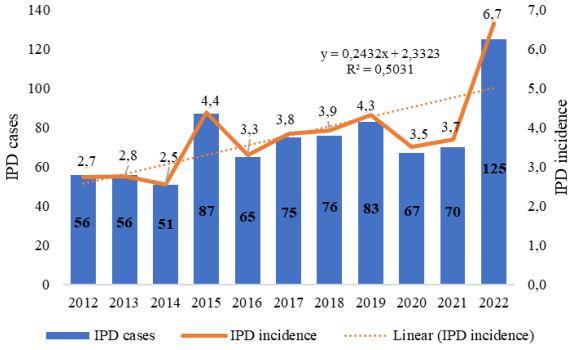


Figure 2.2.a **IPD cases incidence 2012–2022**

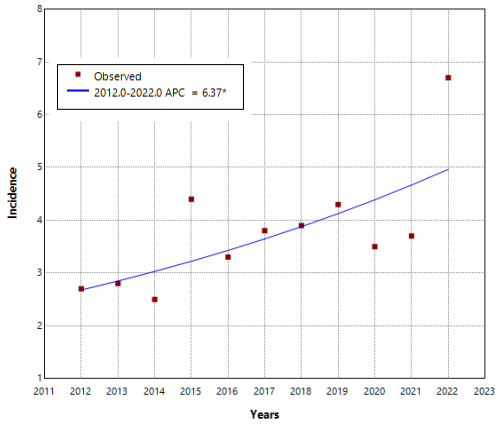


Figure 2.2.b **IPD incidence trends 2012–2022**

Joinpoint regression analysis confirmed that the incidence of invasive pneumococcal disease in Latvia increased significantly over the study period (model slope coefficient, $p = 0.008$). On average, the incidence increased by 6.37% per year, and this trend was statistically significant (APC = 6.37%; 95% CI: 2.67–10.15; $p < 0.0001$) (see Figure 2.2.b).

2.2.2 Incidence of invasive pneumococcal disease in the regions of Latvia

The results showed that, during the study period, the highest number of IPD cases (640) and the highest overall incidence rate (9.36 cases per 100 000 population; 95% CI: 8.65–10.12) were observed in Riga. Moreover, the overall incidence rate in the Riga region was significantly higher than the overall incidence rate in Latvia during the period from 2012 to 2022 ($p < 0.0001$), as well as higher than the overall incidence rate in each of the other regions of Latvia ($p < 0.0001$). Based on the linear regression equation ($y = 0.7884x + 4.5873$, where y denotes the incidence rate per 100 000 population in the Riga region and x denotes year (time period)), it was established that the average annual increase in IPD incidence in the Riga region was approximately 0.7884 cases per 100 000 population. The coefficient of

determination for the linear regression model ($R^2 = 0.6597$) indicates a reliable upward trend in incidence in the Riga region (see Figure 2.3). In addition, *Joinpoint* regression analysis also statistically significantly confirmed an increasing trend in incidence in Riga ($p = 0.001$). On average, the incidence increased significantly by 8.81% per year (APC = 8.81%; 95% CI: 2.49–15.67; $p = 0.0084$) (see Figure 2.4.a). In the Kurzeme region, 34 IPD cases were registered during the study period, and the overall incidence rate was 1.24 cases per 100 000 population (95% CI: 0.92–1.63), which was significantly lower than the overall incidence rate in the Riga region ($p < 0.0001$). Based on the linear regression equation ($y = 0.3065x + 0.5604$, where y denotes the incidence rate per 100 000 population in the Kurzeme region and x denotes year [time period]), it was established that the average annual increase in IPD incidence in this region was approximately 0.3065 cases per 100 000 population. The coefficient of determination for the linear regression model ($R^2 = 0.5312$) indicates a reliable increasing trend in incidence in the Kurzeme region (see Figure 2.3). Furthermore, *Joinpoint* regression analysis also statistically significantly confirmed an increasing trend in incidence in the Kurzeme region ($p = 0.03$). On average, the incidence increased significantly by 22.6% per year (APC = 22.6%; 95% CI: 2.64–46.95; $p = 0.028$) (see Figure 2.4.b).

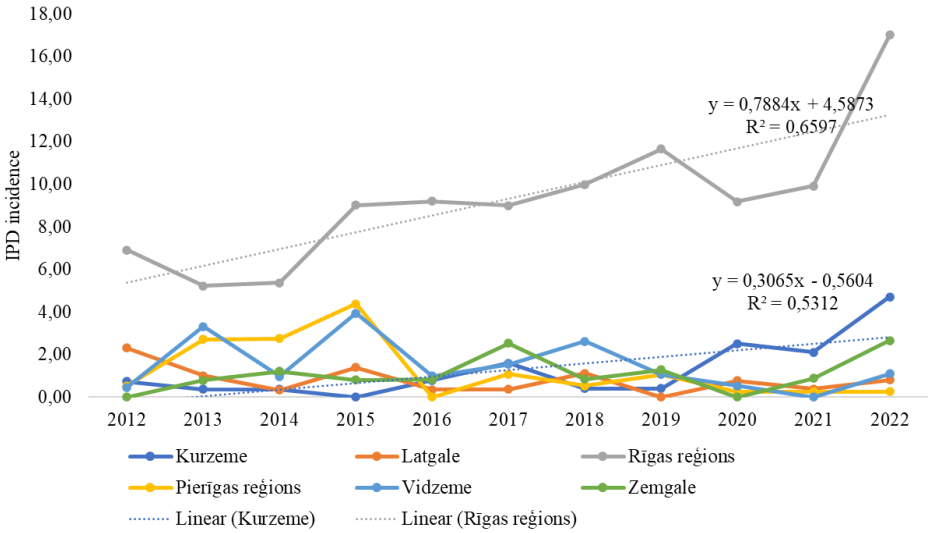


Figure 2.3 **Invasive pneumococcal disease incidence by regions of Latvia**

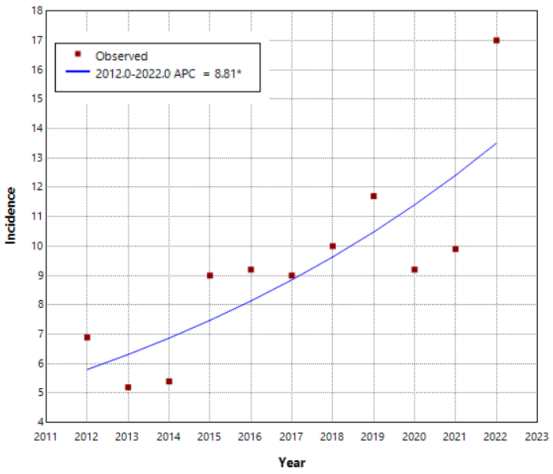


Figure 2.4.a **IPD incidence and its trends in Riga region**

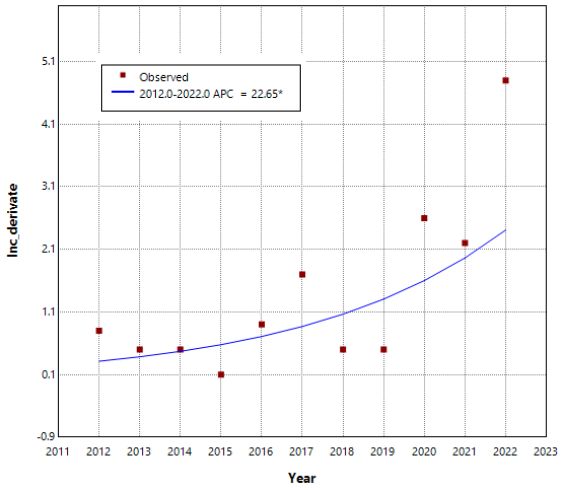


Figure 2.4.b **IPD incidence and its trends in Kurzeme region**

2.2.3 Invasive pneumococcal disease cases and incidence rate by age groups

During the study period, 41 cases of IPD were registered among children aged 0–17 years, accounting for 5.1% of all registered cases (41/811; 95% CI: 3.65–6.80). The mean age in this group was 2.34 years; the minimum age was 0 years, the maximum age was 13 years, and the median age was 2 years. The overall incidence rate during the study period was 1.05 cases per 100 000 population (95% CI: 0.75–1.43). This rate was statistically significantly lower than the incidence rates observed in all other age groups ($p < 0.001$) (see Figure 2.5). In the adult age group of 18–64 years, 451 IPD cases were registered during the study period, representing 55.6% of all recorded cases (451/811; 95% CI: 52.11–59.07). The mean age was 48 years, with a minimum age of 19 years and a maximum age of 64 years; the median age was 50 years. The overall incidence rate in this age group during the study period was 3.4 cases per 100 000 population (95% CI: 3.06–3.68). A total of 319 IPD cases were registered among older adults aged 65 years and above during the study period, accounting for 39.3% of all cases (319/811; 95% CI: 35.95–42.79). The mean age in this group was 76 years, with a minimum age of 65 years and a maximum age of 99 years; the median age was 76 years. The overall incidence rate during the study period was 7.5 cases per 100 000 population (95% CI: 6.72–8.39), which was the highest among all age groups. This rate was statistically significantly higher than the overall incidence rates observed among children aged 0–17 years and adults aged 18–64 years ($p < 0.0001$) (see Figure 2.5).

Based on the linear regression equation ($y = 0.8215x + 2.5408$, where y denotes the incidence rate per 100 000 population among adults aged 65 years and above, and x denotes year [time period]), it was established that the average annual increase in IPD incidence was approximately 0.8215 cases per 100 000 population. The coefficient of determination for

the linear regression model ($R^2 = 0.581$) indicates a reliable upward trend in incidence among individuals aged 65 years and above (see Figure 2.5). *Joinpoint* regression analysis did not identify any inflection points in the dynamics of IPD incidence across age groups, indicating a steady upward trend throughout the study period. A statistically significant increase in incidence was observed only in the 65+ age group ($p = 0.005$). The average annual increase in incidence in this age group was 11.4%, and this trend was statistically significant (APC = 11.40%; 95% CI: 3.85–19.62; $p = 0.0032$) (see Figure 2.6.c). The results of the *Joinpoint* regression analysis did not indicate a statistically significant increasing trend in incidence in the other age groups (see Figures 2.6.a and 2.6.b).

