Tampere University

ALEKSANDRA POLKOWSKA-KRAMEK

Epidemiology of Pneumococcal Meningitis Before and After the Introduction of 10-valent Pneumococcal Conjugate Vaccine (PCV10) in Poland and Finland

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To my dear family and Finnish friends

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My heart will always be in Finland.

ABSTRACT

Streptococcus pneumoniae, or pneumococcus, can cause severe infections such as pneumonia, sepsis, and meningitis. Pneumococcal meningitis is a leading cause of bacterial meningitis worldwide. About 100 distinct *S. pneumoniae* serotypes have been identified. The most important serotypes are included in the available vaccines. In Finland, the 10-valent conjugate vaccine (PCV10) was introduced into the national immunization program in September 2010. Poland introduced PCV10 in January 2017.

For this study, we used national surveillance data to determine the contribution of *S. pneumoniae* to the total burden of bacterial meningitis and evaluate the long-term trends in pneumococcal meningitis in Finland. We also assessed the population-based impact of PCV10 on the epidemiology of pneumococcal meningitis. In Poland, national population-based surveillance data were analyzed to obtain information on the baseline epidemiology of pneumococcal meningitis before the introduction of the first childhood pneumococcal conjugate vaccine, with a particular focus on incidence, serotype distribution, and antimicrobial susceptibility.

During 1998–2014, pneumococcus was the most common cause of bacterial meningitis in Finland. It was also the leading cause of meningitis deaths in adults. The incidence rate of pneumococcal meningitis substantially decreased after the introduction of the conjugate vaccine. Seven years after PCV10 introduction, the overall incidence of pneumococcal meningitis decreased by 27% (95% CI = 12%, 39%), while the incidence of PCV10 serotypes decreased by 68% (95% CI = 57%, 77%). In age groups 0–4 and 50–64 years, overall incidence decreased by 64% and 34%, respectively. In adults ≥65 years of age, an 157% (95% CI = 56%, 342%) increase in non-PCV10 serotypes offset a 69% reduction in PCV10 serotypes. Regardless, the overall mortality rate decreased by 42% (95% CI = 4%, 65%). The overall case fatality proportion was 16% in the pre-PCV10 period and 12% in the PCV10 period ($p = .41$); among persons 50–64 years of age, the case fatality proportion decreased from 25% to 10% ($p = .04$).

In Poland, the annual incidence rate of overall pneumococcal meningitis ranged from 0.21 cases per 100,000 person-years in 2005 to 0.47 in 2015. Substantial regional differences in reported rates were observed. Overall incidence increased by 7% annually (95% CI = 6%, 8%) on average, primarily due to an increase of 3% (95% CI = 2%, 5%) among persons 15–49 years of age, 12% (95% CI = 10%, 13%) among those

50–64 years of age, 18% (95% CI = 16%, 19%) among those 65–74 years of age, and 9% (95% CI = 7%, 10%) among those ≥75 years of age. Overall case fatality proportion ranged from 4% in children <1 year to 31% in adults ≥65 years. PCV10 serotypes were responsible for 46% of all pneumococcal meningitis cases and 75% among children <5 years. However, the proportion of PCV10 serotypes decreased from 52% in 2008–2011 to 41% in 2012–2015. The decline in children <5 years (from 87% to 57%) was more pronounced. Over a quarter of all isolates and half of the isolates in children <5 years were resistant to penicillin. Isolates with decreased susceptibility to cefotaxime constituted 13% of all isolates.

S. pneumoniae was the main contributor to bacterial meningitis in Finland. A substantial reduction in the morbidity and mortality due to pneumococcal meningitis was seen seven years after vaccine introduction. Nevertheless, an important disease burden remains in older adults because of an increase in pneumococcal meningitis caused by non-PCV10 serotypes.

Although pneumococcal meningitis incidence rates were increasing in Poland, the overall and age-specific rates were considerably lower than those reported from other European countries before PCV10 introduction. The proportion of serotypes covered by the PCV10 vaccine during the baseline period was comparable with other European countries before PCV introduction. The low observed rates, considerable regional differences, and high case fatality proportion among the reported cases suggest substantial under ascertainment and underreporting of meningitis cases in Poland. Addressing these limitations and implementing improvements in the surveillance system should be considered when future studies to assess the impact of PCV10 are planned and conducted.

TIIVISTELMÄ

Streptococcus pneumoniae eli pneumokokki voi aiheuttaa vakavan infektion, kuten keuhkokuumeen, verenmyrkytyksen tai aivokalvontulehduksen. Pneumokokki on tärkeimpiä bakteeriperäisen aivokalvontulehduksen (bakteerimeningiitin) aiheuttajia maailmassa. Siitä on tunnistettu sata eri serotyyppiä, joista tärkeimmät on huomioitu pneumokokkirokotteissa. Suomessa 10-valenttinen pneumokokkikonjugaattirokote (PCV10) otettiin kansalliseen rokotusohjelmaan syyskuussa 2010 ja Puolassa tammikuussa 2017.

Tässä tutkimuksessa käytimme kansallisia seurantatietoja arvioidaksemme *S. pneumoniae*:n merkitystä bakteerimeningiitin tautitaakassa sekä arvioidaksemme pneumokokin aiheuttaman aivokalvontulehduksen pitkän aikavälin kehitystä Suomessa. Tarkastelimme myös PCV10:n väestötason vaikutuksia pneumokokin aiheuttaman aivokalvontulehduksen epidemiologiaan. Puolassa käytimme kansallisia, väestöpohjaisia seurantatietoja tutkiaksemme pneumokokin aiheuttaman aivokalvontulehduksen epidemiologiaa ennen ensimmäisen lasten pneumokokkikonjugaattirokotteen käyttöönottoa. Kiinnitimme erityistä huomiota taudin ilmaantuvuuteen, serotyyppijakaumaan ja antibioottiherkkyyteen sekä resistenssin yleisyyteen.

Vuosina 1998–2014 pneumokokki oli yleisin bakteeri, joka aiheutti aivokalvontulehduksia Suomessa. Se oli myös tärkein kuolemaan johtaneen aivokalvontulehduksen aiheuttaja aikuisväestössä. Pneumokokin aiheuttaman aivokalvontulehduksen ilmaantuvuus väheni huomattavasti 10-valenttisen konjugaattirokotteen käyttöönoton jälkeen. Seitsemän vuotta PCV10:n käyttöönoton jälkeen pneumokokin aiheuttaman aivokalvontulehduksen kokonaisilmaantuvuus oli vähentynyt 27 % (95 % luottamusväli, 12–39 %). PCV10-rokotteeseen kuuluvien serotyyppien aiheuttaman aivokalvontulehduksen ilmaantuvuus oli vähentynyt 68 % (95 % luottamusväli, 57–77 %). Ilmaantuvuus vähentyi 64 % alle 5-vuotialla lapsilla ja 34 % 50–64-vuotiailla. Vaikka 65-vuotta täyttäneiden ilmaantuvuus väheni 69 %, laskua PCV10-serotyypien ilmaantuvuudessa kompensoi 157 %:n lisääntyminen muiden kuin PCV10rokoteserotyypien ilmaantuvuudessa. Kuolleisuus kuitenkin väheni 42 % (95 % luottamusväli, 4–65 %). Ennen PCV10 käyttöönottoa tapauskuolleisuus oli 16 %, kun se PCV10 käyttöönoton jälkeen oli 12 % (p=0,41). 50–64-vuotiailla tapauskuolleisuus oli 25 % ennen PCV10 käyttöönottoa ja 10 % se jälkeen (p=0,04).

Puolassa pneumokokkimeninigiitin vuotuinen ilmaantuvuus 100 000 henkilövuotta kohden vaihteli 0,21 tapauksesta vuonna 2005 0,47 tapaukseen vuonna 2015. Ilmaantuvuudessa havaittiin merkittäviä alueellisia eroja. Kokonaisilmaantuvuus lisääntyi keskimäärin 7 % vuosittain (95 % luottamusväli, 6–8 %). Lisääntyminen havaittiin kaikissa ikäryhmissä: 3 %:n nousu (95 % luottamusväli, 2–5 %) 15–49-vuotiailla, 12 % nousu (95 % luottamusväli, 10–13 %) 50–64-vuotiailla, 18 % nousu (95 % luottamusväli, 16–19 %) 65–74-vuotiailla ja 9 % nousu (95 % luottamusväli, 7–10 %) ≥75-vuotiaiden keskuudessa. Tapauskuolleisuus vaihteli 4 %:sta alle 1-vuotiailla lapsilla 31 %:iin ≥65-vuotiailla aikuisilla. PCV10-rokotteeseen kuuluvat 10 serotyyppiä aiheuttivat 46 % kaikista pneumokokkimeningiittitapauksista. Alle 5-vuotialla lapsilla osuus oli 75 %. PCV10-serotyyppien osuus kuitenkin väheni 52 prosentista 41 prosenttiin verrattaessa vuosia 2008–2011 vuosiin 2012–2015. Alle 5-vuotiailla lapsilla väheneminen oli suurempi, 87 prosentista 57 prosenttiin. Yli neljäsosa kaikista bakteerikannoista ja puolet alle 5-vuotiaiden kannoista oli resistenttejä penisilliinille. Bakteerikannoista 13 prosenttia oli herkkyydeltään alentunut kefotaksiimille.

Pneumokokki oli pääasiallinen bakteerimeningiitin aiheuttaja Suomessa tutkimuksen aikana. Pneumokokkimeningiitin sairastuvuuden ja kuolleisuuden huomattava vähentyminen havaittiin pian rokotteen käyttöönoton jälkeen sekä seitsemän vuoden seurannassa. Tästä huolimatta PCV10-rokotteeseen kuulumattomien serotyyppien lisääntyminen aiheuttaa ikäihmisillä edelleen merkittävää sairastuvuutta pneumokokkimeningiittiin.

Vaikka pneumokokkimeningiitin ilmaantuvuus Puolassa lisääntyi tutkimuksen aikana, yleiset ja ikäkohtaiset ilmaantuvuusluvut olivat huomattavasti pienempiä kuin muissa Euroopan maissa ennen PCV10:n käyttöönottoa. PCV10-rokoteserotyyppien aiheuttamien infektioiden osuus kaikista pneumokokkimeningiittitapauksista oli kuitenkin samaa luokkaa kuin muissa Euroopan maissa ennen konjugaattirokotusten aloittamista. Tästä huolimatta ilmoitettujen tapausten vähäinen määrä, merkittävät alueelliset erot ja suuri tapauskuolleisuus viittaavat huomattavaan pneumokokkimeningiitin alidiagnosointiin ja aliraportointiin. Nämä seurantajärjestelmän haasteet tulee Puolassa arvioida ja mahdollisuuksien mukaan ottaa huomioon suunniteltaessa tulevia PCV10 rokotusohjelman vaikuttavuustutkimuksia.

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ABBREVIATIONS

BBB	blood-brain barrier
BCSFB	blood-cerebrospinal fluid barrier
CbpA	choline-binding protein A
CFP	case fatality proportion
CI	confidence interval
CIEP	counterimmunoelectrophoresis
CNS	central nervous system
COPD	chronic obstructive pulmonary disease
CSF	cerebrospinal fluid
CT	computed tomography
DNA	deoxyribonucleic acid
ECDC	European Centre for Diseases Prevention and Control
FN	false negative
FP	false positive
HIV	human immunodeficiency virus
IL-1	interleukin-1
IPD	invasive pneumococcal disease
IR	incidence rate
IRR	incidence rate ratio
IQR	interquartile range
LP	lumbar puncture
MIC	minimum inhibitory concentration
MRI	magnetic resonance imaging
NESp	nonencapsulated Streptococcus pneumoniae
NIDR	National Infectious Diseases Register (Finland)
NIP-NIH	National Institute of Public Health – National Institute of Hygiene (Poland)
NVT	non-vaccine type
NRCBM	National Reference Centre for Bacterial Meningitis (Poland)
P	*p* value

PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PCV20	20-valent pneumococcal conjugate vaccine
PM	pneumococcal meningitis
PIC	personal identity code (Finland)
PIS	population information system (Finland)
PPSV	pneumococcal polysaccharide vaccine
RR	rate ratio
RRR	relative rate reduction
THL	Finnish Institute for Health and Welfare (Finland)
TNFα	tumor necrosis factor alpha
VT	vaccine type

ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, which are referred throughout the text by the Roman numerals given below (I-III).

Publication I Polkowska A, Toropainen M, Ollgren J, Lyytikaïnen O, Nuorti JP. Bacterial meningitis in Finland, 1995-2014: a population-based observational study. *BMJ Open* 2017;0:e015080. doi:10.1136/bmjopen-2016-015080.

Publication II Polkowska A, Skoczyńska A, Paradowska-Stankiewicz I, Stefanoff P, Hryniewicz W, Kuch A, Lyytikäinen O, Nuorti JP. Pneumococcal meningitis before the introduction of 10-valent pneumococcal conjugate vaccine into the National Childhood Immunization Program in Poland. *Vaccine* 2019;37:1365–73. doi:10.1016/j.vaccine.2018.12.028

Publication III Polkowska A, Rinta-Kokko H, Toropainen M, Palmu AA, Nuorti JP. Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland. *Vaccine* 2021;39:3216–24. doi:10.1016/j.vaccine.2021.02.030.

1 INTRODUCTION

Streptococcus pneumoniae is a commensal bacterium that often causes mild upper respiratory system infections and otitis media [1]. However, on rare occasions, it can cause life-threatening invasive disease manifested as septicemia, pneumonia, or meningitis [2]. Pneumococcus is a leading pathogen of bacterial meningitis worldwide [3,4]. Pneumococcal meningitis caused an estimated 83,900 cases and 37,900 deaths among children less than 5 years of age in 2015 [5]. The observed pneumococcal meningitis rates differ globally and over time [5,6]. This variability is partly related to different diagnostic activities and the sensitivity of surveillance systems. The epidemiology of pneumococcal disease is complex due to the occurrence of about 100 distinct serotypes [7]. Nevertheless, only about 20–30 are responsible for most invasive disease cases [8,9].

The burden of pneumococcal meningitis changed after the introduction of the 7-valent conjugate pneumococcal vaccine, which was later replaced by 10- and 13-valent conjugate vaccines [10]. Most studies have reported a substantial decrease in pneumococcal meningitis incidence due to vaccine serotypes in vaccine-eligible children and unvaccinated older adults [11–13]. However, a concomitant increase in cases caused by non-vaccine serotypes was reported in many countries [14]. The magnitude of the changes depended on several factors, such as incidence and serotype distribution before vaccine introduction, vaccine coverage, and the amount of time after vaccine introduction.

This study aimed to examine the role of *S. pneumoniae* in the overall burden of bacterial meningitis and the long-term trend of pneumococcal meningitis in Finland. We also examined the long-term impact of PCV10 on pneumococcal meningitis morbidity and mortality. In addition, we aimed to provide comprehensive baseline information on the epidemiology of pneumococcal meningitis before the introduction of PCV10 into the national immunization program in Poland.

2 LITERATURE REVIEW

2.1 *Streptococcus pneumoniae* microbiology

The bacterium *Streptococcus pneumoniae* was one of the first pathogens identified and described in the golden era of microbiology in the 19th century [15]. It contributed to significant scientific discoveries, such as the concept of humoral immunity, the Gram stain procedure, research on the therapeutic efficacy of penicillin, and the discovery of DNA [15–18]. Independently two researchers, Louis Pasteur and George M. Sternberg, first isolated *S. pneumoniae* in 1881 [16]. Since the isolated bacterium was the most common cause of lobar pneumonia, the term "pneumococcus" was generally used by the late 1880s. In 1920, pneumococcus was officially renamed *Diplococcus pneumoniae*, but because it grows in chains in liquid growth media, a characteristic feature of other members of the *Streptococcus* genus, it was finally named *Streptococcus pneumoniae* in 1974 [19]. Nevertheless, the term "pneumococcal disease" is still used today.

S. pneumoniae is a gram-positive, facultatively anaerobic catalase-negative diplococcus [3]. In the bacterium's surface, three main layers can be identified: the plasma membrane, cell wall, and capsule. Non encapsulated pneumococci are also identified. Based on the capsule's unique chemical structure and polysaccharide and serologic (immunologic) properties, 100 distinct *S. pneumoniae* serotypes belonging to 46 serogroups have been identified [20,21]. Capsular polysaccharides are highly immunogenic, and antibodies against them are serotype specific, but cross-protection against different serotypes can occur due to similarity of capsule polysaccharides [22,23].

2.2 Virulence factors of *Streptococcus pneumoniae*

The capsule is a major virulence factor of *S. pneumoniae* [24], and nearly all clinical isolates of *S. pneumoniae* contain it. The capsule protects against opsonization and phagocytosis, allowing the bacterium to escape the host's immune defense [25]. The capsule is critical for colonization, prevents mechanical removal by mucus, and

reduces exposure to antimicrobials [26,27]. The capsule's structure and thickness determine the bacterium's ability to survive in the bloodstream and cause invasive infection, that is, invasive pneumococcal disease (IPD). Strains with a thick capsule are more virulent, while strains with a thinner capsule are more prone to cause asymptomatic carriage [28]. Although about 100 serotypes exist, only around 20–30 are responsible for most invasive disease cases [8]. *S. pneumoniae* has the ability to undergo capsule switching due to transformation of capsular genes [29]. Nonencapsulated *S. pneumoniae* isolates have primarily been responsible for noninvasive pneumococcal disease, particularly conjunctivitis and otitis media [30,31].

In addition to the capsule other virulence factors that facilitate colonization and survival in the host include surface proteins, toxins and physical structures [32]. The adhesin phosphorylcholine (ChoP) mediates adherence to the receptor for platelet-activating factor (rPAF) that is widely distributed on the epithelial surface of the human nasopharynx [33]. In addition, several proteins on the pneumococcus surface, which are targeted for new vaccine development, such as protein A and protein C (choline-binding protein A, CbpA), are involved in the pathogenicity of *S. pneumoniae* [34,35]. Proteins aid in colonization by adhering to epithelial cell membranes and protect against the host's complement system.

Pneumolysin is well known virulence factor for pneumonia and upper respiratory tract infection [36]. It is produced by all *S. pneumoniae* serotypes and released only when the bacterium undergoes autolysis. Pneumolysin is cytotoxic to ciliated respiratory epithelial cells, slows ciliary beating in organ culture, and causes inflammation by activating complement and inducing the production of tumor necrosis factor alpha (TNFα) and interleukin-1 by human monocytes [37,38]. Pneumolysin's cytotoxic effects can also directly inhibit phagocyte and immune cell function [39]. In contrast to data on pneumolysin's known role in pneumonia and the upper respiratory tract, data on its role in the pathogenesis of meningitis are inconsistent [40]. However, recent studies have suggested that it might cause neuronal cell death and lead to severe neurological sequelae [34,40–43].

Cell wall lysis and the release of pneumolysin, inflammatory peptidoglycan and teichoic acids are initiated by the autolysin LytA [44]. The role of LytB and LytC is not as well described as LytA, but both may play a role in adhesion to epithelial cells by modifying proteins on cell surfaces and by inhibiting the activation of the alternative and classical pathways of the complement system [25,45].

Out of 50 lipoproteins, at least four have been shown to be associated with virulence: pneumococcal surface adhesin A (PsaA), pneumococcal iron acquisition

A (PiA), pneumococcal iron uptake A (PiuA) and pneumococcal iron transporter (PitA). PsA is responsible for the transport of magnesium and zinc into cell and PiA, PiuA, PitA mediate iron uptake [46].

Another example of the pneumococcal virulence factors are immunoglobulin A1 (igA1) protease and hydrogen peroxide. IgA1 protease breaks down human IgA1 into fragments and thus reduces the killing activity of these antibodies [47]. Hydrogen peroxide damages host DNA [48]. It also helps to limit or eliminate competitive bacteria such as *Haemophilus influenzae* and *Neisseria meningitidis* from the same niche [49].

Pneumococcus has also special hair-like structures located on the cell wall- pili. Pili helps to attach to the host epithelial cells in the nasopharynx and lungs [50]. They also provide a protection against phagocytosis by host immune cells [50].

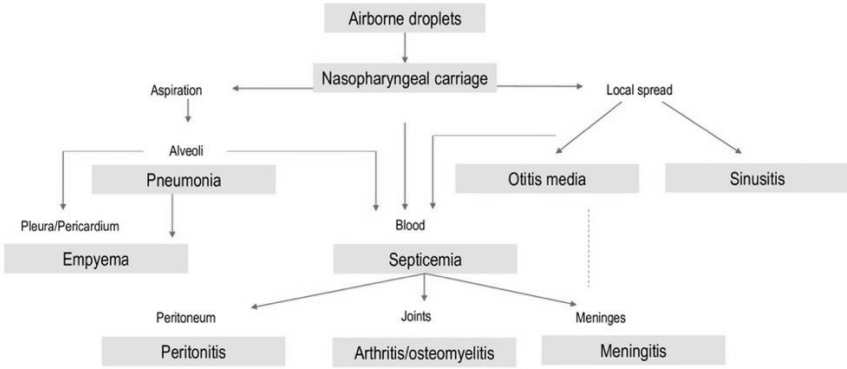
2.3 From carriage to invasive pneumococcal disease

The major reservoir of *S. pneumoniae* is the nasopharynx [1]. Most pneumococci last in the nasopharynx for several weeks to four months and are cleared with no systemic symptoms in the host [1,19]. Duration and colonization rates are highest during the first two years of life and decrease thereafter due to immune system maturation. Carriage rates generally vary from 5%–10% in healthy adults to 20%–40% in healthy children [19,51,52]. However, rates differ in different geographical locations and seasons, with higher carriage during winter months [53]. Host risk factors associated with higher carriage rates include race, particularly Australian Aboriginals and Native Americans [54]; tobacco smoking; alcohol abuse; asthma; and chronic obstructive pulmonary disease (COPD) [55,56].

Transmission of *S. pneumoniae* occurs through direct contact with respiratory secretions or the inhalation of aerosols from asymptomatic carriers or persons with pneumococcal disease [1]. It could also be transmitted indirectly through the contamination of objects with respiratory secretions [57]. Crowded places, such as childcare centers, are a significant risk factor for *S. pneumoniae* acquisition and transmission [58]. In adults, military camps, prisons, nursing homes, and homeless shelters have been associated with higher transmission and occurrence of epidemics [59–62]. The usage of antimicrobials and vaccines also influences carriage rates. The usage of antimicrobials was found to significantly reduce the risk of carriage the following month in a setting with a low prevalence of pneumococcal antimicrobial resistance [63]. The introduction of pneumococcal conjugate vaccines (PCV) was

associated with the decrease in the carriage of vaccine type (VT) pneumococci and the corresponding increase in the carriage of non-vaccine serotypes (NVT) [64,65].

Due to host innate and acquired immune mechanisms, pneumococcal colonization mostly does not proceed to clinical disease [66]. Nevertheless, poor mucosal immune response can result in persistent or recurrent colonization and subsequent infection in some situations [2]. Local spread of *S. pneumoniae* in the upper respiratory system may lead to noninvasive disease such as sinusitis or otitis media, but the aspiration of *S. pneumoniae* from the nasopharynx to the lung alveoli may result in IPD (i.e., pneumonia) or even bacteremia if the bacteria invade the bloodstream [67]. The bacteria can reach the bloodstream through various pathways, including lymphatics, cell damage to the epithelial and endothelial cells, and the direct invasion of endothelial cells [51]. Once in the bloodstream, *S. pneumoniae* spreads into many organs, such as the peritoneum or joints [2]. The central nervous system (CNS) can also be infected: invasion from the blood into the cerebrospinal fluid is thought to occur in the choroid plexus or by crossing the blood-brain barrier in the cerebral capillaries that traverse the subarachnoid space [51].



*Adopted from Bogaert *et al* [2]

Figure 1. Spread of *S. pneumoniae*

Several host characteristics are associated with increased risk of IPD (Table 1). The incidence of IPD has a bimodal age distribution and is highest in young children and older adults [68]. Age is independently associated with risk of invasive pneumococcal disease, even after controlling for other risk factors [69–71]. Greater susceptibility to infection in young children and older adults is related to immune system functioning [72]. The immune system in infants is immature with poor T-cell independent responses to antigens [25]. In addition, immature submucosal glands and surface epithelial secretory cells result in reduced mucociliary clearance and increased colonization [73]. Older age is associated with a decline in efficiency of the immune system (immunosenescence) on one hand, and persistent low-grade inflammation (inflammaging) on the other [74]. Both immunosenescence and inflammaging, as well as an increasing prevalence of underlying medical conditions result in a greater risk of pneumococcal disease in older adults [75].

In immunocompetent persons several medical conditions have been associated with an increased risk of pneumococcal disease and more severe disease. These include chronic heart diseases (e.g. congestive heart failure, cardiomyopathy, arrythmias, cardiovascular and valve diseases), chronic pulmonary diseases (e.g. chronic obstructive pulmonary disease), chronic liver diseases (e.g. cirrhosis) and diabetes mellitus [56,76]. The presence of more than one risk factor is associated with higher risk of IPD than individual risk factor [56].

Immunocompromised persons have highest rates of pneumococcal diseases. People with conditions such as congenital immunodeficiency, diseases of white cells (e.g. leukemia), generalized malignancy, anatomic or functional asplenia, human immunodeficiency virus (HIV) infection, receiving immunosuppressive treatment, or chronic renal failure/nephrotic syndrome, are at high risk of IPD [77,78].

In addition to host factors, socioeconomic, behavioral, and environmental factors also play an important role in susceptibility to disease [79,80]. Crowded living in conditions, malnutrition, alcoholism, and cigarette smoking have been shown to increase the risk of IPD. Air pollution and winter season, low air humidity have also been associated with increased risk of IPD [81].

Table 1. Conditions that predispose to *S. pneumoniae* infection

Host risk factors	Age, <2 or >65 years	
	Male sex	
	Race (Black, American Indian, Alaskan Native)	
	Chronic medical conditions	Congestive heart failure Cardiomyopathy Arrythmias Chronic obstructive pulmonary disease Liver cirrhosis Diabetes mellitus Renal insufficiency Neurological disease Cerebrovascular disease Dementia Decreased cough reflex Cochlear implants
	Immune deficiencies	Hypo- or a-gammaglobulinemia or secondary immunoglobulin deficiency Complement defects, especially C3 Leukemia Lymphoma Functional or anatomical asplenia Human immunodeficiency virus (HIV) infection
Socioeconomic risk factors	Low household income	
	Crowding	
	Institutionalization	
	Malnutrition	
Behavioral risk factors	Cigarette smoking	
	Alcoholism	
Environmental risk factors	High air pollution level	
	Winter season	
	Exposure to environmental tobacco smoke	

Source: Based on review of the literature

2.4 Pneumococcal meningitis

2.4.1 Pathogenesis

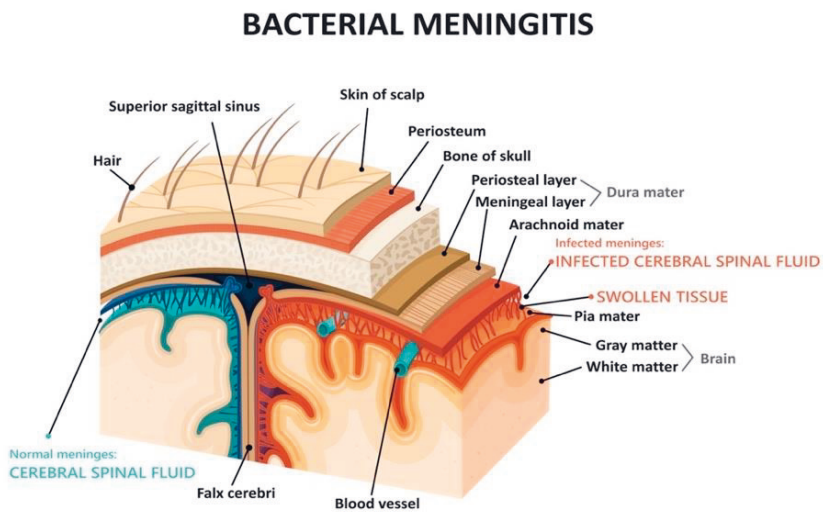
The CNS protection comprises the bony skull, the meninges (with three layers: the outermost dura mater, the arachnoid, and the innermost pia mater), the blood-brain barrier (BBB), and the blood-cerebrospinal fluid barrier (BCSFB) [82–84].

The BBB is a structural and functional barrier formed by cerebromicrovascular endothelial cells, astrocytes, pericytes, and the basement membrane [82]. These cells are characterized by tight junctions with extremely high electrical resistance, which

limits the paracellular flux; sparse pinocytic activity, which limits the transcellular flux; and specific carrier and transport systems [85]. The BBB thus maintains the homeostasis of the neural microenvironment by regulating the passage of molecules and ions and protects the CNS from microorganisms and toxins that might circulate in the blood [86].

The BCSFB is formed by tight junctions between epithelial cells located at the choroid plexus and endothelial cells of veins and venules within the subarachnoid space [83]. The functions of the BCSFB are similar to those of the BBB, with the main differences that cells of the BCSFB secrete CSF from the choroid plexus into the brain ventricular system, and tight junctions between the epithelial cells have a lower electric resistance than BBB cells. The BSCFB might therefore be more vulnerable to microbial penetration than the BBB [85].

Meningitis is an inflammation of the meninges and subarachnoid space, including cerebrospinal fluid in the subarachnoid space and the cerebral ventricles [87] (Figure 2). In severe cases, bacterial invasion into the CNS may also result in the inflammation of cerebral tissue (encephalitis) and spinal cord tissue (myelitis).



Source: Graphicriver.net [paid material]

Figure 2. Bacterial meningitis

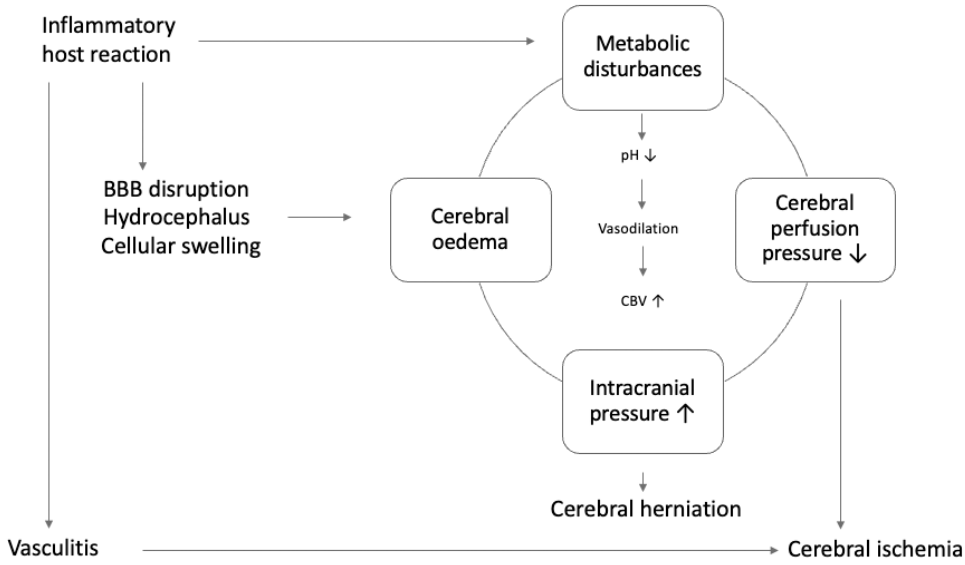
To invade the meninges, the pathogen must break two physiological barriers between the bloodstream and CNS (the BBB and BCSFB) or enter the CNS directly by crossing the external barrier (e.g., during head injury or neurosurgical procedures) or through direct travel of the bacteria to the brain from the nasopharynx via olfactory ensheathing cells or trigeminal nerves [84,88–92].

The initial step that leads to hematogenous pneumococcal meningitis is the colonization of the nasopharynx. Due to the virulence factors described in Section 2.1, *S. pneumoniae* penetrates host cellular barriers to initiate a local infection that can eventually result in systemic spread. High-level bacteremia is considered necessary, although insufficient, for microbial entry into the subarachnoid space [93,94].

Pathogens may cross the BBB and BCSFB via transcellular penetration, paracellular entry, or infected leukocytes from the peripheral circulation (the Trojan horse mechanism) [85]. *S. pneumoniae* crosses the BBB through the transcellular penetration of cerebromicrovascular endothelial cells [95]. Once *S. pneumoniae* has entered the subarachnoid space, it should survive since host defense mechanisms are severely limited in that location: the levels of neutrophils, plasma cells, complement components, and immunoglobulins are low in the normal, uninflamed state [96]. Low concentrations of capsule-specific immunoglobulins and complement factors, together with a paucity of macrophages in the CSF, allow the survival and replication of the bacteria almost as efficiently as in culture broth [85].

S. pneumoniae replication is associated with the release of bacterial products, such as peptidoglycan, and highly immunogenic cell wall fragments. This results in the expression of cytokines, chemokines, and cell-adhesion molecules, proteolytic enzymes, oxidants, cytotoxicity, and apoptosis, which lead to increased BBB permeability and pleocytosis [88]. The host inflammatory reaction and bacterial toxins lead to endothelial injury with loss of cerebrovascular autoregulation, carbon dioxide reactivity of cerebral vessels, and loss of integrity of the BBB [88]. The breakage of the BBB allows plasma to escape into the brain, resulting in vasogenic cerebral edema, followed by an increase in intracranial pressure. Cytotoxic edema can also cause raised intracranial pressure due to an increase in intracellular water following alterations of the cell membrane and loss of cellular homeostasis [97]. Interstitial edema occurs due to the blockade of CSF resorption across the inflamed arachnoid villous system and thus an increase in CSF volume [98]. Finally, the direct bacterial attack and the effects of the inflammatory responses on the cortical blood vessels usually result in the proliferation of the endothelial cells and therefore swelling of the vessel walls and narrowing of their lumen. High intercranial

pressure can cause cerebral herniation or decreased cerebral perfusion, which can ultimately lead to brain injury and death (Figure 3).



BBB: blood-brain barrier, CBV: cerebral blood volume

*From Koedel et al. [88]

Figure 3. Pathophysiological alterations leading to neuronal injury during bacterial meningitis

2.4.2 Diagnosis and clinical presentation

Initial diagnosis of meningitis is based on clinical examination, followed by a lumbar puncture (LP). However, LP is contradicted in patients at risk of brain herniation and those with septic shock or coagulopathy. In addition, before LP is performed, computed tomography (CT) or magnetic resonance imaging (MRI) should be undertaken in patients with signs of brain shift and those with a Glasgow coma scale score <10 [99]. Cytological examination of CSF is helpful in the presumptive diagnosis of acute bacterial meningitis. Classic abnormalities of CSF composition include pleocytosis of mainly polymorphic leukocytes, low glucose concentration, low CSF to blood glucose ratio, and elevated protein levels [100]. In neonates, however, CSF analysis often does not reveal an increased leukocyte count [101].

