



Peter Klemets

Invasive Pneumococcal Infections in Finland before Routine Use of Conjugate Vaccines: Opportunities for Prevention

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**Invasive Pneumococcal Infections
in Finland before Routine Use
of Conjugate Vaccines:
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ACADEMIC DISSERTATION

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ABSTRACT

Background and aims. *Streptococcus pneumoniae* is a leading cause of pneumonia, meningitis and bacteremia worldwide. The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for adults under 65 years with certain chronic medical conditions and for all elderly persons because of high rates of invasive pneumococcal infections (IPI) and increased risk of death. Representative, population-based information about the risk factors and clinical outcome of IPI is limited. National data to determine the disease burden and new risk groups are important for planning vaccination programs. Information about increased risk of IPI among patients with asthma is limited and the characteristics, risk factors, and outcome of infection in patients with nosocomial pneumococcal bacteremia (NPB) seldom appear in large, population-based studies. The objective of this study was to provide baseline data on the epidemiology of IPI in Finland before the introduction of childhood pneumococcal conjugate vaccines with special emphasis on the incidence, risk factors for IPI, outcome, the role of asthma, and healthcare-associated IPI.

Methods. This study was based on national, population-based laboratory surveillance for IPI. Information on all episodes of IPI was collected from the primary diagnostic laboratory. A case with IPI was defined as the isolation of *S. pneumoniae* from blood or cerebrospinal fluid (CSF) or both during 1995-2002. Pneumococcal bacteremia was defined as nosocomial if the first positive blood culture was obtained more than two days after hospital admission or if the patient had been hospitalized for more than two days within seven days of the first positive blood culture. Information about the annual numbers of blood culture and CSF sets processed during the study period were obtained through a survey of all clinical microbiology laboratories. Information on comorbidities and underlying conditions for IPI patients was obtained by linking the IPI surveillance database to other national, population-based health registries using each patient's unique national identity code. For each IPI case with chronic lung disease aged 18-49 years, ten age-, gender-, and health district-matched controls were selected from the Population Information System.

Results: In total, 4357 cases of IPI were identified: 94.2% were bacteremias and 5.7% were meningitis. Of the cases, 58.2% were males, and the median age was 52.6 years. The

overall annualized IPI incidence was 10.6 per 100 000 population. The rate in children under five years was 23.5 per 100 000. Regional pneumococcal bacteremia rates were correlated with blood culture sampling rates ($P= 0.015$), but meningitis rates did not correlate with CSF culture rates. During the study period, the overall annual IPI rate increased by 35.1%, and the annual blood culturing rate increased by 29.6%. Pneumococcal serotypes included in the 7-valent conjugate vaccines caused 69.8% of IPIs among children under five years and 49.5% in adults, respectively. Of the 4357 cases with IPI, those aged 18-49 and 50-64 years accounted for 29.4% and 21.4% of IPI cases, of which 29.0% and 45.7% showed a current indication for PPV23, respectively. Overall, 12.3% of IPI patients died within one month of the first positive culture. Persons aged 18-64 years accounted for 47.4% of all deaths (case-fatality proportion, 11.5%). Of those who died, 46.0% showed no vaccine indication. Overall, 7.4% of cases had a chronic lung disease. After adjustment for other independent risk factors in a conditional logistic regression model, IPI was associated with both low-risk asthma (LRA) (matched OR, 2.8; 95% CI, 2.1-3.6) and high-risk asthma (HRA) (matched OR, 12.3; 95% CI, 5.4-28.0). The adjusted population-attributable risks for HRA and LRA were 0.010 (95% CI, 0.0035-0.017) and 0.039 (95% CI, 0.023-0.055), respectively. Of the 3973 pneumococcal bacteremias, 9.7% had NPB. Patients with NPB were significantly older ($P<0.001$) and were more likely to have at least one high-risk condition (other than age 65 years or older) for which PPV23 is recommended, than were patients with community-associated pneumococcal bacteremias (CAPB). The case-fatality at 28 days was higher in patients with NPB than in CAPBs (23.8% vs. 10.8%, $P<0.001$).