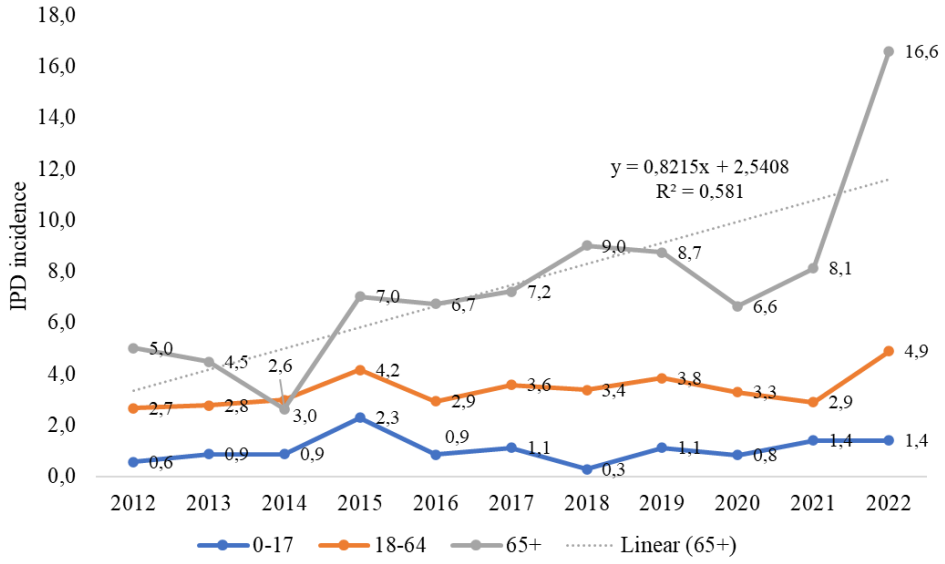


Figure 2.5 **Invasive pneumococcal disease incidence by age groups**

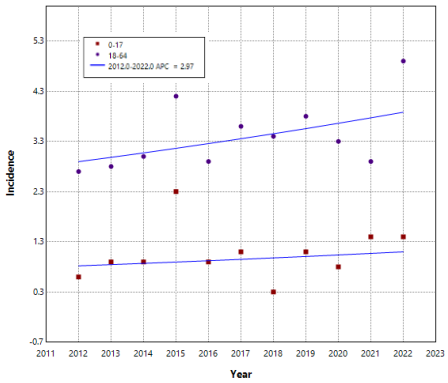


Figure 2.6.a **IPD incidence trends in 0-17 and 18-64 age groups**

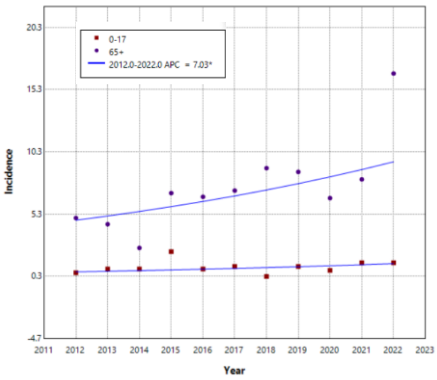


Figure 2.6.b **IPD incidence trends in 0-17 and 65+ age groups**

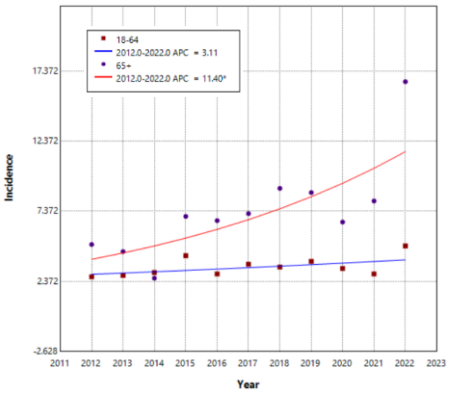


Figure 2.6.c **IPD incidence trends in 18-64 and 65+ age groups**

2.2.4 Invasive pneumococcal disease cases and incidence rates by sex

The incidence rate among men was higher than that among women throughout the study period (see Figure 2.7.a). Based on the linear regression equation ($y = 0.2306x + 1.4191$, where y denotes the incidence rate per 100 000 population among women and x denotes year [time period]), it was established that the average annual increase in IPD incidence among women was approximately 0.2306 cases per 100 000 population. *Joinpoint* regression analysis of IPD incidence trends by sex did not identify any inflection points, indicating a steady increase in incidence over the study period. Among women, the incidence rate increased significantly by an average of 9.1% per year (APC = 9.08% per year; 95% CI: 4.86–13.48; $p = 0.00076$), whereas among men the increase was more gradual and did not reach statistical significance (APC = 4.56% per year; 95%CI: −0.29 to 9.64; $p = 0.062$). The parallelism test indicated statistically significant differences in trend slopes between the sexes, demonstrating that the increase in incidence among women was significantly higher than among men, despite the overall incidence rate remaining higher in men than in women (see Figure 2.7.b).

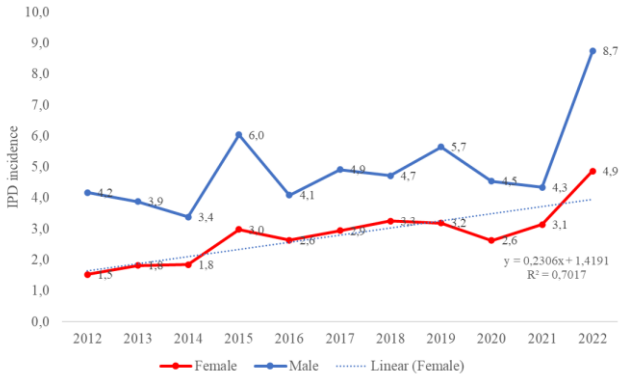


Figure 2.7.a **IPD incidence rate in males and females**

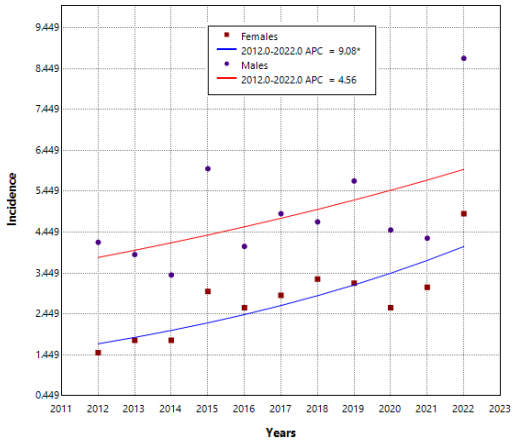


Figure 2.7.b **IPD incidence trends in males and females**

2.3 *Streptococcus pneumoniae* serotypes isolated from patients with invasive pneumococcal disease

Serotypes were identified for the majority of *S. pneumoniae* isolates, 92.7% (752/811; 95% CI: 90.7–94.4). During the analysed period, a total of 55 different *S. pneumoniae* serotypes were identified in the overall study population. Of these, only 18% (10/55) were included in the 10-valent pneumococcal conjugate vaccine (PCV10) used in Latvia during that period. The most frequently detected serotypes throughout the study period were serotype 3 (17.4%, 131/752; 95% CI: 14.8–20.3) and serotype 19A (10.9%, 82/752; 95% CI: 8.8–13.4) (see Table 3.2). Over the study period, a gradual decrease was observed in the proportion of *S. pneumoniae* serotypes included in the PCV10 formulation. *Joinpoint* regression analysis demonstrated a statistically significant downward trend in the proportion of PCV10 serotypes among patients with IPD during the study period ($p = 0.0001$), with the proportion of PCV10 serotypes decreasing significantly by an average of 13.2% per year (APC = −13.2%; 95% CI: −16.28 to −9.95; $p = 0.0001$). In contrast, an upward trend was observed in the proportion of serotypes included in PCV13 but not in PCV10; however, this increase did not reach statistical significance (APC = 5.32% per year; 95% CI: −2.43 to 13.68; $p = 0.160$). The parallelism test indicated that the slopes of the two trends differed significantly ($p = 0.0096$), pointing to a shift in serotype structure during the study period (see Figure 2.8).

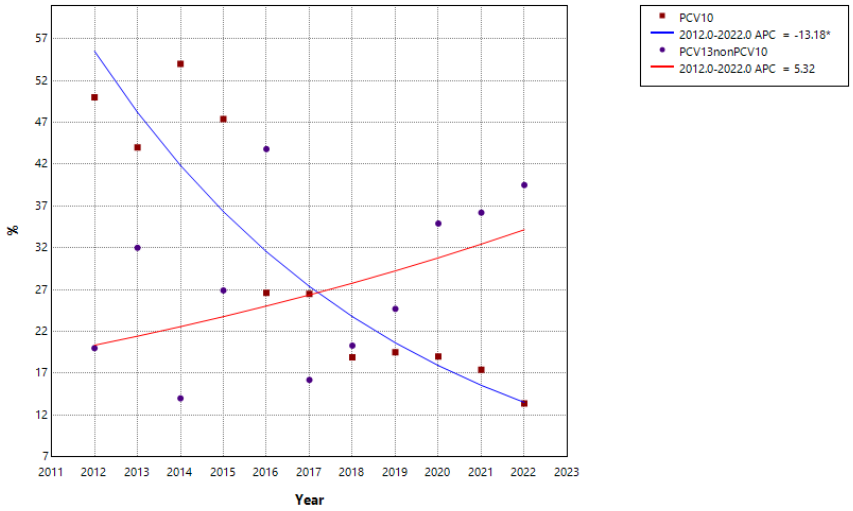


Figure 2.8 **Trends in PCV10 and PCV13 non-PCV10 S. *pneumoniae* serotypes among invasive pneumococcal disease cases in Latvia, 2012–2022**

Joinpoint regression analysis indicated that the observed upward trend in the proportion of serotype 3 during the study period was not statistically significant. For serotype 19A, one inflection point was identified in 2015. During the period 2012–2015, a very steep and statistically significant increase in the proportion of serotype 19A was observed (APC = 274.64% per year; 95% CI: 103.05–847.54; $p < 0.00001$), whereas during the period 2015–2022 a slight increase was identified, which did not reach statistical significance (APC = 7.16% per year; 95% CI: −23.11 to 27.51; $p = 0.589$). Serotype 6C of *S. pneumoniae*, which was not included in any of the vaccines available in Latvia during the study period, began to be identified among registered patients with IPD from 2015 onwards. In 2015, serotype 6C accounted for 1.3% of all identified serotypes (1/78; 95% CI: 0.03–6.94), whereas by 2022 its proportion had increased to 9.2% (11/119; 95% CI: 4.71–15.94). *Joinpoint* regression analysis demonstrated a statistically significant increasing trend in the proportion of serotype 6C. On average, the proportion of serotype 6C increased significantly by 66.3% per year (APC = 66.35%; 95% CI: 28.30–115.58; $p < 0.000001$) (see Figure 2.9.b).