Preliminary identification of a causative pathogen from CSF includes the detection of the bacterium via Gram stain and rapid diagnosis kits, such as latex agglutination tests. Since bacterial antigen tests' sensitivity is limited, the presumptive causative organism should be confirmed by culture or the amplification of bacterial DNA by polymerase chain reaction (PCR) from clinical specimens collected from sterile sites, such as CSF or blood. The CSF culture is the gold standard for diagnosing bacterial meningitis and can identify the causative pathogen in 81%–93% and 76%–88% of patients with pneumococcal meningitis, respectively [102–104]. An advantage of PCR over culture is its usefulness in patients who received intravenous antibiotic treatment before LP, as blood and CSF cultures are often negative in those patients. Although PCR testing is sensitive and specific and allows faster results than culture, it is not routinely performed in settings with low diagnostic capacity. A disadvantage of PCR is that it can sometimes produce false positive blood results in children colonized by pneumococcus [105]. For public health purposes, the serogrouping or serotyping of pneumococcal isolates can be performed. The Quellung reaction or the capsular reaction test is typically used for serotyping. Other methods include latex or coagglutination and counterimmunoelectrophoresis (CIEP) [106].

The clinical presentation of pneumococcal meningitis is indistinguishable from that of another form of bacterial meningitis. Symptoms generally include headache, fever, neck stiffness, and a change in mental status. Almost all patients have at least two of these symptoms, while less than half have all four [107,108]. Nausea and vomiting can also occur. Cranial nerve palsies may occur due to increased intercranial pressure (in approximately 17% of cases). Seizures and focal neurologic deficits can be observed due to brain ischemia in 7%–21% and 29%–42% of patients, respectively [103]. Arterial stroke occurs in up to 30% of patients, cerebral venous thrombosis in 9%, and intracerebral hemorrhage in up to 9% [109]. Systemic complications, such as sepsis and cardiorespiratory failure, are reported in approximately 38% of cases [104,108]. In neonates, the symptoms are nonspecific and include poor feeding, irritability, hyperthermia or hypothermia, hypertonia or hypotonia, and respiratory distress. A bulging fontanelle is seen in one third of neonatal cases and usually occurs late in illness [110].

2.4.3 Treatment

The medical treatment of bacterial meningitis should start as soon as possible, preferably within one hour of presentation to a medical facility [100]. Several studies have confirmed that a delay in initiating antimicrobial treatment is associated with

poor outcome and death [111,112]. A delay in antimicrobial administration of more than six hours after symptom onset was found to be associated with an 8.4-fold greater risk of death [112]. Empiric antimicrobial treatment should be based on patient age and underlying comorbidity. Since antimicrobial-resistant *S. pneumoniae* strains have become increasingly common over the past few decades, local susceptibility patterns should also be considered. The prevalence of *S. pneumoniae* strains not susceptible to penicillin ranges from 7% to over 50% between geographic regions [113,114]. Countries with high penicillin resistance rates include the USA, Canada, China, Croatia, Greece, Italy, Mexico, Pakistan, Poland, Spain, and Turkey [115]. As *S. pneumoniae*, *N. meningitidis*, and *H. influenzae* are the most common causes of meningitis in otherwise healthy adults up to age 60, the recommended initial treatment against bacterial meningitis includes ceftriaxone or cefotaxime together with vancomycin in countries with high microbial resistance rates. Once the CSF culture and antibiotic susceptibility testing results are available, the antimicrobial treatment should be tailored to the specific pathogen. If the *S. pneumoniae* strain is penicillin resistant (minimal inhibitory concentrations (MICs) > 0.06) but cephalosporin-sensitive, cefotaxime or ceftriaxone should be continued. If the *S. pneumoniae* strain is penicillin and cephalosporin resistant, ceftriaxone or cefotaxime and vancomycin should be continued [115].

Despite prompt, adequate antimicrobial treatment, mortality of bacterial meningitis remains high. This is related not only to the effect of the bacteria itself but also because bactericidal antimicrobials lyse the pathogen, causing the release of proinflammatory bacterial components that trigger the host immune response, which in turn contributes to neuronal and brain damage [87]. Adjunctive therapy with dexamethasone (an anti-inflammatory corticosteroid) is thus recommended, along with antimicrobial treatment. Dexamethasone usage during bacterial meningitis, particularly pneumococcal meningitis, revealed a significant reduction in unfavorable outcomes and death in children and adults [116,117]. In *S. pneumoniae* infections, mortality decreased from 34% with placebo to 14% with dexamethasone [116]. In children, corticosteroids reduced severe hearing loss (RR = 0.61, 95% CI = 0.44, 0.86). In adults, corticosteroids significantly protected against death (RR = 0.57, 95% CI = 0.40, 0.81) and short-term neurological sequelae (RR = 0.42, 95% CI = 0.22, 0.87).

2.4.4 Prevention

Since even early treatment of meningitis does not eliminate the risk of unfavorable outcomes, prevention is the most crucial method to reduce the disease's burden and impact. The first attempt to control pneumococcal disease using whole killed pneumococci occurred in South Africa as early as 1911 [118]. Due to further development in immunology, the first pneumococcal vaccines containing purified polysaccharide capsules as antigens were used in the 1920s [119].

The pneumococcal capsular polysaccharide vaccine (PPSV23), approved for use in 1983, is now used. This vaccine contains 23 polysaccharide serotypes (Table 2). In the USA and many European countries, PPSV23 is recommended for persons aged ≥50 years and persons aged ≥2 years who are at increased risk for pneumococcal disease. PPSV23 was found to be effective in preventing invasive disease caused by serotypes in the vaccine. Nonetheless, information on their effect on pneumococcal meningitis alone is scarce [120–122].

In Finland and Poland, PPSV23 is recommended for adults, especially those at risk for pneumococcal infection. However, vaccine coverage is low in both countries.

Pneumococcal capsular polysaccharides are T-cell-independent antigens associated with poor or absent immunogenicity in infants <24 months of age and failure to induce immunological memory at any age [123,124]. The polysaccharide vaccine also has little to no effect on nasopharyngeal and oropharyngeal carriage. The second generation of vaccines in which capsular polysaccharides are conjugated to protein was therefore developed (Table 2). Conjugate vaccines provide significantly increased serotype-specific T-cell-mediated immunity and reduce carriage and invasive disease [125].

The first conjugated vaccine containing seven purified capsular polysaccharides (PCV7) was licensed in 2000 in the USA and 2001 in the EU [125]. In 2009, a 10-valent pneumococcal non-typeable *H. influenzae* protein D conjugate vaccine (PCV10) was licensed in Europe [126]. This vaccine has never been licensed in the USA. In 2010, PCV7 was replaced with the higher-valent 13-valent pneumococcal conjugate vaccine (PCV13). The efficacy of additional serotypes was inferred before licensure from an immunological correlate of protection established for PCV7 serotypes and not based on direct evidence of efficacy [127]. In 2020, the WHO licensed a new low-cost PCV10 vaccine from the Serum Institute of India for use in low- and middle-income countries [128]. In 2021, two new vaccines were licensed:

15- and 20-valent pneumococcal conjugate vaccines. The serotypes included in each vaccine and indications are presented in Table 2.

As of 2017, pneumococcal vaccination programs had been introduced in 140 countries [129]. In Finland, PCV10 vaccination was introduced in the national vaccination program in September 2010. The vaccine is administered free of charge with a 2+1 schedule at 3, 5, and 12 months of age. The vaccine uptake was about 94% in 2011–2018 [130].

In Poland, PCV10 vaccination was introduced into the childhood immunization program in January 2017. The vaccine is administered free of charge with a 2+1 schedule at 2, 4, and 13 months of age. Before 2017, pneumococcal vaccines (PCV10 registered in 2001, PCV10 registered in 2009, and PCV13 registered in 2010, as well as the 23-valent polysaccharide vaccine, PPSV23) were offered free of charge only to children <5 years of age with risk factors. The indications included trauma or central nervous system defects with cerebrospinal fluid (CSF) leakage, chronic heart failure, immunological-hematological diseases, or HIV infection. Local vaccination campaigns, where immunization was available free of charge for all children <2 years of age, were also arranged [131].

Table 2. Vaccines against invasive pneumococcal disease, including pneumococcal meningitis

Manufacturer	Commercial name	Year of FDA approval	Active constituents	Indications/Vaccine schedule
Pfizer	Prevenar 13®	2010	13-valent serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F polysaccharides—conjugated to diphtheria CRM197 protein	- Infants and children from 6 weeks to 5 years of age for the prevention of invasive pneumococcal disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema, and bacteremia) and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F - Children from 6 to 17 years of age and adults 18 years of age and older for the prevention of invasive pneumococcal disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema, and bacteremia) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F
GSK	Synflorix®	2009*	10-valent pneumococcal polysaccharide conjugate vaccine using protein D derived from non-typeable *Haemophilus influenzae* as a carrier protein for eight out of the 10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, and 23F). Serotypes 18C and 19F are conjugated to tetanus toxoid and diphtheria toxoid, respectively.	- Infants and children from 6 weeks up to 5 years of age against invasive pneumococcal disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema, and bacteremia), pneumonia, and acute otitis media caused by *Streptococcus pneumoniae* serotypes 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F, and cross-reactive 19A

Serum Institute of India	Pneumosil	2020	10-valent polysaccharide serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F individually conjugated to non-toxic diphtheria CRM197 protein	- Infants and toddlers from 6 weeks to 2 years of age for the prevention of invasive disease, pneumonia, and acute otitis media caused by *S. pneumoniae* serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, and 23F
Merck	VAXNEUVANCE™	2021	15-valent polysaccharide serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F, and 6B conjugated to CRM197 carrier protein	- Infants, children, and adolescents from 6 weeks to 17 years of age and adults 18 years of age and older for the prevention of invasive disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema, and bacteremia) caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F
Pfizer	Prevenar 20®	2021	20-valent polysaccharide serotypes pneumococcal capsular polysaccharides 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F conjugated to diphtheria CRM197 protein carrier	- Individuals 6 weeks and older against invasive pneumococcal disease (including sepsis, meningitis, bacteremic pneumonia, pleural empyema, and bacteremia) caused by *Streptococcus pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F - Individuals 6 weeks through 5 years of age for the prevention of otitis media caused by *S. pneumoniae* serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F - Individuals 18 years of age and older for the prevention of pneumonia caused by *S. pneumoniae* serotypes 1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 14, 15B, 18C, 19A, 19F, 22F, 23F, and 33F
PPSV23	Pneumovax 23®	1983	23-valent polysaccharide serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F	- Persons 50 years of age or older and persons 2 years of age or older who are at increased risk for pneumococcal disease for the prevention of pneumococcal disease caused by the 23 serotypes contained in the vaccine (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F)

*EFSA approval

2.5 Epidemiology of pneumococcal meningitis

Streptococcus pneumoniae, *H. influenzae*, and *N. meningitidis* are the leading causes of bacterial meningitis worldwide [132,133]. Meningitis accounts for approximately 4%–10% of cases of all invasive pneumococcal disease [134,135]. The burden of pneumococcal meningitis is highest among young children <5 years of age and older adults >65. Among children <5 years of age, pneumococcal meningitis caused about 83,900 cases and 37,900 deaths in 2015 [5]. The global incidence rate of pneumococcal meningitis in children, irrespective of HIV status, was 13 cases per 100,000 children (uncertainty range (UR) = 5–26) and varies substantially by geographical region. The lowest incidence (four cases per 100,000 [uncertainty range = 2–8]) was observed in Europe and the highest (21 cases per 100,000 [uncertainty range = 9–45]) in Africa. The mortality rate was also lowest (one death per 100,000 children [UR = 0–2]) in Europe and the Americas and highest (13 deaths per 100,000 children [UR = 5–28]) in Africa [5].

Pneumococcal meningitis cases and deaths in children <5 years of age estimated for 2015 were lower than those estimated for 2000, when pneumococcal meningitis caused approximately 103,000 cases and 60,500 deaths [6]. The global incidence rate, irrespective of HIV status, was around 17 cases per 100,000 children (UR = 8–21) [6]. The greatest change in incidence (from 38 cases per 100,000 children in 2000 to 21 cases per 100,000 children in 2015) was also observed in Africa.

Pneumococcal meningitis is the most severe bacterial meningitis. Case fatality proportion depends on age, the presence of underlying conditions, and geographic region. It ranges from 10%–37% in high-income countries to over 61% in low-income countries [102].

Pneumococcal meningitis is also associated with long-term sequelae in survivors, such as sensor-motor deficits, hearing loss, and neuro-intellectual impairment. The risk of at least one sequelae is estimated to be 25% (95% CI = 16.2%, 35.4%) to 32% (95% CI = 27.2%, 36.3%) [136,137]. The most commonly reported sequelae after pneumococcal meningitis are hearing loss (9%–21%) and cognitive difficulties (4%–7%) [136].

2.5.1 Effect of conjugate vaccination on pneumococcal meningitis

The epidemiology of pneumococcal meningitis has changed substantially since the introduction of conjugate vaccines (Table 3). Before PCV7 introduction, seven serotypes in the vaccine were responsible for approximately 70%–80% of IPD, including meningitis [138,139]. Since PCV7 introduction, a significant reduction of 41%–95% in vaccine type meningitis has been observed in the pediatric population and other age groups.

In the USA, decreases of 92% in vaccine type (VT) pneumococcal meningitis incidence (from 0.61 cases per 100,000 population in 1998–1999 to 0.05 cases per 100,000 population in 2006–2007) and 26% in any serotype incidence (from 1.09 cases in 1998–1999 to 0.81 cases per 100,000 population in 2006–2007) were observed [140]. In England and Wales, a 95% reduction in VT pneumococcal incidence (from 2.43 cases in 2000–2006 to 0.12 in 2008–2010) and an overall reduction of 44% in pneumococcal meningitis incidence (from 3.18 cases per 100,000 population in 2000–2006 to 1.44 cases in 2008–2010) in children <5 years of age were reported [141]. A similar impact was observed in other European countries, such as Denmark [142], the Netherlands [12], France [143,144], Spain [145], and Sweden [146]. In most PCV7 settings, the decline in meningitis incidence was greatest at three to four years post-introduction and mostly maintained at five years or more [147,148].

Notably, vaccine use resulted in a decrease in pneumococcal meningitis incidence not only in the age groups targeted for vaccination but also in older children and adults who were not immunized [148–150]. In the USA, indirect benefits of PCV7 exceeded direct protective benefits among immunized children, with over twice as many cases of VT IPD, including meningitis, prevented indirectly as directly in 2003 [151]. In other countries, VT pneumococcal meningitis incidence in adults also declined, with a median 67% decrease [152]. However, changes in the unvaccinated population were not immediate. The decline in incidence among 18–49-year-olds becomes statistically significant after seven years of vaccine introduction. Among persons 50–64 years of age and >65, significance was reached between five and six years post-vaccine introduction [148]. PCV7's indirect effects are believed to be caused by the decreased nasopharyngeal carriage of VT strains among vaccinated children, which results in decreased transmission to nonimmunized children and adults (herd immunity).

Nevertheless, along with the decrease in the incidence of vaccine type meningitis, the increase in the prevalence of non-vaccine-type (NVT) carriage and the incidence of NVT pneumococcal meningitis was reported in many settings. The reported increase in vaccine-eligible populations ranged from 104% in France to 273% in the USA [152]. In France, the increase in NVT incidence even abolished the effect on overall incidence six years after PCV7 introduction [143]. An increase in NVT was also observed in vaccine-non-eligible populations. The incidence rise varied from 54% in people 5–64 years of age in the UK to 214% in all adults in Spain [141,153]. These phenomena are known as serotype replacement and replacement disease, respectively. The most commonly increase in serotypes 19A, 1, 3, 7F, 11A, 16F, 22F, and 35B were reported [143,148,154–156].

Higher-valency PCVs have been developed and replaced PCV7 in all immunization programs to address the increase in NVT disease incidence. PCV10 and PCV13 are now widely used.

A systematic review of five studies on PM in Brazil estimated a PCV10 vaccine effectiveness of 13%–87% among children <5 years of age. A 48%–83% decrease in vaccine type PM was observed in children <2 years of age [157]. After three years of PCV10 introduction, no protective effect was observed in unvaccinated age groups. Instead, in adults, a rate increase of 19%–79% was reported [158]. In Colombia, the PM incidence in children <5 years of age decreased from 1.19 cases per 100,000 children in the pre-PCV period to 0.51 in the first year of mass vaccination, remained stable between 0.54 and 0.63 cases per 100,000 children in the following four years, and increased to 1.03 cases per 100,000 children after six years of vaccine introduction [159].

In the Netherlands, after replacement of PCV7 by PCV10, the incidence of PCV7 and PCV10-PCV7 serotypes as causative agents of PM decreased from 0.42 to 0.06 and 0.12 to 0.03, respectively. However, a concomitant increase from 0.45 to 0.68 occurred in the incidence of non-PCV serotypes [160]. In Austria, Bulgaria, and Iceland, PCV10 was the first PCV implemented. Unfortunately, data on the vaccine impact in those countries are scarce. In Iceland, after PC10 implementation, no impact on overall meningitis (any cause) hospitalizations was observed [161]. In Austria and Bulgaria, a significant reduction in vaccine type IPD was observed, but no separate estimates for meningitis were reported [162].

In the USA, early studies on pneumococcal meningitis following the introduction of PCV13 reported that the number of PMs had remained stable [163,164]. However, a study that assessed PCV13's impact four years after vaccine introduction revealed a 39% decrease in overall PM incidence and a 45% decrease in PM rates

among children <2 years of age [165]. In the multicenter European study (SPIDNET), in eight sites using PCV13, the incidence of all type PM in children <5 years of age was lower after PCV13 use than during the PCV7 period. The consecutive decrease in incidence (25%–34%) was observed for up to four years. From the fifth year, the overall effect started to decrease due to a significant increase (79% after seven years) in the incidence of non-PCV13 serotypes. PCV13 vaccine effectiveness against PM vaccine serotypes in children <5 years of age was 96.5% [130]. Decreases of 27.4% in the number of cases of all pneumococcal meningitis and 90.3% in vaccine type PM after PCV13 introduction were observed in France [166]. Other French studies also reported a decrease in overall incidence in the pediatric population [143,167]. Nonsignificant decreases of 27% in all type PM incidence and 93% in vaccine type PM incidence in children <5 years of age were also reported in Israel [168]. In Germany, conflicting results were reported. In one study, no decrease was observed in all type PM or VT incidence in children <2 years of age post-PCV13 introduction [169]. However, the decrease was reported in a long-term trend study, where a significant decrease in meningitis caused by PCV7 and PCV13 serotypes was observed in children <2 years of age [170]. In Spain, the incidence of all type PM in children <15 years of age decreased by 62% within five years following the introduction of PCV13, compared to the PCV7 period, and no significant increase in non-PCV13 serotypes was observed [171]. In England and Wales, the replacement of PCV7 with PCV13 led to a 48% reduction in PM incidence, mainly due to a reduction in cases caused by additional serotypes included in PCV13. Non-PCV13 serotypes remained stable [13].

In the multicenter study that included settings using PCV13 for at least five to seven years, the percentage of remaining pneumococcal meningitis caused by serotypes covered by the vaccine was 14% in children <5 years of age. Serotype 3 was the most commonly found vaccine type, causing 4% of cases in children <5 years of age and 13% in those ≥5. Serotype 15BC was a leading non-PCV13 serotype among children (11.5% of cases) [14]. Serotypes covered by PCV20 were responsible for 43%–47% of PM cases. In settings where PCV10 was used, the most common PCV10-type serotype was 7F, causing 2.1% of cases among children <5 years of age. PCV13 serotypes were responsible for 29.3%–40% of remaining meningitis cases, with 19A as the most common serotype (24% of cases). The second most common serotype was 6C (10% of cases). No difference in the proportion of PCV20 serotypes was observed in PCV10 and PCV13 settings [14].

Table 3. Review of an impact of PCVs on pneumococcal meningitis

Article	Country/area	Age group	Years compared	Incidence* before and after PCV7 introduction (relative difference)	Incidence per PCV subgroup (relative difference)
7-valent PCV					
Hsu 2009 [149]	USA	All	1998–1999 vs. 2004–2005	1.13 vs. 0.79 (−30%)	PCV7: 0.66 vs. 0.18 (−73%)
					Non-PCV7: 0.32 vs. 0.51 (+61%)
		<2 years		10.16 vs. 3.66 (−64%)	PCV7: 8.20 vs. 0.59 (−93%)
					Non-PCV7: 0.77 vs. 2.87 (+275%)
Thigpen 2011 [140]	USA	All	1998–1999 vs. 2006–2007	1.09 vs. 0.81 (−26%)	PCV-7: 0.61 vs. 0.05 (−92%)
					Non-PCV-7: 0.48 vs. 0.77 (+61%)
Castelblanco 2014 [172]	USA	All	1997–2010	0.81 vs. 0.3 (IRR = 0.38)	N/A
Hanquet 2011 [154]	Belgium	<2 years	2002–2003 vs. 2008	19.3 vs. 13.1 (IRR = 0.68)	PCV7: 13.4 vs. 0.0 (IRR = 0)
					Non-PCV7: 5.8 vs. 13.1 (IRR = 2.24)
Ingels 2012 [142]	Denmark	All	2000–2007 vs. 2008–2010	1.57 vs. 1.22 (IRR = 0.78)	PCV7: 0.6 vs. 0.2
		<2 years		13.3 vs. 6.16 (IRR = 0.47)	N/A
Dubos 2007 [173]	France	<18 years	2000–2005	1.65 vs. 0.80 (−53%)	N/A
Alari 2016 [143]	France	All	2001–2003 vs. 2009–2010	28.2 vs. 33.4 cases per month	PCV7: 15.3 vs. 2.2 cases per month
					PCV13-PCV7: 5.5 vs. 9.9 cases per month
					Non-PCV: 7.5 vs. 17.1 cases per month
Ouldali 2018 [174]	France	<15 years	2001–2003 vs. 2010	0.13 vs. 0.12	PCV7: 0.07 vs. 0.01
					PCV13-PCV7: 0.02 vs. 0.05

					Non-PCV: 0.01 vs. 0.03
Lepoutre 2006 [155]	France	AI	2001–2002 vs. 2006	0.9 vs. 0.9 (IRR = 0.98)	N/A
		<2 years		8 vs. 6 (IRR = 0.75)	PCV7: 5.6 vs. 1 (−81%) Non-PCV7: 2.4 vs. 4.9 (+102%)
Bijlsma 2015 [12]	Netherlands	≥16 years	2006–2007 vs. 2010–2011	1 vs. 0.78	PCV7: 0.42 vs. 0.07
					PCV10-PCV7: 0.13 vs. 0.12
					Non-PCV: 0.44 vs. 0.59
Koelman 2022 [160]	Netherlands	≥16 years	2007 vs. 2017–2018	1.7 vs. 0.73 (IRR = 0.69)	PCV7: 0.42 vs. 0.06
Pichon 2013 [156]	UK & Wales	All	2004–2005 vs. 2008–2009	174 vs. 232 cases per year	PCV7: 56% vs. 18%
					PCV13-PCV7: 20% vs. 33%
					Non-PCV13: 25% vs. 49%
Casado-Flores 2008 [145]	Spain	≤14 years	2001 vs. 2006	2.27 vs. 1.29 (−43%)	PCV7: 1.25 vs. 0.27 (−78%)
Gounder 2015 [175]	North American Arctic	All	2000–2004 vs. 2005–2010	10.4 vs. 11.2 case isolates per year	PCV7: 3.8 vs. 1 case isolates per year
					PCV7-PCV13: 1.8 vs. 4 per year
					Non-PCV13: 4.8 vs. 6.2 per year
Imohl 2015 [170]	Germany	All	1992–2006 vs. 2007–2010		PCV7: 44%–64% vs. 19%–23%
					PCV13-PCV7: 19%–22% vs. 33%–38%
					Non-PCV13: 19%–35% vs. 40%–48%
Miller 2011 [141]	England and Wales	<5 years	2000–2006 vs. 2008–2010	IRR = 0.56	PCV7: IRR = 0.05
					Non-PCV7: IRR = 1.77
		≥65 years		IRR = 0.82	PCV7: IRR = 0.30

					Non-PCV7: IRR = 1.19
10-valent PCV					
Article	Country/area	Age group	Years compared	Incidence before and after PCV-10 introduction	Incidence per PCV subgroup
Bijlsma 2016 [12]	Netherlands	≥16 years	2010–2011 vs. 2013–2014	0.78 vs. 0.62	PCV10-PCV7: 0.12 vs. 0.05
					Non-PCV: 0.59 vs. 0.55
Koelman 2022 [160]	Netherlands	≥16 years	2011 vs. 2017		PCV10-PCV7: 0.12 vs. 0.03
Grando 2015 [176]	Brazil	≤2 years	2007 vs. 2012	3.70 vs. 1.84	N/A
Jokinen 2015 [177]	Finland	≤2 years	2010–2013 vs. 2003–2006	−46%	PCV10: −69%
Farfán-Albarracín 2022 [159]	Colombia	<5 years	2011 vs. 2018	0.3 vs. 0.5	
13-valent PCV					
Article	Country/area	Age group	Years compared	Incidence before and after PCV-13 introduction	Incidence per PCV subgroup
Alari 2016 [143]	France	All	2009–2010 vs. 2013–2014	33.4 vs. 21.1 cases per month	PCV13-PCV7: 9.9 vs. 3.9 cases per month
					Non-PCV: 17.1 vs. 16.3 cases per month
Ouldali 2018 [174]	France	<15 years	2010 vs. 2016	0.12 vs. 0.13	PCV13-PCV7: 0.05 vs. 0.01
					Non-PCV: 0.03 vs. 0.06
Lepoutre 2015 [178]	France	All	2008–2009 vs. 2012	1 vs. 0.8 (IRR = 0.83)	N/A
		<2 years		5.6 vs. 4.5 (IRR = 0.81)	N/A
Ben-Shimol 2016 [168]	Israel	<5 years	2000–2008 vs. 2014–2015	4.4 vs. 3.2 (IRR = 0.73)	PCV13: 3.6 vs. 0.3 (IRR = 0.07)
					Non-PCV13: 0.8 vs. 3 (IRR = 3.73)
Jacobs 2017 [165]	U.S.A.	All	2008–2009 vs. 1011–2014	0.62 vs. 0.38 (−39%)	N/A

		<2 years		2.19 vs. 1.20 (−45%)	N/A
Imohl 2015 [170]	Germany	All	2007–2010 vs. 2010–2013		PCV13-PCV7: 33%–38% vs. 7%–23%
					Non-PCV13: 40%–48% vs. 71%–83%
Galanis 2016 [146]	Sweden	All	2005–2007 vs. 2008–2014	10.1 vs. 4.3 (IRR = 0.43)	N/A
Oligbu, 2019 [13]	England and Wales	<5 years	2008–2010 vs. 2015–2016	3.10 vs. 1.22	PCV7: 0.29 vs. 0.03
					PCV13-PCV7: 1.56 vs. 0.09
					Non-PCV13: 1.25 vs. 1.10
		≥65 years	2008–2010 vs. 2015–2016	0.59 vs. 0.27	PCV7: 0.09 vs. 0
					PCV13-PCV7: 0.12 vs. 0.02
					Non-PCV13: 0.27 vs. 0.25
Weiss 2015 [169]	Germany	<16 years	2009 vs. 2012	0.9 vs. 0.7	PCV13: 0.4 vs. 0.2 (−49%)
					Non-PCV7: 0.5 vs. 0.5
		<2 years		3.6 vs. 3.7	PCV13: 2.2 vs. 1.5 (−33%)
					Non-PCV13: 1.4 vs. 2.3 (+59%)
Harboe 2014 [179]	Denmark	<2 years	2008–2010 vs. 2011–2013	IRR = 0.50	N/A
Ruiz-Contreras 2017 [171]	Spain	<15 years	2007–2010 vs. 2010–2015	2.19 vs. 0.81 (−62%)	PCV13-PCV7: 50.8% vs. 14.6%
Chapoutot 2016 [167]	France	<18 years	2008–2010 vs. 2011–2013	1.32 vs. 0.82	
		<2 years		7.32 vs. 2.78	

*Data supplemented and adopted from (Koelman, Brouwer, and van de Beek 2020)

2.5.2 Epidemiology of pneumococcal meningitis in Poland and Finland

In Poland, surveillance system of meningitis, including pneumococcal meningitis, started in the early 1970s. The surveillance system of invasive pneumococcal disease that includes other clinical presentations of the infection, such as bacteremia and pneumonia, was implemented in 2005. Before pneumococcal conjugate vaccine introduction, *S. pneumoniae* was one of the leading causes of meningitis, accounting for approximately 21%–27% of all bacterial meningitis cases in 2007–2016. The overall PM incidence rate ranged from 0.31 to 0.5 cases per 100,000 population [181–190].

Meningitis cases represented 43% of all IPD reported in 2006–2009 and 34% in 2011–2013 [135,191]. This compares to approximately 4%–8% of cases in other European countries, which suggests heavy underreporting of IPD cases in Poland. The notified incidence rate in 2011–2013 was highest among children 0–11 months of age (2.44 cases per 100,000 persons), followed by adults 60–64 years of age (0.66 cases per 100,000 population). In 2011–2013, PCV10 and PCV13 serotypes covered 44% and 78% of all PM cases, respectively. Meningitis was more prevalent in patients infected with serotypes 18C, 15B/C, and 19F than those infected with other serotypes [191].

In Finland, before PCV10's introduction, meningitis constituted 6% of all IPD cases reported in 1995–2002. The overall annualized PM incidence was 0.6 cases per 100,000 population [192]. The highest incidence was reported in children 0–11 months of age (3.9 cases per 100,000 population), almost two-fold the rate for children 1 year of age (2.2 cases per 100,000 population) [193]. No difference in rates by gender was observed. Contrary to that of bacteremia, the incidence of meningitis was stable between 1995 and 2002. PCV10 and PCV13 serotypes were responsible for 59% and 75% of all IPD cases, respectively [193]. Before PCV10 introduction into a national immunization program, the vaccine's effectiveness was first demonstrated in a nationwide cluster-randomized field trial (Finnish Invasive Pneumococcal disease, FinIP) conducted in 2009–2010. Altogether, 47,369 children were enrolled in the study. For VT IPD and IPD, irrespective of serotype, vaccine effectiveness was 100% and 93%, respectively [194]. Vaccine effectiveness was also demonstrated on clinically suspected invasive pneumococcal disease (based on inpatient and outpatient discharge notifications) [195]. However, no data on

meningitis alone was available. A subsequent observational study conducted three years after PCV10 introduction revealed an 80% and a 92% reduction in overall IPD and VT IPD incidence rates in vaccine-eligible children, respectively [177]. In addition, a 48% decrease in overall IPD in unvaccinated children 2–5 years of age was reported. The relative rate reduction in PCV10-type meningitis cases was 69% (95% CI = 10%, 93%). Although the point estimate for the overall decline in pneumococcal meningitis cases was 46%, it was not statistically significant (95% CI = −19%, 78%) [177]. In a study conducted six years after vaccine introduction, overall IPD incidence in vaccine-eligible children decreased by 79%. VT IPD incidence decreased by 94%. PCV10's indirect impact on unvaccinated older children was smaller (33%) due to a less notable reduction in PCV10 serotypes and a slight increase in non-PCV10 serotypes [196]. Unfortunately, no separate estimates for meningitis were available.

3 AIMS OF THE STUDY

This study aimed to estimate the burden and characterize the epidemiology of bacterial meningitis caused by *S. pneumoniae* (pneumococcal meningitis) before and after the introduction of the 10-valent pneumococcal conjugate vaccine (PCV10) in Poland and Finland. The findings provide baseline information for evaluating the impact of pneumococcal vaccine program introduction and guiding the development of future vaccination policies.

The specific objectives were as follows:

I. To evaluate long-term trends in the incidence rates of pneumococcal meningitis and determine the contribution of pneumococcal meningitis to the overall burden of bacterial meningitis in Finland.

II. To assess the baseline epidemiology of pneumococcal meningitis, including long-term trends in incidence rates, serotype distribution, and antimicrobial susceptibility patterns before the introduction of PCV10 in Poland.

III. To assess the long-term effects of infant PCV10 introduction on the direct and indirect protection and serotype distribution of pneumococcal meningitis in Finland.

4 MATERIALS AND METHODS

4.1 Surveillance of meningitis in Finland and Poland

In Finland and Poland, reporting cases of bacterial meningitis, including pneumococcal meningitis, to the national surveillance systems is mandatory.

In Finland (population ~5.5 million), all clinical microbiology laboratories are legally obliged to report microbial isolations from blood and CSF to the National Infectious Diseases Register (NIDR), a population-based electronic laboratory surveillance system maintained by the Finnish Institute for Health and Welfare (THL). Routinely collected information includes the microbe, specimen type, specimen date, date of birth, sex, place of residence, and unique personal identity code (PIC). For findings concerning *S. pneumoniae*, *Streptococcus agalactiae (S. agalactiae)*, *Neisseria meningitidis (N. meningitidis)*, *Listeria monocytogenes* (*L. monocytogenes)*, and *Haemophilus influenzae (H. influenzae)*, multiple notifications with the same PIC and microbe are merged into one case if they occurred within three months of the first notification. Since 2004, information on vital status after the episode has been routinely obtained from Finland's Population Information System (PIS). The PIS is an online database containing information on each permanent resident's name, sex, date of birth, place of residence, and vital status. The PIC can link this database with other healthcare and surveillance registries. In addition to notifying the NIDR, all clinical microbiology laboratories must submit the isolates from reported cases to a THL reference laboratory for species verification and characterization, including serotyping or serogrouping. Since 2004, serotyping results have been linked to NIDR data through the PIC.

Poland (population ~38 million) has two independent passive surveillance systems for monitoring meningitis, including pneumococcal meningitis (Figure 4). The first system is based on physicians' and field laboratories' mandatory reporting of meningitis cases to the local public health authority. Local public health authorities further investigate the case and complete a standardized surveillance report, which includes information on name, surname, date of birth, place of residence, date of disease onset, date of hospital admission, laboratory findings, clinical symptoms, antimicrobial treatment, and disease outcome. Completed cases are reported to the

population-based surveillance system coordinated by the NIPH-NIH every second week. Multiple notifications with the same identification information (name, surname, address, and place of hospitalization) are merged into one case if they refer to the same illness episode. Case-based data are further reported to the European Surveillance System (TESSy) annually. Case-based reports include demographics, diagnosis, hospitalization, specimen, and outcome data.

The second surveillance system is based on field laboratories' voluntary reporting and sending of isolates or clinical specimens to the National Reference Centre for Bacterial Meningitis (NRCBM), which performs serotyping and tests isolates' antimicrobial susceptibility. If available, data on demographic characteristics, antibiotic therapy, vaccination status, clinical symptoms, and disease outcome are collected for all isolates. Since 2010, data from the NIPH-NIH and the NRCBM have been linked using identification information. Notifications of isolates that were sent to the NRCBM but not reported to the NIPH-NIH are actively collected as part of enhanced surveillance.