Conclusions: The true incidence of IPI in Finland may be higher than previously estimated. In the general population of non-elderly adults, two-thirds of invasive infections and one half of fatal cases occur in persons with no recognized PPV23 indication. Asthma is associated with a moderately higher risk of IPI, to which approximately 5% of the disease burden can be attributed. About 10% of all pneumococcal bacteremias were healthcare-associated, and mortality among patients with NPB was over twice as high as among patients with CAPB. Most of the patients with nosocomial disease exhibited underlying conditions for which PPV23 is recommended. The findings of this study emphasize the need for improved prevention efforts against pneumococcal infections through increased use of PPV23 in adult risk groups and introduction of childhood immunization with pneumococcal conjugate vaccine in Finland.

Keywords: asthma, bacteremia, epidemiology, invasive pneumococcal infections, meningitis, nosocomial pneumococcal bacteremia, outcome, public health, risk factors, pneumococcal vaccines

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TIIVISTELMÄ

Tausta ja tavoitteet. *Streptococcus pneumoniae* on maailmanlaajuisesti yleinen keuhkokuumeen, aivokalvotulehduksen ja bakteremian aiheuttaja. Pneumokokki-polysakkaridirokotetta (PPV23) suositellaan kaikille vanhuksille ja alle 65-vuotiaille aikuisille, joilla on perussairautensa vuoksi erityisen suuri riski sairastua ja kuolla invasiiviseen pneumokokki-infektioon (IPI). Edustavaa väestötason tietoa IPI:n riskitekijöistä ja kuolleisuudesta on vähän. Tietoa kansallisen tason tautitaakasta ja uusista riskiryhmistä tarvitaan rokotusohjelmien suunnittelussa. Myös tieto astmapotilaiden riskistä sairastua IPI:in on ristiriitaista ja sairaalasyntyisen pneumokokkibakteremian erityispiirteitä, riskitekijöitä ja kuolleisuutta ei ole aiemmin selvitetty laajoissa väestöpohjaisissa tutkimuksissa. Tämän tutkimuksen tavoitteena oli kerätä perustietoa IPI:n epidemiologiasta Suomessa ennen lapsille suunnatun pneumokokkikonjugaattirokotteen käyttöönottoa. Kiinnostuksen kohteena oli erityisesti IPI:n ilmaantuvuus, riskitekijät ja kuolleisuus sekä astman ja sairaalasyntyisen IPI:n merkitys.

Menetelmät. Tutkimusaineisto perustui kansalliseen, väestöpohjaiseen IPI:n laboratorioseurantaan. IPI-tapaukset kerättiin kliinisen mikrobiologian laboratorioista. IPI-tapauksen määritelmä oli veren ja/tai likvorin positiivinen *S. pneumoniae* -viljelylöydös vuosina 1995–2002. Pneumokokkibakteremia luokiteltiin sairaalasyntyiseksi, jos pneumokokki oli viljelty toisen sairaalahoitopäivän jälkeen otetusta näytteestä tai jos potilas oli ollut sairaalahoidossa kauemmin kuin kaksi päivää edeltävän viikon kuluessa ensimmäisen positiivisen veriviljelynäytteen jälkeen. Kyselytutkimuksella kerättiin tiedot vuosittaisista veri- ja likvoriviljelymääristä kliinisen mikrobiologian laboratorioista. Tiedot potilaan perussairauksista saatiin yhdistämällä IPI-tutkimusaineisto kansallisiin väestöpohjaisiin terveydenhoitorekistereihin henkilötunnuksen avulla. Jokaiselle 18–49-vuotiaalle kroonista keuhkosairautta sairastavalle IPI-tapaukselle valittiin 10 iän, sukupuolen ja asuinpaikan suhteen vakioitua kontrollia väestötietojärjestelmästä.

Tulokset: Kaikkiaan todettiin 4357 IPI-tapausta, joista 94,2 % oli bakteremioita ja 5,7 % aivokalvontulehduksia. Tapauksista 58,2 % oli miehiä ja heidän iän mediaani oli 52,6 vuotta. IPI:n keskimääräinen vuosittainen ilmaantuvuus oli 10,6/100 000