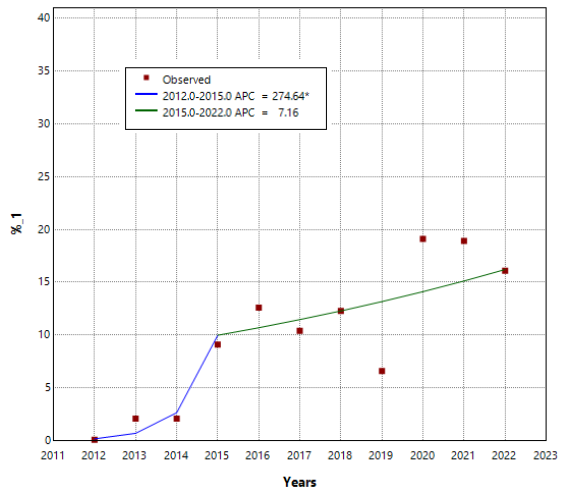


Figure 2.9.a **Trends of *S. pneumoniae* 19A serotype**

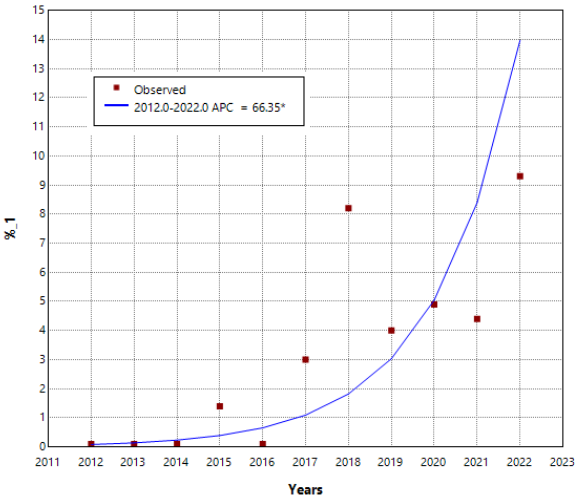


Figure 2.9.b **Trends of *S. pneumoniae* 6C serotype**

Table 2.2

The most frequently identified *S. pneumoniae* serotypes in patients with invasive pneumococcal disease, 2012–2022

***S. pneumoniae* serotype**	**Number of IPD cases, n**	**Proportion of identified serotypes out of the total number of serotypes detected, %**	**95% CI**
3[3,4,5,6]	131	17.4	14.8–20.3
19A[3,4,5,6]	82	10.9	8.8–13.4
4[1,2,3,4,5]	63	8.4	6.5–10.6
8[5,6]	61	8.1	6.26–10.30
19F[2,3,4,5,6]	35	4.7	3.26–6.41
9N[6]	35	4.7	3.26–6.41
6C[6]	29	3.9	2.60–5.49
7F[2,3,4,5,6]	26	3.5	2.27–5.03
22F[4,5,6]	23	3.1	1.95–4.55
23F[2,3,4,5,6]	21	2.8	1.74–4.24
Total number of the most frequent serotyps	506	67.3	63.80–70.63
Other serotypes	246	32.7	29.37–36.20
Total	752	–	–

[1]PCV10
[2] PCV13
[3] PCV15
[4] PCV20
[5] PPSV23
[6] Not covered with vaccins

2.4 Antimicrobial susceptibility of *Streptococcus pneumoniae* serotypes identified in patients with invasive pneumococcal disease

Antimicrobial susceptibility to penicillin, erythromycin, or cefotaxime/ceftriaxone was assessed in 89.9% (729/811; 95% CI: 87.61–91.88) of *S. pneumoniae* isolates obtained from IPD cases. Antimicrobial resistance of *S. pneumoniae* isolates was identified to penicillin, erythromycin, and cefotaxime/ceftriaxone in 3.8% (28/721; 95% CI: 2.60–5.56), 5.4% (39/722; 95% CI: 3.87–7.31), and 1.2% (8/670; 95% CI: 0.52–2.34) of IPD cases, respectively. Resistance to cefotaxime/ceftriaxone was significantly lower than resistance to penicillin ($p = 0.001$) and erythromycin ($p < 0.001$). No significant difference was observed between resistance to penicillin and erythromycin ($p > 0.999$). No statistically significant changes in the overall antimicrobial resistance of *S. pneumoniae* isolates were observed over the study period ($\chi^2 = 17.615$; $p = 0.062$). Likewise, when resistance trends were evaluated separately for each antimicrobial agent under investigation using *Joinpoint* regression analysis, no statistically significant trends were identified during 2012–2022. The highest proportion of resistant *S. pneumoniae* isolates among patients with IPD was observed in the 18–64-year age group (56.4%, 31/55; 95% CI: 42.32–69.70), followed by the age group of 65 years and older (40.0%, 22/55; 95% CI: 27.02–54.09).

2.5 Clinical manifestations in patients with invasive pneumococcal disease

The clinical manifestations of invasive pneumococcal disease were combined into three groups. **Group 1** comprised IPD clinical manifestations "**with meningitis**" (combining meningitis and meningitis with sepsis), accounting for 19.5% of cases (158/811; 95% CI: 16.81–22.38). **Group 2** comprised IPD clinical manifestations "**sepsis**" (IPD with sepsis only), representing 52.4% of cases (425/811; 95% CI: 48.90–55.89). **Group 3** comprised IPD clinical manifestations "**with pneumonia**" (including the groups "Sepsis with pneumonia" and "Invasive pneumonia"), accounting for 28.1% of cases (228/811; 95% CI: 25.04–31.34).

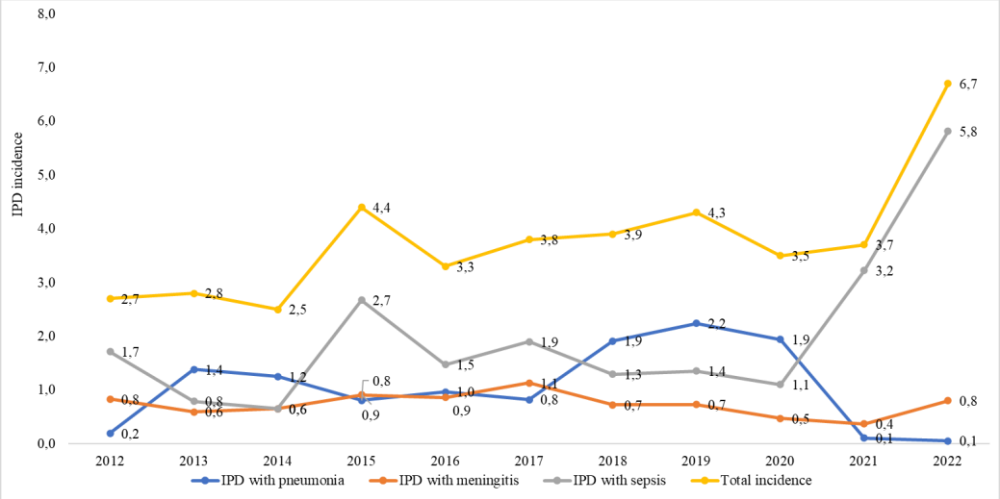


Figure 2.10 **Incidence of clinical manifestations of invasive pneumococcal disease, 2012–2022**

Joinpoint regression analysis of the incidence of clinical manifestations of IPD during the period from 2012 to 2022 did not indicate any statistically significant temporal trends for any of the clinical manifestations analysed.

Over the study period, the overall incidence rate of IPD with meningitis was 0.7 cases per 100 000 population, which was statistically significantly lower than that of the clinical manifestation with pneumonia ($p < 0.003$) and with sepsis ($p < 0.0001$). The overall incidence rate of the clinical manifestation with sepsis was 2.0 cases per 100 000 population, which was statistically significantly higher than that observed for the other clinical manifestations ($p < 0.0001$). The overall incidence rate of IPD with pneumonia was 1.1 cases per 100 000 population, which was statistically significantly higher than that of IPD with meningitis ($p < 0.0003$), but statistically significantly lower than that of IPD with sepsis ($p < 0.0001$) (see Figure 2.10).

2.6 Fatal outcomes in patients with invasive pneumococcal disease

During the period from 2012 to 2022, a total of 279 fatal outcomes were registered among patients with invasive pneumococcal disease, corresponding to case fatality rate of 34.4% (279/811; 95% CI: 31.21–37.74). The results of the *Joinpoint* regression analysis indicated a statistically significant increasing trend in the number of fatal cases (slope coefficient, $p = 0.0159$). Furthermore, the annual number of fatal cases increased significantly by an average of 9.59% per year (APC = 9.59%; 95% CI: 3.56–17.43; $p = 0.0016$) (see Figure 2.11a). *Joinpoint* regression analysis stratified by sex showed that, although one inflection point was identified in 2020 in both men and women, accompanied by a sharp increase in the number of deaths, this increase did not reach statistical significance (see Figure 2.11.b).