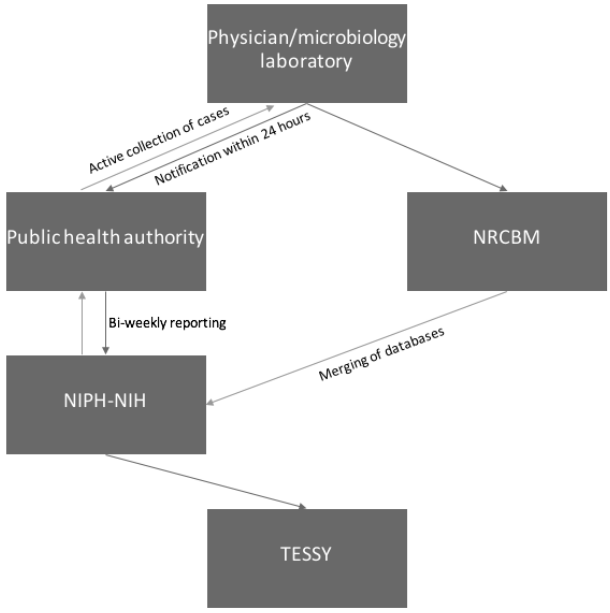


Figure 4. Surveillance system of pneumococcal meningitis in Poland

4.2 Data sources

For Objectives I and III, Finnish data on bacterial meningitis cases caused by *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes*, or *H. influenzae* were obtained from the NIDR. Serotype data were also obtained from this database. The case's vital status within 30 days of the first positive CSF or blood culture was acquired from the PIS. Data on discharge diagnosis (Objective III) were obtained from the national hospital discharge register (the Care Register for Health Care at THL). Data from the PIS were used as denominators for the incidence calculations.

For Objective II, data on the number of pneumococcal meningitis cases in Poland, their demographics (age and sex), and disease outcomes were collected from the NIPH-NIH database. Year of notification was obtained from the date of onset of symptoms or, if unavailable, the specimen collection date. Through linkage with the NRCBM databases (based on identification information), data on serotypes and antimicrobial susceptibility of those cases were collected.

4.3 Case definitions

For Objective I, a case of bacterial meningitis was defined as a patient from which *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes*, or *H. influenzae* was isolated from CSF, with notification to the NIDR from 1995 through 2014.

For Objective II, a case of pneumococcal meningitis was defined as a patient from which *S. pneumoniae* was isolated in CSF, with notification to the NIP-NIH from 2005 through 2015.

For Objective III, a case of pneumococcal meningitis was defined as a patient from which *S. pneumoniae* was isolated in CSF or blood and who received an ICD-10 hospital discharge diagnosis G00.0, G.001, G.002, or G00.9 within 30 days before or after the blood culture date, with notification to the national hospital discharge register from 2004 through 2017.

4.4 Serotyping

In Finland (Objectives I and III), *S. pneumoniae* isolates were serotyped by latex agglutination or counterimmunoelectrophoresis supplemented with the Quellung

reaction until 2009. Since 2010, isolates have been serotyped by multiplex PCR supplemented with the Quellung reaction if needed [106]. All serotype 6A isolates from 2004–2009 were retested to distinguish serotypes 6C and 6D, and since 2010, serotype 6C and 6D identifications have been performed routinely.

In Poland (Objective II), *S. pneumoniae* isolates from CSF were serotyped using the Pneumotest-Latex kit (Statens Serum Institut, Copenhagen, Denmark), PCR, or sequencing. Serotypes not successfully identified by the above methods were subjected to the Quellung test at the Statens Serum Institut (Denmark) in 2008, whereafter in 2009–2015, it was performed at the National Reference Center for Streptococci in Aachen (Germany).

4.5 Antimicrobial susceptibility

To assess the antimicrobial susceptibility of pneumococcal meningitis isolates (objective II), MICs for penicillin and cefotaxime were determined by the ETEST (AB Biodisk-bioMérieuxc) or M.I.C. Evaluator (Oxoid-Thermo Fisher) according to manufactures instructions.

For the interpretation of MIC data, the EUCAST 2015 breakpoints for meningitis cases were applied (European Committee on Antimicrobial Susceptibility Testing, EUCAST, Breakpoint tables for interpretation of MICs and zone diameters. Version 5.0, 2015). Pneumococcal meningitis isolates were categorized as susceptible (S) (MIC ≤0.06 for penicillin and ≤0.5 for cefotaxime), intermediate (I), or resistant (R). The intermediate and resistant isolates were collectively referred to as non-susceptible.

4.6 Serotype distribution and diversity

The proportions of *S. pneumoniae* isolates according to the causative serotypes were calculated. *S. pneumoniae* serotypes were grouped (without cross-reaction assumptions) as follows: PCV10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, and 23F), PCV13 serotypes (PCV10 serotypes and serotypes 3, 6A, and 19A), and PPSV23 serotypes (PCV10 serotypes and serotypes 3, 19A, 2, 8, 9N, 10A, 11A, 12F, 15B, 17F, 20, 22F, and 33F) (Table 4). Three additional serotypes in PCV13 (3, 6A, and 19A) were placed in a separate group: PCV13–PCV10. In addition, PCV20-PCV13 serotypes refer to seven new serotypes (8, 10A, 11A, 12F, 15B, 22F, and

33F) to those present in PCV13. Serotypes different than those present in PCV13 were categorized as non-PCV13. For the serotype proportion calculation in the denominator, cases with missing serotype information were also included. Any culture-confirmed PM included cases with missing serotype information. Serotypes 15B and 15C were grouped as 15B/C because of the reported reversible switching between these serotypes [197].

Table 4. Grouping of *S. pneumoniae* serotypes

Serotype	PCV10	PCV13	PCV20	PPSV23
1	X	X	X	X
4	X	X	X	X
5	X	X	X	X
6B	X	X	X	X
7F	X	X	X	X
9V	X	X	X	X
14	X	X	X	X
18C	X	X	X	X
19F	X	X	X	X
23F	X	X	X	X
3		X	X	X
6A		X	X	X
19A		X	X	X
2				X
8			X	X
9N				X
10A			X	X
11A			X	X
12F			X	X
15B			X	X
17F				X
20				X
22F			X	X
33F			X	X

4.7 Study design

Three population-based observational studies were performed (Objectives I, II, III). In the first study (Objective I), proportions and age-specific annual incidence rates (IRs) were calculated for five main pathogens responsible for bacterial meningitis and reported to the NIDR during 2004–2014: *S. pneumoniae*, *S. agalactiae*,

N. meningitidis, *L. monocytogenes*, and *H. influenzae*. Data from the Finnish PIS were used as denominators.

In the second study (Objective II), to assess the baseline epidemiology of pneumococcal meningitis in Poland, annual and age-specific pneumococcal meningitis IRs were calculated using data from the Polish Central Statistical Office as denominators. The study population comprised all residents registered in Poland between January 1, 2005, and December 31, 2015.

The third study (Objective III) was a before-after study. Serotype- and age-specific pneumococcal meningitis IRs, related 30-day mortality rates, and CFPs were calculated. Pneumococcal meningitis cases with sampling dates from July 1, 2004, to June 30, 2017, and notification to the NIDR were included in the analysis. The pre-PCV10 period (baseline period) was defined as July 1, 2004, to June 30, 2010, while the PCV10 period was defined as July 1, 2011, to June 30, 2017. The transition year (July 1, 2010, to June 30, 2011) was excluded from the study. Data from the Finnish PIS were used as denominators.

4.8 Statistical analysis

In the first study (Objective I), the Poisson regression was used to test for a log-linear trend in IRs of bacterial meningitis in Finland from 1995 through 2014. Incidence rate ratios (IRRs), their 95% confidence intervals (95% CI), and p values for yearly changes were calculated using time (year) as a continuous explanatory variable in the Poisson model. When appropriate, negative binomial regression was used to correct for data overdispersion. The Wilcoxon rank-sum test was used to compare the age distribution of cases across years.

In the second study, negative binomial regression was used to assess the baseline epidemiology of pneumococcal meningitis in Poland (Objective II) and test for a trend in IRs during 2005–2015 while correcting for overdispersion. The Newey-West method was applied to adjust for autocorrelation. Rate ratios (RRs), their 95% CIs, and p values for yearly changes were calculated using time (year) as a continuous explanatory variable in the model. Case fatality proportion (CFP) by age group was calculated as the number of cases resulting in death divided by all reported cases. The chi-square test was used to assess changes in CFP between 2005–2010 and 2011–2015. A $p < 0.05$ was considered statistically significant.

In the third study (Objective III), the Poisson regression was used to compare pneumococcal meningitis incidence and mortality rates between the pre-PCV10 and PCV10 periods in Finland. Rate differences and their 95% CIs were calculated from parameter estimates using the delta method. Relative rate reduction (RRR) was defined as (1 − incidence rate ratio) x 100%, comparing the pre-PCV10 and PCV10 periods. The proportions and IRs of serotype groups in the pre-PCV10 period were compared to those in the last epidemiological year of the study (July 1, 2016–June 30, 2017) to assess changes in *S. pneumoniae* serotype distribution over time. The 30-day CFP (Objectives I and III) was defined as the number of pneumococcal meningitis cases resulting in death within 30 days of the first positive culture divided by all cases. The chi-square test was applied to assess changes in CFP over time. A $p < 0.05$ was considered statistically significant. All analyses were performed with STATA version 13, R version 3.4.2, and MS Excel 2013.

4.9 Ethical considerations

In Finland, the data used for the study I and III were collected as part of national routine surveillance in Finland, which falls under the existing mandate of the THL. Only authorized users had access to the data. In study I no formal Institutional Review Board review was required. Personal identifiers were removed after linkage with vital status data. Data used in study III were de-identified and permission to use the register data for research was obtained from the relevant register controllers at THL (THL/1090/6.02.00/2013) and THL Institutional Review Board approved the study.

In Poland, the data used for study II were collected as part of national routine surveillance, which falls under the existing mandate of the NIPH-NIH and NRCBM. No formal institutional review board review was required for study II in Poland. Permission to use the register data for research was obtained from the relevant data custodians in the NIPH-NIH and NRCBM. Personal identifiers were removed after linkage with serotype information and vital status data.

5 RESULTS

5.1 Contribution of pneumococcal meningitis to the burden of bacterial meningitis in Finland (I)

From 1995 to 2014, 1,361 cases of bacterial meningitis caused by *S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, *L. monocytogenes*, or *H. influenzae* were reported in Finland (mean IR = 1.29 cases per 100,000 person-years). The median age of all bacterial meningitis cases was 36 years. The IR was higher in men than women (1.52 vs. 1.07 cases per 100,000 person-years, IRR = 1.4, 95% CI = 1.3, 1.6).

S. pneumoniae was the most common etiology throughout the study period, except for 1995–1998, when *N. meningitidis* was the primary pathogen (Figure 5). Pneumococcal meningitis was identified in 611 cases (45% of all bacterial meningitis cases), with a mean IR of 0.58 cases per 100,000 person-years. The median age of pneumococcal meningitis cases was 48 years, and 57% of cases were male (male to female IRR = 1.4, 95% CI = 1.2, 1.6) (Table 5).

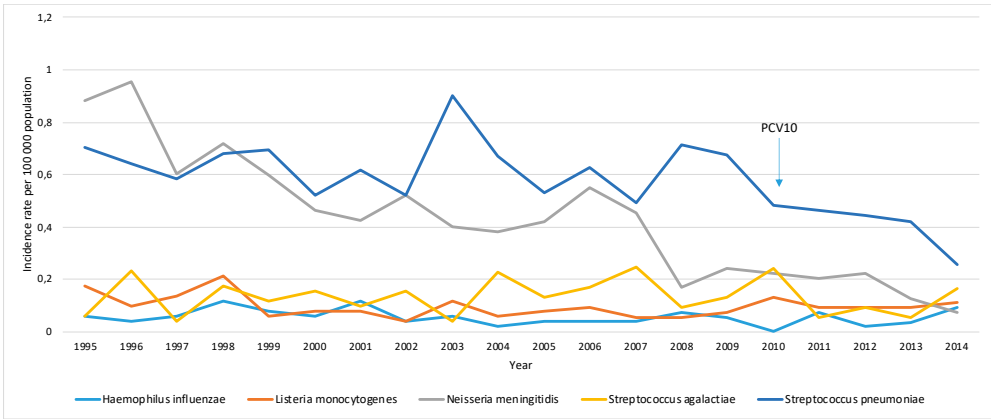


Figure 5. Incidence rate (per 100,000 person-years) of bacterial meningitis by year and pathogen in Finland, 1995–2014

Children <2 years of age accounted for 20% of all bacterial meningitis cases and had the highest mean IR. The most common pathogen in this age group was *S. agalactiae*; *S. pneumoniae* was the second most common etiological agent (3.52 cases per 100,000 person-years), causing 31% (83/268) of cases.

Children 2–4 years of age constituted 5% of all bacterial meningitis cases and had the second highest mean IR. *S. pneumoniae* was also the second most common pathogen in this age group, after *N. meningitidis* (Figure 6).

Children 5–17 years of age accounted for 9% (130/1361) of all bacterial meningitis cases and had the lowest mean IR of all age groups. *N. meningitidis* and *S. pneumoniae* were the main etiologies.

Adults 18–49 years of age constituted 30% of all bacterial meningitis cases. *N. meningitidis* and *S. pneumoniae* caused most of these cases.

Adults 50–64 years of age accounted for 20% of bacterial meningitis cases, of which *S. pneumoniae* caused 68%.

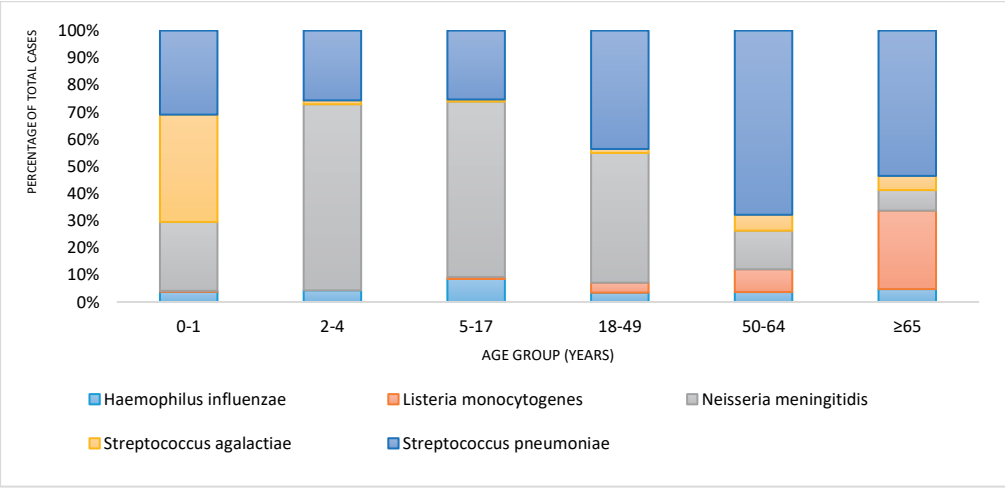


Figure 6. Proportions of bacterial meningitis cases caused by *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, and *S. pneumoniae* by age group in Finland, 1995–2014

In adults ≥65 years of age, 211 cases (15%) of bacterial meningitis occurred. *S. pneumoniae* was the main etiological agent, accounting for 53% (113/211) of the cases.

During 2004–2014, 633 bacterial meningitis cases were reported, and 65 deaths within 30 days of culture were registered. This corresponds to a mean CFP of 10%

(65/633). No significant change in 30-day CFP was observed between 2004–2009 (11%, 43/402) and 2010–2014 (10%, 22/231) (p = .22). The overall CFP ranged from 2% in children <2 years of age to 19% in adults ≥65. *S. pneumoniae* was associated with 58% (38/65) of all fatal cases and had the second highest CFP (12%; 38/308) after *L. monocytogenes* (22%; 11/50). All pneumococcal meningitis deaths but one occurred in adults ≥18 years of age. *S. pneumoniae* was the major cause of death in this age group (37/55 deaths).

Table 5. Characteristics of bacterial meningitis cases caused by *H. influenzae*, *L. monocytogenes*, *N. meningitidis*, *S. agalactiae*, and *S. pneumoniae* in Finland, 1995–2014

	Streptococcus pneumoniae	*Neisseria meningitidis*	*Streptococcus agalactiae*	*Listeria monocytogenes*	*Haemophilus influenzae*	Total
No. of cases (% of total)	611 (45%)	450 (33%)	141 (10%)	101 (8%)	58 (4%)	1361 (100%)
Number of cases per age group (mean incidence rate per 100,000 person-years)						
<2 years	83 (3.52)	68 (2.89)	106 (4.50)	1 (0.04)	10 (0.42)	268 (11.38)
2–4 years	18 (0.50)	48 (1.33)	1 (0.03)	0 (0)	3 (0.08)	70 (1.94)
5–17 years	33 (0.20)	84 (0.52)	1 (0.01)	1 (0.01)	11 (0.07)	130 (0.80)
18–49 years	178 (0.40)	195 (0.43)	6 (0.01)	15 (0.03)	14 (0.03)	408 (0.91)
50–64 years	186 (0.88)	39 (0.18)	16 (0.08)	23 (0.11)	10 (0.05)	274 (1.30)
≥65 years	113 (0.66)	16 (0.09)	11 (0.06)	61 (0.35)	10 (0.06)	211 (1.23)
All	611 (0.58)	450 (0.43)	141 (0.13)	101 (0.10)	58 (0.06)	1361 (1.29)
No. of cases (male/female)	347/264	268/182	70/71	71/30	28/30	784/577
Median age, years (IQR)	48 (28–62)	18 (4–35)	0 (0)	68 (56–74)	29 (6–54)	36 (5–58)
CFP (deaths/cases)*	12.3 % (38/308)	8.6% (14/163)	2.3% (2/86)	22% (11/50)	0% (0/26)	10.3% (65/633)

*Data on cases reported during 2004–2014

5.2 Long-term trend in the incidence rate of bacterial meningitis, including pneumococcal meningitis in Finland (I)

The mean IRs of all bacterial meningitis cases in Finland ranged from 1.97 cases per 100,000 person-years in 1996 to 0.70 in 2014, with a mean annual decrease of 4% (95% CI = −3%, −5%). The overall decline included an annual change of 2% (95% CI = −4%, −1%) among children <2 years of age, 8% (95% CI = −12%, −4%) among children 5–17 years of age, 7% (95% CI = −8%, −5%) in adults 18–49, and 4% (95% CI = −6%, −2%) in adults 50–64 years of age. Among older adults ≥65 years of age, an annual change of −1% was not statistically significant (95% CI = −4%, 1%) (Table 6).

The mean IR of pneumococcal meningitis decreased from 0.70 cases per 100,000 person-years in 1995 to 0.26 in 2014, which represented a mean decrease of 2% (95% CI = −4%, −1) per year, primarily due to declines of 7% (95% CI = −13%, −1%) and 4% (95% CI = −6%, 1%) in the age groups 5–17 years and 18–49 years, respectively. In older adults 50–64 and ≥65 years of age, the mean annual decreases were 2% (95% CI = −4, 2) and 1% (95% CI = −4, 2), respectively (Table 6). However, the confidence intervals of both estimates included 0.

Of the 308 pneumococcal meningitis cases reported during 2004–2014, serotype information was available for 296 (96%). The proportion of overall cases caused by PCV10 serotypes decreased from 61% (35/57) in 2004–2005 to 5% (9/36) in 2013–2014, including a decrease from 75% (9/12) to 20% (1/5) in children <2 years of age. In 2014, no meningitis cases were caused by PCV10 serotypes.

The mean IR of *N. meningitidis* meningitis decreased from 0.88 cases per 100,000 person-years in 1995 to 0.07 in 2014; the mean annual decrease was 9% (95% CI = −7%, −10%). The decline occurred in all age groups except in persons <2 and ≥65 years of age. The incidence rate decreased annually by 6% (95% CI = −1%, −10%), 8% (95% CI = −3%, −14%), 10% (95% CI = −8%, −13%), and 12% (95% CI = −8%, −13%) in the age groups 2–4 years, 5–17 years, 18–49 years, and 50–64 years, respectively (Table 6). During 2004–2014, information on *N. meningitidis* serogroups was available for 99% of cases (161/163). Serogroup B accounted for 85% (137/161) of isolates, C for 11% (17/161), and Y for 4% (7/161). In children <2 years, serogroup B caused 96% (26/27) of cases. MCV-4 and MenB vaccine serogroups caused 15% (24/161) and 85% (137/161) of all cases, respectively.

The mean IR of meningitis caused by *H. influenzae* ranged from 0 cases per 100,000 person-years in 2010 to 0.25 in 2007. Mean annual IR changes overall and in specific age groups were not statistically significant (Table 6). In 2004–2014, non-encapsulated *H. influenzae* accounted for 69% (18/26), serotype f for 23% (6/26), and type b for 8% (2/26) of isolates.

The mean IR of meningitis caused by *S. agalactiae* ranged from 0.06 cases per 100,000 person-years in 1995 to 0.17 in 2014. Overall rates and age-specific rates of *S. agalactiae* did not change significantly (Table 6)

Overall and age-specific mean IRs of *L. monocytogenes* meningitis did not vary significantly during the study period (Table 6), ranging from 0.04 to 0.21 cases per 100,000 person-years.

Table 6. Incidence rates (IR) per 100,000 person-years, number of cases (*N*), and mean annual relative change (95% CI) in the incidence of bacterial meningitis according to age group (years), 1995–2014, Finland

Age group	1995–1999	2000–2004	2005–2009	2010–2014	1995–2014	1995–2014
	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	% change (95% CI)*
Streptococcus pneumoniae						
<2	4.32 (26)	4.43 (25)	3.05 (18)	2.33 (14)	3.52 (83)	−4 (−7; 0)
2–4	0.63 (6)	0.35 (3)	0.69 (6)	0.33 (3)	0.50 (18)	−1 (−8; 7)
5–17	0.31 (13)	0.26 (11)	0.17 (7)	0.05 (2)	0.20 (33)	−7 (−13; −1)
18–49	0.50 (59)	0.48 (54)	0.32 (35)	0.27 (30)	0.40 (178)	−4 (−6; −1)
50–64	0.91 (41)	1 (52)	0.99 (56)	0.65 (37)	0.88 (186)	−2 (−4; 1)
≥65	0.67 (25)	0.57 (23)	0.89 (39)	0.51 (26)	0.66 (113)	−1 (−4; 2)
All	0.55 (170)	0.65 (168)	0.61 (161)	0.41 (112)	0.58 (611)	−2 (−4; −1)
Neisseria meningitidis						
<2	3.83 (23)	4.07 (23)	1.36 (8)	2.33 (14)	2.89 (68)	−4 (−8; 0)
2–4	1.98 (19)	1.27 (11)	1.38 (12)	0.66 (6)	1.33 (48)	−6 (−10; −1)
5–17	0.88 (37)	0.38 (16)	0.60 (24)	0.18 (7)	0.52 (84)	−8 (−14; −3)
18–49	0.79 (93)	0.41 (46)	0.38 (42)	0.13 (14)	0.43 (195)	−10 (−13; −8)
50–64	0.33 (15)	0.29 (15)	0.12 (7)	0.04 (2)	0.18 (39)	−12 (−17; −6)
≥65	0.16 (6)	0.07 (3)	0.09 (4)	0.06 (3)	0.09 (16)	−7 (−14; 2)
All	0.62 (193)	0.44 (114)	0.37 (97)	0.17 (46)	0.43 (450)	−9 (−10; −7)
Haemophilus influenzae						
<2	0.67 (4)	0.53 (3)	0.34 (2)	0.17 (1)	0.42 (10)	−7 (−17; 4)
2–4	0 (0)	0.35 (3)	0 (0)	0 (0)	0.08 (3)	NA
5–17	0.12 (5)	0.10 (4)	0 (0)	0.05 (2)	0.07 (11)	−8 (−17; 3)
18–49	0.03 (4)	0.02 (2)	0.02 (2)	0.05 (6)	0.03 (14)	5 (−5; 15)
50–64	0.07 (3)	0.06 (3)	0.04 (2)	0.04 (2)	0.05 (10)	−3 (−13; 8)
≥65	0.05 (2)	0 (0)	0.16 (7)	0.02 (1)	0.06 (10)	1 (−9; 12)
All	0.06 (18)	0.06 (15)	0.05 (13)	0.04 (12)	0.06 (58)	−2 (−7; 2)

Age group	1995–1999	2000–2004	2005–2009	2010–2014	1995–2014	1995–2014 % change
	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	(95% CI)*
Streptococcus agalactiae						
<2	4.16 (25)	4.25 (24)	5.43 (32)	4.16 (25)	4.50 (106)	0 (−3; 5)
2–4	0.10 (1)	0 (0)	0 (0)	0 (0)	0.03 (1)	NA
5–17	0 (0)	0.02 (1)	0 (0)	0 (0)	0.01 (1)	NA
18–49	0.02 (2)	0.01 (1)	0.01 (1)	0.02 (2)	0.01 (6)	1 (−12; 16)
50–64	0.09 (4)	0.04 (2)	0.12 (7)	0.05 (3)	0.08 (16)	1 (−9; 8)
≥65	0 (0)	0.17 (7)	0.02 (1)	0.06 (3)	0.06 (11)	−2 (−11; 9)
All	0.10 (32)	0.13 (35)	0.15 (41)	0.12 (33)	0.13 (141)	0 (−3; 3)
Listeria monocytogenes						
<2	0.17 (1)	0 (0)	0 (0)	0 (0)	0.04 (1)	NA
2–4	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	NA
5–17	0.02 (1)	0 (0)	0 (0)	0 (0)	0.01 (1)	NA
18–49	0.08 (9)	0.03 (3)	0 (0)	0.03 (3)	0.03 (15)	−11 (−19; −3)
50–64	0.22 (10)	0.06 (3)	0.11 (6)	0.07 (4)	0.11 (23)	−6 (−13; 1)
≥65	0.37 (14)	0.32 (13)	0.30 (13)	0.42 (21)	0.35 (61)	0 (−4; 4)
All	0.11 (35)	0.07 (19)	0.07 (19)	0.10 (28)	0.10 (101)	−2 (−5; 1)
Total bacterial meningitis						
<2	13.14 (79)	13.28 (75)	10.18 (60)	8.99 (54)	11.38 (268)	−2 (−4; −1)
2–4	2.71 (26)	1.97 (17)	2.07 (18)	0.98 (9)	1.94 (70)	−5 (−10; 0)
5–17	1.33 (56)	0.77 (32)	0.77 (31)	0.28 (11)	0.80 (130)	−8 (−12; −4)
18–49	1.43 (167)	0.94 (106)	0.73 (80)	0.50 (55)	0.91 (408)	−7 (−8; −5)
50–64	1.63 (73)	1.44 (75)	1.37 (78)	0.84 (48)	1.30 (274)	−4 (−6; −2)
≥65	1.25 (47)	1.15 (46)	1.46 (64)	1.07 (54)	1.23 (211)	−1 (−4; 1)
All	1.45 (448)	1.35 (351)	1.25 (331)	0.85 (231)	1.29 (1361)	−4 (−3; −5)

*Mean annual relative change in incidence calculated by Poisson regression or negative binomial regression

5.3 Incidence and long-term trend of pneumococcal meningitis before PCV10 introduction in Poland (II)

During 2005–2015, 1,435 pneumococcal meningitis cases were reported to the NIPH-NIH in Poland. The median age of cases was 48 years (IQR 25–60 years). The male-to-female incidence rate ratio was 1.85 (IR = 0.45 vs. 0.24 cases per 100,000 person-years).

The mean annual IR was 0.34 cases per 100,000 person-years. The highest IR was reported in children <1 year of age, followed by the age groups 1–4 years and 65–74 years (Table 7). The reported IRs among young children <1 year of age exemplified substantial variation across the years. Substantial geographical variation also occurred in the reported mean IR, ranging from 0.18 cases in Podlaskie to 0.52 in Pomorskie.

The overall pneumococcal meningitis IR increased steadily from 0.21 cases per 100,000 person-years in 2005 to 0.47 in 2015, which represented an average increase

of 7% per year (95% CI = 6%, 8%), primarily due to annual increases of 3% (95% CI = 2%, 5%) among persons 15–49 years of age, 12% (95% CI = 10%, 13%) among those 50–64 years of age, 18% (95% CI = 16%, 19%) among those 65–74 years of age, and 9% (95% CI = 7%, 10%) among those ≥75 years of age. Trends in other age groups were not statistically significant (Table 7).

The overall CFP was 20% (281/1,435) and varied from 4% (4/90) in children <1 year of age to 31% (71/226) in persons ≥65 years of age. The mean overall CFP was higher in 2005–2010 (22%) than in 2011–2015 (18%) ($p = .052$).

Table 7. Annual incidence rate (IR) per 100,000 person-years, number of cases (N) of pneumococcal meningitis according to age group (years), and mean annual relative change in incidence, 2005–2015, Poland

AGE GROUP	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2005–2015	2005–2015 % CHANGE*
	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	IR (N)	(95% CI)
<1	1.94 (7)	1.64 (6)	0.52 (2)	1.94 (8)	2.12 (9)	3.59 (15)	2.77 (11)	1.56 (6)	3.26 (12)	2.18 (8)	1.66 (6)	2.12 (90)	4 (−3, 11)
1–4	0.35 (5)	0.56 (8)	0.77 (11)	0.68 (10)	0.53 (8)	0.77 (12)	1.20 (20)	0.60 (10)	0.36 (6)	0.45 (7)	0.85 (13)	0.65 (110)	2 (−4, 8)
5–14	0.24 (11)	0.14 (6)	0.29 (12)	0.25 (10)	0.31 (12)	0.21 (8)	0.29 (11)	0.13 (5)	0.27 (10)	0.26 (10)	0.21 (8)	0.24 (103)	0 (−6, 6)
15–49	0.14 (27)	0.18 (35)	0.26 (51)	0.20 (38)	0.24 (47)	0.23 (44)	0.22 (42)	0.16 (30)	0.32 (60)	0.20 (38)	0.29 (54)	0.22 (466)	4 (1, 7)
50–64	0.32 (22)	0.34 (24)	0.29 (22)	0.40 (31)	0.40 (31)	0.46 (37)	0.69 (57)	0.47 (39)	0.67 (55)	0.77 (62)	0.72 (57)	0.51 (437)	10 (7, 14)
65–74	0.20 (6)	0.17 (5)	0.32 (9)	0.22 (6)	0.54 (15)	0.44 (12)	0.33 (9)	0.53 (15)	0.94 (28)	0.47 (15)	0.92 (31)	0.47 (151)	16 (10, 22)
≥75	0.14 (3)	0.27 (6)	0.30 (7)	0.13 (3)	0.34 (8)	0.20 (5)	0.28 (7)	0.35 (9)	0.31 (8)	0.34 (9)	0.37 (10)	0.28 (75)	6 (−1, 44)
ALL**	0.21 (81)	0.24 (90)	0.30 (114)	0.28 (106)	0.34 (130)	0.35 (133)	0.41 (157)	0.30 (114)	0.46 (179)	0.39 (149)	0.47 (179)	0.34 (1,432)	7 (5, 9)

* Mean annual relative change in incidence calculated by Poisson regression or negative binomial regression

** Information on age was missing for three cases

5.4 Serotype distribution of pneumococcal meningitis isolates before PCV10 introduction in Poland (II)

Of the 1,149 pneumococcal meningitis cases reported to the NIPH-NIH during 2008–2015, 676 (59%) CSF isolates were sent to the NRCBM for serotyping. Of the 676, 672 (99%) belonged to 48 different *S. pneumoniae* serotypes or serogroups, while four isolates were non-typeable. The most common serotypes were 3 (11%; 71/676), 19F (10%; 65/676), 14 (9%; 58/676), and 23F (6%; 40/676). No significant differences in serotype distribution between 2008–2011 and 2012–2015 were observed. The exception was an increase in the proportion of serotypes 19A (from 2% in 2008–2011 to 6% in 2012–2015, $p = .0106$) and 23B (from 0% in 2008–2011 to 3% in 2012–2015, $p = .003$).

The serotypes in PCV10, PCV13, and PPSV23 accounted for 46% (309/676), 62% (419/676), and 83% (563/676) of all isolates, respectively. Between 2008–2011 and 2012–2015, a significant decrease in the proportion of cases caused by PCV10 serotypes, from 52% to 41% ($p = .0044$), occurred. No significant changes in proportions of PCV13 ($p = .0630$), PPSV23 ($p = .0848$), PCV13-PCV10 ($p = .16$), and PPSV23 unique serotypes ($p = .54$) were observed.

Of the 112 isolates reported in children <5 years of age, the most common were serotypes 14 (21%, 23/112), 19F (20%, 22/112), 6B (13%, 14/112), 23F (8%, 9/112), 9V (5%, 6/112), and 15B/C (5%, 5/112). PCV10, PCV13, and PPSV23 serotypes accounted for 75% (84/112), 80% (90/112), and 93% (104/112) of isolates, respectively (Table 8). Concerning the distribution of serotypes between 2008–2011 and 2012–2015, the proportion of PCV10 serotypes declined from 87% to 57% ($p = .0004$), the proportion of PCV13 serotypes from 91% to 64% ($p = .0003$), and the proportion of PPSV23 serotypes from 96% to 89% ($p = .15$).

Table 8. Serotype distribution (%) of pneumococcal meningitis isolates among persons <5 years of age reported to the NIP-NIH, 2008–2015, Poland

	2008	2009	2010	2011	2012	2013	2014	2015	2008–2015
Cases reported to NIP-NIH	18	17	27	31	16	18	15	19	161
No. (%) of isolates sent to the NRCBM and serotyped	15 (83)	13 (76)	19 (70)	21 (68)	9 (56)	13 (72)	10 (67)	12 (63)	112 (67)
No. of different serotypes	8	6	7	8	9	9	8	8	25
PCV10/PCV13 serotypes									
1	0	0	0	0	0	7.7	0	0	0.9
4	0	0	0	4.8	0	0	10	0	1.8
5	0	0	0	0	0	0	0	0	0
6B	20	7.7	21.1	9.5	11.1	7.7	0	16.7	12.5
7F	13.3	7.7	0	0	0	0	0	0	2.7
9V	0	0	5.3	19	11.1	0	0	0	5.4
14	13.3	23.1	26.3	33.3	0	23.1	20	8.3	20.5
18C	6.7	15.4	0	0	11.1	0	0	0	3.6
19F	6.7	38.5	21.1	19	11.1	23.1	20	16.7	19.6
23F	20	0	10.5	4.8	11.1	7.7	10	0	8
Additional PCV13 serotypes									
3	0	0	0	0	0	0	0	8.3	0.9
6A	0	7.7	10.5	0	0	0	0	0	2.7
19A	0	0	0	0	0	0	0	16.7	1.8
Other serotypes									
15B/C	13.3	0	0	0	11.1	0	0	16.7	4.5
10A	0	0	5.3	4.8	11.1	7.7	0	0	3.6
8	0	0	0	0	0	7.7	0	8.3	1.8
22F	6.7	0	0	0	0	0	0	8.3	1.8
11A	0	0	0	4.8	0	0	0	0	0.9
12F	0	0	0	0	11.1	0	0	0	0.9
33F	0	0	0	0	0	0	10	0	0.9
9N	0	0	0	0	0	0	10	0	0.9
27	0	0	0	0	0	0	10	0	0.9
38	0	0	0	0	0	0	10	0	0.9
23B	0	0	0	0	0	7.7	0	0	0.9
24F	0	0	0	0	0	7.7	0	0	0.9
35F	0	0	0	0	11.1	0	0	0	0.9
PCV10 serotypes	80	92.3	84.2	90.5	55.6	69.2	60	41.7	75.0
PCV13-PCV10 serotypes	0	7.7	10.5	0	0	0	0	25	5.4
Non-PCV13 serotypes	20	0	5.3	9.5	44.4	30.8	40	33.3	19.6

Among individuals ≥5 years of age (564 isolates), the most common isolates belonged to serotypes 3 (12%; 70/564), 19F (8%; 43/564), 14 (6%; 35/564), 4 (6%; 33/564), 23F (6%; 31/564), and 19A (5%; 27/564). PCV10, PCV13, and PPSV23 serotypes accounted for 40% (225/564), 58% (329/564), and 81% (459/564) of isolates, respectively (Table 9). No significant changes in the proportion of PCV10, PCV13, non-PCV10, non-PCV13, and PCV13-PCV10 serotypes occurred between 2008–2011 and 2012–2015.