henkilövuotta. Alle 5-vuotiailla lapsilla ilmaantuvuus oli 23,5/100 000. Alueelliset pneumokokkibakteremiaesiintyvyydet korreloivat veriviljelyottoaktiviteetin kanssa ($P=0.015$), kun taas aivokalvotulehduksen ja likvorviljelyjen välillä ei vastaavaa yhteyttä todettu. Tutkimusjakson aikana vuosittainen IPI-ilmaantuvuus lisääntyi 35,1 % ja vuosittaiset veriviljelymäärät 29,6 %. Alle 5-vuotiailla 7-valenttiseen konjugaattirokotteeseen kuuluvat serotyypit aiheuttivat 69,8 % IPI-tapauksista ja aikuisilla vastaavasti 49,5 %. Kaikista IPI-tapauksista 29,4 % esiintyi 18–49-vuotiailla ja 21,4 % 50–64-vuotiailla: 18–49-vuotiaista 29,0 %:lla ja 50–64-vuotiaista 45,7 %:lla oli PPV23-rokoteindikaatio. IPI-tapauksista 12,3 % kuoli kuukauden kuluessa ensimmäisen positiivisen viljelynäytteen jälkeen. Kuolleista 47,4 % kuului ikäryhmään 18–64 (tappavuus, 11,5 %). Menehtyneistä 46,0 %:lla ei ollut PPV23-rokoteindikaatiota. Kaikista tapauksista 7,4 %:lla oli krooninen keuhkosairaus. Kun muut itsenäiset riskitekijät oli huomioitu logistisessa regressiomallissa riski sairastua IPI:in liittyi sekä matalan riskin astmaan (kaltaistettu vetosuhde, 2,8; 95 % luottamusväli, 2,1-3,6) että korkean riskin astmaan (kaltaistettu vetosuhde, 12,3; 95 % luottamusväli, 5,4-28,0). Korkean riskin astman ylimääräosuus väestössä oli 0,010 (95 % luottamusväli, 0,0035-0,017) ja matalan riskin astman 0,039 (95 % luottamusväli, 0,023-0,055). Sairaalasentyinen pneumokokkibakteremia todettiin 9,7 %:lla pneumokokkibakteremiatapauksista ($n=3973$): verrattuna avohoidon tapauksiin sairaalasentyiset olivat merkitsevästi iäkkäämpiä ja heillä oli vähintään yksi riskitekijä (muu kuin ikä ≥ 65 vuotta), johon PPV23-rokotetta suositellaan annettavaksi. Tappavuus 28 päivän sisällä oli sairaalasentyisillä pneumokokkibakteremiatapauksilla merkitsevästi korkeampi kuin avohoidon tapauksilla (23,8 % vs. 10,8 %, $P < 0.001$).

Yhteenveto: IPI:n ilmaantuvuus on todennäköisesti aiempia arvioita korkeampi. Työikäisten keskuudessa kaksikolmasosaa infektioista ja puolet kuolemista esiintyy henkilöillä, joilla ei ole PPV23-rokoteindikaatiota. Astmaan liittyy kohtalaisen suuri riski sairastua IPI:in ja se kattaa noin 5 % IPI:n kokonaistautitaakasta. Noin 10 % kaikista pneumokokkibakteremiatapauksista oli sairaalasentyisiä ja niihin liittyvä kuolleisuus oli suurempi kuin muualla saatuun liittyvä. Suurimmalla osalla sairaalasentyisistä tapauksista oli joku PPV23-rokoteindikaation mukainen perussairaus. Tämän tutkimuksen tulokset korostavat pneumokokki-infektioiden ennaltaehkäisyyn tehostamisen tärkeyttä Suomessa pneumokokkirokottein.

Asiasanat: aivokalvotulehdus, astma, bakteremia, epidemiologia, invasiiviset pneumokokki-infektiot, kuolleisuus, pneumokokkirokotteet, riskitekijät, sairaalasentyinen pneumokokkibakteremia

ABBREVIATIONS

ABC	Active Bacterial Core surveillance (USA)
AIDS	Acquired immunodeficiency syndrome
ARD	Alcohol-related diseases
CAPB	Community-associated pneumococcal bacteremia
CDC	Centers for disease control and prevention (USA)
CFP	Case-fatality proportion
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CSF	Cerebrospinal fluid
HAART	Highly active antiretroviral therapy
HCD	Healthcare district
HIV	Human immunodeficiency virus
HR	Hazard ratio
HRA	High risk asthma
ICD	International classification of diseases
IPI	Invasive pneumococcal infections
KELA	National social insurance institution
LRA	Low risk asthma
MOR	Matched odds ratio
NIDR	National infectious diseases register
NPB	Nosocomial pneumococcal bacteremia
OR	Odds ratio
PAR	Population-attributable risk
PCV7	7-valent pneumococcal conjugate vaccine

PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPV23	23-valent pneumococcal polysaccharide vaccine
RR	Relative risk
SPB	<i>Streptococcus pneumoniae</i> bacteremia
SPM	<i>Streptococcus pneumoniae</i> meningitis