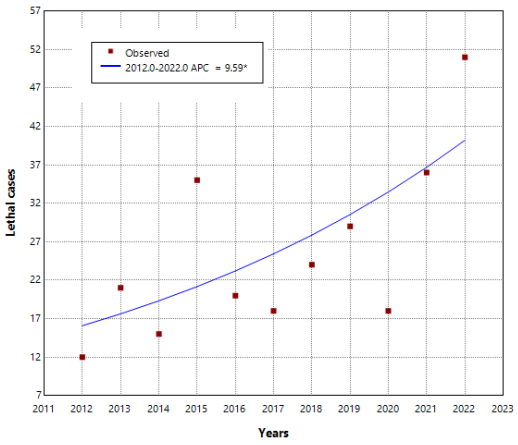


Figure 2.11.a **IPD cases with fatal outcome, 2012.–2022**

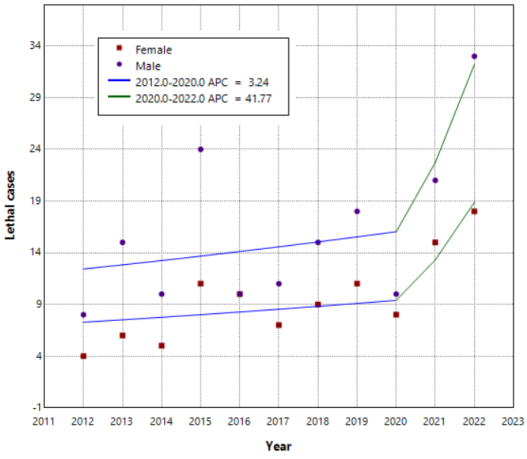


Figure 2.11.b **IPD cases with fatal outcome in males and females, 2012.–2022**

2.6.1 Age and sex of patients with fatal outcomes of invasive pneumococcal disease

The highest case fatality during the analysed period was observed among patients with IPD aged 65 years and above, reaching 45.7% (146/319; 95% CI: 40.21–51.41). Among patients aged 18–64 years, the case fatality rate was 29.3% (132/451; 95% CI: 25.11–33.70), whereas only one fatal outcome was registered among children during the study period, corresponding to 2.4% of all IPD cases in this age group (1/41; 95% CI: 0.06–12.86). Moreover, the differences between age groups were statistically significant. When comparing sexes, a higher case fatality rate during the study period was observed among men, at 35.9% (175/488; 95% CI: 31.60–40.29), however, the difference between the sexes was not statistically significant. In both women and men, higher case fatality was observed among patients with IPD aged 65 years and above, and the differences between age groups were statistically significant. The results of the univariable logistic regression analysis indicated that, during the study period, patients with IPD aged 65 years and above had statistically significantly higher odds of a fatal outcome following invasive pneumococcal disease than patients in the other two age groups.

2.6.2 Isolated *Streptococcus pneumoniae* Serotypes and Their Antimicrobial Susceptibility in Patients with Fatal Outcomes of Invasive Pneumococcal Disease

During the study period, 94.98% (265/279; 95% CI: 91.72–97.23) of all *S. pneumoniae* isolates obtained from patients with fatal IPD outcomes were serotyped. Among deceased patients, the most frequently identified *S. pneumoniae* serotypes were serotype 3 (19.2%, 51/265; 95% CI: 14.68–24.52), serotype 19A (13.6%, 36/265; 95% CI: 9.70–18.31), and serotype 8 (7.9%, 21/265; 95% CI: 4.97–11.86). These three serotypes were identified in 40.7% of deceased patients with determined *S. pneumoniae* serotypes (108/265; 95% CI:

34.78–46.94). Certain *S. pneumoniae* serotypes, namely 10F (1 case), 17A (1 case), 28A (1 case), 33 (1 case), and 37 (2 cases), were detected exclusively among IPD patients with fatal outcomes. When *S. pneumoniae* serotypes were grouped according to their inclusion in pneumococcal vaccine formulations, higher case fatality was observed among patients with IPD caused by *S. pneumoniae* serotypes included in PCV13 but not in PCV10 (serotypes 3, 6A, and 19A), compared with patients infected with serotypes included in PCV10, namely 41.55% (91/219; 95% CI: 34.95–48.39) and 28.27% (60/210; 95% CI: 22.57–35.19), respectively. During the study period, no statistically significant difference was found between fatal outcomes among IPD patients with resistant *S. pneumoniae* isolates and those without antimicrobial resistance, 30.9% (17/55; 95% CI: 19.15–44.81) and 34.7% (262/756; 95% CI: 31.26–38.17), respectively.

2.6.3 Clinical manifestations in patients with fatal invasive pneumococcal disease outcomes

During the study period, the highest case fatality was observed among IPD patients with the clinical manifestation of pneumonia (pneumonia with sepsis and invasive pneumonia), reaching 37.7% (86/228; 95% CI: 31.41–44.36). However, the differences between the clinical manifestation groups were not statistically significant.

2.6.4 Multivariable analysis for determining the odds of fatal outcome

Univariable logistic regression analysis was performed to examine the associations between fatal IPD outcome and selected factors separately, including:

- age group (0–17, 18–64, 65+ years);
- sex (male, female);
- IPD clinical manifestations (“sepsis”, “with meningitis”, and “with pneumonia”);
- *S. pneumoniae* serotypes grouped according to inclusion in pneumococcal vaccine formulations (PCV10, PCV13, PCV15, PCV20, PPSV23, and non-vaccine serotypes);
- resistance to at least one of the antimicrobial agents under investigation:
  - resistance to penicillin (resistant/not tested/susceptible),
  - resistance to erythromycin (resistant/not tested/susceptible),
  - resistance to ceftriaxone/cefotaxime (resistant/not tested/susceptible).

The regression analysis demonstrated that patients with IPD aged 65 years and above had statistically significantly higher odds of fatal IPD outcome than those aged 18–64 years (crude OR = 2.04; 95% CI: 1.41–2.75; $p < 0.001$). Patients whose IPD was caused by the group of serotypes included in PCV13 (serotypes 3, 6A, and 19A) but not included in PCV10 also

had statistically significantly higher odds of fatal IPD outcome than patients infected with serotypes included only in PCV10 (crude OR = 1.75; 95% CI: 1.17–2.62; $p = 0.006$).

After adjustment for the interrelationships between factors by including in the model those variables with crude odds ratios greater than one (age group, resistance to erythromycin, resistance to ceftriaxone/cefotaxime, sex, *S. pneumoniae* serotype group, and the clinical manifestations "sepsis" and "with pneumonia"), the statistically significant association between fatal IPD outcome and infection caused by the serotype group included in PCV13 was no longer observed in the multivariable logistic regression model. The odds of fatal IPD outcome were increased among men (adjusted OR = 1.43; 95% CI: 1.03–2.00; $p = 0.03$), as well as among individuals aged 65 years and above (adjusted OR = 2.16; 95% CI: 1.55–3.00; $p < 0.001$), compared with individuals aged 18–64 years. No other factors showed a statistically significant association with the odds of fatal IPD outcome in the multivariable regression model.

2.7 Comorbidities in patients with invasive pneumococcal disease and their association with fatal outcomes

2.7.1 Presence of at least one of the studied comorbidities in patients with invasive pneumococcal disease

During the study period, at least one of the studied and previously described comorbidities was identified in 34.0% (276/811; 95% CI: 30.77–37.41) of patients with IPD. As observed for the individual diseases, the proportion of IPD cases among patients with at least one of the studied comorbidities varied from year to year. The highest proportion of IPD cases with comorbidities was observed in 2020, at 41.8% (28/67; 95% CI: 29.85–54.48), whereas the lowest proportion was recorded in 2012, at 19.6% (11/56; 95% CI: 9.24–30.05). The results indicate that the increase over time in the proportion of IPD cases among patients with at least one comorbidity was statistically significant ($\chi^2 = 18.659$, $p = 0.045$). *Joinpoint* regression analysis likewise confirmed a statistically significant increasing trend in the number of adult IPD cases among patients with at least one comorbidity ($p = 0.001$). The number of cases increased significantly by an average of 10.9% per year (APC = 10.95%; 95% CI: 2.28–22.39; $p = 0.015$).

Case fatality in patients with invasive pneumococcal disease and at least one comorbidity

During the study period, the case fatality rate among IPD patients with at least one comorbidity was 34.4% (95/276; 95% CI: 28.83–40.35), which was identical to the overall case fatality rate (34.4%). Among patients in whom no comorbidity was identified, the case fatality rate was likewise 34.4% (184/535; 95% CI: 30.37–38.39). After adjustment for sex and age

group, the presence of at least one comorbidity was not independently associated with a fatal outcome in patients with IPD (adjusted OR = 0.86; 95% CI: 0.63–1.19; $p = 0.882$).

2.7.2 HIV/AIDS in patients with invasive pneumococcal disease

HIV/AIDS as an underlying diagnosis was registered in 50 of 811 IPD patients, corresponding to 6.2% (95% CI: 1.61–8.05). However, owing to the small absolute number of cases, differences in the proportion of such patients between years were not statistically significant ($\chi^2 = 9.57$, $p = 0.478$).

Case fatality in patients with invasive pneumococcal disease and an hiv/aids diagnosis

During the study period, the case fatality rate among IPD patients with an HIV/AIDS diagnosis was 18.0% (9/50; 95% CI: 8.58–31.44), whereas among patients without HIV/AIDS it was 35.5% (270/761; 95% CI: 32.08–39.00). However, these results were influenced by the relatively small number of cases in the HIV/AIDS group, which reduced statistical power. After adjustment for sex and age group, HIV/AIDS diagnosis was not independently associated with a fatal outcome (adjusted OR = 0.49; 95% CI: 0.23–1.03; $p = 0.532$).

2.7.3 Oncological Diseases in Patients with Invasive Pneumococcal Disease

Cancer as an underlying diagnosis was registered in 13.7% (111/811; 95% CI: 11.39–16.25) of all patients with IPD. The results of the *Joinpoint* regression analysis indicated a statistically significant increasing trend in the number of IPD patients with oncological diseases (slope coefficient, $p = 0.001$) (see Figure 2.12a).