Table 9. Serotype distribution (%) of pneumococcal meningitis isolates among persons ≥5 years of age, 2008–2015, Poland

	2008	2009	2010	2011	2012	2013	2014	2015	2008–2015
Cases reported to NIP-NIH	88	113	106	126	98	161	134	160	986
No. (%) of isolates sent to the NRCBM and serotyped	37 (42)	66 (58)	66 (62)	59 (47)	57 (58)	96 (60)	90 (67)	93 (58)	564 (57)
No. of different serotypes	20	31	26	28	21	32	28	31	49
PCV10/PCV13 serotypes									
1	0	0	1.5	1.7	0	2.1	1.1	2.2	1.2
4	5.4	6.1	7.6	3.4	7	6.3	6.7	4.3	5.9
5	0	0	0	0	0	0	0	0	0
6B	5.4	1.5	3	6.8	3.5	4.2	5.6	2.2	3.9
7F	2.7	0	1.5	3.4	0	2.1	5.6	0	2
9V	8.1	3	3	1.7	1.8	5.2	1.1	3.2	3.2
14	8.1	6.1	9.1	3.4	5.3	5.2	6.7	6.5	6.2
18C	2.7	6.1	7.6	3.4	8.8	5.2	1.1	2.2	4.4
19F	10.8	3	13.6	6.8	10.5	7.3	5.6	6.5	7.6
23F	5.4	3	7.6	5.1	8.8	6.3	3.3	5.4	5.5
Additional PCV13 serotypes									
3	10.8	10.6	10.6	20.3	12.3	9.4	17.8	8.6	12.4
6A	0	1.5	1.5	0	1.8	2.1	0	2.2	1.2
19A	2.7	1.5	1.5	6.8	3.5	8.3	6.7	4.3	4.8
Other serotypes									
8	8.1	1.5	3	1.7	5.3	2.1	2.2	5.4	3.4
10A	5.4	3	3	0	5.3	1	2.2	7.5	3.4
22F	0	1.5	3	3.4	7	1	4.4	5.4	3.4
9N	2.7	4.5	1.5	1.7	1.8	4.2	2.2	4.3	3
11A	2.7	3	6.1	3.4	0	3.1	3.3	1.1	2.8
15B/C	5.4	3	0	5.1	3.5	5.2	0	2.2	2.8
12F	2.7	12.1	0	1.7	1.8	1	1.1	2.2	2.7
17F	0	1.5	0	1.7	3.5	0	0	0	0.7
33F	0	0	0	1.7	1.8	0	1.1	0	0.5
20	2.7	3	1.5	0	3.5	0	2.2	0	1.4
2	0	1.5	0	0	0	0	0	0	0.2
23A	2.7	1.5	0	0	0	3.1	3.3	5.4	2.3
23B	0	0	0	0	0	2.1	5.6	5.4	2.1

	2008	2009	2010	2011	2012	2013	2014	2015	2008–2015
6C	0	3	0	1.7	0	1	3.3	2.2	1.6
15A	0	1.5	1.5	1.7	1.8	1	1.1	1.1	1.2
6A	0	1.5	1.5	0	1.8	2.1	0	2.2	1.2
31	0	3	0	1.7	0	1	0	1.1	0.9
Other**	5.4	12.1	10.6	11.9	0	8.3	6.7	7.5	8
PCV10 serotypes	48.6	28.8	54.5	35.6	45.6	43.8	36.7	32.3	39.9
PCV13-PCV10 serotypes	13.5	13.6	13.6	27.1	17.5	19.8	24.4	15.1	18.4
Non-PCV13 serotypes	37.8	57.6	31.8	37.3	36.8	36.5	38.9	52.7	41.7

** Serotypes, other than those presented in the table, that occurred <10 times in 2005–2015 in Poland. Non-typeable isolates (n = 4) were included.

5.5 Antimicrobial susceptibility of pneumococcal meningitis isolates before PCV10 introduction in Poland (II)

Of the 669 pneumococcal meningitis isolates with available data on penicillin susceptibility from 2008–2015 in Poland, 28% (189/669) were resistant to this antimicrobial (MIC > 0.06 mg/L). Resistance to penicillin was common among serotypes 19A (90%; 26/29), 9V (79%; 19/24), 19F (72%; 47/65), 14 (69%; 40/58), and 6B (66%; 23/35). No statistically significant change in the overall proportion of penicillin-resistant isolates was reported in 2008–2011 (29%) vs. 2012–2015 (27%) (p = .57). Among children <5 years of age, 53% (58/110) of isolates were resistant to penicillin compared to 23% (131/559) among persons ≥5 years of age (p < .0001). Among children <5 years of age, the serotypes with the highest proportion of penicillin resistance were 9V (100%; 6/6), 19A (100%; 2/2), 23B (100%; 1/1), 19F (82%; 18/22), 14 (70%; 16/23), 6A (67%; 2/3), and 23F (56%; 5/9).

Isolates with decreased susceptibility to cefotaxime (MIC > 0.5 mg/L) constituted 13% (90/670) of all isolates tested in 2008–2015. Non-susceptibility to cefotaxime was highest among serotypes 19A (59%; 17/29), 35B (50%; 1/2), 19F (46%; 30/65), 14 (43%, 25/58), 23F (25%, 10/40), and 9V (21%, 5/24). The overall proportion of cefotaxime non-susceptibility did not change significantly between 2008–2011 and 2012–2015, 14% (40/295) and 13% (50/375), respectively (p = .7066). Among children <5 years of age, 22% (24/110) of isolates were non-susceptible to cefotaxime compared to 13% (70/560) among persons ≥5 years of age (70/560) (p = .0052). The highest proportion of cefotaxime non-susceptible isolates in children <5 years of age was identified in serotypes 19A (100%, 2/2), 23F (44%, 4/9), 14 (43%, 10/23), and 19F (36%, 8/22).

5.6 Changes in the overall pneumococcal meningitis incidence rates after PCV10 introduction in Finland (III)

Altogether, 451 culture-confirmed pneumococcal meningitis cases were reported to the NIDR from July 1, 2004, to June 30, 2017 (excluding the transition period of July 1, 2011–June 30, 2011). The median age of cases was 57 years (IQR 40–64 years). Of the 451 cases, 257 occurred in the pre-PCV10 period, while 194 occurred during the PCV10 period. Twenty-eight percent of pneumococcal meningitis cases in the pre-PCV10 period and 30% in the PCV10 period were identified based on positive blood culture and an ICD10 bacterial meningitis discharge diagnosis. The remaining cases were identified based on positive CSF culture only.

The overall annual pneumococcal meningitis IR varied from 0.44 cases per 100,000 person-years in 2016–2017 to 1.07 in 2008. Between the pre-PCV10 and PCV10 periods, the mean overall annual IR of pneumococcal meningitis decreased by 27%, from 0.81 cases per 100,000 person-years to 0.59 (IRR = 0.73, 95% CI = 0.61, 0.88) (Table 10). Compared to the pre-PCV10 period, in the PCV10 period, the pneumococcal meningitis IR decreased by 64% in children 0–4 years of age (IRR = 0.36, 95% CI = 0.19, 0.63) and 34% in adults 50–64 years of age (IRR = 0.66, 95% CI = 0.47, 0.90). In all adults ≥18 years of age, the pneumococcal meningitis IR decreased by 19%, from 0.82 cases per 100,000 person-years to 0.67 (IRR = 0.81, 95% CI = 0.66, 0.99). In other age groups, the point estimates decreased, but confidence intervals included 1 (Table 10).

Table 10. Overall number (*N*) and incidence rates of pneumococcal meningitis and the corresponding relative and absolute rate reductions according to age group, based on the comparison of the pre-PCV10 period vs. the PCV10 period, Finland

Age group (years)	Pre-PCV10 period incidence rate per 100,000 person-years (N)	PCV10 period incidence rate per 100,000 person-years (N)	PCV10 period vs. pre-PCV10 period		
			Incidence rate ratio (95% CI)	Relative rate reduction (%) (95% CI)	Absolute rate reduction per 100,000 person-years (95% CI)
0–4	2.35 (41)	0.84 (15)	0.36 (0.19, 0.63)	64.45 (37.21, 80.94)	1.52 (0.68, 2.35)
5–17	0.19 (9)	0.09 (4)	0.46 (0.13, 1.42)	53.86 (−41.69, 87.5)	0.1 (−0.05, 0.25)
18–49	0.40 (53)	0.31 (40)	0.76 (0.50, 1.14)	24.05 (−14.22, 49.89)	0.1 (−0.05, 0.24)
50–64	1.38 (93)	0.90 (61)	0.66 (0.47, 0.90)	34.46 (9.74, 52.75)	0.47 (0.11, 0.83)
≥65	1.17 (61)	1.15 (74)	0.99 (0.70, 1.39)	1.37 (−38.79, 29.65)	0.02 (−0.38, 0.41)
All	0.81 (257)	0.59 (194)	0.73 (0.61, 0.88)	26.81 (11.87, 39.31)	0.22 (0.09, 0.35)

5.7 Changes in the serotype-specific pneumococcal meningitis incidence rates after infant PCV10 introduction in Finland (III)

Overall, pneumococcal meningitis IR caused by PCV10 serotypes decreased by 68%, from 0.50 cases per 100,000 person-years in the pre-PCV10 period to 0.16 in the PCV10 period (Table 11). In children 0–4 years of age, the IR decreased by 87%, from 2.07 cases per 100,000 person-years in the pre-PCV10 period to 0.28 in the PCV10 period. In adults 18–49 and 50–64 years of age, the IR decreased by 63%, from 0.27 cases per 100,000 person-years to 0.10, and 63%, from 0.68 cases per 100,000 person-years to 0.25, respectively. Among older adults ≥65 years of age, the IR of PCV10-serotype pneumococcal meningitis decreased by 69%, from 0.71 cases per 100,000 person-years to 0.22.

The IR of pneumococcal meningitis caused by PCV13 serotypes also decreased in all age groups. However, pneumococcal meningitis caused by the three serotypes exclusively in PCV13 (3, 6A, and 19A) increased in adults 18–49 years, but the absolute rate change was minimal (0.04/100,000) (Table 11).

The overall IR of non-PCV10 serotype pneumococcal meningitis increased by 54%, from 0.28 cases per 100,000 person-years in the pre-PCV10 period to 0.43 in the PCV10 period. This was mainly due to an increase in IR of 157% in adults ≥65 years of age, from 0.36 cases in the pre-PCV10 period to 0.94 in the PCV10 period.

The overall IR of non-PCV13 serotypes increased by 57%, from 0.21 cases per 100,000 person-years to 0.34, primarily due to increases in children 0–4 years of age and adults ≥65 (Table 11).

Table 11. Serotype-specific incidence rates, the number of cases (*N*) of pneumococcal meningitis, and the corresponding relative and absolute rate reductions according to age group, based on the comparison of the pre-PCV10 period vs. the PCV10 period, Finland

Age group (years)	Pre-PCV10 period incidence rate/ 100,000 person-years (N)	PCV10 period incidence rate/ 100,000 person-years (N)	PCV10 period vs. pre-PCV10 period		
			Incidence rate ratio (95% CI)	Relative rate reduction (%) (95% CI)	Absolute rate reduction/100,000 person-years (95% CI)
PCV10-serotypes					
0–4	2.07 (36)	0.28 (5)	0.14 (0.05, 0.31)	86.5 (68.64, 95.36)	1.79 (1.07, 2.51)
5–17	0.10 (5)	0.06 (3)	0.62 (0.13, 2.54)	37.71 (−153.87, 87.22)	0.04 (−0.08, 0.16)
18–49	0.27 (35)	0.10 (13)	0.37 (0.19, 0.69)	62.62 (31.13, 80.94)	0.17 (0.06, 0.27)
50–64	0.68 (46)	0.25 (17)	0.37 (0.21, 0.63)	63.07 (36.87, 79.41)	0.43 (0.2, 0.66)
≥65	0.71 (37)	0.22 (14)	0.31 (0.16, 0.56)	69.24 (44.42, 83.92)	0.49 (0.24, 0.75)
All	0.50 (159)	0.16 (52)	0.32 (0.23, 0.43)	68.29 (56.96, 77.02)	0.34 (0.25, 0.43)
Non-PCV10 serotypes					
0–4	0.23 (4)	0.56 (10)	2.43 (0.81, 8.86)	−142.94 (−785.68, 18.74)	−0.33 (−0.74, 0.08)
5–17	0.08 (4)	0.02 (1)	0.26 (0.01, 1.75)	74.05 (−75.45, 98.67)	0.06 (−0.03, 0.15)
18–49	0.13 (17)	0.21 (27)	1.60 (0.88, 2.99)	−59.83 (−198.81, 12.06)	−0.08 (−0.18, 0.02)
50–64	0.67 (45)	0.64 (43)	0.96 (0.63, 1.45)	4.51 (−45.16, 37.27)	0.03 (−0.24, 0.3)
≥65	0.36 (19)	0.94 (60)	2.57 (1.56, 4.42)	−156.74 (−341.56, −56.36)	−0.57 (−0.86, −0.28)
All	0.28 (89)	0.43 (141)	1.54 (1.18, 2.01)	−53.62 (−100.91, −18.08)	−0.15 (−0.24, −0.06)
PCV13-serotypes					
0–4	2.18 (38)	0.34 (6)	0.15 (0.06, 0.34)	84.66 (66.35, 94.17)	1.85 (1.1, 2.59)
5–17	0.15 (7)	0.06 (3)	0.45 (0.10, 1.6)	55.51 (−60.04, 90.41)	0.08 (−0.05, 0.21)
18–49	0.27 (36)	0.15 (19)	0.53 (0.30, 0.91)	46.89 (8.54, 70.13)	0.13 (0.02, 0.24)
50–64	0.81 (55)	0.46 (31)	0.56 (0.36, 0.87)	43.68 (13.16, 64.13)	0.36 (0.09, 0.62)
≥65	0.84 (44)	0.37 (24)	0.44 (0.27, 0.72)	55.65 (27.77, 73.43)	0.47 (0.18, 0.76)
All	0.57 (180)	0.25 (83)	0.45 (0.34, 0.58)	55.29 (42.23, 65.68)	0.31 (0.21, 0.41)

Age group (years)	Pre-PCV10 period incidence rate/ 100,000 person-years (N)	PCV10 period incidence rate/ 100,000 person-years (N)	PCV10 period vs. pre-PCV10 period		
			Incidence rate ratio (95% CI)	Relative rate reduction (%) (95% CI)	Absolute rate reduction/100,000 person-years (95% CI)
Non-PCV13 serotypes					
0–4	0.12 (2)	0.50 (9)	4.37 (1.1, 28.7)	−337.29 (−2768.43, −12.7)	−0.39 (−0.75, −0.02)
5–17	0.04 (2)	0.02 (1)	0.52 (0.02, 5.42)	48.09 (−441.95, 97.59)	0.02 (−0.05, 0.09)
18–49	0.12 (16)	0.16 (21)	1.32 (0.69, 2.57)	−32.08 (−157.05, 30.81)	−0.04 (−0.13, 0.05)
50–64	0.53 (36)	0.43 (29)	0.81 (0.49, 1.31)	19.5 (−31.03, 50.97)	0.1 (−0.13, 0.34)
≥65	0.23 (12)	0.78 (50)	3.39 (1.87, 6.67)	−238.75 (−566.6, −86.85)	−0.55 (−0.8, −0.3)
All	0.21 (68)	0.34 (110)	1.57 (1.16, 2.13)	−56.85 (−113.12, −16.28)	−0.12 (−0.2, −0.04)
PCV13-PCV10 serotypes (3, 6A, 19A)					
0–4	0.12 (2)	0.06 (1)	0.49 (0.02, 5.07)	51.41 (−407.28, 97.74)	0.06 (−0.13, 0.25)
5–17	0.04 (2)	0 (0)	0 (0, 1.62)	100 (−61.61, 100)	0.04 (−0.02, 0.1)
18–49	0.01 (1)	0.05 (6)	6.04(1.03,114.04)	−503.82 (−11303.5, −3.15)	−0.04 (−0.08, 0)
50–64	0.13 (9)	0.21 (14)	1.55 (0.68, 3.73)	−55.45 (−273.16, 31.81)	−0.07 (−0.21, 0.07)
≥65	0.13 (7)	0.16 (10)	1.16 (0.45, 3.20)	−16.14 (−219.85, 55.39)	−0.02 (−0.16, 0.12)
All	0.07 (21)	0.10 (31)	1.43 (0.83, 2.53)	−43.14 (−152.46, 17.22)	−0.03 (−0.07, 0.02)
PPSV23 unique serotypes					
0–4	0 (0)	0.22 (4)	-	-	−0.22 (−0.44, 0)
5–17	0.02 (1)	0.021 (1)	1.04 (0.04, 26.25)	−3.82 (−2525.4, 95.89)	0 (−0.06, 0.06)
18–49	0.06 (8)	0.08 (11)	1.38 (0.56, 3.57)	−38.37 (−257.43, 43.99)	−0.02 (−0.09, 0.04)
50–64	0.27 (18)	0.21 (14)	0.78 (0.38, 1.56)	22.28 (−55.78, 62.01)	0.06 (−0.1, 0.22)
≥65	0.13 (7)	0.33 (21)	2.44 (1.09, 6.19)	−143.9 (−519.26, −8.77)	−0.19 (−0.36, −0.02)
All	0.11 (34)	0.16 (51)	1.45 (0.95, 2.26)	−45.45 (−126.28, 5.33)	−0.05 (−0.1, 0.01)
Serotype 3					
0–4	0.06 (1)	0.06 (1)	0.97 (0.04, 24.57)	2.82 (−2357.41, 96.16)	0 (−0.16, 0.16)
5–17	0.04 (2)	0 (0)	0 (0, 1.62)	100 (−61.61, 100)	0.04 (−0.02, 0.1)
18–49	0 (0)	0.02 (2)	-	-	−0.02 (−0.04, 0.01)
50–64	0.04 (3)	0.04 (3)	1.0 (0.19, 5.40)	0.07 (−439.95, 81.51)	0 (−0.07, 0.07)
≥65	0.08 (4)	0.06 (4)	0.81 (0.19, 3.44)	18.7 (−243.84, 80.78)	0.01 (−0.08, 0.11)
All	0.03 (10)	0.03 (10)	0.97 (0.40, 2.36)	3.04 (−136.28, 60.21)	0 (−0.03, 0.03)

Age group (years)	Pre-PCV10 period incidence rate/ 100,000 person-years (N)	PCV10 period incidence rate/ 100,000 person-years (N)	PCV10 period vs. pre-PCV10 period		
			Incidence rate ratio (95% CI)	Relative rate reduction (%) (95% CI)	Absolute rate reduction/100,000 person-years (95% CI)
Serotype 6A					
0–4	0.06 (1)	0 (0)	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
5–17	0 (0)	0 (0)	-	-	-
18–49	0.01 (1)	0.01 (1)	1.01 (0.04, 25.45)	−0.64 (−2444.9, 96.02)	0 (−0.02, 0.02)
50–64	0.07 (5)	0.09 (6)	1.20 (0.36, 4.16)	−19.91 (−316.09, 63.88)	−0.01 (−0.11, 0.08)
≥65	0.08 (3)	0.06 (2)	0.81 (0.19, 3.44)	18.7 (−243.84, 80.78)	0.01 (−0.08, 0.11)
All	0.03 (10)	0.03 (9)	0.87 (0.35, 2.17)	12.73 (−116.51, 65.33)	0 (−0.02, 0.03)
Serotype 6C					
0–4	0 (0)	0.11 (2)	-	-	−0.11 (−0.27, 0.04)
5–17	0 (0)	0 (0)	-	-	-
18–49	0 (0)	0.03 (4)	-	-	−0.03 (−0.06, 0)
50–64	0.02 (1)	0.04 (3)	3.0 (0.38, 60.61)	−199.79 (−5960.6, 61.62)	−0.03 (−0.09, 0.03)
≥65	0.04 (2)	0.09 (6)	2.44 (0.56, 16.65)	−143.9 (−1564.69, 43.8)	−0.06 (−0.15, 0.04)
All	0.01 (3)	0.05 (15)	4.85 (1.6, 20.93)	−384.82 (−1993.23, −60)	−0.04 (−0.06, −0.01)
Serotype 19A					
0–4	0 (0)	0 (0)	-	-	-
5–17	0 (0)	0 (0)	-	-	-
18–49	0 (0)	0.02 (3)	-	-	−0.02 (−0.05, 0)
50–64	0.02 (1)	0.07 (5)	5 (0.81, 95.73)	−399.65 (−9472.7, 19.42)	−0.06 (−0.13, 0.01)
≥65	0 (0)	0.06 (4)	-	-	−0.06 (−0.12, 0)
All	0 (1)	0.04 (12)	11.64 (2.3, 211.9)	−1063.6 (−21,099, −129.3)	−0.03 (−0.06, −0.01)
Serotype 22F					
0–4	0 (0)	0.06 (1)	-	-	−0.06 (−0.17, 0.05)
5–17	0 (0)	0 (0)	-	-	-
18–49	0.03 (4)	0.02 (3)	0.76 (0.15, 3.42)	24.52 (−242.4, 85.13)	0.01 (−0.03, 0.05)
50–64	0.04 (3)	0.10 (7)	2.33 (0.65, 10.82)	−133.17 (−981.94, 35.18)	−0.06 (−0.15, 0.03)
≥65	0.06 (3)	0.16 (10)	2.71 (0.83, 12.09)	−171 (−1108.77, 17.1)	−0.1 (−0.21, 0.02)
All	0.03 (10)	0.06 (21)	2.04 (0.98, 4.52)	−103.62 (−351.53, 1.71)	−0.03 (−0.07, 0)

5.8 Changes in pneumococcal meningitis serotype distribution after infant PCV10 introduction in Finland (III)

In the final epidemiological year of the study there were 24 serotyped pneumococcal isolates. No cases were reported in children 5–17 years of age. In the pre-PCV10 period, pneumococcal meningitis cases caused by PCV10 serotypes in persons 0–4 and 18–49 years of age accounted for 90% (36/40) and 67% (35/52) of all typed isolates, respectively. By the final epidemiological year of the study, no cases caused by those serotypes were reported in these age groups. In adults aged 50–64 and ≥65 years of age, PCV10 serotypes caused 51% (46/91) and 66% (37/56) of meningitis cases in the pre-PCV10 period and 33% (2/6) and 7% (1/14) in the last study year.

The proportion of meningitis caused by PCV13-PCV10 serotypes in persons 0–4 and 50–64 years of age decreased to 0%, from 5% (2/40) and 10% (9/91), respectively. However, in adults 18–49 and ≥65 years of age, this proportion increased from 2% (1/52) to 50% (1/2) and from 13% (7/56) to 14% (2/14), respectively.

The proportion of non-PCV13 serotypes increased in children 0–4 years of age (from 5% [2/40] to 100% [2/2]) and adults 18–49 years of age (from 31% [16/52] to 50% [1/2]), 50–64 (from 40% [36/91] to 67% [4/6]), and ≥65 years of age (from 21% [12/56] to 79% [11/14]).

Unique PCV20 serotypes constituted 50% (3/6) and 50% (7/14) of all isolates in adults 50–64 and ≥65 years of age in the last study year, compared to 12% (11/91) and 9% (5/56) pre-PCV10 introduction. In the two youngest age groups, no cases were caused by those serotypes before PCV10 introduction or in the last year.

In all adults ≥18 years of age, between the pre-PCV10 period and 2016–2017, the proportion of PCV10 serotypes decreased from 59% to 14%. The proportion of non-PCV13 serotypes thus increased from 32% in the pre-PCV10 period to 73% in 2016–2017.

In 2016–2017, the serotypes causing most cases were 22F, 6C, and 23A (Figure 7).

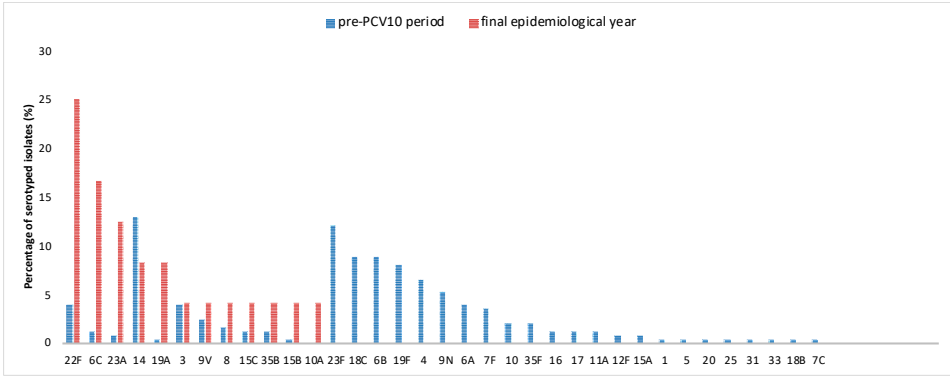


Figure 7. Proportions (%) of individual *S. pneumoniae* serotypes to overall pneumococcal meningitis cases before PCV10 introduction and in 2016–2017 (the final epidemiological year of the study), Finland

5.9 Changes in mortality risk after infant PCV10 introduction in Finland (III)

During the study period, 64 pneumococcal meningitis-related deaths occurred within 30 days of the first positive CSF or blood culture. All deaths but one were in adults >18 years of age (Table 12). Compared to that in the pre-PCV10 period, the overall mortality rate of pneumococcal meningitis decreased by 42% (95% CI = 4%, 65%), from 0.13 deaths per 100,000 person-years to 0.07 in the PCV10 period. This was primarily due to a 66% (95% CI = 31%, 85%) reduction in the mortality rate of PCV10 serotype pneumococcal meningitis (Table 12), particularly in persons 50–64 years of age (a reduction of 80% [95% CI = 39%, 95%]).

The overall CFPs during the pre-PCV10 and PCV10 periods were 16% and 12%, respectively (p = .41). The CFP in persons 50–64 years of age decreased from 25% in the pre-PCV10 period to 10% in the PCV10 period (p = .04).

In adults ≥18 years of age, the pneumococcal meningitis-related mortality rate decreased by 41% between the pre-PCV10 and PCV10 periods (95% CI = 3%, 65%), from 0.16 deaths per 100,000 person-years to 0.09, mainly due to a 65% decrease (95% CI = 29%, 85%) in the mortality rate of PCV10 serotype pneumococcal meningitis. The CFPs in the pre-PCV10 and PCV10 periods were 19% and 14%, respectively (p = .61).

Table 12. Mortality rates (number of deaths, *N*) and case fatality proportion (CFP) of pneumococcal meningitis and the corresponding relative and absolute rate reductions based on comparison of the pre-PCV10 period vs. the PCV10 period, Finland

Age group (years)	Pre-PCV10 period		PCV10 period		Pre-PCV10 period vs. PCV10 period		
	Mortality/100,000 person-years (N)	CFP (%)	Mortality/100,000 person-years (N)	CFP (%)	Mortality rate ratio	Relative rate reduction, %	Absolute rate reduction/ 100,000 person-years
Any culture confirmed							
0–4	0.06 (1)	2.4	0 (0)	0.0	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
5–17	0 (0)	0.0	0 (0)	0.0	-	-	-
18–49	0.05 (6)	11.3	0.04 (5)	12.5	0.84 (0.24, 2.78)	16.14 (−178.45, 75.83)	0.01 (−0.04, 0.06)
50–64	0.34 (23)	24.7	0.09 (6)	9.8	0.26 (0.10, 0.60)	73.93 (39.92, 90.37)	0.25 (0.1, 0.41)
65	0.19 (10)	16.4	0.20 (13)	17.6	1.06 (0.47, 2.48)	−5.69 (−147.59, 53.51)	−0.01 (−0.17, 0.15)
All	0.13 (40)	15.6	0.07 (24)	12.4	0.58 (0.35, 0.96)	41.82 (4.26, 65.4)	0.05 (0, 0.1)
PCV10-serotypes							
0–4	0.06 (1)	2.8	0 (0)	0.0	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
5–17	0 (0)	0.0	0 (0)	0.0	-	-	-
18–49	0.03 (4)	11.4	0.02 (3)	23.1	0.76 (0.15, 3.42)	24.52 (-242.4, 85.13)	0.01 (−0.03, 0.05)
50–64	0.22 (15)	32.6	0.04 (3)	17.6	0.2 (0.05, 0.61)	80.01 (39.44, 95.37)	0.18 (0.05, 0.3)
65	0.12 (6)	16.2	0.05 (3)	21.4	0.41 (0.09, 1.54)	59.35 (−54.08, 91.42)	0.07 (−0.04, 0.17)
All	0.08 (26)	16.4	0.03 (9)	17.3	0.34 (0.15, 0.69)	66.44 (31, 85.14)	0.05 (0.02, 0.09)
Non-PCV10 serotypes							
0–4	0 (0)	0.0	0 (0)	0.0	-	-	-
5–17	0 (0)	0.0	0 (0)	0.0	-	-	-
18–49	0.02 (2)	11.8	0.02 (2)	7.4	1.01 (0.12, 8.39)	−0.64 (−738.79, 87.93)	0 (−0.03, 0.03)
50–64	0.12 (8)	17.8	0.04 (3)	7.0	0.38 (0.08, 1.30)	62.53 (−29.56, 91.79)	0.07 (−0.02, 0.17)
≥65	0.08 (4)	21.1	0.16 (10)	16.7	2.03 (0.68, 7.41)	−103.25 (−640.99, 32.01)	−0.08 (−0.2, 0.04)
All	0.04 (14)	15.7	0.05 (15)	10.6	1.04 (0.50, 2.18)	−3.89 (−117.65, 50.1)	0 (−0.03, 0.03)
PCV13-serotypes							
0–4	0.06 (1)	2.6	0 (0)	0.0	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
5–17	0 (0)	0.0	0 (0)	0.0	-	-	-
18–49	0.03 (4)	11.1	0.02 (3)	15.8	0.76 (0.150, 3.42)	24.52 (−242.4, 85.13)	0.01 (−0.03, 0.05)
50–64	0.25 (17)	30.9	0.07 (5)	16.1	0.29 (0.10, 0.74)	70.61 (25.7, 90.34)	0.18 (0.04, 0.31)

Age group (years)	Pre-PCV10 period		PCV10 period		Pre-PCV10 period vs. PCV10 period		
	Mortality/100,000 person-years (N)	CFP (%)	Mortality/100,000 person-years (N)	CFP (%)	Mortality rate ratio	Relative rate reduction, %	Absolute rate reduction/ 100,000 person-years
≥65	0.12 (6)	13.6	0.05 (3)	12.5	0.41 (0.09, 1.54)	59.35 (−54.08, 91.42)	0.07 (−0.04, 0.17)
All	0.09 (28)	15.6	0.03 (11)	13.3	0.38 (0.18, 0.74)	61.91 (25.62, 81.84)	0.05 (0.02, 0.09)
Non-PCV13 serotypes							
0–4	0 (0)	0.0	0 (0)	0.0	-	-	-
5–17	0 (0)	0.0	0 (0)	0.0	-	-	-
18–49	0.02 (2)	12,5	0.02 (2)	9,5	1.01 (0.12, 8.39)	−0.64 (−738.79, 87.93)	0 (−0.03, 0.03)
50–64	0.09 (6)	16,7	0.02 (1)	3,4	0.17 (0.01, 0.98)	83.35 (2.51, 99.12)	0.07 (0, 0.15)
≥65	0.08 (4)	33,3	0.16 (10)	20,0	2.03 (0.68, 7.41)	−103.25 (−640.99, 32.01)	−0.08 (−0.2, 0.04)
All	0.04 (12)	17,6	0.04 (13)	11,8	1.05 (0.48, 2.34)	−5.04 (−133.53, 52.35)	0 (−0.03, 0.03)
PCV13-PCV10 serotypes (3, 6A, 19A)							
0–4	0 (0)	0,0	0 (0)	0,0	-	-	-
5–17	0 (0)	0,0	0 (0)	-	-	-	-
18–49	0 (0)	0,0	0 (0)	0,0	-	-	-
50–64	0.03 (2)	22,2	0.03 (2)	14,3	1 (0.12, 8.33)	0.07 (−732.9, 88.01)	0 (−0.06, 0.06)
≥65	0 (0)	0,0	0 (0)	0,0	-	-	-
All	0.01 (2)	9,5	0.01(2)	6,5	0.97 (0.12, 8.08)	3.04 (−708.18, 88.37)	0 (−0.01, 0.01)
PPSV23 unique serotypes							
0–4	0 (0)	-	0 (0)	0,0	-	-	-
5–17	0 (0)	0,0	0 (0)	0,0	-	-	-
18–49	0.02 (2)	25,0	0.02 (2)	18,2	1.01 (0.12, 8.39)	−0.64 (−738.79, 87.93)	0 (−0.03, 0.03)
50–64	0.04 (3)	16,7	0.02 (1)	7,1	0.33 (0.02, 2.60)	66.69 (−160.17, 98.35)	0.03 (−0.03, 0.09)
≥65	0.08 (4)	57,1	0.08 (5)	23,8	1.02 (0.27, 4.11)	−1.63 (−310.59, 73.11)	0 (−0.1, 0.1)
All	0.03 (9)	26,5	0.02 (8)	15,7	0.86 (0.32, 2.25)	13.81 (−125.43, 67.64)	0 (−0.02, 0.03)

6 DISCUSSION

6.1 Summary of findings across studies

Our population-based study documented that for almost 20 years, *S. pneumoniae* was the leading cause of bacterial meningitis in Finland, even four years after PCV10 introduction (Study I). Nevertheless, pneumococcus's contribution to the bacterial meningitis burden varied by year and age group. It was the second most common cause of meningitis in young children <2 years of age and the leading cause in adults >50 years of age. The incidence rate of pneumococcal meningitis was 1.4-fold higher in men than women. *S. pneumoniae* was the leading cause of death in bacterial meningitis during the study period and had the second highest case fatality proportion.

The study conducted seven years after the infant PCV10 program introduction revealed a substantial reduction in the burden of pneumococcal meningitis in Finland (Study III). The overall incidence of PCV10 serotype meningitis decreased in vaccine-eligible children and unvaccinated adults. However, a significant disease burden remains in older adults because of an increase in pneumococcal meningitis caused by non-PCV10 serotypes.