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles referred to in the text by their Roman numerals:

- I** Klemets P, Lyytikäinen O, Ruutu P, Kaijalainen T, Leinonen M, Ollgren J, J. P Nuorti. Trends and geographical variation in invasive pneumococcal infections in Finland. *Scand J Infect Dis.* 2008; 40 (8): 621-28
- II** Klemets P, Lyytikäinen O, Ruutu P, Ollgren J, J. P Nuorti. Invasive *Streptococcus pneumoniae* infections among persons with and without underlying medical conditions: rethinking prevention strategies. *BMC Infect Dis* 2008; 8: 96
- III** Klemets P, Lyytikäinen O, Ruutu P, Ollgen J, Kaijalainen T, Leinonen M, Nuorti J.P. Risk of invasive pneumococcal infections among adults with asthma (submitted)
- IV** Lyytikäinen O, Klemets P, Ruutu P, Kaijalainen T, Rantala M, Ollgen J, Nuorti J.P. Defining the population-based burden of invasive pneumococcal bacteremia. *Arch Intern Med.* 2007; 167 (15): 1635-40

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1 INTRODUCTION

Streptococcus pneumoniae (pneumococcus) is a leading cause of pneumonia, meningitis, and bacteremia worldwide and affects mainly young children, the elderly, and persons with certain underlying medical conditions. Pneumococcal infections are estimated to be responsible for 1-2 million deaths in children every year and likely for a similar number among adults (1). For more than 120 years, the study of *Streptococcus pneumoniae* and pneumococcal infections has played a central role in the development of a scientific basis for the control of infectious diseases (2-4). Infections of the middle ear, tracheobronchial tree, and lung stem from the direct spread of the bacteria from the nasopharynx. Pneumococcus may also cause systemic infections and invasive pneumococcal infection (IPI) in which *S. pneumoniae* is isolated from the bloodstream or other normally sterile sites such as cerebrospinal fluid (CSF), synovial or pleural fluids (5).

The reported incidence and serotype distribution for IPI varies globally and over time. Differences in observed rates of IPI between countries and jurisdictions may stem from differences in diagnostic activity and surveillance systems, population demographics, and the prevalence of risk factors for IPI (6, 7). Few studies (8, 9) have evaluated the relationship between the incidence of IPI and blood culturing rates in different catchment areas and over time, and to my knowledge, none have assessed the relationship between IPI and CSF culturing rates.

The 23-valent pneumococcal polysaccharide vaccine (PPV23) is recommended for all adults aged 65 years and older as well as for younger adults with certain chronic medical conditions because of their high disease rates and increased risk of death (10-12). Estimates of the effectiveness of PPV23 against IPI, although somewhat inconsistent, are generally highest among otherwise healthy young adults (13-16), but lower among persons with multiple underlying medical conditions and immunosuppression (17, 18). Available information from representative, population-based studies on the outcome of IPI is limited. Case fatality has generally been defined as in-hospital mortality without extended follow-up after discharge from the hospital (10, 11).

Chronic obstructive pulmonary diseases (COPD) is an established risk factor for IPI (19), but asthma is not universally accepted as an indication for PPV23 (20), and available information about the higher risk of IPI among persons with asthma is limited.

Streptococcus pneumoniae predominantly causes community-acquired respiratory tract, central nervous system, and bloodstream infections, but its role in healthcare-

associated infections remains poorly defined (21, 22). Institutional outbreaks of IPI and multidrug-resistant *S. pneumoniae* have been reported, and the prevalence of antimicrobial resistant strains may be higher in older adults living in long-term care facilities (23-27). Among such adults, IPI is an important cause of illness and death, thus underscoring the need for better prevention efforts through immunization (28).

The purpose of this study was to provide comprehensive baseline information on the epidemiology of IPI in Finland before the introduction of routine childhood immunization with pneumococcal conjugate vaccine. Linking population-based surveillance data collected during the eight-year study period with data available in national healthcare registries enabled us to define the pneumococcal disease burden as well as the incidence, established and new risk factors, clinical outcome, and the contribution of healthcare-associated pneumococcal infections. This study also points to the multiple opportunities for preventing pneumococcal infections in Finland where the use of pneumococcal vaccines has thus far been minimal.