Case Fatality in Patients with Invasive Pneumococcal Disease and Oncological Diagnoses

During the study period, the case fatality rate among IPD patients with oncological diagnoses was 39.6% (44/111; 95% CI: 30.48–49.37), which was higher than the overall case fatality rate (34.4%). By comparison, the case fatality rate among patients without oncological diagnoses was 33.6% (235/700; 95% CI: 30.08–37.21). After adjustment for sex and age group, oncological diagnoses were not independently associated with a fatal outcome (adjusted OR = 0.94; 95% CI: 0.61–1.45; $p = 0.79$). Given that in some years the number of fatal outcomes was zero, a small continuity correction was applied before performing *Joinpoint* regression by adding 0.1 to each case count in order to avoid zero values and ensure correct model estimation. Following this correction, *Joinpoint* regression analysis demonstrated a statistically significant increasing trend in fatal outcomes among IPD patients with oncological diagnoses (slope coefficient, $p = 0.018$). Fatal outcomes in IPD patients with oncological diagnoses increased

significantly by an average of 15.2% per year (APC = 15.2%; 95% CI: 2.79–35.30; $p = 0.022$) (see Figure 2.12b).

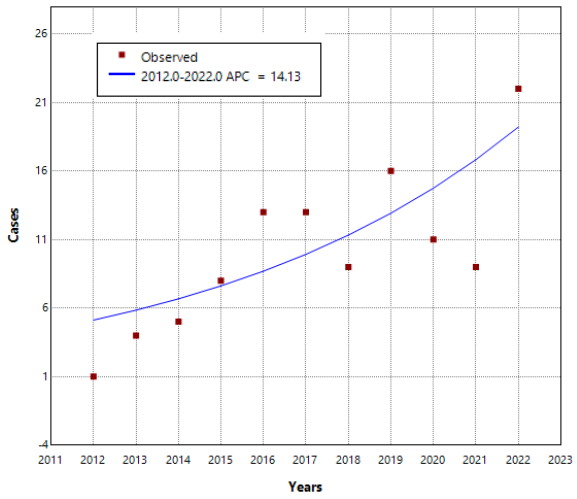


Figure 2.12.a **IPD trends among patients with oncological diagnoses**

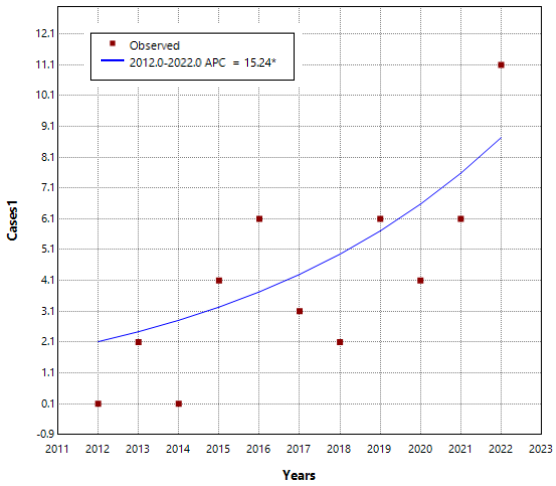


Figure 2.12.b **IPD fatal outcomes trends among patients with oncological diagnoses**

2.7.4 Diabetes mellitus in patients with invasive pneumococcal disease

Diabetes mellitus was present in 10.1% (82/811; 95% CI: 8.35–12.66) of all patients with IPD. The results indicate that differences in the proportion of IPD cases among patients with diabetes mellitus across years were not statistically significant ($\chi^2 = 13.07$, $p = 0.220$).

Case fatality in patients with invasive pneumococcal disease and diabetes mellitus

During the study period, the case fatality rate among IPD patients with diabetes mellitus was 40.2% (33/82; 95% CI: 29.56–51.66), which was higher than the overall case fatality rate (34.4%). Among patients without diabetes mellitus, the case fatality rate was 33.7% (729/246; 95% CI: 30.32 – 37.31). The statistical significance of these findings was influenced by the relatively small number of cases in the group of IPD patients with diabetes mellitus. After adjustment for sex and age group, fatal outcome in IPD patients was not independently associated with diabetes mellitus (adjusted OR = 1.04; 95% CI: 0.64–1.70; $p = 0.85$). The case fatality rate among IPD patients with diabetes mellitus fluctuated over time; however, these changes were not statistically significant ($\chi^2 = 15.6$, $p = 0.112$).

3.7.5. Tuberculosis in patients with invasive pneumococcal disease

Tuberculosis was registered in 4.6% (37/811; 95% CI: 3.23–6.23) of patients with IPD. No statistically significant differences were identified in the number or proportion of tuberculosis cases among IPD patients across age groups, sex groups, or groups of clinical manifestations of IPD.

Case fatality in patients with invasive pneumococcal disease and tuberculosis

During the study period, the case fatality rate among IPD patients with tuberculosis was 29.7% (11/37; 95% CI: 15.87–46.98), which was lower than the overall case fatality rate (34.4%) and lower than the case fatality rate among patients without tuberculosis, which was 34.63% (268/774; 95% CI: 31.27–38.10). The statistical reliability of these findings was affected by the relatively small number of cases in the group of IPD patients with tuberculosis. The proportion of fatal cases among IPD patients with tuberculosis was relatively low, and fluctuations in case numbers were not statistically significant ($\chi^2 = 7.664$, $p = 0.662$). No statistically significant differences were found with respect to temporal variation in case fatality, age and sex groups, the distribution of identified *S. pneumoniae* serotypes, or clinical manifestations.

3.7.6. Hepatitis C virus infection in patients with invasive pneumococcal disease

During the study period, hepatitis C virus infection was identified as a comorbidity in 8.1% of the analysed IPD patients (66/811; 95% CI: 6.35–10.24). No statistically significant differences were found in the number or proportion of hepatitis C virus infection cases among IPD patients across age groups, sex groups, or groups of clinical manifestations of IPD.

Case fatality in patients with invasive pneumococcal disease and hepatitis C virus infection

During the study period, 17 IPD patients with hepatitis C virus infection died, corresponding to a case fatality rate of 25.8% (95% CI: 15.78–38.01), which was lower than the overall case fatality rate (34.4%) and lower than that observed among patients without hepatitis C virus infection, namely 35.17% (262/745; 95% CI: 31.74–38.72). No statistically significant differences were found with respect to temporal variation in case fatality, age and sex groups, the distribution of identified *S. pneumoniae* serotypes, or clinical manifestations.

Multivariable logistic regression analysis demonstrated that the comorbidities examined in patients with IPD were not statistically significantly associated with fatal outcome, either in the crude model or in the model adjusted for sex and age.

3 Discussion

The present Doctoral Thesis characterised the incidence of invasive pneumococcal disease in Latvia during the period from 2012 to 2022, identified the *S. pneumoniae* serotypes detected in patients with IPD and their susceptibility to antibacterial agents, and analysed the associations between fatal IPD outcomes and patient related demographic and health characteristics. Invasive pneumococcal disease is not included as a separate diagnosis in the 10th revision of the International Classification of Diseases (ICD-10). Nevertheless, the term is widely used in scientific publications, as well as in documents issued by the World Health Organization, the European Centre for Disease Prevention and Control, and other international organisations. The term *invasive pneumococcal disease* is used to denote invasive infections caused by *S. pneumoniae* that are coded in ICD-10 according to their specific clinical manifestation, for example, A40.3 – *Streptococcus* pneumoniae sepsis, or G00.1 – pneumococcal meningitis. Possibly, taking into account the public health importance of IPD, consideration could be given to its inclusion as a distinct subgroup in future revisions of the ICD.

Compared with other European countries, the incidence of invasive pneumococcal disease in Latvia remained moderate until 2021, ranging from 2.5 to 4.3 cases per 100 000 population. However, in 2022, a marked increase in incidence was observed, reaching 6.7 cases per 100 000 population and exceeding both the average rate reported in the European Union (5.1) and those observed in the neighbouring countries Lithuania (3.3) and Estonia (2.6) (ECDC, 2025). Two pronounced increases in IPD incidence were observed during the analysed period, namely in 2015 and 2022. These peaks may be explained not only by a true increase in disease occurrence, but also, at least in part, by improvements in case notification. In both years, the Centre for Disease Prevention and Control of Latvia implemented educational interventions directed at healthcare professionals, reminding them of the requirement to report cases, which may have contributed to more complete case notification. In addition, the increase observed in 2022 may also be attributable to the lifting of non-pharmaceutical interventions introduced during the COVID-19 pandemic (Facciola et al., 2023; Lee et al., 2024). Epidemiological surveillance data on IPD in Latvia indicate that the increase in incidence observed by 2023 continued beyond the study period, reaching 7.9 cases per 100 000 population (149 cases). However, the incidence pattern recorded in 2024 and 2025 is more indicative of year to year fluctuation with 6.5 cases per 100 000 population (122 cases) reported in 2024 and 7.6 cases per 100 000 population (141 cases) in 2025.

The data analysis demonstrated that the most unfavourable epidemiological situation during the study period was observed in Riga, where both a higher incidence of invasive pneumococcal disease and one of the highest increasing trends were identified in comparison

with other regions of Latvia. According to the *Joinpoint* regression analysis, the incidence of IPD in Riga increased significantly by an average of 8.81% per year. These regional differences may be attributable both to disparities in healthcare infrastructure and to possible differences in the diagnosis and reporting of IPD cases. Given that the largest inpatient healthcare institutions are concentrated in the Riga region and that the National Microbiology Reference Laboratory is also located there, the diagnostic capacity for IPD is likely to be greater, thereby facilitating more complete reporting to the surveillance network. Data from the Kurzeme region likewise indicated a statistically significant increasing trend in incidence during the study period. However, the annual incidence rates in this region were not among the highest observed in Latvia.