The study conducted in Poland described 10-year baseline epidemiologic characteristics of pneumococcal meningitis cases reported to the national surveillance system before the introduction of universal PCV10 vaccination (Study II). The study demonstrated an increasing trend in reported rates of pneumococcal meningitis, primarily among persons >15 years of age. Substantial geographical variation also occurred in the mean pneumococcal meningitis incidence rate. During the study period, PCV10 serotypes caused almost half of all cases and three quarters of cases in children <5 years of age. The average proportion of penicillin-resistant isolates, especially in children <5 years of age, was high.

6.2 Burden of bacterial meningitis, with a particular focus on pneumococcal meningitis, during two decades of surveillance in Finland

Our study confirmed that most of the bacterial meningitis burden over 20 years was attributable to *S. pneumoniae* and *N. meningitidis*. However, the overall incidence of both pathogens decreased significantly during the study period.

The annual pneumococcal meningitis rates fluctuated from 0.55 to 0.61 cases per 100,000 population before PCV10 introduction and decreased to 0.41 shortly after PCV10 introduction in 2011–2014. The timing of the reduction and change in causative serotypes suggested PCV10 influence. A study conducted seven years after vaccine introduction confirmed a significant vaccine impact.

Interestingly, the observed decline in the overall incidence was greatest in meningococcal meningitis despite no routine meningococcal vaccination program. During the study period, serogroup B was dominant in Finland. This serogroup has circulated largely in Europe, Australia, and the Americas [198,199]. Similar decreases in the incidence of meningitis caused by *N. meningitidis* serogroup B in the absence of the vaccination were observed in other countries, such as the Netherlands and the USA [200–202]. The reasons for this decline are unclear. It might be related to changes in environmental and behavioral factors, such as smoking prohibition in public places. However, the concurrent increase observed in other meningococcal serotypes does not support this explanation. Other possible reasons include population immunity to circulating strains and a natural cyclical pattern of meningococcal serogroup distribution [203,204]. In addition, the impact of quadrivalent vaccine use on military recruits in Finland is uncertain, as no relevant research exists.

The burdens of *H. influenzae*, *L. monocytogenes*, and *S. agalactiae* did not change significantly over the 20 years. The conjugate vaccination program against *H. influenzae* type b was introduced in Finland as early as 1986 and practically eliminated meningitis caused by vaccine type *H. influenzae* [205]. The study indicates that vaccine impact remained during the study period, with only two cases of meningitis caused by vaccine type. Moreover, no strong signals for serotype replacement have occurred in meningitis cases. Similar findings were observed in other countries with established HiB vaccination programs and high vaccination coverage [5,206]. *S. agalactiae* was the most common cause of meningitis in young children <2 years of age (median age of cases = 0 years). Since a vaccine against group B Streptococcus is still in the phase two clinical trial, the only available

prevention strategy involves screening and intrapartum antimicrobial prophylaxis [207]. Nevertheless, this control measure is ineffective for late-onset infections in infants.

The common observation for *L. monocytogenes*, *N. meningitidis*, and *S. pneumoniae* was that higher incidence rates were reported in men compared to women. While the reasons are unknown, they may be related to the higher prevalence of underlying conditions (e.g., liver diseases, including alcoholic cirrhosis) and behavioral factors (e.g., smoking and alcoholism) among men [208,209].

The case fatality proportion for overall bacterial meningitis did not differ significantly between 2004–2009 and 2010–2014. This might be related to the shift in the mean age of cases to older age groups. Older age is associated with a higher prevalence of comorbid conditions and a worse prognostic [210]. *S. pneumoniae* was the most common cause of death in adults and had the second highest CFP (12%) after *L. monocytogenes* (22%). Interestingly, seven years after PCV10 introduction, the mortality rate and case fatality proportion were reduced among pneumococcal meningitis cases.

6.3 Impact of infant PCV10 vaccination on pneumococcal meningitis in Finland

The national surveillance data analysis seven years after PCV10 introduction revealed a substantial impact of the vaccination program on pneumococcal meningitis morbidity and mortality. The incidence of PCV10 serotype meningitis in all age groups decreased by 68%, which resulted in a 27% reduction in the overall PM incidence. In vaccine-eligible children <5 years of age, a 64% and an 87% reduction in the overall and PCV10 serotype incidence, respectively, was observed. In 2017, no PCV10 serotype meningitis cases were reported. Serotype 6A pneumococcal meningitis incidence was low and did not change after PCV10 introduction. The findings also suggest substantial indirect effects of vaccination since incidence rates of meningitis caused by PCV10 serotypes decreased in vaccinated children and non-vaccinated adults. In persons 18–49 and 50–64 years of age, the rates decreased by 63%. Despite the decline in PCV10 serotype incidence, no significant decrease in overall PM incidence in persons ≥65 years of age was observed after vaccine introduction. This was related to the serotype replacement by non-PCV10 serotypes observed in this age group.

During the PCV10 period, no pneumococcal meningitis deaths occurred in children. In older adults 50–64 years of age, the pneumococcal mortality rate was reduced by 74% and the case fatality proportion by 15%. This reduction was mostly due to significantly fewer deaths caused by PCV10 serotypes.

Comparing our findings with other populations is difficult due to differences in the baseline serotype distribution of meningitis cases, use of different PCVs, and potential secular trends. However, the magnitude of the overall effect was comparable to those of other European countries using PCV13 (a decrease of approximately 25%–48% in the general population and approximately 60%–70% in children <5 years of age) [13,166,211].

Decreases in mortality attributable to pneumococcal meningitis were also observed in other countries after the introduction of PCV10 or PCV13 vaccination [172,212]. The explanation might be the lower invasive potential of the remaining pneumococcal serotypes and changes in the clinical practice, such as the use of adjunctive dexamethasone therapy [116].

6.4 Serotype replacement in pneumococcal meningitis after PCV10 introduction in Finland

The 54% increase in the overall incidence of non-PCV10 serotypes seven years after vaccine introduction suggests serotype replacement. The increase was particularly prominent in adults ≥65 years of age (157%), resulting in no net impact of PCV10 on the disease burden in this age group. Overall, the main replacement serotypes during the vaccination period (2011–2017) were 19A and 6C, although the increases varied by age group. In the final study year (2017), non-PCV10 serotypes 22F, 6C, and 23A caused most PM cases.

Our observations are consistent with recent reports from other settings with mature PCV10/13 programs, where non-vaccine serotypes have increased and become the most common cause of meningitis [213]. In PCV10-using settings, the top serotypes causing meningitis were 19A, 6C, and 3 [14]. Although early studies indicated potential cross-protection of 19F for 19A in PCV10-using settings, recent studies do not support these findings. In contrast, our study and other recent studies suggest vaccine-induced serotype replacement in PCV10 settings such as Brazil, Austria, Canada, and Belgium [162,214–216]. Serotype 6C has also been found as an emerging serotype in PCV10 settings [14]. It is especially concerning, as this serotype appeared to be more often non-susceptible to tetracycline and erythromycin than

other serotypes [217,218]. In PCV13 settings, no increases in serotype 6C have been reported, probably due to the cross-protection from 6A included in PCV13 [214]. Interestingly, we did not observe an increase in serotype 3 PM, although it was found to be one of the leading replacement serotypes in IPD cases in Finland [219] and other PCV10/13-using sites. This might be related to the small number of meningitis cases caused by this serotype before PCV10 introduction.

The mechanism of serotype replacement is not entirely understood. The change in the serotype distribution may be related to filling the ecological niche created by the disappearance of vaccine serotypes due to host immunity or capsular switching [220]. According to a hypothesis called "Red Queen," streptococcus rapidly adapts to changes in human immunity shortly after PCV vaccination and increases its serotype diversity. This is followed by a decrease in the diversity within the next three to five years and dominance of nonvaccine serotypes that were at low levels before vaccine introduction [221].

6.5 Comparing the effects of PCV10 pediatric vaccination on pneumococcal meningitis and invasive pneumococcal disease in Finland

Studies conducted three, six, and nine years after the introduction of PCV10 into Finland's national immunization program have documented a substantial impact of vaccination on invasive pneumococcal disease (bacteremic pneumonia, bacteremia, and meningitis) burden in adults and children. In vaccine-eligible children, the vaccination resulted in a reduction of 79% in overall IPD incidence and 94% in IPD caused by PCV10 serotypes [196,219,222]. However, vaccine impact on pneumococcal meningitis was smaller and amounted to a 64% and an 87% reduction of overall and PCV10 serotypes incidence, respectively (Study III).

In adults ≥18 years, contrary to meningitis incidence rates, IPD ones were increasing before PCV10 introduction [219]. Nine years after vaccine implementation, the observed incidence rate of PCV10 serotype IPD, after adjustment for the pre-PCV10 trend, was 90% lower than the expected rate without the PCV program. The overall IPD incidence was estimated to be 30% lower [219]. This compares to a reduction of approximately 65% in PCV10 serotype PM incidence and 30% in overall PM incidence in adults.

The estimated smaller impact of vaccination on PCV10 type PM could be related to the different and more diverse serotype distribution before PCV10 introduction

and potentially higher invasiveness of some non-vaccine serotypes for meningitis compared to other clinical presentations [9,166]. The observed changes in non-vaccine serotype rates support this hypothesis. The incidence of IPD caused by non-PCV10 serotypes in vaccine-eligible children increased by 85% within three years and 53% within six years of PCV10 introduction, although the absolute numbers were small [177,196]. This compares to a 143% increase in non-PCV10 type pneumococcal meningitis seven years after vaccine introduction. The difference was even more pronounced in adults ≥65 years of age, with a 70% increase in NVT for IPD and 157% for meningitis [219]. The increases were driven by serotypes 3, 19A, and 22F for IPD and serotypes 19A, 6C, and 23A for meningitis.

Although the differences in the PCV used in the vaccination program limit comparability, a more substantial reduction in the disease incidence of non-meningitis compared to meningitis was also observed in other studies. In Israel, PCV7/PCV13's impact was smaller in overall meningitis than non-meningitis, especially in children ≤2 years of age [168]. In Germany, after PCV10/PCV13 introduction, a more pronounced incidence reduction in children was also observed for non-meningitis compared to meningitis, particularly in children <2 years of age [169]. For these two studies, researchers suggested that meningitis cases were younger than non-meningitis cases and that the proportion of non-vaccine serotypes was higher for meningitis before PCV introduction [168,169]. The lower age of meningitis cases could be related to the higher prevalence of underlying conditions and lower vaccine effectiveness in these patients. Our study could not assess these questions because clinical and risk factor data were unavailable.

6.6 Summary of the baseline epidemiology of pneumococcal meningitis before PCV10 introduction in Poland

In Poland, as in other countries, the highest pneumococcal meningitis incidence rates were reported in young children and older adults. Although the incidence rates were lower in the working-age population, they contributed to the highest number of cases. The overall incidence rate ranged from 0.21 cases per 100,000 population in 2005 to 0.47 in 2015, with substantial geographical differences between reported rates within the country (up to three-fold). Although incidence rates were increasing, the observed overall and age-specific incidence rates of pneumococcal meningitis were considerably lower than those reported in other high-income countries, such

as Finland [192] and the Netherlands [223], before PCV10 introduction. The difference was largest among older adults.

Low overall pneumococcal meningitis rates suggest considerable underreporting and underascertainment of cases, particularly in adults. Substantially lower incidences, compared with other EU countries, were also observed for invasive pneumococcal disease (in 2014, the overall IPD incidence in Poland was 1.9 cases per 100,000 population vs. an average of 4.8 in the EU) [224]. Underreporting is likely related to low surveillance sensitivity, especially in some regions of the country. Underascertainment of cases might be related to frequent administration of antimicrobials immediately after diagnosis and thus negative culture results [191]. Nonetheless, underascertainment of meningitis cases was less pronounced than in bacteremia/sepsis cases. The ratio of meningitis cases to all IPD is much higher in Poland than in other countries with better surveillance (approximately 30% vs. 6%–10%), which indicates insufficient blood culturing practices [191]. The observed increasing trend in meningitis incidence likely reflects changes in the surveillance system during the study period. Since 2010, data from two surveillance systems have been matched, resulting in more identified cases. However, the effect of secular trends cannot be excluded.

The overall case fatality proportion of pneumococcal meningitis was 20%, ranging from 4% in children <1 year of age to 31% in adults ≥65. The observed CFPs were almost two-fold higher than in Finland before PCV10 introduction. Again, this finding might be associated with insufficient surveillance and bias due to more frequent reporting of severe cases, with a higher mortality risk.

The most common serotypes were 3, 19F, 14, and 23F. In vaccine-eligible children <5 years of age, the most common were serotypes 14, 19F, 6B, and 23F. The highest case fatality proportions for serotypes identified at least 20 times during the study period were for 14, 19F, 6B, and 23F. PCV10 serotypes were responsible for 46% of all pneumococcal meningitis cases and 75% among children <5 years of age. Notably, the overall proportion of PCV10 serotypes decreased from 52% in 2008–2011 to 41% in 2012–2015 without a routine vaccination program. The decline was more profound in children <5 years of age, from 87% to 57%, respectively.

The potential PCV10 vaccine coverage during the baseline period was comparable to those of other countries before they introduced PCV, accounting for 62%–72% of meningitis cases in children <5 years of age [14]. The 2012–2015 decline in the proportion of PCV10 serotypes cannot be explained by vaccine use in the private sector or risk groups, as the estimated vaccine coverage was <1% [225]. This change was probably associated with secular trends, and indeed, the proportion

of non-PCV10 serotypes increased from 13% to 43%, mostly due to serotypes 19A and 23B.

Our study also demonstrated the vital role of PCV13 unique serotypes in the overall burden of pneumococcal meningitis. Serotype 3 was most prevalent in adults, and serotype 19A has become more common in recent years, which suggests a potential benefit of introducing a higher-valent vaccine. However, this should be interpreted cautiously. Recent studies indicate lower vaccine effectiveness against serotype 3 in mature PCV13 programs with high vaccination coverage than for other vaccine serotypes [127,130,226]. A possible explanation is the distinct features of serotype 3, such as the bountiful production of capsules and surface electronegativity [227,228]. In addition, immunotolerance after repeated vaccination is considered [229]. The herd effect in adults is also unclear, with some studies observing no impact of the PCV13 on this serotype in the non-vaccinated population [14], most likely due to no effect of the vaccine on the nasopharyngeal carriage [230]. In PCV13-using settings, serotype 19A was rarely identified as the cause of meningitis [14]. However, concerning serotype 3, in some studies, PCV13 vaccine effectiveness against this serotype was lower than for other vaccine serotypes [231]. It was the most commonly reported vaccine failure [231].

Reported levels of resistance to penicillin were concerning. Over a quarter of all isolates and half of isolates in children <5 years of age were resistant to penicillin. Most penicillin-resistant isolates were caused by serotypes 19A, 9V, 19F, and 14, targeted by the PCV13 vaccine. The observed prevalence of resistance was comparable to the average for IPD isolates in European countries [232]. Serotypes 19A, 14, and 19F were also associated with resistance in other countries [233]. Several studies have revealed that PCV introduction reduced the nasopharyngeal carriage of penicillin-resistant strains and the disease burden caused by those serotypes [234,235].

6.7 Considerations for evaluating the PCV10 vaccination program in Poland

One should consider several factors when assessing the impact of PCV10 vaccination program introduction in Poland. First, the previously described limitations of the surveillance system should be formally evaluated, especially as the new electronic-based reporting replaced paper-based reports. Second, because of underreporting, the relatively low observed rates will result in a smaller reduction in

the absolute number of cases compared to other European countries, which may affect the health and economic benefits estimated in the cost-effectiveness analysis of the vaccination program. In addition, due to the increasing trend before PCV introduction, the choice of the analytical method might affect the estimated vaccine impact and indirect effects. Before-after analysis will be characterized by smaller differences in observed and expected incidence rates and smaller or no indirect effects since pre-vaccine trends may be averaged out. In the Polish context, the method of choice might be interrupted time series (ITS) analysis, where the increased trend in the baseline period can be adjusted for [196,219].

Finally, secular trends in the circulating serotypes should also be considered when evaluating the vaccination's impact on serotype distribution and potential serotype replacement. This should be especially highlighted for serotype 19A.

6.8 Strengths and limitations of the studies

A major strength of all studies in this dissertation was the use of nationwide population-based surveillance data from Finland and Poland. Finland's laboratory-based electronic surveillance system allows near-complete case ascertainment and serotyping of pneumococcal meningitis isolates at the THL reference laboratory. Moreover, including pneumococcal meningitis cases based on hospital discharge data and positive blood culture increased the sensitivity of case identification.

However, findings from those studies should be interpreted considering potential limitations. First, a passive surveillance system in Poland likely led to the underreporting of pneumococcal meningitis cases. Second, including only CSF culture-confirmed cases in the analysis, potentially underestimating the number of cases. Furthermore, the changes in the surveillance system from matching cases from passive and laboratory surveillance could affect the trends in reported cases. In Finland, the design of the observational before-after study to assess the impact of the vaccination is susceptible to potential bias due to secular trend, potential changes in clinical practices, and the prevalence of risk factors. In addition, we had no individual vaccination records. However, no significant changes in meningitis case ascertainment occurred, and contrary to the incidence of bloodstream infection, no increasing trend in the incidence of pneumococcal meningitis was observed before PCV implementation [193]. We thus did not adjust for trend in our analysis. Due to a lack of clinical data in our studies, we could not account for the effects of potential changes in treatment practices or the prevalence of underlying diseases. Finally, the

analysis of case fatality proportions and mortality rates may have been influenced by the cause of death data being unavailable. However, other studies have revealed that most deaths due to meningitis occur within 14 days; we therefore assumed that they are attributable to pneumococcal meningitis [236].

6.9 Conclusions

For over two decades, *Streptococcus pneumoniae* was the leading bacterial cause of meningitis in Finland. It is also one of the most severe forms of bacterial meningitis. The use of infant PCV10 immunization had a significant role in reducing the burden of pneumococcal meningitis. Vaccination provided significant direct and indirect protection for vaccine type meningitis and associated mortality. However, because of the serotype replacement by non-PCV10 serotypes, a substantial disease burden remains in older adults.

In Poland, the baseline epidemiology of pneumococcal meningitis suggests reasonable PCV10 serotype coverage and potential benefits of reducing antimicrobial non-susceptibility. Nonetheless, the identified limitations of the surveillance system may hinder future vaccine evaluation studies.

Our studies suggest that the 13-valent conjugate vaccine might have a higher serotype coverage than PCV10, especially in older adults. However, as discussed earlier, this should be interpreted cautiously due to reports of limited vaccine effectiveness and duration of protection against serotype 3 [231]. In addition, vaccination of older adults with PCV13 has not been found cost-effective [237].

The dynamic serotype replacement of *S. pneumoniae* poses challenges for effective vaccination strategies, especially in the long term. Continuous surveillance is essential during pre-vaccination and after vaccine introduction to monitor trends and assess candidate serotypes in future PCVs in development.

6.10 Future directions

Due to the observed shift into non-vaccine serotypes, new vaccination strategies with expanded serotype coverage have been developed. The recently licensed PCV15 and PCV20 formulation protects children and adults against up to seven additional serotypes that were found to be associated with high prevalence, antibiotic resistance, heightened disease severity, and invasive potential [238]. In mature

PCV10/13 settings, PCV20 serotypes constituted over half of the remaining pneumococcal meningitis [14]. In Finland, 50% of all isolates in adults 50–64 and ≥65 years of age in the last study year were serotypes in PCV20. In the two youngest age groups, no cases were caused by these serotypes before PCV10 introduction or in the last year. Additional studies are thus needed to assess the potential benefits and cost-effectiveness of higher-valency vaccines.

Based on relevant data and experience with the PCV7/10/13 programs, *S. pneumoniae*, in response to the introduction of higher-valency conjugate vaccines, might continue its evolution and develop selective advantages over new replacing serotypes. Alternative prevention approaches are therefore needed. These include protein-based vaccines targeting different potential surface proteins, such as protein A or C or pneumolysin, or even whole-cell vaccines containing killed or live attenuated pneumococci [239,240]. Although promising, both methods are at the early stages of clinical development.

In summary, despite efforts to combat pneumococcus, it will continue challenging the next generation of epidemiologists and public health microbiologists. However, this should not prevent the current generation from establishing an ambitious goal: defeating meningitis. New vaccines should be effective and affordable, as the highest burden of meningitis is in low-income countries. This is reflected in the WHO's "Defeating Meningitis by 2030" global road map, which defines the plan to tackle the leading causes of bacterial meningitis, including pneumococcal meningitis [241]. I can only hope that this dream comes true.

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Bacterial meningitis in Finland, 1995–2014: a population-based observational study

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ABSTRACT

Objectives Bacterial meningitis remains an important cause of morbidity and mortality worldwide. Its epidemiological characteristics, however, are changing due to new vaccines and secular trends. Conjugate vaccines against *Haemophilus influenzae* type b and *Streptococcus pneumoniae* (10-valent) were introduced in 1986 and 2010 in Finland. We assessed the disease burden and long-term trends of five common causes of bacterial meningitis in a population-based observational study.

Methods A case was defined as isolation of *S. pneumoniae*, *Neisseria meningitidis*, *Streptococcus agalactiae*, *Listeria monocytogenes* or *H. influenzae* from cerebrospinal fluid and reported to national, population-based laboratory surveillance system during 1995–2014. We evaluated changes in incidence rates (Poisson or negative binomial regression), case fatality proportions (χ^2) and age distribution of cases (Wilcoxon rank-sum).

Results During 1995–2014, *S. pneumoniae* and *N. meningitidis* accounted for 78% of the total 1361 reported bacterial meningitis cases. *H. influenzae* accounted for 4% of cases (92% of isolates were non-type b). During the study period, the overall rate of bacterial meningitis per 1 00 000 person-years decreased from 1.88 cases in 1995 to 0.70 cases in 2014 (4% annual decline (95% CI 3% to 5%). This was primarily due to a 9% annual reduction in rates of *N. meningitidis* (95% CI 7% to 10%) and 2% decrease in *S. pneumoniae* (95% CI 1% to 4%). The median age of cases increased from 31 years in 1995–2004 to 43 years in 2005–2014 (p=0.0004). Overall case fatality proportion (10%) did not change from 2004 to 2009 to 2010–2014.

Conclusions Substantial decreases in bacterial meningitis were associated with infant conjugate vaccination against pneumococcal meningitis and secular trend in meningococcal meningitis in the absence of vaccination programme. Ongoing epidemiological surveillance is needed to identify trends, evaluate serotype distribution, assess vaccine impact and develop future vaccination strategies.

Strengths and limitations of this study

- ► This study describes the epidemiological characteristics of >1300 cases of bacterial meningitis reported to national surveillance during 20 years in Finland.
- ► The study provides clinically important information on the changing distribution of pathogens and age of cases.
- ► The study documents the sustained population impact of infant conjugate vaccination against *Haemophilus influenzae* type b; and introduction of 10-valent pneumococcal conjugate vaccination on reducing the burden of bacterial meningitis, as well as decline in meningococcal meningitis due to secular trend. As the data were from laboratory-based surveillance system, clinical information such as severity or treatment was not available.
- ► Incidence rate of bacterial meningitis may be underestimated since cases diagnosed by PCR or antigen detection and culture-negative meningitis cases diagnosed based on clinical symptoms and findings were not included in the dataset.

INTRODUCTION

Despite the availability of vaccines, antibiotics and advances in intensive care, bacterial meningitis remains an important cause of morbidity and mortality worldwide. Persistent neurological sequelae including hearing loss, neuropsychological impairment or seizures are reported in 10%–30% of survivors.[1] The case fatality proportion (CFP) ranges from 5% to 30% for different bacteria.[2 3]

Globally, *Streptococcus pneumoniae*, *Neisseria meningitidis* and *Haemophilus influenzae* are the most important causes of bacterial meningitis, particularly in young children.[4 5] Among neonates, the most common cause of bacterial meningitis is *S. agalactiae*,[2 6] while *Listeria monocytogenes* is important in newborns and elderly persons with comorbidities.[7] However, the leading organisms causing bacterial meningitis vary by age of the patient, time and geographical location.[5] As the choice of empirical antimicrobial treatment for bacterial meningitis should be based on local epidemiology, patient's age, presence of risk factors and regional resistance patterns,[8–10] population-based

surveillance data are important to help in formulating clinical guidelines.

The introduction of effective protein conjugate vaccines against *H. influenzae* type b (Hib), *S. pneumoniae* and *N. meningitidis* has changed the epidemiology of bacterial meningitis in many countries.[11 12] In Finland, universal vaccination against Hib since 1986 resulted in rapid elimination of the disease[13] and introduction of the 10-valent pneumococcal conjugate vaccine (PCV10) in September 2010 has resulted in substantial reduction in vaccine-type invasive disease.[14 15] Meningococcal conjugate vaccines (MCVs) have not been introduced into Finnish National Vaccination Programme (NVP). However, meningococcal polysaccharide vaccine has been offered to military conscripts since 1982.

To provide information for developing future prevention strategies and to help in formulating clinical guidelines, we conducted a population-based observational study to determine the contribution of specific pathogens to the total bacterial meningitis disease burden and to assess long-term trends in the incidence of common aetiologies in Finland during 1995–2014.

MATERIALS AND METHODS

Data sources

Since 1995, all clinical microbiology laboratories in Finland have had legal obligation to report microbial isolations from blood and/or cerebrospinal fluid (CSF) to the National Infectious Diseases Register (NIDR)—a population-based, electronic laboratory surveillance system maintained by the National Institute for Health and Welfare (THL). Routinely collected information include the microbe, specimen date, date of birth, sex, place of residence and unique Personal Identity Code (PIC). For blood or CSF findings concerning *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes* or *H. influenzae*, multiple notifications with the same PIC and microbe are merged into one case if they occurred within 3 months of the first notification. Since 2004, information on vital status after episode is routinely obtained from the Population Information System. All clinical microbiology laboratories also submit isolates from reported cases to THL reference laboratories for species verification and characterisation of the isolates including serotyping or serogrouping. Since 2004, serotyping results are linked to NIDR notifications by using the PIC. Antimicrobial susceptibility data were not available.

Case definitions

We defined a case of bacterial meningitis as isolation of *S. pneumoniae*, *S. agalactiae*, *N. meningitidis*, *L. monocytogenes* or *H. influenzae* from CSF and notified to NIDR from 1995 through 2014.

For cases reported during 2004–2014, we calculated the pathogen-specific 30-day CFP as number of cases resulting in death within 30 days from the first positive CSF culture, divided by all cases.

We calculated the proportions of *S. pneumoniae*, *N. meningitidis* and *H. influenzae* cases due to vaccine-preventable serotypes/serogroups during 2004–2014. Serotypes covered in PCV10 are the following: 1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F; the 13-valent PCV13 adds serotypes 3, 6A and 19A. Vaccine-preventable meningococcal serogroups include those in the quadrivalent MCV (MCV-4, A, C, W and Y) and serogroup B isolates targeted by novel protein-based vaccines (MenB). For *H. influenzae*, type b was considered vaccine preventable.

Statistical analysis

By using data from the Population Information System as denominators, we calculated pathogen-specific and age-specific annual incidence rates. Poisson regression was used to test for log-linear trend in rates of bacterial meningitis during 1995–2014. Incidence rate ratios (IRRs), their 95% CI and p values for yearly changes were calculated using time (year) as a continuous explanatory variable in the Poisson model. When appropriate, we used negative binomial regression to correct for overdispersion of data. To compare age distribution of cases across years, we used Wilcoxon rank-sum test. To assess changes in CFP, we used χ^2 analyses; p value <0.05 was considered statistically significant. All analyses were done with STATA version 13 and Microsoft Excel 2013.

Ethical considerations

Data used in the analysis were collected as a part of national routine surveillance which falls under the existing mandate of THL. No formal Institutional Review Board review was required for this study. Personal identifiers were removed after linkage with vital status data.

RESULTS

Overall incidence rates of bacterial meningitis

From 1995 to 2014, 1361 cases of bacterial meningitis caused by *S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, *L. monocytogenes* or *H. influenzae* were reported (mean incidence rate, 1.29 cases/100 000 person-years, table 1). *S. pneumoniae* and *N. meningitidis* were the most common aetiologies accounting for 78% (1061/1361) of cases. The median age of cases increased from 31 years in 1995–2004 to 43 years in 2005–2014 (p=0.0004). Rates were higher in men than women (1.52 vs 1.07 cases/100 000 person-years; IRR 1.4, 95% CI 1.3 to 1.6)).

The mean annual rates of all bacterial meningitis ranged from 1.97 in 1996 to 0.70 cases/100 000 person-years in 2014, with an annual decrease of 4% (95% CI −3% to −5%, table 1). During 2004–2014, 65 patients died within 30 days from culture (CFP, 10% (65/633)). There was no change in 30-day CFP from 2004–2009 (11% (43/402) to 2010–2014 (10% (22/231), p=0.22.

Characteristic of bacterial meningitis by age group

Children <2 years of age accounted for 20% of cases (268/1361) and had the highest incidence rate (11.38 cases/100 000 person-years, table 1). The most common

Table 1 Number of cases (n), incidence rates per 100 000 person-years (IR) and mean annual relative change in incidence of bacterial meningitis, according to age group (years), Finland, 1995–2014

	1995–1999		2000–2004		2005–2009		2010–2014		1995–2014		1995–2014	
	n	IR	n	IR	n	IR	n	IR	n	IR	% change*	95% CI
Streptococcus pneumoniae												
<2	26	4.32	25	4.43	18	3.05	14	2.33	83	3.52	−4	−7 to 0
2–4	6	0.63	3	0.35	6	0.69	3	0.33	18	0.50	−1	−8 to 7
5–17	13	0.31	11	0.26	7	0.17	2	0.05	33	0.20	−7	−13 to 1
18–49	59	0.50	54	0.48	35	0.32	30	0.27	178	0.40	−4	−6 to 1
50–64	41	0.91	52	1.00	56	0.99	37	0.65	186	0.88	−2	−4 to 1
≥65	25	0.67	23	0.57	39	0.89	26	0.51	113	0.66	−1	−4 to 2
All age groups	170	0.55	168	0.65	161	0.61	112	0.41	611	0.58	−2	−4 to 1
Neisseria meningitidis												
<2	23	3.83	23	4.07	8	1.36	14	2.33	68	2.89	−4	−8 to 0
2–4	19	1.98	11	1.27	12	1.38	6	0.66	48	1.33	−6	−10 to −1
5–17	37	0.88	16	0.38	24	0.60	7	0.18	84	0.52	−8	−14 to −3
18–49	93	0.79	46	0.41	42	0.38	14	0.13	195	0.43	−10	−13 to −8
50–64	15	0.33	15	0.29	7	0.12	2	0.04	39	0.18	−12	−17 to −6
≥65	6	0.16	3	0.07	4	0.09	3	0.06	16	0.09	−7	−14 to 2
All age groups	193	0.62	114	0.44	97	0.37	46	0.17	450	0.43	−9	−10 to −7
Haemophilus influenzae												
<2	4	0.67	3	0.53	2	0.34	1	0.17	10	0.42	−7	−17 to 4
2–4	0	0.00	3	0.35	0	0.00	0	0.00	3	0.08	NA	NA
5–17	5	0.12	4	0.10	0	0.00	2	0.05	11	0.07	−8	−17 to 3
18–49	4	0.03	2	0.02	2	0.02	6	0.05	14	0.03	5	−5 to 15
50–64	3	0.07	3	0.06	2	0.04	2	0.04	10	0.05	−3	−13 to 8
≥65	2	0.05	0	0.00	7	0.16	1	0.02	10	0.06	1	−9 to 12
All age groups	18	0.06	15	0.06	13	0.05	12	0.04	58	0.06	−2	−7 to 2
S. agalactiae												
<2	25	4.16	24	4.25	32	5.43	25	4.16	106	4.50	0	−3 to 5
2–4	1	0.10	0	0.00	0	0.00	0	0.00	1	0.03	NA	NA
5–17	0	0.00	1	0.02	0	0.00	0	0.00	1	0.01	NA	NA

Continued

Table 1 Continued

	1995–1999		2000–2004		2005–2009		2010–2014		1995–2014		1995–2014	
	n	IR	n	IR	n	IR	n	IR	n	IR	% change*	95% CI
18–49	2	0.02	1	0.01	1	0.01	2	0.02	6	0.01	1	−12 to 16
50–64	4	0.09	2	0.04	7	0.12	3	0.05	16	0.08	1	−9 to 8
≥65	0	0.00	7	0.17	1	0.02	3	0.06	11	0.06	−2	−11 to 9
All age groups	32	0.10	35	0.13	41	0.15	33	0.12	141	0.13	0	−3 to 3
Listeria monocytogenes												
<2	1	0.17	0	0.00	0	0.00	0	0.00	1	0.04	NA	NA
2–4	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	NA	NA
5–17	1	0.02	0	0.00	0	0.00	0	0.00	1	0.01	NA	NA
18–49	9	0.08	3	0.03	0	0.00	3	0.03	15	0.03	−11	−19 to −3
50–64	10	0.22	3	0.06	6	0.11	4	0.07	23	0.11	−6	−13 to 1
≥65	14	0.37	13	0.32	13	0.30	21	0.42	61	0.35	0	−4 to 4
All age groups	35	0.11	19	0.07	19	0.07	28	0.10	101	0.10	−2	−5 to 1
Total bacterial meningitis												
<2	79	13.14	75	13.28	60	10.18	54	8.99	268	11.38	−2	−4 to 1
2–4	26	2.71	17	1.97	18	2.07	9	0.98	70	1.94	−5	−10 to 0
5–17	56	1.33	32	0.77	31	0.77	11	0.28	130	0.80	−8	−12 to −4
18–49	167	1.43	106	0.94	80	0.73	55	0.50	408	0.91	−7	−8 to −5
50–64	73	1.63	75	1.44	78	1.37	48	0.84	274	1.30	−4	−6 to −2
≥65	47	1.25	46	1.15	64	1.46	54	1.07	211	1.23	−1	−4 to 1
All age groups	448	1.45	351	1.35	331	1.25	231	0.85	1361	1.29	−4	−3 to −5

*Mean annual relative change in incidence calculated by Poisson regression or negative binomial regression.
NA, not applicable.