2 REVIEW OF THE LITERATURE

2.1.1 Background (*Streptococcus pneumoniae*)

In the 1880s, *Streptococcus pneumoniae* was recognized as the major cause of pneumonia. During the 20th century, the bacterium has played a central role in the history of microbiology and humoral immunology, as well as in the discovery of DNA (29-31). The organism was almost simultaneously isolated and grown in laboratories in the USA and France by Sternberg and Pasteur, respectively, in 1880. The late 1880s saw the introduction of the term *pneumococcus* and the official name *Diplococcus pneumoniae*. In 1974, the organism was reclassified as *Streptococcus pneumoniae* on the basis of its growth in chains in liquid media (32).

S. pneumoniae is a gram-positive coccus that grows in chains and is catalase-negative. It produces pneumolysin, a toxin that breaks down hemoglobin, thus causing alpha-hemolysis on blood agar. Further, the bacterium is characterized by its susceptibility to optochin and solubility in bile salts.

Almost all clinical isolates of *S. pneumoniae* contain an external polysaccharide capsule. To date, 91 distinct capsules are known. Types that are antigenically related to each other are included in groups (e.g. 19F, 19A, 19B, and 19C), whereas types with no close relationship to other types are designated with numbers only (33). The polysaccharide capsule is of great importance for virulence (34).

Pneumococcus is a commensal member of the oral streptococci and is primarily carried asymptotically (35-37). The bacterium colonizes the nasopharynx and can be isolated from 5% to 10% of healthy adults and from 20% to 40% of healthy children. The rate of colonization seems to be seasonal, peaking in mid-winter (38). On the other hand, a better-known characteristic of this organism is its association with widespread morbidity and mortality. Infection usually takes place as a result of the spread of the bacteria to cavities from which they are not readily cleared (e.g. sinuses, Eustachian tubes, and bronchi). Viral infection, environmental factors, such as cigarette smoke or other toxic substances, and allergies may impair the clearance of the organism, and thus promote infection. Pneumococci may also directly interact with surface receptors on epithelial and mucosal cells and enter the blood stream (39), thus causing invasive infection. IPI is defined as an infection in which *S. pneumoniae* is isolated from blood, CSF, or other normally sterile sites (e.g. pleural, peritoneal, and synovial fluids).

2.1.2 Public health impact

S. pneumoniae is a leading cause of infection-related morbidity and mortality. The organism is endemic worldwide and causes a wide range of diseases ranging from non-severe upper-respiratory infections to severe, life-threatening invasive infections.

The World Health Organization (WHO) has estimated that 1.6 million people die annually from pneumococcal disease, an estimate that includes the death of 0.7-1 million children under five years (40). The disease burden is remarkable. In the USA, *S. pneumoniae* is the most common cause of otitis media, accounting for more than 16 million medical visits annually. Prior to the introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) in the USA, pneumococcus was responsible for 500 000 cases of pneumonia, 60 000 cases of bacteremia, 3 000 cases of meningitis, and 200 childhood deaths annually (41). The FinOM study (42) reports that 40 000 episodes of pneumococcal otitis media occur annually in Finland among children under two years. A study by Heiskanen-Kosma (43) identifies the incidence of pneumococcal pneumonia in children under five years as 8.6 cases per 1 000, which translates to approximately 2 500 cases of pneumonia annually. Among the elderly, the burden of pneumococcal pneumonia is even greater, with an incidence of 14.8 per 1 000 in those aged 60 years or older (44). A review by Mulholland estimated that 70% of severe pneumonia is of pneumococcal origin (45). In some countries, empyema and pulmonary abscesses have become more common as a complication of particularly pneumococcal pneumonia since the 1990s (46-49). In a report from a pediatric tertiary care clinic in Finland, the prevalence of empyema among cases of uncomplicated pneumonia increased from 0.5% to 3.3% during 1991-2006. *S. pneumoniae* was verified from pleural fluid in 46% of the empyema cases (50).

Of all documented IPI among adults, more than 90% are bacteremias and 5% to 10% are meningitis (51). Of all bacteremic infections in Finland during 1995-2004, *S. pneumoniae* was the fourth most common isolate among those aged 15-64 years and the sixth most common among those aged 65 years or older, thus accounting for 10% to 12% and 5% to 7% of cases, respectively (52). In England and Wales, pneumococcus is the third most common isolate reported from blood cultures of patients of all ages and the most common in children in the USA (53). Other clinical manifestations of IPI, such as peritonitis, septic arthritis, and purulent pericarditis, are rare, constituting 2% to 5% of cases (54-58). In children, the clinical presentation of IPI has been bacteremia with no focus in 57% to 71% of cases, pneumonia in 10% to 15% of cases, and meningitis in 8% to 14% of cases (59-62).