The findings of the present Doctoral Thesis indicate that the highest incidence of invasive pneumococcal disease was observed in two particularly susceptible age groups: infants under one year of age and older adults aged 65 years and above. This bimodal age distribution of IPD incidence is frequently observed at the global level, across European countries, and within the EU/EEA region as a whole (ECDC, 2025; Henriques-Normark & Tuomanen, 2013; Pilishvili et al., 2010). The high incidence during the first year of life may be explained by the immaturity of the infant immune system and the waning protection conferred by maternally derived antibodies. Other investigators have also attributed this pattern to the high prevalence of nasopharyngeal carriage of *S. pneumoniae* and the intensity of transmission during this age period (Bogaert et al., 2004), as well as to the limited capacity of infants to mount effective immune responses to capsular polysaccharide antigens early in life, which increases susceptibility until completion of the primary PCV vaccination series (Basha et al., 2014). Social and care-related factors, such as early attendance at preschool institutions and household overcrowding, may further facilitate bacterial colonisation and increase the risk of IPD (Hjuler et al., 2007). WHO recommendations likewise emphasise the particularly high burden of IPD among children under two years of age and the importance of early vaccination (WHO, 2019). The high incidence of IPD among older adults aged 65 years and above is associated with age-related decline in immune function, as well as with the presence of chronic comorbidities. It is particularly noteworthy that an increasing trend in IPD incidence was observed in the age group of 65 years and above during the study period. This trend may be attributable to several factors, including population ageing, increasing prevalence of chronic diseases, and potentially insufficient vaccination coverage in this age group (Cheong & Song, 2024).

The results of the Doctoral Thesis also indicate statistically significant sex differences in IPD epidemiology in Latvia. When the sex groups were compared, a higher incidence was observed among men, whereas a statistically significant increasing trend in IPD incidence was

identified among women. Higher IPD incidence rates among men have also been reported in other EU/EEA countries (ECDC, 2025). Possible explanations include differences in immune response, lifestyle related factors such as smoking and alcohol consumption, occupational risk factors, or differences in risk behaviour. At the same time, the increasing incidence trend observed specifically among women points to the need for further investigation of the temporal dynamics of sex related differences in IPD.

Vaccination against pneumococcal infection was first introduced into the Latvian National Immunisation Programme in 2010, with the inclusion of PCV7, which was replaced by PCV10 in 2012 and remained in active use until the end of 2023. The pneumococcal vaccination schedule consists of three doses administered to children at 2, 4, and 12–15 months of age (Regulation, 2000). It should be noted that, during the study period, both PCV13 and PCV15 were available in Latvia. However, these vaccines were not included in the national immunisation schedule and could only be obtained privately at individual expense. PCV13 was authorised in the European Union in December 2009 and was most likely available in Latvia from 2010. PCV15 was authorised in the European Union in December 2021 and was most likely available in Latvia from 2022. As data on vaccination coverage for these vaccines are unavailable, their impact on the incidence of IPD could not be assessed precisely within the framework of the present study. The successive introduction of the conjugate vaccines PCV7 and PCV10 into the National Immunisation Programme substantially influenced the distribution of detected *S. pneumoniae* serotypes among patients with IPD. The findings of this Doctoral Thesis indicate that, during the study period, the proportion of IPD cases caused by *S. pneumoniae* serotypes included in PCV10 declined. At the same time, an increase was observed in the proportion of IPD cases caused by *S. pneumoniae* serotypes included in PCV13, PCV15, and PPV23, but not in PCV10. PCV13, PCV15, and PPV23 were not available within the Latvian immunisation programme during the study period. These findings are consistent with observations reported in other countries and support the phenomenon of serotype replacement, whereby the decline in circulation of vaccine covered serotypes in the population is accompanied by an increase in the prevalence of non-vaccine serotypes. In many instances, serotype replacement is relative in nature, reflecting a mathematically proportional increase in the share of serotypes not included in the vaccine used in the immunisation programme, rather than the emergence of entirely new serotypes. For example, in Canada, following the introduction of PCV into the vaccination programme, a statistically significant increase was observed in the proportion of IPD cases caused by *S. pneumoniae* serotypes not included in the vaccine used, rising from 42% in the pre-vaccination period to 73.3% after the introduction of PCV13 ($p = 0.002$). The authors concluded that the introduction of PCV effectively reduced

the number of vaccine-type IPD cases, but at the same time created ecological space for the spread of serotypes not included in the vaccine formulation (Murad et al., 2022). Similar trends were also observed in Spain, where, following the inclusion of PCV13 in the childhood immunisation programme, the number of IPD cases caused by *S. pneumoniae* serotypes included in PCV13 declined by 88% in children and by 59% in the adult population, whereas the proportion of IPD cases caused by serotypes not covered by the vaccine increased substantially (De-Miguel et al., 2021). Likewise, in Austria, after the introduction of PCV10 into the vaccination programme, the proportion of *S. pneumoniae* serotype 19A among IPD cases increased from 3% to 6–7% (Paulke-Korinek, 2014), whereas in Finland, following PCV10 implementation, serotypes 19A (30%) and 3 (19%) became the dominant serotypes among IPD cases (Jokinen et al., 2015). The findings of the present Doctoral Thesis confirm these international observations. Following the introduction of PCV10, the proportion of IPD cases caused by *S. pneumoniae* serotypes included in PCV10 decreased, whereas the proportion of cases caused by *S. pneumoniae* serotypes included in PCV13 but not in PCV10, such as serotypes 3 and 19A, increased. As demonstrated by the present analysis, the proportion of serotype 3 among all identified serotypes in Latvia was 17.5% in 2012 (7/40; 95% CI: 7.34–32.78), rising to 21.8% in 2022 (26/119; 95% CI: 14.8–30.35). Similarly, serotype 19A, which accounted for only 2% of IPD cases in 2013 (1/50; 95% CI: 0.05–10.65), reached 15.9% in 2022 (19/119; 95% CI: 9.89–23.81). Moreover, serotype 19A began to appear among patients with IPD only from year 2013. Such serotype replacement poses potential long term challenges for public health. Newly dominant serotypes are often associated with a more severe clinical course of IPD, as observed in Latvia with the increasing prevalence of serotypes 3 and 19A, thereby increasing healthcare costs and complicating treatment because of antimicrobial resistance.

Beginning in 2015, *S. pneumoniae* serotype 6C, which is not included in any of the currently available pneumococcal vaccines, began to be identified among patients with IPD in Latvia. Its proportion among all identified serotypes was 1.3% in 2015 (1/78; 95% CI: 0.03–6.94), but increased to 9.2% in 2022 (11/119; 95% CI: 4.71–15.94). This increase indicates the emergence of *S. pneumoniae* serotype not covered by PCV in the epidemiology of IPD. A similar pattern has been reported in the United States, where the dominant *S. pneumoniae* serotypes among patients with IPD were serotypes 3, 22F, 20, 35, and 23A, with freqvency of 12.2%, 10.3%, 9.6%, 9.0%, and 7.7%, respectively, while a substantial proportion of IPD cases (17.9%) were caused by serotypes not included in the pneumococcal vaccines available at that time (Schulz et al., 2022). This underscores the need for vaccines with broader serotype coverage in order to reduce the public health burden of IPD more effectively (L. Grant

et al., 2023). To mitigate the trend of *S. pneumoniae* serotype replacement and broaden protection against IPD, Latvia introduced PCV15, a vaccine with extended serotype coverage, into the National Immunisation Schedule in 2024. In addition to the serotypes covered by PCV10, this vaccine includes serotypes 3, 19A, 6A, 22F, and 33F, thereby expanding coverage and potentially reducing the impact of serotype replacement. As meantioned previously, the findings of the Doctoral Thesis indicate that the most frequently identified *S. pneumoniae* serotypes among patients with IPD in Latvia during the study period were serotype 3 (17.4%) and serotype 19A (10.9%), which is broadly consistent with international trends following the introduction of PCV vaccination into national immunisation programmes. The data analysis also revealed differences in dominant serotypes according to age group. Among patients with IPD of working age (18–64 years), in addition to the dominant serotypes 3 (16.7%) and 19A (8.0%), serotype 4 also accounted for a considerable proportion of cases (13.1%). Studies from other countries have likewise shown that the presence of serotype 4 is associated with age below 65 years (Kellner JD et al., 2021). The occurrence of this serotype among IPD patients aged 18–64 years may also be related to its clinical characteristics, such as potentially greater invasiveness in adults, or to the fact that this age group did not constitute the primary target population for childhood vaccination and therefore may not have benefited from herd immunity against serotype 4 to the same extent as vaccinated children. Similarly, a study conducted in the United States reported an increase in IPD caused by serotype 4 among adults, particularly among people experiencing homelessness, indicating that serotype dynamics may vary according to population characteristics and risk factors (Beall et al., 2021). However, in the present Doctoral Thesis, owing to the relatively small number of cases with *S. pneumoniae* serotypes identified, the differences between serotypes and serotype groups did not reach statistical significance.

The analysis of *S. pneumoniae* antimicrobial susceptibility conducted within the framework of this Doctoral Thesis for the period from 2012 to 2022 in Latvia revealed a comparatively low level of resistance to the antimicrobial agents investigated when compared with other countries. Overall, resistance was reported in 7.5% of IPD cases. More specifically, non-susceptibility to penicillin was identified in 3.8% of cases, to erythromycin in 5.4%, and to cefotaxime/ceftriaxone in only 1.2% of cases. Furthermore, during the study period, a favourable trend towards declining resistance to penicillin and erythromycin was observed in Latvia, although these changes did not reach statistical significance. By contrast, resistance to cefotaxime/ceftriaxone increased over time, from zero in 2012 to 2.4% in 2022. Antimicrobial resistance in Latvia remains substantially lower than that reported in many other countries. For example, studies conducted in Korea have documented penicillin resistance rates ranging

from 26.6% to 37.2%, while erythromycin resistance was exceptionally high, reaching 80.3% (Kim et al., 2023; Kim et al., 2018). Similarly, high levels of resistance to penicillin (57–70%) and erythromycin (38%) have been reported in Turkey (Hascelik et al., 2023). This pattern may, at least in part, be explained by vaccination programmes and their influence on circulating serotypes. Although the findings of the present study did not demonstrate statistically significant associations between *S. pneumoniae* antimicrobial resistance and fatal outcome in patients with IPD, similar observations have also been reported in other scientific studies (Tao et al., 2022). At the same time, other studies have identified antimicrobial resistance as an independent factor for unfavorable outcome (Navarro-Torne et al., 2015). These diferencies between studies may be attributable to differences in the definition of resistance, the proportion of resistant isolates, the age distribution of patients with IPD, and the presence of chronic comorbidities. In the present doctoral study, the absence of such an association is most likely explained by the small number of resistant isolates, which limited statistical power. Although the situation in Latvia during the study period may be regarded as favourable, particularly with respect to the very low level of resistance to cephalosporins, the phenomenon of serotype replacement and the circulation of multidrug-resistant strains, such as serotype 19A, necessitate continuous resistance surveillance and rational antibiotic use.