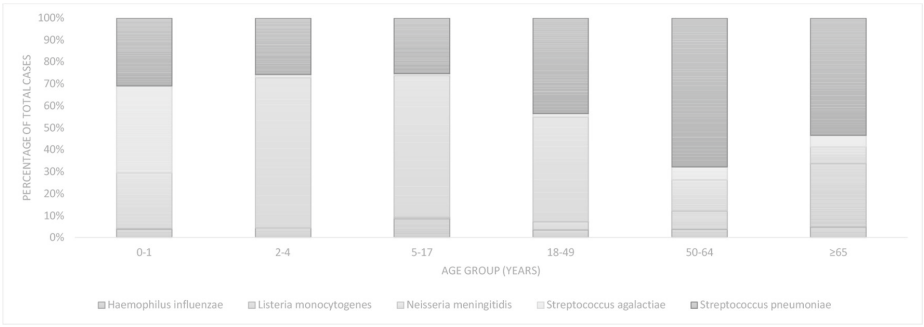

Figure 1 Proportions of bacterial meningitis cases caused by five pathogens according to age group, Finland, 1995–2014.

pathogens in this age group were *S. agalactiae* (4.50 cases/100 000 person-years) and *S. pneumoniae* (3.52 cases/100 000 person-years, figure 1). From 1995 to 2014, the rate of bacterial meningitis in this age group decreased by 2% annually (95% CI −4% to −1%, table 1). The average 30-day CFP in 2004–2014 was 2% (3/140). In children 2–4 years of age, 70 cases (5%) of bacterial meningitis were reported during 1995 to 2014 (1.94 cases/100 000 person-years). The most common pathogens in this age group were *N. meningitidis* (1.33 cases/100 000 person-years) and *S. pneumoniae* (0.50 cases/100 000 person-years, table 1). During the study period, the rate of all meningitis did not change significantly (table 1). The 30-day CFP in 2004–2014 was 14% (4/128); all four deaths were due to *N. meningitidis*.

Children 5–17 years of age accounted for 130 cases (9%) of bacterial meningitis and had the lowest rate (0.80 cases/100 000 person-years, table 1). *N. meningitidis* and *S. pneumoniae* were the main causes (0.52 and 0.20 cases/100 000 person-years, respectively, figure 1). From 1995 to 2014, the rate of bacterial meningitis decreased by 8% annually (95% CI −12% to −4%, table 1). The 30-day CFP was 7% (3/45); all three fatal cases were due to *N. meningitidis*.

Adults 18–49 years of age accounted for 408 cases (30%) of bacterial meningitis (0.91 cases/100 000 person-years, table 1). *N. meningitidis* and *S. pneumoniae* caused most of the cases (figure 1), with incidence rates 0.43 and 0.40 cases/100 000 person-years, respectively. During 1995–2014, the overall rate decreased by 7% annually (95% CI −8% to −5%, table 1). The 30-day CFP was 8% (13/152), with nine deaths due to *S. pneumoniae* infection.

Among persons 50–64 years of age, there were 274 cases (20%) of bacterial meningitis (1.30 cases/100 000 person-years, table 1), of which 186 cases (68%) were caused by *S. pneumoniae* (0.88 cases/100 000 person-years, figure 1). During the study period, the overall rate decreased by 4% annually (95% CI −6% to −2%, table 1). The 30-day CFP was 13% (18/143), with most fatal cases attributable to *S. pneumoniae* (16 deaths).

In adults ≥65 years of age, there were 211 cases (15%) of bacterial meningitis (1.23 cases/100 000 person-years, table 1). *S. pneumoniae* caused 53% (113/211) of the cases (0.66 cases/100 000 person-years), followed by *L. monocytogenes*. There was no significant change in the overall rate during 1995–2014 (table 1). This age group had the highest 30-day CFP (19%, 24/125). Half of the fatal cases were due to *S. pneumoniae* (12 deaths); *L. monocytogenes* caused 10 deaths.

Causes of bacterial meningitis

Streptococcus pneumoniae

From 1995 to 2014, 611 cases of pneumococcal meningitis were reported. Median age was 48 years; 57% of cases were male (male to female IRR, 1.4 95% CI 1.2 to 1.6, table 2). The overall annual rate per 100 000 person-years decreased from 0.70 in 1995 to 0.26 in 2014 (figure 2), a 2% annual decrease (95% CI −4% to −1%, table 1).

The incidence of pneumococcal meningitis decreased annually by 4% (95% CI −7% to 0%), 7% (95% CI −13% to −1%) and 4% (95% CI −6% to −1%) in age groups <2 years, 5–17 years and 18–49 years, respectively. During 2004–2014, *S. pneumoniae* accounted for 58% (38/65) of fatal cases (30-day CFP 12%, 38/308).

Of the 308 pneumococcal meningitis cases reported during 2004–2014, information on serotype was available for 296 (96%). The proportion of cases caused by PCV10 serotypes decreased from 61% (35/57) in 2004–2005 to 15% (9/36) in 2013–2014. PCV13 serotypes accounted for 70% (40/57) cases in 2004–2005 and 44% (16/36) in 2013–2014. In children less than 2 years, proportion of meningitis cases caused by PCV10 serotypes decreased from 75% (9/12) in 2004–2005 to 20% (1/5) in 2013–2014. In 2014, no meningitis cases were caused by PCV10 serotypes.

Neisseria meningitidis

During the study period, meningococcal meningitis accounted for 450 cases (0.43 cases/100 000 person-years) (table 1). Median age was 18 years and 60% of cases were male (male to female IRR 1.5, 95% CI 1.3 to 1.9, table 2). The overall annual incidence per 100 000 person-years decreased from 0.88 in 1995 to 0.07 in 2014; the annual decrease was −9% (95% CI −7% to −10%, table 1). The decline occurred in all age-groups except in <2 years

Table 2 Characteristics of bacterial meningitis cases, Finland, 1995–2014

Characteristics	*S. pneumoniae*	*N. meningitidis*	*S. agalactiae*	*L. monocytogenes*	*H. influenzae*	Total
Gender, no of cases (% of total)						
Male	347 (57)	268 (60)	70 (50)	71 (70)	28 (48)	784 (58)
Female	264 (43)	182 (40)	71 (50)	30 (30)	30 (52)	577 (42)
Age (years)						
Median	48	18	0	68	29	36
IQR	28–62	4–35	0	56–74	6–54	5–58
Case fatality*						
No of deaths (no of cases)	38 (308)	14 (163)	2 (86)	11 (50)	0 (26)	65 (633)
Case fatality proportion (%)	12.3	8.6	2.3	22	0	10.3

*Data are for cases reported during 2004–2014.

and ≥65 years of age. The incidence decreased annually by 6% (95% CI −1% to −10%), 8% (95% CI −3% to −14%), 10% (95% CI −8% to −13%) and 12% (95% CI −8% to −13%) in age groups 2–4 years, 5–17 years, 18–49 years and 50–64 years, respectively. The overall 30-day CFP was 9% (14/163) and ranged from 3% (1/29) among children aged 0–1 years to 21% (4/19) among children aged 2–4 years.

During 2004–2014, information on *N. meningitidis* serogroups was available for 99% of cases (161/163). Serogroup B accounted for 85% (137/161) of isolates, C 11% (17/161) and Y 4% (7/161). In children <2 years, serogroup B caused 96% (26/27) of cases. MCV-4 and MenB vaccine serogroups caused 15% (24/161) and 85% (137/161) of all cases, respectively.

Haemophilus influenzae

From 1995 to 2014, 58 cases of *H. influenzae* were reported (0.06 cases/100 000 person-years, table 1). Median age was 29 years and male to female IRR was 1.0 (95% CI 0.6 to 1.7, table 2). The incidence rate ranged from 0.0 cases per 100 000 person-years in 2010 to 0.25 cases in 2007 (figure 2). Rates in all age groups were stable. From 2004 to 2014, there were no deaths due to *H. influenzae*.

In 2004–2014, non-encapsulated *H. influenzae* accounted for 69% (18/26) , serotype f 23% (6/26) and type b 8% (2/26) of isolates.

Streptococcus agalactiae

Infection with *S. agalactiae* accounted for 141 cases of meningitis (0.13 cases/100 000 person-years), including 24 early-onset cases and 78 late-onset cases (table 1). The median age of cases was 30 days; male to female IRR was 1.03 (95% CI 0.7 to 1.4) (table 2). During the study

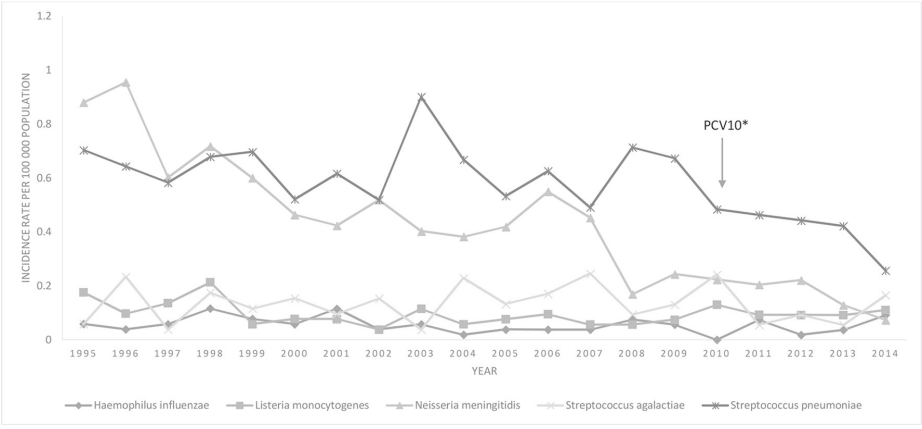

Figure 2 Incidence rate (per 100 000 person-years) of bacterial meningitis by year and pathogen, Finland, 1995–2014.

period, annual rates ranged from 0.06 cases/100 000 person-years in 1995 to 0.17 cases in 2014 (figure 2), but overall rates of *S. agalactiae* did not change significantly (p=0.97, table 1). During 2004–2014, the 30-day CFP was 2% (2/86).

Listeria monocytogenes

During the study period, *L. monocytogenes* caused 101 cases of meningitis (0.13 cases/100 000 person-years), mostly among elderly persons (median age, 68 years). Of cases, 70% were men (male to female IRR 2.5, 95% CI 1.6 to 3.9, table 2). Overall incidence rates of *Listeria* meningitis did not vary significantly during the study period, ranging from 0.04 to 0.21/100 000 person-years (table 1). The overall 30-day CFP was 22% (11/50) and 28% (10/36) in persons ≥65 years of age.

DISCUSSION

During 1995–2014, the most common causes of bacterial meningitis in Finland were *S. pneumoniae* and *N. meningitidis*. However, contribution of specific pathogens to the disease burden varied substantially by age. As in other developed countries, *S. agalactiae* was the most common cause of bacterial meningitis in children <1 years of age.[6] The mean age of cases increased significantly during the study period mainly because of the decrease in incidence in children associated with PCV10 programme and declining secular trend in meningococcal meningitis.

During the study period, significant declines were seen in overall incidence of bacterial meningitis—primarily due to decreases in rates of *N. meningitis* and *S. pneumoniae*. Of interest, the decrease in incidence of *N. meningitidis* was greater than for pneumococcal meningitis, although there is no routine vaccination programme for meningococcal disease in Finland. Changes in rates of meningococcal disease have also been observed in other countries in Europe and worldwide.[16 17] The reasons for these declines in incidence are not clear but may be related to population immunity to circulating strains, changes in colonising organisms in the nasopharynx or increasing use of influenza vaccine. Also, changes in behavioural risk factors such as lower prevalence of smoking or crowding might contribute.[18 19] In some countries, decreases were related to meningococcal vaccination. After the introduction of conjugate serogroup C meningococcal vaccine, vaccine serogroup disease nearly disappeared in England[20] and the Netherlands.[21] Direct and indirect (herd protection) vaccine effects were also reported from other European countries including Spain, Ireland and Belgium.[22 23] Immunisation of high risk groups with recently licensed protein-based vaccines targeted against meningococcal serogroup B might also be considered in Finland. However, updated cost-effective analysis is needed for decision-making about introduction of meningococcal vaccination programs.

Before the introduction of PCV10, considerable variation in pneumococcal meningitis incidence rates was seen. As there were no major changes in surveillance or diagnostic practices in Finland, these changes may be related to emergence of new serotypes, selective pressure from antibiotic use or natural fluctuation in serotypes.[24–26] The decline in pneumococcal meningitis incidence in children <2 years of age was associated with introduction of PCV10 in the NVP in 2010[15]; PCV10 serotypes in this age group were significantly reduced and by 2014 no vaccine serotype meningitis cases were reported. In vaccine-eligible children, the overall rate of pneumococcal meningitis was reduced by 46% as a result of a 69% reduction in PCV10-type meningitis.[15] Many studies in USA and Europe have also documented significant declines in the incidence of pneumococcal meningitis in both vaccinated and unvaccinated groups after introduction of PCV programmes.[11 12 27–29] In Finland, it might be possible to achieve further reductions with higher valency conjugate vaccine formulations.

The incidence rate of *L. monocytogenes*, *N. meningitidis* and *S. pneumoniae* was higher in men than women. *L. monocytogenes* meningitis cases were 2.5 times more likely to be men. Higher rates of listeriosis in males have also been observed in other studies.[7] However, the reasons are unknown, but may be related to higher prevalence of underlying conditions, alcoholism among men and liver diseases (including alcoholic cirrhosis).[30] In pneumococcal and meningococcal meningitis, possible reasons may be higher prevalence of underlying medical conditions,smoking and alcoholism.[31] As listeriosis is primarily transmitted through contaminated food, important prevention efforts include health education about dietary guidelines for high risk groups, such as pregnant women and the elderly.[32]

The overall 30-day CFP for meningitis did not change significantly during 1995–2014. However, the unchanged CFP may be related to the altered age distribution of cases. Older age is associated with higher risk of poor outcome.[33] In addition, pathogen distribution has changed and the case fatality for meningococcal meningitis is lower compared with pneumococcal meningitis. The small number of fatal cases in our study did not allow assessing changes in CFP by age group and pathogen. The 30-day CFP was highest for *L. monocytogenes* (22%), which is comparable with results from the Netherlands and Spain.[7 34] Most of the fatal cases of bacterial meningitis in persons ≥50 years were attributable to *S. pneumoniae*. Cases who had pneumococcal meningitis were older than those who were infected with other encapsulated bacteria and likely had higher prevalence of comorbidities increasing the risk of pneumococcal infection and poor outcome.[35] Because of lack of clinical data, we could not assess the potential impact of treatment changes, such as dexamethasone use, on case fatality. The relatively high CFP emphasises the importance of immediate initiation of treatment and supportive care after diagnosis to improve outcome of bacterial meningitis.

As expected, *H. influenzae* was the least common cause of bacterial meningitis. However, the stable number of cases

over 20 years suggest existence of small group of individuals with risk factors for *H. influenzae* (such as chronic respiratory disease and impaired immunity).[36] Conjugate vaccination has nearly eliminated Hib meningitis in many high-income countries.[37 38] However, changes in the epidemiology of invasive *H. influenzae* have been observed and currently most cases occur in adults[39] and non-encapsulated, non-typable *H. influenzae* have dominated since 2004.

Because the data on laboratory confirmed cases are transmitted electronically directly from the clinical microbiology laboratories' database to the national surveillance database, a strength of our study is comprehensive case ascertainment. In addition, almost all isolates of *N. meningitidis*, *H. influenzae* and *S. pneumoniae* (98%) were available for serotyping/grouping at THL reference laboratory. However, our study has several limitations. As the data were from laboratory-based surveillance system, information on clinical presentation or treatment was not available. Therefore, culture-negative meningitis cases diagnosed on the basis of clinical symptoms and findings were not included in the analysis dataset. In addition, cases diagnosed by PCR or antigen detection were not included. As CSF cultures are negative in 11%–30% of patients with bacterial meningitis,[40] the total number of meningitis cases is underestimated. Another limitation is that NIDR database does not include information on the cause of death. However, most of deaths associated with bacterial meningitis occur early (within 14 days of admission), suggesting that they were related to the infection.[41]

In conclusion, this study describes the epidemiological characteristics of >1300 cases of bacterial meningitis reported to national surveillance over 20 years. It documents the sustained population impact of infant conjugate vaccination against Hib and introduction of PCV on reducing burden of bacterial meningitis as well as decline in meningococcal meningitis due to secular trend. However, disease burden had shifted to older people and no changes in the overall proportion of fatal cases were seen. Data on changes in causative organisms and age distribution for meningitis cases are important for evaluating clinical guidelines for empirical antibiotic therapy in bacterial meningitis. Continued epidemiological surveillance is necessary to monitor changing trends and serotype distribution, assessing the impact of vaccination programs and developing future vaccination strategies.

Contributors Study concept and design: AP, OL, PN. Acquisition of data: MT, JO, OL, PN. Analysis and interpretation of data: AP, MT, JO, OL, PN. Drafting of the manuscript: AP, PN. Critical revision of the manuscript for important intellectual content: AP, MT, JO, OL, PN. Statistical analysis: AP, JO. Obtained funding: PN. Study supervision: PN. Final approval: AP, MT, JO, OL, PN.

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Competing interests None declared.

Ethics approval Data used in the analysis were collected as a part of surveillance and infection control activities which falls under the existing mandate of the National Institute for Health and Welfare (THL).

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement No additional data are available.

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Bacterial meningitis in Finland, 1995• 2014: a population-based observational study

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Pneumococcal meningitis before the introduction of 10-valent pneumococcal conjugate vaccine into the National Childhood Immunization Program in Poland

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Pneumococcal meningitis before the introduction of 10-valent pneumococcal conjugate vaccine into the National Childhood Immunization Program in Poland

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ABSTRACT

Background: Poland introduced the 10-valent conjugate pneumococcal vaccine (PCV10) into the childhood immunization program in January 2017. During previous decades, considerable changes had occurred in the surveillance system for invasive pneumococcal disease. Therefore, to provide baseline data on pneumococcal diseases before PCV10 introduction, we evaluated the epidemiology of pneumococcal meningitis (PM), the only syndrome monitored consistently since 1970.

Methods: Based on laboratory-confirmed cases reported during 2005-2015, we calculated the reported rates, serotypes distribution and antimicrobial resistance of pneumococcal meningitis isolates. Data from the mandatory national surveillance system was linked with data on cerebrospinal fluid isolates submitted to the National Reference Centre for Bacterial Meningitis. We used negative binomial regression with Newey West method to test for trend in rates of pneumococcal meningitis notified during 2005-2015 and Chi-squared test to assess changes in the serotype distribution from 2008-2011 to 2012-2015.

Results: From 2005 to 2015, the overall reported incidence of PM increased from 0.21 to 0.47 cases per 100,000 population, average yearly increase of 7% (rate ratio 1.07; 95% CI 1.06–1.08). The increase was primarily due to annual increase of 3% (1.02–1.05) among 15–49 years of age, 12% (95% CI: 1.10–1.13) among 50–64 years of age, 18% (95% CI: 1.16–1.19) among persons 65–74 years of age and 9% (95% CI 1.07–1.10) among persons ≥75 years of age. In children <5 years of age, serotypes included in PCV10 and PCV13 accounted for 75% and 80% of reported isolates, respectively. From 2008-2011 to 2012-2015, the proportion of PM cases caused by PCV10 serotypes decreased from 52% to 41% ($p < 0.01$). Overall, 28% of isolates were resistant to penicillin and 13% were non-susceptible to cefotaxime.

Conclusions: The introduction of PCV10 into national immunization program may have considerable impact on disease burden, especially on number of cases caused by isolates non-susceptible to antimicrobials.

1. Background

Streptococcus pneumoniae, along with *Neisseria meningitidis* and *Haemophilus influenzae* type b (Hib) [1–4], are most common causes of bacterial meningitis worldwide. In developed countries, case fatality for pneumococcal meningitis (PM) varies from 5% to 20% and sequelae such as hearing loss, seizures or focal neurological deficits occur in up to 50% survivors [1,5–7]. The disease affects mostly young children, the elderly and individuals with chronic illnesses [1]. Due to severity of the condition and established surveillance systems, PM is considered a reliable indicator of *S. pneumoniae* disease burden and long-term trends, allowing for international comparisons [8,9]. Epidemiology of pneumococcal meningitis has changed in many countries after implementation of seven-valent conjugate pneumococcal vaccine (PCV7), which later was replaced by 10- or 13-valent conjugate pneumococcal vaccines (PCV10, PCV13) [10–13]. The treatment of pneumococcal infections is complicated by increasing prevalence of clinical iso-

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lates of *S. pneumoniae* that are non-susceptible to first line antibiotics, primarily β-lactams [1,14]. The occurrence of non-susceptibility varies among countries, and may be as high as 40%-80% in certain geographic locations [15–18].

In January 2017, Poland introduced PCV10 into the childhood immunization program. The vaccine is currently administered free of charge in a 2 + 1 schedule at 2, 4 and 13 months of age for children born after 1st January 2017. Before 2017, pneumococcal vaccines (PCV10, PCV13 and the 23-valent polysaccharide vaccine, PPSV23) were given free of charge only to children ≤5 years of age with risk factors. The indications included trauma or defects of central nervous system with cerebrospinal fluid (CSF) leakage, chronic heart failure, immunological-hematological diseases or HIV infection. In addition, some municipalities had organized vaccination at own cost for children registered as residents. In 2015, the vaccine uptake (including children with risk factors receiving any type of pneumococcal vaccine or vaccinated at the cost of their parents) was approximately 10% [19].

Poland introduced mandatory surveillance of PM and other bacterial meningitis in 1970. The system is supervised by two institutions: the National Institute of Public Health- National Institute of Hygiene (NIPH-NIH) and the reference laboratory - the National Reference Centre for Bacterial Meningitis (NRCBM). In this system, physicians and laboratories report isolations of *S. pneumoniae* from normally sterile sites. In our study, we analyzed baseline data on the epidemiology of pneumococcal meningitis before introduction of PCV10 into the childhood vaccination program in Poland. To provide data for evaluating the impact of PCV10 vaccination program in the future, the specific aims included assessing the reported rates, serotype distribution and antimicrobial resistance of pneumococcal meningitis isolates.

2. Materials and methods

2.1. Surveillance of pneumococcal meningitis

In Poland, there are two independent passive surveillance systems for monitoring PM. The first system, based on mandatory reporting by physicians, is operated by NIPH-NIH. The second, consisting of voluntary reporting by laboratories is led by NRCBM. In 2005, Poland implemented EU case definition for invasive pneumococcal disease (IPD) and extended the scope of reporting to other manifestations of IPD, than meningitis [20]. Physicians are obliged by law to notify to the local public health authority each suspect IPD case within 24 h. Microbiological laboratories who isolate *S. pneumoniae* or detect *S. pneumoniae* nucleic acid from normally sterile site from patients also report to the local public health authority. Local public health authorities complete paper-based, standardized surveillance reports for each clinical case of PM and notify it biweekly to a population-based surveillance system coordinated by the NIPH-NIH. Multiple notifications with the same identification information (name, surname, address, place of hospitalization) are merged into one case, if they refer to the same illness episode.

Laboratory-based surveillance of PM since 1997 is operated by the NRCBM which receives clinical materials for PCR, the pneumococcal isolates, performs serotyping, and tests antimicrobial susceptibility of isolates. Data on demographic characteristics, antibiotic therapy, vaccination status, clinical symptoms, and the disease outcome, if already available, are collected for all isolates.

Since 2010, data from the NIPH-NIH and the NRCBM have been linked by using identification information and submitted to the European Surveillance System (TESSy) maintained by the European Centre for Disease Prevention and Control (ECDC). Notifications of materials and isolates, which were sent to the NRCBM but not reported to the NIPH, are actively collected as part of an enhanced surveillance. The schematic presentation of surveillance systems of pneumococcal meningitis is depicted in the Graph 1.

2.2. Data sources

Data on number of cases, their demographics (age, sex), outcome of the disease and districts where cases were reported, were collected from the population-based surveillance database coordinated by the NIPH-NIH. Year of notification was acquired from the date of onset of symptoms or, if unavailable, specimen collection date. After linkage with the NRCBM databases (based on identification information), data on serotypes and antimicrobial susceptibility of those cases was collected.

2.3. Study design

We performed an observational, population-based study. The study population consisted of all residents living in Poland between 1 January 2005 and December 2015.

2.4. Case definition

We defined a case of pneumococcal meningitis as isolation of *S. pneumoniae* from CSF during 2005-2015 and notified to the NIP-NIH.

2.5. Reported rates and trend

Data were stratified into seven age groups (<1 year, 1–4 years, 5–14 years, 15–49 years, 50–64 years, 65–74 years, ≥75 years). Annual, age-specific and district-specific reported rates per 100,000 were calculated using data from the Central Statistical Office as denominators.

To test trend in rates during 2005-2015 and correct for overdispersion of data, we used negative binomial regression. To adjust for autocorrelation, we used Newey West method. Rate ratios (RR), their 95% confidence intervals (CI) and p-values for yearly changes were calculated using time (year) as a continuous explanatory variable in the model.

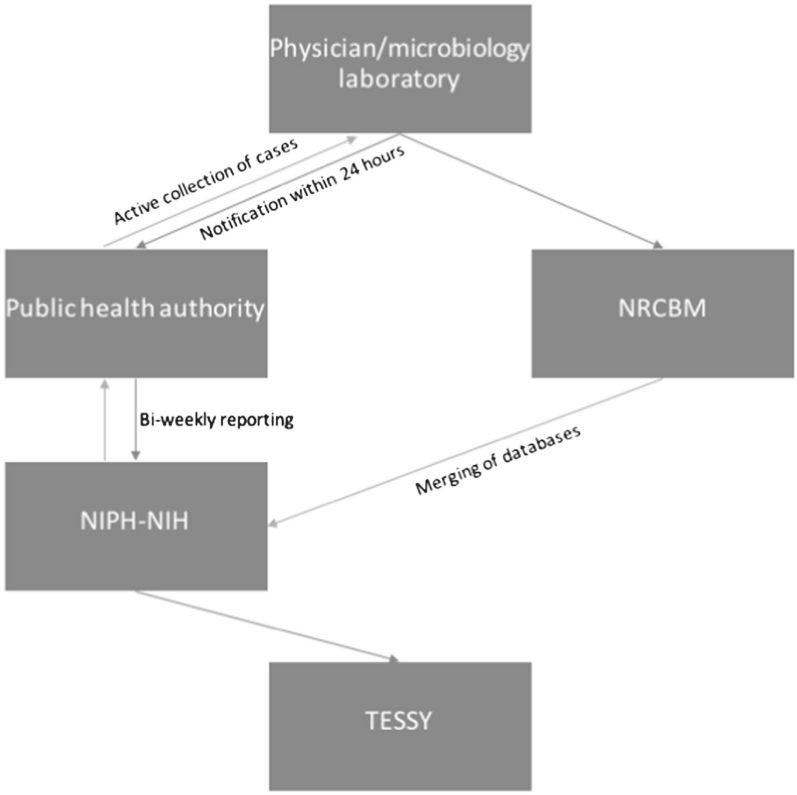
2.6. Case fatality proportion

We calculated case fatality proportion (CFP) by age group as a number of cases resulting in death, divided by all reported cases. To assess changes in CFP between 2005 and 2010 and 2011-2015, we used chi-square test; p-value < 0.05 was considered statistically significant.

2.7. Serotype distribution and diversity

We calculated proportions of *S. pneumoniae* isolates by vaccine-serotypes. The 10-valent pneumococcal conjugate vaccine contains serotypes 1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F and 23F; the 13-valent pneumococcal conjugate vaccine adds serotypes 3, 6A, and 19A. Those three additional serotypes were defined as PCV13 - PCV10. The 23-valent pneumococcal polysaccharide vaccine contains 12 serotypes in common with PCV13 and 11 unique serotypes (2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F). The non-vaccine types were categorized as non-PCV10 and non-PCV13. Serotypes 15B and 15C were grouped together as 15B/C because of the reported reversible switching between these serotypes, which makes differentiation difficult [21]. We used chi-squared test to assess changes in the serotype distribution between 2008-2011 and 2012-2015.

To assess the diversity of reported serotypes, we used the Simpson's index of diversity (D) [22]. D refers to the probability that two



Graph 1. Surveillance system of pneumococcal meningitis in Poland. NRCBM- National Reference Centre for Bacterial Meningitis; NIPH-NIH- National Institute of Public Health- National Institute of Hygiene; TESSy- The European Surveillance System. Blue line- standard surveillance; Green line- Enhanced surveillance. (For interpretation of the references to colour in this gure legend, the reader is referred to the web version of this article.)

randomly selected isolates have different serotypes. We de ned D as:

$$D = \frac{N}{(N-1)} \times \left[1 - \sum_{i=1}^{m} \left(\frac{n_i}{N}\right)^2\right]$$

where, N is the total number of pneumococcal meningitis cases (sample size), n is the number of cases with serotype i, m is the total number of serotypes [23].

2.8. Serotyping

S. pneumoniae CSF isolates sent to the NRCBM were serotyped using Pneumotest-Latex kit (Statens Serum Institut, Copenhagen, Denmark), PCR or sequencing. Serotypes not identi ed by the above methods were subjected to the Neufeld Quellung test in the Statens Serum Institut in 2008, and in the National Reference Center for Streptococci in Aachen, Germany in 2009-2015, as previously described [24].

2.9. Antimicrobial susceptibility

Minimal inhibitory concentrations (MICs) for penicillin and cefotaxime were determined by the Etest (AB Biodisk-bioMérieux) or MICEvaluators (Oxoid-Thermo Fisher) according to manufactures instructions.

For the interpretation of MICs data, the EUCAST 2015 breakpoints for meningitis cases were applied [25]. Pneumococcal meningitis isolates were categorized as susceptible (S), intermediate (I), and resistant (R). The intermediate and resistant isolates were collectively referred to as non-susceptible.

2.10. Data analysis

All analyses were done with STATA version 13 (STATA Corp., Texas, USA) and Microsoft Excel 2013.

2.11. Ethical considerations

Data used in the analysis were collected as a part of national routine surveillance activities which fall under the existing mandate of the NIPH-NIH and the NRCBM. No formal approval of Institutional Review Board was required for this non-interventional study [26]. Identi cation data (names, addresses) were removed after matching with vital status or serotype.

3. Results

3.1. Descriptive analysis

From January 2005 until December 2015, a total of 1435 cases of pneumococcal meningitis were noti ed to the NIPH-NIH. Information on age was available for 1432 (99.8%) cases. The median age of cases was 48 years (interquartile range (IQR), 25-60 years), and 63% (910/1435) were male. Fourteen percent (200/1432) of

cases were in children under 5 years of age and 16% (226/1432) were adults ≥65 years. The overall case fatality proportion was 20% (281 deaths) and varied from 4% (4/90) in children under 1 year of age to 31% (71/226) in people ≥65 years of age. Most of the deaths occurred within 30 days of symptom onset (81%, 228/281). The CFP was higher in 2005-2010 (22%) than in 2011-2015 (18%) (p = 0.052).

3.2. Reported rates of pneumococcal meningitis and trends

The highest rate was among children under 1 year of age, followed by 1–4 years of age and people 50–64 years of age (Table 1). The reported rates in the youngest age group were characterized by substantial variation, from 0.52 cases per 100,000 person-years in 2007 to 3.59 cases per 100,000 person-years in 2010. The overall rate increased steadily from 0.21 cases per 100,000 person-years in 2005 to 0.47 cases per 100,000 person-years in 2015. This represented an average increase by 7% per year (RR 1.07, 95% CI: 1.06–1.08), primarily due to annual increase by 3% (1.02–1.05) among 15–49 years of age, 12% (95% CI: 1.10–1.13) among 50–64 years of age, 18% (95% CI: 1.16–1.19) among persons 65–74 years of age and 9% (95% CI 1.07–1.10) among ≥75 years of age. Trends in other age groups were not statistically significant (Table 1). Male to female rate ratio was 1.85 (0.45 cases/100,000 person-years vs. 0.24 cases/100,000 person-years). There were geographical differences in the reported rates notified in 2005-2015, ranging from 0.18 cases per 100,000 person-years in district 10, to 0.52 cases per 100,000 person-years in district 11 (Fig. 1). The reported rate was higher in urban areas, than rural (0.38 cases per 100,000 person-years and 0.28 cases per 100,000 person-years, respectively).

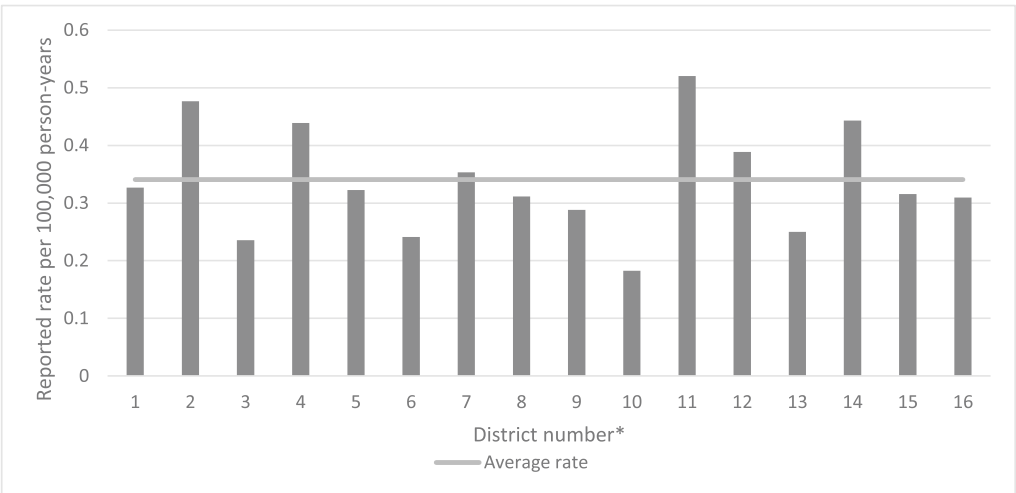
3.3. Serotype distribution of pneumococcal meningitis isolates

Of the 1149 PM cases reported to the NIPH-NIH in 2008-2015, 676 (59%) CSF isolates were sent to the NRCBM. The proportion of isolates sent to the NRCBM varied from 49% in 2008 to 67% in 2015. Of the 676 isolates available for serotyping, 672 belonged to 48 different serotypes or serogroups; 4 isolates were non-typeable. The most common serotypes were 3 (71 isolates, 11% of all isolates), 19F (65, 10%), 14 (58, 9%) and 23F (40, 6%). There were no significant differences in serotype distribution between

Table 1
Rates and number of cases of pneumococcal meningitis according to age group (years) and mean annual relative change in incidence, 2005-2015, Finland.

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2005–2015	% Change* (95%CI)
<1	1.94 (7)	1.64 (6)	0.52 (2)	1.94 (8)	2.12 (9)	3.59 (15)	2.77 (11)	1.56 (6)	3.26 (12)	2.18 (8)	1.66 (6)	2.12 (90)	4 (−2 to 10)
1–4	0.35 (5)	0.56 (8)	0.77 (11)	0.68 (10)	0.53 (8)	0.77 (12)	1.20 (20)	0.60 (10)	0.36 (6)	0.45 (7)	0.85 (13)	0.65 (110)	3 (−1 to 8)
5–14	0.24 (11)	0.14 (6)	0.29 (12)	0.25 (10)	0.31 (12)	0.21 (8)	0.29 (11)	0.13 (5)	0.27 (10)	0.26 (10)	0.21 (8)	0.24 (103)	−1 (−3 to 0)
15–49	0.14 (27)	0.18 (35)	0.26 (51)	0.20 (38)	0.24 (47)	0.23 (44)	0.22 (42)	0.16 (30)	0.32 (60)	0.20 (38)	0.29 (54)	0.22 (466)	3 (2 to 5)
50–64	0.32 (22)	0.34 (24)	0.29 (22)	0.40 (31)	0.40 (31)	0.46 (37)	0.69 (57)	0.47 (39)	0.67 (55)	0.77 (62)	0.72 (57)	0.51 (437)	12 (10 to 13)
65–74	0.20 (6)	0.17 (5)	0.32 (9)	0.22 (6)	0.54 (15)	0.44 (12)	0.33 (9)	0.53 (15)	0.94 (28)	0.47 (15)	0.92 (31)	0.47 (151)	18 (16 to 19)
≥75	0.14 (3)	0.27 (6)	0.30 (7)	0.13 (3)	0.34 (8)	0.20 (5)	0.28 (7)	0.35 (9)	0.31 (8)	0.34 (9)	0.37 (10)	0.28 (75)	9 (7 to 10)
Total	0.21 (81)	0.24 (90)	0.30 (114)	0.28 (106)	0.34 (130)	0.35 (133)	0.41 (157)	0.30 (114)	0.46 (179)	0.39 (149)	0.47 (179)	0.34 (1432)	7 (6 to 8)

* Mean annual relative change in incidence calculated by negative binomial regression with Newey West method.