Antibiotic resistance is an increasing public health problem in many countries. In Europe, the resistance pattern has a dynamic character. During 1999-2007, penicillin non-susceptibility of *S. pneumoniae* (PNSP) is increasing in Turkey and Finland; on the other hand, it is decreasing in some countries, among those three countries showing the highest PNSP rates in 2006 (63). Erythromycin non-susceptibility is becoming more prevalent in several countries. In Finland this increase is very pronounced (6% in 1999 vs. 26% in 2007), and severe cases of IPI and pneumonia have been detected due to failure of initial macrolide treatment (63-65).

2.1.3 Surveillance

The surveillance system of IPI greatly impacts the reported incidence rates and mortality of the disease. Surveillance systems differ considerably between countries, and particularly between developing and developed ones. This fact makes country-based and even regional comparison complicated. The kind of information the surveillance is based on is fundamental to interpreting the results. Issues of importance are whether the surveillance is active or passive, nationwide, regional or sentinel-based, statutory or voluntary. Further, whether the system relies on laboratory-based data, clinical surveillance, or a combination of both, and whether cases are defined with non-culture or culture methods or both, is crucial.

In the USA, the Active Bacterial Core surveillance (ABCs) at the Centers for Disease Control and Prevention (CDC) provides comparable national data on the incidence of IPI in ten Emerging Infections Program Network sites, representing a population of over 28 million (66). Surveillance for IPI in Europe is very heterogeneous, and several countries lack surveillance systems altogether (67). Large differences in reported disease incidence may reflect both true differences as well as variations in patient and healthcare factors, including surveillance. A number of European countries lack serotype information, which is critical to ascertaining the coverage of PCV7 and other pneumococcal vaccines. Although a large number of IPI episodes are reported through surveillance in Europe, reported IPI rates vary greatly between countries (67-69).

An important difference between IPI rates reported in the USA and those reported by European surveillance systems stems from blood culture practice. In Europe, most positive pneumococcal blood cultures have been taken from hospitalized patients with a more severe disease, whereas in the USA, a significant proportion (79% among children under two years) of IPI isolates comes from outpatients with a milder disease (53, 68, 70).

2.1.4 Incidence

Data from population-based studies carried out in different parts of the world show that the overall rate of IPI is about 15 per 100 000 persons (38). Estimates suggest that a more correct figure in North America and Europe may be more than 40 per 100 000 (33, 71, 72). The age-distribution of IPI is typically bimodal with the highest peaks in newborns and infants up to two years and in adults over 65 years. The shape of the incidence curve remains unchanged compared to that of the preantibiotic era, although the overall incidence of IPI in the population has declined markedly (38). Few studies have reported incidence rates among non-elderly adults aged 18-64 years even though this age group contributes to the largest absolute number of cases (73-76) (Table 1). Before the introduction of PCV7 in the USA, the annual incidence among children 6-11 months was 235, and 166.9 per 100 000 in children under two years, respectively (10, 77); in the U.K., the incidence is 21.1-36.2 per 100 000 children under one year (78). Among the elderly (over 65 years) in developed countries, the incidence of IPI has been estimated at 50 per 100 000 persons (69). For the same age-group during the pre-conjugate vaccine era, higher rates were reported from the USA (19, 74, 79-82) and lower rates from Europe (78). Particularly among children, geographical variations in incidence can be attributed to variations in blood culture practices as described in section 2.1.3. Studies have also shown that variation in blood culture sampling rates can explain differences in IPI or *S. pneumoniae* bacteremia (SPB) rates within geographical regions, as illustrated in Southwestern England and Finland (8, 9, 83). Because a vast majority of adult patients with IPI also have bacteremic pneumococcal pneumonia, variation in the frequency with which blood cultures are obtained in pneumonia patients may explain many of these differences (74, 84, 85).

Rising trends in bacteremia and mostly stable *S. pneumoniae* (SPM) rates have been reported in Sweden, Norway, Scotland, UK, South Carolina, USA and Denmark during 1989-1994, (79, 86-89). In contrast, declining observed rates of pneumococcal bacteremia were reported in Denmark during 1995-1999 (90), but rising rates of IPI were again reported during 2000-2005, due mainly to a rise in bacteremia rates (91). Following large-scale immunization against *Hemophilus influenzae* type b in children, *S. pneumoniae* has become the most common cause of bacterial meningitis. The incidence of SPM in the developed world has remained stable at around 0.5-1.0 per 100 000 (92, 93).