The findings of the Doctoral Thesis indicate that higher case fatality was observed among those patients with IPD in whom *S. pneumoniae* serotypes 3 (38.9%), 19A (43.9%), and 8 (34.4%) were identified. These three serotypes were detected in 39.4% (108/274) of all fatal cases in which *S. pneumoniae* was serotyped. Findings from other studies likewise confirm that *S. pneumoniae* serotype 3 is associated with a higher risk of death among patients with IPD (Nikolova et al., 2024). Similar results were reported in a study conducted in Madrid, in which *S. pneumoniae* serotypes 3 and 8 were responsible for multiple fatal cases, with case fatality rates of 13.8% and 6.8%, respectively (De Miguel et al., 2021). During the study period, one fatal outcome was observed in a one-year-old child with IPD in whom *S. pneumoniae* serotype 3 was identified. When serotypes were grouped according to their inclusion in PCV, the PCV13 serotypes (3, 6A, and 19A) accounted for a substantial proportion of all fatal cases, particularly in the age group of 65 years and above (Moore et al., 2015; Pilishvili et al., 2010). This points to the high virulence of these serotypes and their capacity to cause severe forms of IPD (Moore et al., 2015). Inthe present Doctoral Thesis, when serotypes were grouped according to vaccine composition, patients in whom PCV13 serotypes not included in PCV10 (such as serotypes 3 and 19A) were identified had statistically significantly higher odds of fatal outcome than patients in whom PCV10 serotypes were identified (crude OR 1.75; 95% CI: 1.17–2.62; $p = 0.006$). These findings suggest that the PCV10 vaccine used in Latvia did not provide

sufficient protection against clinically important serotypes associated with higher case fatality. However, owing to the small number of cases in each group, no statistically significant association with fatal outcomes was observed when serotypes 3 and 19A were analysed separately. A high case fatality rate (34.8%) was also observed among patients in whom *S. pneumoniae* serotypes not included in the vaccines used in Latvia were identified. This indicates that, despite the vaccination programme, a risk of fatal outcome from non-vaccine serotypes persists. Similar findings have been reported in studies from other countries, which concluded that serotype replacement may lead to an increasing spread of emerging serotypes not covered by vaccine formulations (Reslan, 2022; Weinberger et al., 2010). This underscores the need for continuous monitoring of *S. pneumoniae* serotypes and for periodic updation of vaccine composition.

The results of the Doctoral Thesis confirm age as an important risk factor for IPD case fatality. Higher case fatality was observed among patients aged 65 years and above compared both with children aged 0–17 years and with working-age adults aged 18–64 years. Overall case fatality in the senior group reached 45.8%, whereas in the 18–64 year age group it was 29.3%, and among children it was 2.4%. Multivariable logistic regression analysis further confirmed that the odds of fatal outcome in patients with IPD in this age group were 30 times higher than in children (adjusted OR 30.6, $p < 0.001$) and two times higher than in adults aged 18–64 years (adjusted OR 2.1, $p < 0.001$). This may be explained by several biological and clinical factors, including the higher prevalence of chronic diseases, including multimorbidity, age-related decline in immune function, and a more severe clinical course of IPD in the senior population. After adjustment only for the comorbidities investigated, this pattern remained unchanged: patients with IPD aged 65 years and above had higher odds of fatal outcome than those aged 18–64 years (adjusted OR 1.9, $p < 0.001$). This confirms the observed relationship that age is an important independent factor associated with fatal IPD outcome. Findings from other studies similarly indicate that higher IPD case fatality is observed among older individuals (Chen et al., 2021; Cheong & Song, 2024; de Boer et al., 2024). When the data were analysed by sex, the multivariable analysis, male sex showed a statistically significant association with higher case fatality (adjusted OR 1.41; $p = 0.041$).

The doctoral study also described the prevalence of some chronic comorbidities and their impact on the IPD outcome. Among all patients with IPD during the study period, 13.7% had oncological diagnoses, 10.1% had diabetes mellitus, 6.2% had HIV/AIDS, 8.1% had hepatitis C virus infection, and 4.6% had tuberculosis. The results of the *Joinpoint* regression analysis indicated a statistically significant increasing trend in the number of cases in IPD with oncological diseases ($p = 0.01$). The highest case fatality rates were observed among IPD

patients with diabetes mellitus (40.2%) and among those with oncological diseases (39.6%). A study conducted in the Netherlands likewise demonstrated that case fatality among IPD patients with oncological comorbidity was 1.6 times higher than among patients without oncological diagnoses (adjusted OR 1.60; 95% CI: 1.34–1.91) (Garcia Garrido et al., 2021). This supports the hypothesis that patients with immunosuppression and chronic diseases are at increased risk of severe forms of IPD and death. However, univariable regression analysis did not demonstrate a statistically significant association between any of the individual comorbidities investigated and fatal outcome.

3.1 Limitations of the doctoral study

The relatively small number of IPD cases within each comorbidity and clinical manifestation group most likely reduced the statistical power of the analysis. The associations of oncological disease and diabetes mellitus with fatal outcome could not be demonstrated statistically in the present study. In addition, the data available from VISUMS and the disease registers did not permit comprehensive assessment of comorbidity severity or treatment received. For example, patients with HIV/AIDS were not stratified according to the severity of immunodeficiency, such as CD4 cell count or receipt of antiretroviral therapy, both of which substantially influence the course and outcome of infection. A similar limitation applies to patients with diabetes mellitus, in whom the degree of metabolic control was not taken into account, despite its likely relevance to IPD outcome. Likewise, treatment availability and effectiveness were not assessed for other comorbidity groups, such as tuberculosis or hepatitis C virus infection. Other important study limitations are related to the specific characteristics of the diagnostic and surveillance systems. One of the principal limitations of the present study is the potential for underreporting within the surveillance system. Underreporting of infectious disease cases may also be influenced by laboratory diagnostic challenges in Latvia. At present, there are no unified guidelines for hospital laboratories regarding specimen logistics. Some hospitals perform primary diagnostic testing in their own laboratories before forwarding isolates to the National Microbiology Reference Laboratory and information regarding the validation of these procedures is limited. Moreover, PCR, which is the more sensitive diagnostic method, is not routinely used in regional laboratories, and even in NMRL practice bacterial isolation is generally prioritised over molecular methods. Such an approach may affect the identification and registration of new cases.

It should also be noted that, owing to data availability constraints, a comprehensive analysis of vaccination status among patients with IPD could not be performed within this Doctoral Thesis as complete information was available only for children. For adults and older adults, vaccination status data for patients with IPD were not available in VISUMS. This

limitation is directly related both to the process of epidemiological investigation of IPD, which relies on information exchange between healthcare professionals and epidemiologists, and to the practice of recording vaccination data. During the study period, the recording of privately paid vaccinations in outpatient medical records was not carried out in a uniform and systematic manner. During the epidemiological investigation of IPD cases, epidemiologists contacted both the treating physicians in the hospital and the patients' family physicians. However, within family physician practices, information on vaccination against pneumococcal infection was generally available only for children, because childhood vaccination is strictly regulated within the national immunisation schedule and is state funded, usually being administered directly by the family physician. Family physicians are also required to report on vaccines used, which contributes to documentation of vaccination and to vaccine accounting. By contrast, vaccination of adults and older adults against pneumococcal infection during the study period was available only as a paid service. It was provided both in family physician practices and outside them, for example in vaccination centres or other healthcare institutions. In cases where vaccination was performed outside the family physician's practice, patients did not always inform their family physician. Consequently, adult vaccination data may not be fully reflected in outpatient medical records or in official reports (Regulation, 2000). This practice has contributed to incomplete data on adult vaccination coverage in Latvia. The situation has been partially improved only by changes introduced in 2024, requiring healthcare professionals to register all administered vaccinations electronically in the national E-health portal (Regulation, 2000). In the future, this development should provide substantially more complete and accurate information on vaccination status and enable more detailed analysis of the impact of vaccination on IPD in different age groups.

The comparatively low level of *S. pneumoniae* resistance identified in this Doctoral Thesis (7.5%) among patients with IPD may reflect a combination of methodological factors. For example, during the study period, the spectrum of antibiotics selected for antimicrobial susceptibility testing was limited because surveillance data were reported in accordance with ECDC TESSy reporting requirements. The TESSy system requires mandatory reporting of *S. pneumoniae* susceptibility to penicillin, erythromycin, and cefotaxime/ceftriaxone, but does not include other antimicrobial classes, which may lead to an apparently lower overall resistance burden. This limitation may substantially affect comprehensive assessment of the true burden of antimicrobial resistance in the Latvian population. Future studies should therefore consider broadening the antimicrobial panel to include clinically relevant agents such as levofloxacin, linezolid, moxifloxacin, and vancomycin, in order to provide a more complete picture of the *S. pneumoniae* resistance profile. It should also be noted that, in some years,

the number of *S. pneumoniae* isolates tested for antimicrobial susceptibility was limited. Furthermore, interpretive breakpoints for resistance may differ depending on the standards applied by the laboratory performing susceptibility testing in the country, whether EUCAST or another system. These issues warrant further investigation in future studies of the course and outcomes of IPD in Latvia. An additional limitation of the study is the observed decline in the proportion of resistant *S. pneumoniae* isolates, which is inconsistent with findings from several other countries, where resistance has shown an increasing trend (J. S. Kim et al., 2021; Torumkuney et al., 2016; Wasserman, 2021). This discrepancy most likely reflects the surveillance and laboratory diagnostic limitations described above. At the same time, the multivariable analysis did not demonstrate statistically significant associations between the PCV13nonPCV10 serotype group, resistant *S. pneumoniae* isolates, or clinical manifestations of IPD and fatal outcome, which is likely attributable to limited statistical power due to small sample size and to possible heterogeneity of clinical manifestations. Nevertheless, the literature indicates that the risk of fatal outcome in IPD is substantially increased by severe disease, particularly the clinical presentation of sepsis (Chen et al., 2021). Likewise, *S. pneumoniae* serotypes 3 and 19A, which belong to the PCV13 non-PCV10 group, have been identified in the scientific literature as independent and statistically significant predictors of fatal IPD outcome (Albrich et al., 2025; Darkwah et al., 2025), a finding that was not confirmed in the present doctoral study.