*1- Dolnośląskie, 2- Kujawsko-pomorskie, 3- Lubelskie, 4- Lubuskie, 5- Łódzkie, 6- Małopolskie, 7- Mazowieckie, 8- Opolskie, 9- Podkarpackie, 10- Podlaskie, 11- Pomorskie, 12- Śląskie, 13- Świętokrzyskie, 14- Warmińsko-mazurskie, 15- Wielkopolskie, 16- Zachodniopomorskie

Fig. 1. Reported rate of pneumococcal meningitis by district, Poland, 2005-2015. *1- Dolnośląskie, 2- Kujawsko-pomorskie, 3- Lubelskie, 4- Lubuskie, 5- Łódzkie, 6- Małopolskie, 7- Mazowieckie, 8- Opolskie, 9- Podkarpackie, 10- Podlaskie, 11- Pomorskie, 12- Śląskie, 13- Świętokrzyskie, 14- Warmińsko-mazurskie, 15- Wielkopolskie, 16- Zachodniopomorskie.

2008 and 2011 and 2012-2015, except an increase in serotype 19A (increase from 2% in 2008-2011 to 6% in 2012-2015, p = 0.0106) and 23B (from 0% to 3%, p = 0.0027). The serotypes present in PCV10, PCV13 and PPSV23 accounted for 46% (309/676), 62% (419/676) and 83% (563/676) of all isolates, respectively. Between 2008-2011 and 2012-2015, there was signi cant decrease in the proportion of cases caused by PCV10 serotypes, from 52% to 41% (p = 0.0044), respectively. There were no signi cant changes in proportions of PCV13 (p = 0.0630) and PPSV23 (p = 0.0848), PCV13-PCV10 (p = 0.1622) and PPSV23 unique serotypes (p = 0.5409).

Among serotypes identi ed at least 20 times during the study period, the highest CFP was found for serotype 4 (34%, 12 deaths/35 isolates), 8 (29%, 6/21), 22F (29%, 6/21) and 10A (22%, 5/23). However, the observed differences in CFPs were not statistically signi cant.

Of the 112 isolates noti ed in children under 5 years of age, most common were serotypes 14 (n = 23, 21%), 19F (n = 22, 20%), 6B (n = 14, 13%), 23F (n = 9, 8%), 9 V (n = 6, 5%) and 15B/C (n = 5, 5%) (Table 2). There were no signi cant changes in frequency of particular serotypes between 2008-2011 and 2012-2015. PCV10, PCV13 and PPSV23 serotypes accounted for 75% (84/112), 80% (90/112) and 93% (104/112) of isolates, respectively. Comparing the distribution of serotypes in 2008-2011 to 2012-2015, the proportion of PCV10 serotypes declined from 87% to 57% (p = 0.0004); PCV13 serotypes decreased from 91% to 64% (p = 0.0003), PPSV23 serotypes decreased from 96% to 89% (p = 0.1511) and the proportion of non-PCV10 serotypes increased from 13% to 43% (p = 0.0004), non-PCV13 from 9% to 36% (p = 0.0003) and PCV13-PCV10 serotypes from 4% to 7% (p = 0.4860).

Among individuals ≥5 years of age (564 isolates), the most common were serotypes 3 (n = 70, 12%), 19F (n = 43, 8%), 14 (n = 35, 6%), 4 (n = 33, 6%), 23F (n = 31, 6%) and 19A (n = 27, 5%) (Table 3). PCV10, PCV13 and PPSV23 serotypes accounted for 40% (225/564), 58% (329/564) and 81% (459/564) of isolates, respectively. There were no signi cant changes in proportion of PCV10, PCV13 or non-PCV10, non-PCV13 and PCV13-PCV10 serotypes between 2008-2011 and 2012-2015.

Simpson's index of diversity was 0.894 and 0.954 in children <5 years of age and individuals ≥5 years, respectively.

3.4. Antimicrobial susceptibility

Data for antimicrobial susceptibility were available for 670 pneumococcal meningitis isolates (99.1%) reported in 2008-2015. Overall, 28% (189/669) of isolates were resistant to penicillin (MIC > 0.06 mg/L). There was no signi cant change in the frequency of penicillin resistant isolates reported in 2008-2011 and 2012-2015 (29% and 27% respectively, p = 0.5671). Resistance to penicillin was common among serotypes 19A (26/29, 90%), 9 V

Table 2
Serotypes distribution (%) of pneumococcal meningitis isolates among persons <5 years of age reported to the NIP-NIH, 2008-2015, Poland.

	2008	2009	2010	2011	2012	2013	2014	2015	2008–2015
No. of cases reported to the NIP-NIH	18	17	27	31	16	18	15	19	161
No. and proportion (%) of isolates sent to the NRCBM and serotyped	15 (83)	13 (76)	19 (70)	21 (68)	9 (56)	13 (72)	10 (67)	12 (63)	112 (67)
no. of different serotypes	8	6	7	8	9	9	8	8	25
simpson D' index	0.914	0.821	0.860	0.838	1.000	0.923	0.956	0.939	0.894
PCV10/PCV13 serotypes									
1	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.9
4	0.0	0.0	0.0	4.8	0.0	0.0	10.0	0.0	1.8
5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6B	20.0	7.7	21.1	9.5	11.1	7.7	0.0	16.7	12.5
7F	13.3	7.7	0.0	0.0	0.0	0.0	0.0	0.0	2.7
9V	0.0	0.0	5.3	19.0	11.1	0.0	0.0	0.0	5.4
14	13.3	23.1	26.3	33.3	0.0	23.1	20.0	8.3	20.5
18C	6.7	15.4	0.0	0.0	11.1	0.0	0.0	0.0	3.6
19F	6.7	38.5	21.1	19.0	11.1	23.1	20.0	16.7	19.6
23F	20.0	0.0	10.5	4.8	11.1	7.7	10.0	0.0	8.0
Additional PCV13 serotypes									
3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	8.3	0.9
6A	0.0	7.7	10.5	0.0	0.0	0.0	0.0	0.0	2.7
19A	0.0	0.0	0.0	0.0	0.0	0.0	0.0	16.7	1.8
Other serotypes									
15B/C	13.3	0.0	0.0	0.0	11.1	0.0	0.0	16.7	4.5
10A	0.0	0.0	5.3	4.8	11.1	7.7	0.0	0.0	3.6
8	0.0	0.0	0.0	0.0	0.0	7.7	0.0	8.3	1.8
22F	6.7	0.0	0.0	0.0	0.0	0.0	0.0	8.3	1.8
11A	0.0	0.0	0.0	4.8	0.0	0.0	0.0	0.0	0.9
12F	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	0.9
33F	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
9N	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
27	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
38	0.0	0.0	0.0	0.0	0.0	0.0	10.0	0.0	0.9
23B	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.9
24F	0.0	0.0	0.0	0.0	0.0	7.7	0.0	0.0	0.9
35F	0.0	0.0	0.0	0.0	11.1	0.0	0.0	0.0	0.9
Percentage of all isolates									
PCV10 serotypes	80.0	92.3	84.2	90.5	55.6	69.2	60.0	41.7	75.0
Non-PCV10 serotypes	20.0	7.7	15.8	9.5	44.4	30.8	40.0	58.3	25.0
PCV13 serotypes	80.0	100.0	94.7	90.5	55.6	69.2	60.0	66.7	80.4
PCV13-PCV10 serotypes	0.0	7.7	10.5	0.0	0.0	0.0	0.0	25.0	5.4
Non-PCV13 serotypes	20.0	0.0	5.3	9.5	44.4	30.8	40.0	33.3	19.6
PPSV23 serotypes	100.0	92.3	89.5	100.0	88.9	84.6	80.0	100.0	92.9
PPSV23 unique serotypes	20.0	0.0	5.3	9.5	33.3	15.4	20.0	33.3	15.2
Non-PPSV23 serotypes	0.0	0.0	0.0	0.0	11.1	15.4	20.0	0.0	4.5

Table 3
Serotypes distribution (%) of pneumococcal meningitis isolates among persons ≥ 5 years of age reported to the NIPH-NIH, 2008-2015, Poland.

	2008	2009	2010	2011	2012	2013	2014	2015	2008–2015
No. of cases reported to the NIP-NIH	88	113	106	126	98	161	134	160	986
No. of isolates (%) sent to NRCBM and serotyped	37 (42)	66 (58)	66 (62)	59 (47)	57 (58)	96 (60)	90 (67)	93 (58)	564 (57)
No. of different serotypes	20	31	26	28	21	32	28	31	49
Simpson D' index	0.961	0.962	0.947	0.943	0.949	0.960	0.943	0.963	0.954
PCV10/PCV13 serotypes									
1	0.0	0.0	1.5	1.7	0.0	2.1	1.1	2.2	1.2
4	5.4	6.1	7.6	3.4	7.0	6.3	6.7	4.3	5.9
5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
6B	5.4	1.5	3.0	6.8	3.5	4.2	5.6	2.2	3.9
7F	2.7	0.0	1.5	3.4	0.0	2.1	5.6	0.0	2.0
9V	8.1	3.0	3.0	1.7	1.8	5.2	1.1	3.2	3.2
14	8.1	6.1	9.1	3.4	5.3	5.2	6.7	6.5	6.2
18C	2.7	6.1	7.6	3.4	8.8	5.2	1.1	2.2	4.4
19F	10.8	3.0	13.6	6.8	10.5	7.3	5.6	6.5	7.6
23F	5.4	3.0	7.6	5.1	8.8	6.3	3.3	5.4	5.5
Additional PCV13 serotypes									
3	10.8	10.6	10.6	20.3	12.3	9.4	17.8	8.6	12.4
6A	0.0	1.5	1.5	0.0	1.8	2.1	0.0	2.2	1.2
19A	2.7	1.5	1.5	6.8	3.5	8.3	6.7	4.3	4.8
Other serotypes									
8	8.1	1.5	3.0	1.7	5.3	2.1	2.2	5.4	3.4
10A	5.4	3.0	3.0	0.0	5.3	1.0	2.2	7.5	3.4
22F	0.0	1.5	3.0	3.4	7.0	1.0	4.4	5.4	3.4
9N	2.7	4.5	1.5	1.7	1.8	4.2	2.2	4.3	3.0
11A	2.7	3.0	6.1	3.4	0.0	3.1	3.3	1.1	2.8
15B/C	5.4	3.0	0.0	5.1	3.5	5.2	0.0	2.2	2.8
12F	2.7	12.1	0.0	1.7	1.8	1.0	1.1	2.2	2.7
17F	0.0	1.5	0.0	1.7	3.5	0.0	0.0	0.0	0.7
33F	0.0	0.0	0.0	1.7	1.8	0.0	1.1	0.0	0.5
20	2.7	3.0	1.5	0.0	3.5	0.0	2.2	0.0	1.4
2	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.2
23A	2.7	1.5	0.0	0.0	0.0	3.1	3.3	5.4	2.3
23B	0.0	0.0	0.0	0.0	0.0	2.1	5.6	5.4	2.1
6C	0.0	3.0	0.0	1.7	0.0	1.0	3.3	2.2	1.6
15A	0.0	1.5	1.5	1.7	1.8	1.0	1.1	1.1	1.2
6A	0.0	1.5	1.5	0.0	1.8	2.1	0.0	2.2	1.2
31	0.0	3.0	0.0	1.7	0.0	1.0	0.0	1.1	0.9
Other**	5.4	12.1	10.6	11.9	0.0	8.3	6.7	7.5	8.0
Percentage of all isolates									
PCV10 serotypes	48.6	28.8	54.5	35.6	45.6	43.8	36.7	32.3	39.9
Non-PCV10 serotypes	51.4	71.2	45.5	64.4	54.4	56.3	63.3	67.7	60.1
PCV13 serotypes	62.2	42.4	68.2	62.7	63.2	63.5	61.1	47.3	58.3
PCV13-10 serotypes	13.5	13.6	13.6	27.1	17.5	19.8	24.4	15.1	18.4
Non-PCV13 serotypes	37.8	57.6	31.8	37.3	36.8	36.5	38.9	52.7	41.7
PPSV23 serotypes	91.9	75.8	84.8	83.1	94.7	79.2	80.0	73.1	81.4
PPSV23 unique serotypes	29.7	34.8	18.2	20.3	33.3	17.7	18.9	28.0	24.3
Non-PPSV23 serotypes	8.1	24.2	15.2	16.9	5.3	20.8	20.0	26.9	18.6

** Serotypes other than presented in the table, that occurred less than 10 times in 2005-2015 in Poland. Non-typeable isolates (n = 4) were included.

(19/24, 79%), 19F (47/65, 72%), 14 (40/58, 69%) and 6B (23/35, 66%). Among children <5 years of age, 53% (58/110) of the isolates were resistant to penicillin compared with 23% among persons ≥5 years of age (p < 0.0001). Serotypes with high proportion of penicillin resistance were: 19A (2/2, 100%), 9 V (6/6, 100%), 23B (1/1, 100%), 19F (18/22, 82%), 14 (16/23, 70%), 6A (2/3, 67%) and 23F (5/9, 56%).

Isolates with decreased susceptibility to cefotaxime (MIC > 0.5 mg/L) constituted 13% (90/670) of isolates tested in 2008-2015. The frequency of cefotaxime non-susceptibility did not change signi cantly between 2008-2011 (14%) and 2012-2015 (13%) (p = 0.7066). Non-susceptibility to cefotaxime was highest among isolates of serotypes 19A (17/29, 59%), 35B (1/2, 50%), 19F (30/65, 46%), 14 (25/58, 43%), 23F (10/40, 25%) and 9 V (5/24, 21%). Among children <5 years of age, 22% (24/110) of isolates were non-susceptible to cefotaxime compared with 12% among persons ≥5 years of age (p = 0.0052). The highest proportion of cefotaxime non-susceptible isolates was identi ed in serotypes 19A (2/2, 100%), 23F (4/9, 44%), 14 (10/23, 43%) and 19F (8/22, 36%).

4. Discussion

Our study described comprehensive 10-year baseline epidemiologic characteristics of PM cases reported to the national surveillance system (NIPH-NIH) in Poland before the introduction of universal PCV10 vaccination. To date, the analysis of epidemiology of PM was conducted only by the NRCBM and was limited to submitted isolates. There was an increasing trend in reported rates of pneumococcal meningitis, primarily among persons older than 15 years. During the study period almost half of the cases were caused by PCV10 serotypes. The average penicillin resistance of isolates was signi cantly higher among children less than 5 years of age and higher than in most European countries.

The age distribution of reported cases in Poland was similar to that noti ed in other European countries, with children below 5 years of age and persons ≥65 years of age having highest reported rates. Although the rates observed in our study (average 0.34 cases per 100,000 person-years) were higher than in the previous Polish studies [27,28], the overall and age-speci c rates were

considerably lower than those reported from other countries before introduction of pneumococcal conjugate vaccines, such as Finland [29], the Netherlands [30], England and Wales [31], Austria [32] or USA [10]. The low rates for pneumococcal meningitis in Poland may be due to low surveillance sensitivity or frequent administration of antibiotics immediately after clinical diagnosis or suspicion of meningitis, resulting in negative culture results [28]. The largest differences in reported rates between Poland and other European countries were among the elderly, suggesting considerable underreporting in this age group. This hypothesis is supported by the ndings from the prospective study conducted in 124 pediatric hospitals or wards in ve randomly selected districts in Poland during 2003-2004 [33]. The rates of pneumococcal meningitis were estimated to be 3.8 cases/ 100,000 person-years in children <5 years of age and 4.1 in children <2 years of age, respectively. The study showed that 108 out of 134 cases of laboratory-con rmed invasive pneumococcal disease were culture-negative and therefore serotyping data was available for 26 isolates only. Additionally, 28% children were treated with antibiotics before blood or CSF sampling. Relatively low reported rates should be taken into account when designing future vaccine effectiveness or impact studies or conducting evaluations of the economic and health bene ts of the PCV10 vaccination program. Underestimated burden of meningitis will affect the absolute number of cases prevented/reduced after conjugate vaccine introduction.

The increasing rates of pneumococcal meningitis from 0.21 cases per 100,000 person-years in 2005 to 0.47 cases per 100,000 person-years in 2015 may re ect changes and systematic improvements in the surveillance system for IPD. Historically, epidemiological surveillance of IPD in Poland was limited to meningitis cases, which have been routinely reported by physicians since 1970. The implementation of EU case de nition for IPD in 2005 [20], allowed collection of data on whole spectrum of clinical manifestations of IPD and thus improved surveillance sensitivity. In addition, active searching of cases reported to the NRCBM but not reported to the NIPH, increased the number of reported cases included in the national surveillance data. The signi cant increase in rate was reported primarily among persons $\geq$15 years of age. This may be related to better case ascertainment and reporting in this age group. However, in uence of secular trends cannot be excluded. The reason for the substantial variation in reported rates in children <1 years of age, between 2007 (0.5 cases per 100,000 person-years) and 2010 (3.59 cases per 100,000 person-years) is unknown, since there were no outbreaks reported. During the study period, changes in reported rates among children <15 years of age were not statistically signi cant. This might be related to small number of cases, uctuations in reported rates which affect the possibility to observe linear trend, or to other factors.

Changes in clinical practice also might have in uenced the increased number of observed cases. However, in Poland, as in most European countries, cerebrospinal uid (CSF) collection is a standard procedure in suspected pneumococcal meningitis [34]. Thus, epidemiology of PM is likely to be less affected by changes in clinical practice than IPD incidence where blood culturing practices for diagnosis of pneumonia can in uence observed rates [9,35]. Taking into account changes in surveillance system, the data on observed trends should be interpreted with caution.

The observed lower CFP in 2011-2015 comparing to 2005-2010, might be related to better surveillance, since more cases with less severe disease could have been reported. In addition in 2011, the national guidelines for diagnostic and treatment of bacterial meningitis were edited under umbrella of the National Programme for Antibiotic Protection by the National Medicines Institute [34].

The serotype distribution of pneumococcal meningitis isolates was characterized by considerable heterogeneity, especially among persons $\geq$5 years of age. Higher heterogeneity in older age groups has also been observed in other countries [36]. As in other countries before implementation of vaccination, the most common serotypes in children were 14, 19F, 23F [37,38]. In adults, serotype 3 was most common. Findings from other studies indicated that serotype 3 is commonly isolated in meningitis and associated with unfavorable outcomes [39]. The highest CFPs were reported for serotypes 4, 8, 22F and 10A. In a Danish nationwide population-based study, serotypes 4, 8, 22F were also found to be associated with higher 30-day mortality in meningitis patients [40]. There was signi cant increase in the proportion of serotype 19A and 23B reported in 2012-2015, compared with 2008-2011. In children <5 years of age, the most common were serotypes 14 and 19F. Both serotypes are targeted by available vaccines. In children <5 years of age, serotypes targeted by PCV10 and PCV13 accounted for higher proportion of all reported isolates, than in individuals $\geq$ 5 years of age. However, in children < 5 years of age, proportion of PCV10 and PCV13 serotypes decreased signi cantly from 2012-2015 to 2008-2010. It is dif cult to assess the impact of local vaccination programs on the rise in non-PCV serotypes, because detailed data on vaccine coverage in speci c time and regions were unavailable. These results indicate high potential for prevention of meningitis cases by PCV10, PCV13 and PPSV23 vaccines.

A number of studies have documented a signi cant decline in the reported rates of PM in the PCV vaccinated children. Some studies have shown the decrease in incidence also in older children and adults not targeted by vaccine, through herd effect. However, decrease in incidence due to the vaccine serotypes resulted in an increase in PM caused by non-vaccine serotypes [23]. In countries where PCV7 or PCV10 has been used in the infant vaccination programs, number of serotype 19A cases has increased both in children and adults, becoming one of the most common cause of meningitis. In contrast, after implementation of infant PCV13, the number of serotype 19A cases decreased signi cantly among both vaccinated and unvaccinated population groups [41]. However, increases in proportion of a wide variety of non-PCV13 serotypes have been seen after PCV13 introduction. In Germany, a signi cant increase in percentage of serotypes 12F, 15C, 22F, 23B and 35B was observed in children, after PCV introduction. In adults, increases in percentage of serotypes 6C, 12F, 15B, 22F, 23A, 23B and 35B were observed [42]. In France, after PCV13 introduction increase in frequency of serotypes 12F, 24F, 23B, 10A, 15A and 6C was observed [43]. However, results of herd effect and serotype replacement were not consistent in all countries. To allow assessment of changes in serotype distribution and potential serotype replacement in Poland, ongoing surveillance on circulating strains is essential.

The average penicillin resistance of isolates amounted 28% and was signi cantly higher among children less than 5 years of age. There were no substantial changes in penicillin resistance during the study period. Poland along with Romania, Malta and Iceland, has one of the highest proportion of IPD isolates resistant to penicillin. In Europe there is wide variation in antimicrobial susceptibility of pneumococcal isolates [44]. Differences are likely related to diversity in circulating strains, antibiotic use, vaccination policy, diagnostic capacity and access to healthcare. In our study, most of penicillin resistant isolates were targeted by PCV13. Several studies have demonstrated that vaccination with pneumococcal conjugate vaccines (PCV7, PCV10 and PCV13) reduced the nasopharyngeal carriage of penicillin-resistant *S. pneumoniae* and thus pneumococcal resistance in vaccinated and unvaccinated population [45–47]. Prevention is especially important since antimicrobial resistance has been associated with worse clinical outcomes in patients with pneumococcal meningitis [48].

In addition to low sensitivity, the surveillance system for pneumococcal meningitis in Poland has several other limitations. Our study shows substantial regional variation in reported rates. This

suggests considerable underreporting in some districts (district 10, 3, 6, 13) and important areas for improvement. In addition, during 2008-2015 less than 60% of isolates reported to the NIPH-NIH were sent to the NRCBM and serotyped. Formal evaluation of the surveillance system should be performed before conducting vaccine effectiveness or impact studies. This is especially important because of the planned change from paper-based to electronic based reporting surveillance system. Changes in surveillance can affect sensitivity of surveillance and quality of surveillance data. Media attention for pneumococcal disease after introduction of PCV10 could possibly improve awareness of IPD and result in further increase in the number of reported cases.

The strength of the study is a population-based design and all residents are entitled to free acute healthcare. Pneumococcal meningitis is a severe and life-threatening condition, thus each case is hospitalized. However, several limitations of this study should be noted. In the analysis only CSF culture-confirmed cases were included. Cases diagnosed on the basis of other laboratory methods such as PCR or antigen detection from CSF or blood culture with clinical symptoms of meningitis, were excluded from the study. This may have led to underestimation of the number of cases. The trend in reported rates was probably affected by the matching of cases captured by the two surveillance systems, initiated in 2010. However, the separate analysis of cases passively reported only was not possible due to lack of register of actively collected cases in 2010-2014, and thus different form of reporting. Since the outcome of the disease was collected by the public health authority, there is a possibility that some fatal cases were not captured, if the death occurred after the collection of the data or the patients was moved to another hospital.

5. Conclusions

This is the first study assessing long term trends of pneumococcal meningitis cases reported to mandatory surveillance system in Poland. The reported incidence of pneumococcal meningitis increased in persons $\geq$15 years of age. In children <5 years of age, serotypes included in PCV10 and PCV13 accounted for 75% and 80% of reported isolates, respectively. The introduction of PCV10 into national immunization program may have considerable impact on disease burden, especially on number of cases caused by isolates non-susceptible to antimicrobials.

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Conflict of interest statement

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PUBLICATION III

Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland

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Long-term population effects of infant 10-valent pneumococcal conjugate vaccination on pneumococcal meningitis in Finland

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ABSTRACT

Background: No previous studies have reported long-term follow-up of ten-valent pneumococcal conjugate vaccine (PCV10) program impact on pneumococcal meningitis (PM). We assessed the effects of infant PCV10 program on PM incidence, mortality and serotype distribution in children and adults during 7 years after introduction.

Methods: We conducted a population-based observational study. A case of PM was defined as isolation of *Streptococcus pneumoniae* from cerebrospinal fluid or, a patient with *S. pneumoniae* isolated from blood and an ICD-10 hospital discharge diagnosis of bacterial meningitis within 30 days before or after positive culture date. We compared age- and serotype-specific incidence and associated 30-day mortality rates in 2011–2017 (PCV10 period) with those in 2004–2010 (pre-PCV10 baseline) by using Poisson regression models. Absolute rate differences and 95% confidence intervals (CIs) were calculated from the parameter estimates by using delta method.

Results: During the PCV10 period, the overall incidence of PCV10 serotype meningitis decreased by 68% (95%CI 57%-77%), and the overall PM incidence by 27% (95%CI: 12%-39%). In age groups 0–4, 50–64, and $\geq$ 18 years, the overall PM incidence was reduced by 64%, 34% and 19%, respectively. In adults $\geq$ 65 years of age, a 69% reduction in PCV10 serotypes was offset by 157% (56%-342%) increase in non-PCV10 serotypes. The overall PM-related mortality rate decreased by 42% (95%CI 4%-65%). Overall case fatality proportion (CFP) was 16% in pre-PCV10 period and 12% in PCV10 period ($p = 0.41$); among persons 50–64 years the CFP decreased from 25% to 10% ($p = 0.04$).

Conclusions: We observed substantial impact and herd protection for vaccine-serotype PM and associated mortality after infant PCV10 introduction. However, in older adults $\geq$ 65 years of age, PM burden remains unchanged due to serotype replacement.

1. Introduction

Streptococcus pneumoniae remains a leading cause of bacterial meningitis worldwide [1]; an estimated 83 900 cases (36,100–169,000) of pneumococcal meningitis (PM) occurred in 2015 in children under 5 years of age [2]. It is the most severe form of invasive pneumococcal disease (IPD), characterized by 8% to 50% case-fatality and frequent long-term complications in survivors [3]. Approximately half of the cases suffer sequalae such as hearing loss, seizures and cognitive impairments [4,5]. Incidence rates are highest in young children and the elderly, but the disease affects all age groups [6].

Decreases in PM incidence in children have been reported after introduction of 7-, 10- and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, PCV13) into infant immunization programs [7–15]. Many studies have also reported herd protection against PM in unvaccinated population groups, especially older adults. However, reductions in vaccine serotypes were often offset by increases in non-vaccine serotypes (serotype replacement) [16–19].

In September 2010, Finland introduced PCV10 in the National Vaccination Programme (NVP) with a 2 + 1 schedule (3, 5 and 12 months of age). PCV10 effectiveness against invasive pneumococcal disease (IPD) due to vaccine serotypes (VT IPD) in children was first demonstrated in a large cluster-randomized trial (FinIP)

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conducted in 2009–2012. For VT IPD and IPD irrespective of serotype, vaccine effectiveness was 100% and 93%, respectively [20]. A subsequent surveillance study conducted 3 years after PCV10 introduction, showed a reduction by 80% of overall IPD rate in vaccine-eligible children and 48% reduction in unvaccinated children 2 to 5 years of age [21]. The early estimate for relative rate reduction in PCV10-type meningitis cases was 69% (95%CI 10% to 93%). However, the point estimate for overall reduction in pneumococcal meningitis cases (46%) was not statistically significant (95%CI − 19% to 78%)[21]. In a long term follow-up study six years after vaccine introduction, the overall IPD incidence had decreased by 79% in vaccine-eligible children and 33% in unvaccinated, older children [22].

No previous studies have reported long-term follow-up of PCV10 impact on pneumococcal meningitis in children and adults. We assessed the population effects of the infant PCV10 program on pneumococcal meningitis incidence and mortality after 7 years of vaccine introduction in a national study.

2. Methods

2.1. Surveillance on pneumococcal meningitis

The Population Information System of Finland is an online database containing information on name, sex, date of birth, place of residence and vital status of about 5.5 million permanent residents. This database can be linked with other health care and surveillance registries by using personal identity code (PIC). Since 1995, all clinical microbiology laboratories are obliged by law to report isolation of *Streptococcus pneumoniae* or detection of *S. pneumoniae* nucleic acid in blood or cerebrospinal fluid (CSF) to the National Infectious Diseases Register (NIDR), a population- based electronic laboratory surveillance system, maintained by the Finnish Institute for Health and Welfare (THL)[23]. Multiple notifications of IPD with the same PIC are merged into single case, if they occurred within 3 months from the first report. All clinical microbiology laboratories are also obliged to submit *S. pneumoniae* isolates from reported cases to THL reference laboratory for species verification and characterization.

2.2. Laboratory methods

Until 2009, pneumococcal isolates were serotyped by latex agglutination and/or counterimmunoelectrophoresis supplemented with Quellung reaction. During 2010–2017, isolates were serotyped by sequential multiplex PCRs supplemented with Quellung reaction, if needed [24]. All serotype 6A isolates from 2004 to 2009 were re-tested to distinguish serotype 6C and 6D. Since 2010, serotype 6C and 6D identification have been done routinely. Serotyping results have been routinely linked with the surveillance database by using PIC since 2004.

2.3. Study design and data sources

We conducted a population-based observational before-after study. Culture confirmed cases reported to NIDR with date of sampling from July 1, 2004 to June 30, 2017 were included in the analysis. The pre-PCV10 baseline period was defined as time-period from July 1, 2004 to June 30, 2010, and PCV10-period as time-period from July 1, 2011 to June 30, 2017. We excluded the transition year from July 1, 2010 to June 30, 2011. The case's vital status within 30 days from the first positive CSF or blood culture was obtained from The Population Information System. Cause of death data were not available. Data on discharge diagnoses were obtained from the national hospital discharge register (the Care Register for Health Care at THL).

2.4. Case definitions

A case of PM was defined as isolation of *S. pneumoniae* from CSF or a patient with *S. pneumoniae* isolated from blood and an ICD-10 hospital discharge diagnosis G00.0, G.001, G.002 or G00.9 within 30 days before or after collection of culture positive specimen.

Cases were categorized into five groups according to the causative serotypes: PCV10 serotype PM (1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, 23F), PCV13 serotype PM (PCV10 + 3, 6A, 19A), PM caused by serotypes unique to the 23-valent pneumococcal polysaccharide vaccine (PPSV23) (2, 8, 9 N, 10A, 11A, 12F, 15B, 17F, 20, 22F, 33F), non-vaccine type PM (NVT; serotypes not included in PCV10, PCV13, PPSV23 vaccines), and any culture-confirmed PM.

Because other studies have shown increases or inconclusive results related to serotypes 3, 6A, 6C, 19A, 22F after PCV introduction, cases of these serotypes were analyzed separately.

2.5. Statistical analysis

We calculated total and serotype-specific incidence rates, related 30-day mortality rates and case fatality proportions of PM overall and in specific age groups (0–4 years; 5–17 years; 18–49 years; 50–64 years; ≥65 years; ≥18 years) during the study periods. Data from The Population Information System were used as denominators. The case fatality proportion (CFP) was defined as number of cases resulting in death within 30 days from the first positive culture divided by all cases. To assess changes in CFP, we used chi-square test. Statistical significance was deemed at the 5% level.

Comparisons of PM incidence and mortality rates between pre-PCV10 baseline and PCV10-periods were performed by using Poisson regression models. Absolute rate differences and their 95% CIs were calculated from the parameter estimates by using delta method. Relative rate reduction (RRR) was defined as (1- incidence rate ratio) × 100%, comparing the pre-PCV10 baseline period and PCV10-period. All analyses were conducted with R version 3.4.2 and MS Excel 2013.

To assess changes in serotype distribution we compared the proportions of vaccine serotype groups in the pre-PCV10 period and in the final epidemiological year of the study (July 1, 2016 - June 30, 2017).

2.6. Ethical considerations

Data used in the study were de-identified and permission to use the register data for research was obtained from the relevant register controllers at THL (THL/1090/6.02.00/2013). THL Institutional Review Board approved the study.

3. Results

3.1. Changes in pneumococcal meningitis incidence rates

3.1.1. Overall incidence rates

A total of 451 culture-confirmed PM cases were reported during the study period (median age 57 years, IQR 40–66 years). Of the cases, 257 occurred during the pre-PCV10 baseline period and 194 during PCV10 period. The overall annual incidence rate varied from 1.07 cases per 100,000 person-years in 2008–2009 to 0.44 in 2016–2017 (Fig. 1). During the pre-PCV10 period and PCV10-period, 28% and 30% of cases were identified based on positive blood culture and ICD10-coded bacterial meningitis discharge

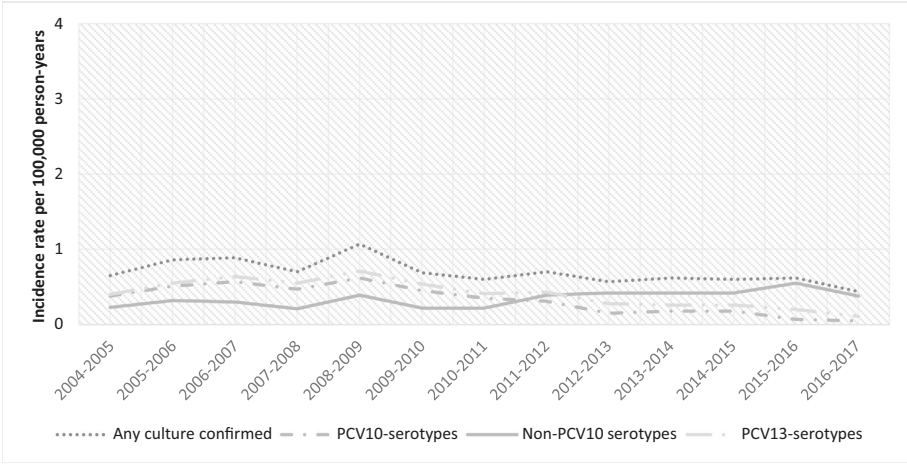


Fig. 1. Annual pneumococcal meningitis incidence rate per 100,000 person-years, according to the causing serotype, 2004–2017, Finland.

diagnosis, respectively; the rest of the PM cases were identified based on positive CSF culture. The overall PM incidence rate decreased by 27% from 0.81 cases during pre-PCV10 period to 0.59 cases per 100,000 person-years in the PCV10 period (IRR 0.73; 95%CI: 0.61–0.88). Compared with the baseline period, incidence decreased by 64% in children 0–4 years of age (IRR 0.36, 95%CI 0.19–0.63) and by 34% in adults 50–64 years of age (IRR 0.66, 95%CI 0.47–0.90). In all adults ≥ 18 years of age, the PM incidence rate decreased by 19% from 0.82 cases to 0.67 cases per 100,000 person-years (IRR 0.81; 95%CI 0.66–0.99). In other age groups, the point estimates decreased, but confidence intervals included one (Table 1).