3.2 Strengths of the Doctoral Thesis

This Doctoral Thesis provides the first comprehensive analysis of IPD epidemiology, case fatality, and the factors influencing these outcomes in Latvia during the period from 2012 to 2022. The study findings clearly demonstrate an overall increasing trend in IPD incidence, largely driven by serotype replacement and the increasing circulation of highly virulent serotypes not included in PCV10, particularly serotypes 3 and 19A, following the introduction of PCV10. The Doctoral Thesis identified the principal risk groups for fatal outcome, namely older adults aged 65 years and above, men, and patients infected with serotypes included in PCV13 but not covered by PCV10. The results provide strong scientific justification for Latvia's recent decision to transition to the broader-spectrum PCV15 vaccine in the childhood immunisation programme. At the same time, the findings highlight the critical need to develop and implement targeted vaccination strategies for adult risk groups, particularly older adults and patients with oncological diseases, among whom incidence showed statistically significant increasing trends, as well as patients with diabetes mellitus, among whom IPD case fatality was the highest. Although the available data did not permit detailed analysis of comorbidities in patients with IPD, such as CD4 cell count in patients with HIV/AIDS or cancer

type, stage, and/or remission status, the analysis nevertheless makes a substantial contribution by characterising the overall burden of IPD among patients with the comorbidities studied and by enabling comparison of case fatality across clinically relevant risk groups. Effective future control of the burden of IPD will require continuous epidemiological surveillance of IPD and microbiological surveillance of *S. pneumoniae*. Such surveillance will make it possible to monitor the impact of the new vaccine on serotype distribution and antimicrobial resistance. The insights generated by this work may be used to support evidence-based public health decision-making aimed at reducing the burden of IPD in the Latvian population.

Based on the findings of the Doctoral Thesis, the hypotheses proposed in the study were partially confirmed.

The first hypothesis, namely that *the incidence of invasive pneumococcal disease in Latvia shows an increasing trend*, was partially confirmed. The study findings, based on *Joinpoint* regression analysis, demonstrated a statistically significant increasing trend in IPD incidence ($p = 0.008$), with incidence increasing significantly by an average of 6.37% per year ($p = 0.0001$). However, when examined in greater detail, the increasing trend was not uniform across demographic and geographical strata. *Joinpoint* regression analysis confirmed a statistically significant increase in IPD incidence in the Riga region ($p = 0.001$), where incidence increased significantly by an average of 8.81% per year ($p = 0.008$), and in the Kurzeme region ($p = 0.03$), where incidence increased significantly by 22.6% per year ($p = 0.028$). In the age group of 65 years and above, a statistically significant increase in IPD incidence was identified ($p = 0.005$), with incidence increasing significantly by an average of 11.4% per year ($p = 0.0032$). A statistically significant increasing trend was also observed among women, with an average annual increase of 9.1% ($p = 0.0007$), but not among men.

The second hypothesis, namely that case fatality among patients with invasive pneumococcal disease is associated with demographic factors and disease course-related factors, including both chronic diseases and the clinical manifestations of IPD, was likewise partially confirmed. The findings of the Doctoral Thesis demonstrated a strong and statistically significant association between case fatality and demographic factors. Patients aged 65 years and above had significantly higher odds of fatal outcome than both patients with IPD aged 18–64 years and children. In addition, in the multivariable analysis, male sex was confirmed as an independent risk factor for case fatality (OR 1.41; $p = 0.041$). By contrast, the associations identified between case fatality and disease course-related factors did not reach statistical significance. No statistically significant association was found between fatal outcome and any of the comorbidities investigated, including oncological disease, tuberculosis, diabetes mellitus, and hepatitis C virus infection, nor was any statistically significant association identified

between fatal IPD outcomes and specific clinical manifestations such as sepsis, meningitis, or pneumonia.

The third hypothesis, namely that case fatality among patients with invasive pneumococcal disease is associated with infection caused by vaccine-non-covered and antimicrobial-resistant S. pneumoniae serotypes, was also partially confirmed. A statistically significant association between case fatality and PCV13 vaccine serotypes, which were not included in the Latvian childhood immunisation schedule during the study period, was identified only in the univariable regression analysis. This finding indicated that patients infected with PCV13 serotypes had 75% higher odds of fatal outcome than those infected with PCV10 serotypes (crude OR 1.75; $p = 0.006$). However, after adjustment for age and sex, this association no longer remained statistically significant (adjusted OR 1.05, $p = 0.07$). No association was identified between antimicrobial resistance and fatal outcome among patients with IPD.

Conclusions

1 A statistically significant increasing trend in the incidence of invasive pneumococcal disease was observed in Latvia during the study period, predominantly in the Riga and Kurzeme regions. A statistically significant increase in incidence was also identified among women and among older adults aged 65 years and abov;

2 Among patients with IPD for whom an *S. pneumoniae* serotype was identified, the proportion of serotypes included in PCV10 decreased significantly during the study period, whereas the proportion of serotypes included in PCV13 but not in PCV10, as well as serotypes not included in any pneumococcal vaccine, increased. During the study period, *S. pneumoniae* serotypes 3 (17.4%) and 19A (10.9%) were the most frequently identified both among patients with IPD overall and among those with fatal IPD outcomes. In the age group 18–64, *S. pneumoniae* serotype 4 was also among the dominant serotypes. *S. pneumoniae* serotypes 37, 10F, 17A, 28A, and 33 were detected exclusively among patients with fatal IPD outcomes. Patients with IPD caused by *S. pneumoniae* serotypes included in PCV13 but not in PCV10 had statistically significantly higher odds of fatal outcome in the crude model. No association was found between antimicrobial resistance and fatal outcome among patients with IPD;

3 The clinical manifestation "**sepsis**" was identified significantly more frequently among patients with IPD, whereas case fatality was higher among patients with the clinical manifestation "**with pneumonia**"; however, these differences did not reach statistical significance. Overall, no statistically significant associations were identified between the clinical manifestations of IPD and fatal IPD outcome;

4 During the study period, statistically significant increasing trends were observed in the number of IPD patients with oncological diseases. In addition, *S. pneumoniae* serotypes 10F, 11, 28A, and 5 were detected exclusively among IPD patients with oncological diagnoses. No statistically significant associations were identified between the studied comorbidities, or the presence of at least one of the specified comorbidities, and fatal IPD outcome;

5 Statistically significantly higher odds of fatal outcome were identified among patients with IPD aged 65 years and above, as well as among men.

Proposals

Based on the findings of the Doctoral Thesis, several recommendations have been developed with the aim of reducing the burden of invasive pneumococcal disease in Latvia.

1 The study findings demonstrated the high frequency of serotypes not covered by PCV10, particularly serotypes 3 and 19A, and their association with fatal outcomes, provide strong scientific evidence for the decision in the year 2024 to change PCV10 to PCV15 with broader *S. pneumoniae* serotype spectrum in the childhood immunisation programme. It is essential to ensure continuity of this strategy and, in the future, to evaluate the introduction of vaccines with even broader serotype coverage on the basis of continuous surveillance data. The Doctoral Thesis clearly identified adults aged 65 years and above as a group with both high incidence and a statistically significant increasing trend in IPD incidence. Therefore, publicly funded vaccination against pneumococcal infection should be introduced for this risk group. Furthermore, given the statistically significant increase in IPD cases among patients with oncological diseases, indicates the inclusion of pneumococcal vaccination in the *Plan for the improvement of healthcare services in oncology*. That would represent a targeted and evidence based measure to strengthen protection in this vulnerable population.
2 In order to evaluate the impact of the new vaccination strategy and to respond promptly to changes in the epidemiological situation, the surveillance system should be further strengthened. This should include both the implementation of 100% serotyping of all *S. pneumoniae* isolates obtained from patients with IPD, in order to timely detect serotype replacement trends, and the expansion of the antimicrobial resistance monitoring panel. The current surveillance data on three antibiotic panel provides only limited insight. Therefore, its extension to include other clinically relevant antimicrobial agents would facilitate the development of more precise national treatment guidelines and enable the timely detection of emerging resistance threats.
3 Greater emphasis should be placed on the education and active involvement of healthcare professionals. Clinical guidelines for family physicians and other specialists should be updated and disseminated, focusing on the targeted identification of adult IPD risk groups and the active recommendation of vaccination. In addition, regular professional education courses should be ensured.

The implementation of these recommendations would make it possible to establish an evidence based and comprehensive system capable of substantially reducing the burden of invasive pneumococcal disease in Latvia.

List of publications, reports and patents on the topic of the Thesis

Publications:

1. Savrasova, L., Villerusa, A., Zeltina, I., Krumina, A., Cupeca, H., Balasegaram, S., Greve, M., Savicka, O., Selderina, S., Galajeva, J., & Dushacka, D. (2025). *Streptococcus pneumoniae* serotypes and factors associated with antimicrobial resistance in Invasive pneumococcal disease cases in Latvia, 2012-2022. *Frontiers in public health*, *13*, 1501821. https://doi.org/10.3389/fpubh.2025.1501821

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Reports and theses at international congresses and conferences:

1. Savrasova, L., Cupeca, H., Villerusa, A., Zeltina, I., Krumina, A., Galajeva, J. 2023. Invasive Pneumococcal Disease Epidemiology in Latvia, 2017–2021. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences "Knowledge for Use in Practice": Abstracts, 29.–31.03.2021, 162.
2. Cupeca, H., Savrasova, L., Villerusa, A., Zeltina, I., Krumina, A., Gardovska, D. 2023. Invasive Pneumococcal Disease and S. pneumoniae Carriage in Hospitalised Children in Latvia 2018–2022. Rīga Stradiņš University International Research Conference on Medical and Health Care Sciences "Knowledge for Use in Practice": Abstracts, 29.–31.03.2021, 809
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