3.1.2. Serotype-specific incidence rates

Compared with the pre-PCV10 baseline period the incidence of meningitis caused by PCV10 serotypes decreased by 68%, from 0.50 to 0.16 cases per 100,000 person-years (Table 1). In children 0–4 years of age, the incidence rate of PCV10-serotype PM decreased by 87% from 2.07 to 0.28 cases per 100,000 person-years. In adults 18–49 and 50–64 years of age the rates decreased by 63%, from 0.27 to 0.10 cases per 100,000 person-years and by 63% from 0.68 to 0.25 cases per 100,000 person-years, respectively. Among adults ≥ 65 years of age the incidence rate of PCV10-serotype PM decreased by 69%, from 0.71 to 0.22 cases per 100,000 person-years. In all these four age groups, the incidence of PM caused by PCV13-serotypes also decreased (Table 1). Overall incidence of non-PCV10 serotype PM increased by 54% from 0.28 to 0.43 cases per 100,000 person-years. This was mainly due to increase by 157% in adults ≥ 65 years of age, from 0.36 cases in pre-PCV10 period to 0.94 cases per 100,000 person-years in PCV10-period. Overall incidence of non-PCV13 serotypes increased by 57% from 0.21 to 0.34 cases per 100,000, primarily due to increases in children 0–4 years of age and adults ≥ 65 years of age (Table 1). Supplement Fig. 1 shows annual incidence rates by age group. In the whole population, the incidence of serotypes 19A and 6C PM increased, but the absolute rate differences were small (0.03 and 0.04 cases per 100,000 person-years, respectively). PM caused by serotypes 3 and 6A did not change in any age group. PM caused by the three serotypes in PCV13 but not in PCV10 (3, 6A, 19A) increased in adults 18–49 years, but the absolute rate change was minimal (0.04/100,000). Table 1 shows the detailed data on changes in serotype-specific incidence rates.

In adults ≥ 18 years of age, incidence of PCV10 and PCV13 serotype PM decreased by 64% from 0.47 to 0.17 cases per 100,000 person-years and by 47% from 0.54 to 0.28 cases per 100,000 person-years, respectively. Incidence of non-PCV10 PM increased by 54%, but the absolute rate change was small. This was primarily due to increase in serotype 6C from 0.01 to 0.05 cases per 100,000 person-years, and 19A from 0.004 to 0.05 cases per 100,000 person-years. Rates of meningitis caused by PPSV23 unique serotypes were 0.13 and 0.18 cases per 100,000 person-years during pre-PCV10 and PCV10 periods, respectively. In adults ≥ 65 years of age, the incidence rate of PPSV23 unique serotypes increased from 0.13 to 0.33 cases per 100,000 person-years.

3.1.3. Changes in serotype distribution

By the final epidemiological year of the study (2016–2017), the proportion of PCV10 serotypes had reduced from 88%, 56% and 66% of all isolates in pre-PCV10 period to 0%, in persons 0–4 years, 5–17 years and 18–49 years of age, respectively (Fig. 2). The proportion of meningitis caused by PCV13-PCV10 serotypes decreased in persons 0–4 years (from 5% to 0%), 5–17 years (from 22% to 0%) and 50–64 years of age (from 10% to 0%). In adults 18–49 years of age and ≥ 65 years of age the proportion of PCV13-PCV10 serotypes increased from 2% to 50% and from 12% to 14%, respectively.

The proportion of PPSV23 unique serotypes dropped in adolescents 5–17 years of age and adults 18–49 years of age from 11% and 15% of all isolates to 0% in the last epidemiological year, respectively. The proportion of PPSV23 unique serotypes increased in persons 50–64 years of age (from 19% to 50%) and in people ≥ 65 years of age (from 12% to 43%). In persons 50–64 years of age, the proportion of NVT serotype PM had decreased from 22% to 17%. In adults ≥ 65 years of age, the proportion of NVT PM increased from 16% to 36% (Fig. 2).

In adults ≥ 18 years of age, comparing 2016–2017 to the pre-PCV10 period, the proportion of PCV10 serotypes decreased from 57% to 14%. On the contrary, there was an increase from 16% to 41% in proportion of PPSV23 unique serotypes. The proportion of NVT serotypes increased from 19% in pre-PCV10 to 41% in 2016–2017 (Fig. 2).

In 2016–2017, the serotypes causing most cases were 22F, 6C and 23A (Fig. 3). Compared with the pre-PCV10 period, these serotypes also had the largest increases (Fig. 3).

Table 1
Incidence rates of pneumococcal meningitis (PM) and the corresponding relative and absolute rate reduction according to age group, based on the comparison of the pre-PCV10 period vs PCV10 period, Finland.

	Age group (years)	Pre-PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period vs. Pre-PCV10 period		
				Incidence rate ratio	Relative rate reduction (%)	Absolute rate reduction/100,000 person-years
Any culture confirmed PM						
	0–4	2.35 (41)	0.84 (15)	**0.36 (0.19, 0.63)**	**64.45 (37.21, 80.94)**	**1.52 (0.68, 2.35)**
	5–17	0.19 (9)	0.09 (4)	0.46 (0.13, 1.42)	53.86 (−41.69, 87.5)	0.1 (−0.05, 0.25)
	18–49	0.40 (53)	0.31 (40)	0.76 (0.50, 1.14)	24.05 (−14.22, 49.89)	0.1 (−0.05, 0.24)
	50–64	1.38 (93)	0.90 (61)	**0.66 (0.47, 0.90)**	**34.46 (9.74, 52.75)**	**0.47 (0.11, 0.83)**
	>=65	1.17 (61)	1.15 (74)	0.99 (0.70, 1.39)	1.37 (−38.79, 29.65)	0.02 (−0.38, 0.41)
	All*	0.81 (257)	0.59 (194)	**0.73 (0.61, 0.88)**	**26.81 (11.87, 39.31)**	**0.22 (0.09, 0.35)**
PCV10-serotypes						
	0–4	2.07 (36)	0.28 (5)	**0.14 (0.05, 0.31)**	**86.5 (68.64, 95.36)**	**1.79 (1.07, 2.51)**
	5–17	0.10 (5)	0.06 (3)	0.62 (0.13, 2.54)	37.71 (−153.87, 87.22)	0.04 (−0.08, 0.16)
	18–49	0.27 (35)	0.10 (13)	**0.37 (0.19, 0.69)**	**62.62 (31.13, 80.94)**	**0.17 (0.06, 0.27)**
	50–64	0.68 (46)	0.25 (17)	**0.37 (0.21, 0.63)**	**63.07 (36.87, 79.41)**	**0.43 (0.2, 0.66)**
	>=65	0.71 (37)	0.22 (14)	**0.31 (0.16, 0.56)**	**69.24 (44.42, 83.92)**	**0.49 (0.24, 0.75)**
	All	0.50 (159)	0.16 (52)	**0.32 (0.23, 0.43)**	**68.29 (56.96, 77.02)**	**0.34 (0.25, 0.43)**
Non-PCV10 serotypes						
	0–4	0.23 (4)	0.56 (10)	2.43 (0.81, 8.86)	−142.94 (−785.68, 18.74)	−0.33 (−0.74, 0.08)
	5–17	0.08 (4)	0.02 (1)	0.26 (0.01, 1.75)	74.05 (−75.45, 98.67)	0.06 (−0.03, 0.15)
	18–49	0.13 (17)	0.21 (27)	1.60 (0.88, 2.99)	−59.83 (−198.81, 12.06)	−0.08 (−0.18, 0.02)
	50–64	0.67 (45)	0.64 (43)	0.96 (0.63, 1.45)	4.51 (−45.16, 37.27)	0.03 (−0.24, 0.3)
	>=65	0.36 (19)	0.94 (60)	**2.57 (1.56, 4.42)**	**−156.74 (−341.56, −56.36)**	**−0.57 (−0.86, −0.28)**
	All	0.28 (89)	0.43 (141)	**1.54 (1.18, 2.01)**	**−53.62 (−100.91, −18.08)**	**−0.15 (−0.24, −0.06)**
PCV13-serotypes						
	0–4	2.18 (38)	0.34 (6)	**0.15 (0.06, 0.34)**	**84.66 (66.35, 94.17)**	**1.85 (1.1, 2.59)**
	5–17	0.15 (7)	0.06 (3)	0.45 (0.10, 1.6)	55.51 (−60.04, 90.41)	0.08 (−0.05, 0.21)
	18–49	0.27 (36)	0.15 (19)	**0.53 (0.30, 0.91)**	**46.89 (8.54, 70.13)**	**0.13 (0.02, 0.24)**
	50–64	0.81 (55)	0.46 (31)	**0.56 (0.36, 0.87)**	**43.68 (13.16, 64.13)**	**0.36 (0.09, 0.62)**
	>=65	0.84 (44)	0.37 (24)	**0.44 (0.27, 0.72)**	**55.65 (27.77, 73.43)**	**0.47 (0.18, 0.76)**
	All	0.57 (180)	0.25 (83)	**0.45 (0.34, 0.58)**	**55.29 (42.23, 65.68)**	**0.31 (0.21, 0.41)**
Non-PCV13 serotypes						
	0–4	0.12 (2)	0.50 (9)	**4.37 (1.13, 28.68)**	**−337.29 (−2768.43, −12.7)**	**−0.39 (−0.75, −0.02)**
	5–17	0.04 (2)	0.02 (1)	0.52 (0.02, 5.42)	48.09 (−441.95, 97.59)	0.02 (−0.05, 0.09)
	18–49	0.12 (16)	0.16 (21)	1.32 (0.69, 2.57)	−32.08 (−157.05, 30.81)	−0.04 (−0.13, 0.05)
	50–64	0.53 (36)	0.43 (29)	0.81 (0.49, 1.31)	19.5 (−31.03, 50.97)	0.1 (−0.13, 0.34)
	>=65	0.23 (12)	0.78 (50)	**3.39 (1.87, 6.67)**	**−238.75 (−566.6, −86.85)**	**−0.55 (−0.8, −0.3)**
	All	0.21 (68)	0.34 (110)	**1.57 (1.16, 2.13)**	**−56.85 (−113.12, −16.28)**	**−0.12 (−0.2, −0.04)**
PCV13-PCV10 serotypes (3, 6A, 19A)						
	0–4	0.12 (2)	0.06 (1)	0.49 (0.02, 5.07)	51.41 (−407.28, 97.74)	0.06 (−0.13, 0.25)
	5–17	0.04 (2)	0 (0)	0 (0, 1.62)	100 (−61.61, 100)	0.04 (−0.02, 0.1)
	18–49	0.01 (1)	0.05 (6)	**6.04 (1.03, 114.04)**	**−503.82 (−11303.54, −3.15)**	**−0.04 (−0.08, 0)**
	50–64	0.13 (9)	0.21 (14)	1.55 (0.68, 3.73)	−55.45 (−273.16, 31.81)	−0.07 (−0.21, 0.07)
	>=65	0.13 (7)	0.16 (10)	1.16 (0.45, 3.20)	−16.14 (−219.85, 55.39)	−0.02 (−0.16, 0.12)
	All	0.07 (21)	0.10 (31)	1.43 (0.83, 2.53)	−43.14 (−152.46, 17.22)	−0.03 (−0.07, 0.02)
PPSV23 unique serotypes						
	0–4	0 (0)	0.22 (4)	–	–	−0.22 (−0.44, 0)
	5–17	0.02 (1)	0.021 (1)	1.04 (0.04, 26.25)	−3.82 (−2525.4, 95.89)	0 (−0.06, 0.06)
	18–49	0.06 (8)	0.08 (11)	1.38 (0.56, 3.57)	−38.37 (−257.43, 43.99)	−0.02 (−0.09, 0.04)
	50–64	0.27 (18)	0.21 (14)	0.78 (0.38, 1.56)	22.28 (−55.78, 62.01)	0.06 (−0.1, 0.22)
	>=65	0.13 (7)	0.33 (21)	**2.44 (1.09, 6.19)**	**−143.9 (−519.26, −8.77)**	**−0.19 (−0.36, −0.02)**
	All	0.11 (34)	0.16 (51)	1.45 (0.95, 2.26)	−45.45 (−126.28, 5.33)	−0.05 (−0.1, 0.01)
3						
	0–4	0.06 (1)	0.06 (1)	0.97 (0.04, 24.57)	2.82 (−2357.41, 96.16)	0 (−0.16, 0.16)
	5–17	0.04 (2)	0 (0)	0 (0, 1.62)	100 (−61.61, 100)	0.04 (−0.02, 0.1)
	18–49	0 (0)	0.02 (2)	–	–	−0.02 (−0.04, 0.01)
	50–64	0.04 (3)	0.04 (3)	1.0 (0.19, 5.40)	0.07 (−439.95, 81.51)	0 (−0.07, 0.07)
	>=65	0.08 (4)	0.06 (4)	0.81 (0.19, 3.44)	18.7 (−243.84, 80.78)	0.01 (−0.08, 0.11)
	All	0.03 (10)	0.03 (10)	0.97 (0.40, 2.36)	3.04 (−136.28, 60.21)	0 (−0.03, 0.03)
6A						
	0–4	0.06 (1)	0 (0)	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
	5–17	0 (0)	0 (0)	–	–	–
	18–49	0.01 (1)	0.01 (1)	1.01 (0.04, 25.45)	−0.64 (−2444.9, 96.02)	0 (−0.02, 0.02)
	50–64	0.07 (5)	0.09 (6)	1.20 (0.36, 4.16)	−19.91 (−316.09, 63.88)	−0.01 (−0.11, 0.08)
	>=65	0.08 (4)	0.06 (4)	0.81 (0.19, 3.44)	18.7 (−243.84, 80.78)	0.01 (−0.08, 0.11)
	All	0.03 (10)	0.03 (9)	0.87 (0.35, 2.17)	12.73 (−116.51, 65.33)	0 (−0.02, 0.03)

(*continued on next page*)

Table 1 (*continued*)

	Age group (years)	Pre-PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period Incidence rate per 100,000 person-years (N)	PCV10 period vs. Pre-PCV10 period		
				Incidence rate ratio	Relative rate reduction (%)	Absolute rate reduction/100,000 person-years
6C						
	0–4	0 (0)	0.11 (2)	–	–	−0.11 (−0.27, 0.04)
	5–17	0 (0)	0 (0)	–	–	
	18–49	0 (0)	0.03 (4)	–	–	−0.03 (−0.06, 0)
	50–64	0.02 (1)	0.04 (3)	3.0 (0.38, 60.61)	−199.79 (−5960.57, 61.62)	−0.03 (−0.09, 0.03)
	>=65	0.04 (2)	0.09 (6)	2.44 (0.56, 16.65)	−143.9 (−1564.69, 43.8)	−0.06 (−0.15, 0.04)
	All	0.01 (3)	0.05 (15)	**4.85 (1.6, 20.93)**	**−384.82 (−1993.23, −60)**	**−0.04 (−0.06, −0.01)**
19A						
	0–4	0 (0)	0 (0)	–	–	–
	5–17	0 (0)	0 (0)	–	–	–
	18–49	0 (0)	0.02 (3)	–	–	−0.02 (−0.05, 0)
	50–64	0.02 (1)	0.07 (5)	5.00 (0.81, 95.73)	−399.65 (−9472.74, 19.42)	−0.06 (−0.13, 0.01)
	>=65	0 (0)	0.06 (4)	–	–	−0.06 (−0.12, 0)
	All	0.00 (1)	0.04 (12)	**11.64 (2.29, 211.99)**	**−1063.56 (−21099.18, −129.33)**	**−0.03 (−0.06, −0.01)**
22F						
	0–4	0 (0)	0.06 (1)	–	–	−0.06 (−0.17, 0.05)
	5–17	0 (0)	0 (0)	–	–	
	18–49	0.03 (4)	0.02 (3)	0.76 (0.15, 3.42)	24.52 (−242.4, 85.13)	0.01 (−0.03, 0.05)
	50–64	0.04 (3)	0.10 (7)	2.33 (0.65, 10.82)	−133.17 (−981.94, 35.18)	−0.06 (−0.15, 0.03)
	>=65	0.06 (3)	0.16 (10)	2.71 (0.83, 12.09)	−171 (−1108.77, 17.1)	−0.1 (−0.21, 0.02)
	All	0.03 (10)	0.06(21)	2.04 (0.98, 4.52)	−103.62 (−351.53, 1.71)	−0.03 (−0.07, 0)

* Includes cases with missing serotype information.

3.1.4. Case fatality proportions and mortality rates

We identified 64 PM-related deaths which occurred within 30 days of the first positive culture (40 deaths in pre-PCV10 period and 24 deaths in PCV10-period). All identified deaths, except one, were in adults ≥ 18 years of age (Table 2). Compared with the pre-PCV10 baseline period, the overall mortality rate related to all PM decreased by 42% (95%CI 4%-65%) from 0.13 to 0.07 deaths per 100,000 person-years. This was primarily due to 66% (95%CI 31%-85%) reduction in mortality rate for PCV10 serotype PM (Table 2), particularly in persons 50–64 years of age (reduction by 80% (95%CI 39%-95%)). The overall CFPs during the pre-PCV10 period and PCV10 period were 16% and 12%, respectively (p = 0.41). The CFP in persons 50–64 years of age decreased from 25% in pre-PCV10 period to 10% in PCV10-period (p = 0.04).

In adults ≥ 18 years of age, the PM-related mortality rate decreased by 41% (95%CI 3%-65%) from 0.16 to 0.09 deaths per 100,000 person-years, mainly due to decrease by 65% (95%CI 29%-85%) in mortality rate for PCV10 serotype PM. The CFPs in pre-PCV10 period and PCV10 period were 19% and 14%, respectively (p = 0.61).

4. Discussion

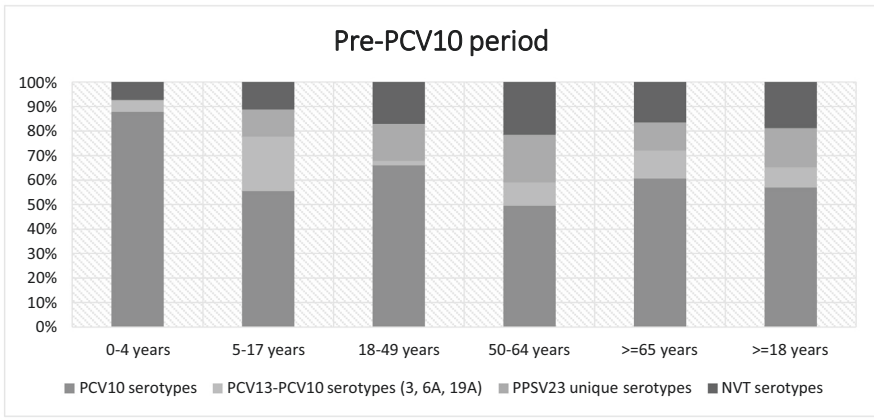
Seven years of infant PCV10 program has resulted in substantial reduction in the burden of pneumococcal meningitis in Finland. The overall incidence of PCV10 serotype meningitis was reduced by 68% and, consequently, the overall PM incidence by 27%. In vaccine-eligible children, there was an 87% reduction in the incidence of PCV10 serotype cases and in 2017, no PCV10 serotype meningitis cases were seen. The overall PM-related mortality rate was reduced by 42%. The case fatality proportion decreased from 25% to 10% in persons 50–64 years. However, an important burden of disease remains in older adults because of an increase in PM caused by non-PCV10 serotypes.

Our study suggests substantial herd effect of vaccination, since incidence rates of PCV10 serotypes cases decreased not only in vaccinated children, but also in non-vaccinated population groups including older adults ≥ 65 years of age. However, because of serotype replacement, no net impact of PCV10 on disease burden was seen in the older adult age group. In the final study year, the significant decrease in PCV10 serotype PM was offset mostly by disease caused by serotype 22F (included in PPSV23) and non-vaccine serotypes such as 6C and 23A. This suggests relatively small potential benefits of PCV13 vaccination for older adults and a potential advantage of PPSV23 in terms of covered serotypes.

Serotype replacement has been widely reported after introduction of pneumococcal vaccines. After PCV7 introduction, meningitis cases caused by non-PCV7 serotypes emerged, particularly serotypes 1, 3, 7F, 19A and 22F [25–28]. After introduction of higher valency vaccines, significant reductions in PM have been reported among children < 5 years in France, England and Wales and Israel due to decreases in the additional serotypes included in PCV13 [14,29,30]. Among U.S. children and Israeli adults, the number of PM cases remained almost unchanged despite a decrease in the proportion of PCV13 serotypes after PCV13 introduction [16,31]. The most frequent emerging non-PCV13 serotypes during PCV13 vaccination period have been 8 and 12F in England and Wales [29]; 12F, 24F, 23B and 10A in France [14]; 12F, 16F, 6C, 23A, 23B, and 24F in Israel [16]; and 22F and 35B among U.S. children [31]. In the US, serotype 19A continued to be the most common PM serotype after three years of infant PCV13 vaccination program [31]. In Brazil where PCV10 was implemented, PM in children decreased significantly after introduction. Non-PCV10 serotypes 12F, 10A, 15B and 18B were reportedly most prevalent during PCV10 period [32].

In our study, the incidence of serotype 6A PM was low and did not change after PCV10 introduction. In PCV10-period, however, we saw an increase in serotype 6C in adults ≥ 18 years of age. Emergence of this IPD serotype has been noted also in other settings, including those using PCV13 [16,33].

Regardless of age, PM incidence of serotype 3 has not changed in PCV10 period. In Brazil, increase in serotype 3 was found in patients aged over 18 years with a diagnosis other than meningitis [19]. In Israel, serotype 3 PM increased after PCV13 introduction



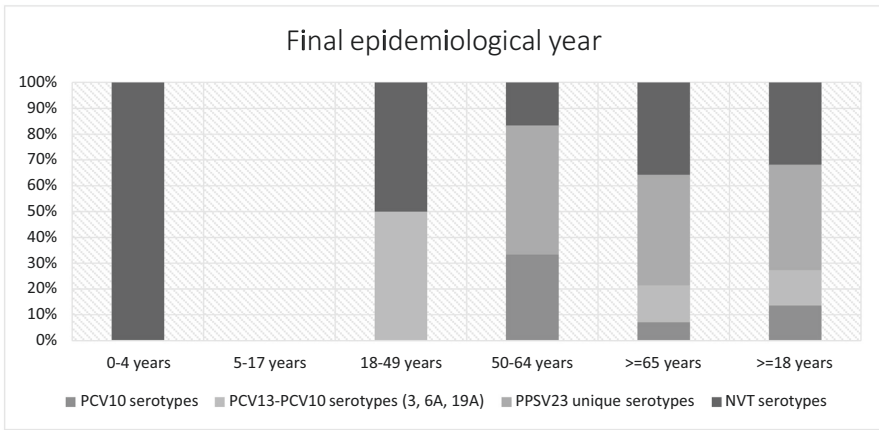


Fig. 2. Proportions of pneumococcal meningitis (PM) according to serotype in age groups in the pre-PCV10 period and in the final epidemiological year (2016–2017) of the study, Finland.

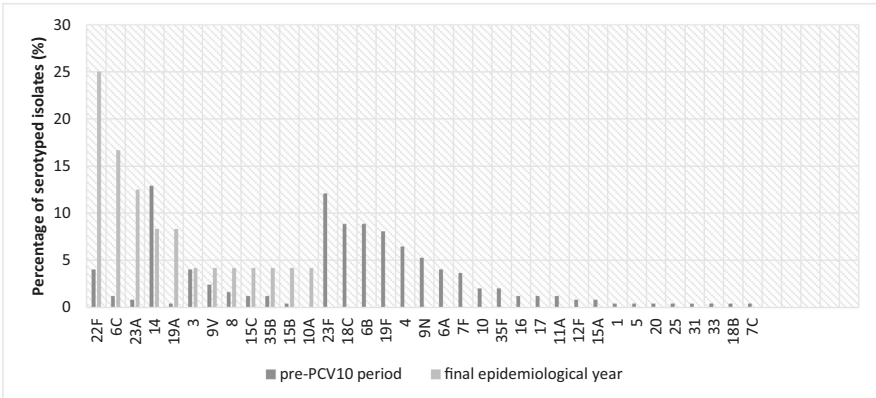


Fig. 3. Contribution (percentage) of individual *Streptococcus pneumoniae* serotypes to pneumococcal meningitis cases for all age groups before PCV10 introduction and in the final epidemiological year of the study (2016–2017), Finland.

Table 2
Mortality rates of pneumococcal meningitis (PM) and the corresponding relative and absolute rate reduction, based on the comparison of the pre-PCV10 period vs PCV10 period, Finland.

		Pre-PCV10 period		PCV10 period		Pre-PCV10 period vs PCV10 period		
	Age group (years)	Mortality/ 100,000 person-years (N)	CFP (%)	Mortality/ 100000 person-years (N)	CFP (%)	Mortality rate ratio	Relative rate reduction, %	Absolute rate reduction/ 100,000 person-years
Any culture confirmed								
	0–4	0.06 (1)	2.4	0 (0)	0.0	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.05 (6)	11.3	0.04 (5)	12.5	0.84 (0.24, 2.78)	16.14 (−178.45, 75.83)	0.01 (−0.04, 0.06)
	50–64	0.34 (23)	24.7	0.09 (6)	9.8	**0.26 (0.10, 0.60)**	**73.93 (39.92, 90.37)**	**0.25 (0.1, 0.41)**
	>=65	0.19 (10)	16.4	0.20 (13)	17.6	1.06 (0.47, 2.48)	−5.69 (−147.59, 53.51)	−0.01 (−0.17, 0.15)
	All	0.13 (40)	15.6	0.07 (24)	12.4	**0.58 (0.35, 0.96)**	**41.82 (4.26, 65.4)**	**0.05 (0, 0.1)**
PCV10-serotypes								
	0–4	0.06 (1)	2.8	0 (0)	0.0	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.03 (4)	11.4	0.02 (3)	23.1	0.76 (0.15, 3.42)	24.52 (−242.4, 85.13)	0.01 (−0.03, 0.05)
	50–64	0.22 (15)	32.6	0.04 (3)	17.6	**0.2 (0.05, 0.61)**	**80.01 (39.44, 95.37)**	**0.18 (0.05, 0.3)**
	>=65	0.12 (6)	16.2	0.05 (3)	21.4	0.41 (0.09, 1.54)	59.35 (−54.08, 91.42)	0.07 (−0.04, 0.17)
	All	0.08 (26)	16.4	0.03 (9)	17.3	**0.34 (0.15, 0.69)**	**66.44 (31, 85.14)**	**0.05 (0.02, 0.09)**
Non-PCV10 serotypes								
	0–4	0 (0)	0.0	0 (0)	0.0	–	–	–
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.02 (2)	11.8	0.02 (2)	7.4	1.01 (0.12, 8.39)	−0.64 (−738.79, 87.93)	0 (−0.03, 0.03)
	50–64	0.12 (8)	17.8	0.04 (3)	7.0	0.38 (0.08, 1.30)	62.53 (−29.56, 91.79)	0.07 (−0.02, 0.17)
	>=65	0.08 (4)	21.1	0.16 (10)	16.7	2.03 (0.68, 7.41)	−103.25 (−640.99, 32.01)	−0.08 (−0.2, 0.04)
	All	0.04 (14)	15.7	0.05 (15)	10.6	1.04 (0.50, 2.18)	−3.89 (−117.65, 50.1)	0 (−0.03, 0.03)
PCV13-serotypes								
	0–4	0.06 (1)	2.6	0 (0)	0.0	0 (0, 5.87)	100 (−487.09, 100)	0.06 (−0.06, 0.17)
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.03 (4)	11.1	0.02 (3)	15.8	0.76 (0.150, 3.42)	24.52 (−242.4, 85.13)	0.01 (−0.03, 0.05)
	50–64	0.25 (17)	30.9	0.07 (5)	16.1	**0.29 (0.10, 0.74)**	**70.61 (25.7, 90.34)**	**0.18 (0.04, 0.31)**
	>=65	0.12 (6)	13.6	0.05 (3)	12.5	0.41 (0.09, 1.54)	59.35 (−54.08, 91.42)	0.07 (−0.04, 0.17)
	All	0.09 (28)	15.6	0.03 (11)	13.3	**0.38 (0.18, 0.74)**	**61.91 (25.62, 81.84)**	**0.05 (0.02, 0.09)**
Non-PCV13 serotypes								
	0–4	0 (0)	0.0	0 (0)	0.0	–	–	–
	5–17	0 (0)	0.0	0 (0)	0.0	–	–	–
	18–49	0.02 (2)	12,5	0.02 (2)	9,5	1.01 (0.12, 8.39)	−0.64 (−738.79, 87.93)	0 (−0.03, 0.03)
	50–64	0.09 (6)	16,7	0.02 (1)	3,4	**0.17 (0.01, 0.98)**	**83.35 (2.51, 99.12)**	**0.07 (0, 0.15)**
	>=65	0.08 (4)	33,3	0.16 (10)	20,0	2.03 (0.68, 7.41)	−103.25 (−640.99, 32.01)	−0.08 (−0.2, 0.04)
	All	0.04 (12)	17,6	0.04 (13)	11,8	1.05 (0.48, 2.34)	−5.04 (−133.53, 52.35)	0 (−0.03, 0.03)
PCV13-PCV10 serotypes (3, 6A, 19A)								
	0–4	0 (0)	0,0	0 (0)	0,0	–	–	–
	5–17	0 (0)	0,0	0 (0)	–	–	–	–
	18–49	0 (0)	0,0	0 (0)	0,0	–	–	–
	50–64	0.03 (2)	22,2	0.03 (2)	14,3	1.00 (0.12, 8.33)	0.07 (−732.9, 88.01)	0 (−0.06, 0.06)
	>=65	0 (0)	0,0	0 (0)	0,0			
	All	0.01 (2)	9,5	0.01(2)	6,5	0.97 (0.12, 8.08)	3.04 (−708.18, 88.37)	0 (−0.01, 0.01)
PPSV23 unique serotypes								
	0–4	0 (0)	–	0 (0)	0,0	–	–	–
	5–17	0 (0)	0,0	0 (0)	0,0	–	–	–
	18–49	0.02 (2)	25,0	0.02 (2)	18,2	1.01 (0.12, 8.39)	−0.64 (−738.79, 87.93)	0 (−0.03, 0.03)
	50–64	0.04 (3)	16,7	0.02 (1)	7,1	0.33 (0.02, 2.60)	66.69 (−160.17, 98.35)	0.03 (−0.03, 0.09)
	>=65	0.08 (4)	57,1	0.08 (5)	23,8	1.02 (0.27, 4.11)	−1.63 (−310.59, 73.11)	0 (−0.1, 0.1)
	All	0.03 (9)	26,5	0.02 (8)	15,7	0.86 (0.32, 2.25)	13.81 (−125.43, 67.64)	0 (−0.02, 0.03)

[16]. Serotype 3 has been a common replacing serotype in adult IPD. Study results regarding direct PCV13 effectiveness against IPD serotype 3 have been inconsistent, and some suggest poor immunogenicity and effectiveness [34–38]. Several reports on IPD suggest no indirect protection from PCV13 against serotype 3 [39,40].

In our study, no cases of serotype 19A PM were seen in children, but its incidence increased significantly in adults $\geq$ 18 years of age. These findings are consistent with other studies [41]. In many European countries and the US after PCV7 introduction, serotype 19A emerged as the most common replacing serotype causing meningitis [42]. Emergence of this serotype might be related to high prevalence of 19A carriage during pre-vaccination period, antimicrobial non-susceptibility and capsular switching [43]. Continuous surveillance will be essential in determining whether serotype replacement will lead to increases in serotype 19A meningitis in Finland.

PCV10 vaccination has had an impact not only on morbidity, but also on PM-associated mortality. The overall PM-associated mortality rate was reduced by 42%. In the PCV10 period, there were no deaths related to PM in children < 18 years. In adults 50–64 years of age, where the burden of disease is high, PM-associated mortality rate was reduced by 74% and case fatality by 15%. The reduction in PM related mortality was mostly due to decrease in PCV10 serotype-related fatal cases. These results are consistent with other studies conducted with either PCV13 or PCV10 in the US and Brazil [44,45]. The reduction in PM associated mortality and overall CFP might be due to lower invasive potential

of the replacing pneumococcal strains and/or changes in clinical practice, such as use of adjunctive dexamethasone therapy [46,47].

Some limitations should be considered with our data. First, the observational before-after comparison study design is susceptible to bias due to secular trends, potential changes in reporting system, clinical practices and prevalence of risk factors. The estimated magnitude and precision of herd effects of pediatric PCV programs depends on the choice of analytical methodology. For datasets where, upward trends in overall IPD were reported before vaccine introduction, substantially larger estimated herd effects might be observed in interrupted time series (ITS) analysis, than in before-after analysis. In such a situation, before-after analysis is characterized by smaller differences in observed and expected IRRs and smaller or no herd effects, since pre-vaccine trends are averaged out [48]. In Finland there have been no major changes in meningitis case ascertainment since 1995 and no trend in PM incidence was observed before PCV10 introduction [49]. Therefore, we choose not to adjust for trend in our analysis. Information of comorbidities and treatment were not available in surveillance data. Secondly, we did not have information on cause of deaths. However, most of the deaths associated with bacterial meningitis occurred early (within 14 days of admission), suggesting that they were related to the infection. Due to very small number of fatal cases, it was not possible to assess the association between particular serotype and risk of death. According to the National vaccination register, the uptake of adult PCV13 vaccinations was about 8% and that of PPSV23 about 2% during the study period. It is therefore unlikely that adult vaccinations influenced the results.

The study has several strengths. First, we used data from national, laboratory-based surveillance system that allows near complete case ascertainment and serotyping. The linking of the National Infectious Diseases Register database with the Population Information System of Finland allows conducting whole population analyses and provides accurate population denominators. In addition, Inclusion of PM cases based on ICD-10 discharge data and positive blood culture results increased the sensitivity of case definition and reduced misclassification

In conclusion, our study contributes to the evidence-base of PCV10 impact on PM in vaccinated children and herd effects on vaccine type PM in unvaccinated age groups. Importantly, substantial reductions in both PM incidence and associated mortality rates were seen in working-age adults 50–64 years of age among whom the PM burden was high. In older adults $\geq$ 65 years of age, however, the burden remains unchanged because of serotype replacement. Cost-effectiveness studies of higher-valency infant and adult vaccination strategies should be considered to achieve optimal vaccination program for prevention of pneumococcal meningitis.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [The Finnish Institute for Health and Welfare has received research funding from GlaxoSmithKline Vaccines for the conduct of a nationwide effectiveness trial of the 10-valent pneumococcal conjugate vaccine, and from Pfizer, Inc. and Sanofi Pasteur, Inc. for non-pneumococcal research. Hanna Rinta-Kokko, Arto A. Palmu and Maija Toropainen are co-investigators in these studies. The other authors have no conflicts to disclose. The current study was entirely publicly funded.].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.02.030.

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