The incidence also varies according to ethnicity and race. In the pre-conjugate vaccine era in the USA, black adults had a three-fold to five-fold higher overall rate of SPB than did whites (74, 75, 79, 94, 95). Studies have shown that Australian

Table 1. Summary of nationwide and large population-based studies on invasive pneumococcal infections (IPI), *S. pneumoniae* bacteremia (SPB), and meningitis (SPM)

Country, publication year	Time period	Region	Age (years)	No. of cases	Annual incidence per 100 000		CFP (%)	Remarks	Reference
					IPI	SPB/SPM			
Australia, 2003	1997-2001	New South Wales metropolitan area	All	3033	Regional variation 10.7-22.0		13.6% No underlying disease: 1% (< 15yrs) 4% (15-64 yrs) 17% (> 65 yrs) With disease: 4% (< 15 yrs) 14% (15-64 yrs) 29% (> 65 yrs) 8.6%	54% exhibited a PPV23 indication	(106)
Australia, 2002	2001	Nationwide	All	1681	8.6 Regional variation: 5.6-48.5	SPM 0.6		PCV7 introduced in late 2001	(107)
Czech Republic, 2008	1997-2006	Nationwide	All	1236	2.3-4.3	SPM Notifications 0.4-0.6 Laboratory 0.6-1.6		Routine notification of IPI and laboratory surveillance	(108)
Denmark, 2004	1992-2001	North Jutland county Population 496 000	>15	628	NA		DM vs. non-DM 11.1% vs. 16.5% at 30 days 16.0% vs. 19.5% at 90 days	Comparison between DM and non-DM IPI cases	(109)
Denmark, 2002	1995-1999	Nationwide	All	5452	1996:27 1999:17				(90)
Denmark, 2008	2000-2005	Nationwide	All	6478	15.4-20.7	SPM 1.2-1.6		Increase due to rise in number of bacteremia cases	(91)

Country, publication year	Time period	Region	Age (years)	No. of cases	Annual incidence per 100 000		CFP (%)	Remarks	Reference
					IPI	SPB/SPM			
France, 2001	1994-1998	Puy-de-Dôme Population 600 000	All	214	IPI 1994: 5.5 1998: 9.3	SPM 0.6	21.5% (at 30 days from IPI diagnosis)	Factors increasing risk of death: age, gender, underlying disease, severity of illness	(110)
Iceland, 2005	1975-2004	Nationwide	All	933	1975-1989: 8.3 1990-2004: 16.7		17% 25% (≥ 16 yrs) SPM 25%	Study of recurrent IPI (n = 36) 94% had predisposing condition; only 26% of eligible cases received PPV23	(111)
International, 2000	1993-1995	Huntington, USA Manchester, UK Barcelona Halifax, Canada Stockholm Population ~2 million	≥ 18	460			US and Spain 20%, UK 13%, Sweden 8%, Canada 6%, SPM 26%, pneumonia without meningitis 19% vs. 7% (≥ 2 vs. 1 lobe) 9% (Norway) 20% (Greenland) 27% (Iceland)	Rate (%) of meningitis in the different centers was similar (6%-9%) and in accordance with that of previous studies. Blood cultures in Stockholm occurred with ~50% of the frequency in other centers; 2% were vaccinated with PPV23.	(105)
International, 2008	2000-2005	Nationwide/ regional Finland, Northern Sweden, Norway, Iceland, Greenland	All	Finland: 4049 N. Sweden: 88 Norway: 5744 Iceland: 274 Greenland: 69 144	11.6 9.1 16.2 14.6 19.8 6.6				(112)
Ireland, 2003 Israel, 1997	1999 1993-1995	Nationwide Nationwide 92% of population	All ≥ 16	603	14.5		27.8%	Laboratory study (susceptibility, serotyping)	(113) (114)

Country, publication year	Time period	Region	Age (years)	No. of cases	Annual incidence per 100 000	CFP (%)	Remarks	Reference
					IPI	SPB/SPM		
Italy, 2005	2001	Population in Piemonte 4.3 million, and in Puglia, 4.1 million	All	Piemonte 135 Puglia 24	Piemonte 3.1 Puglia 0.6	26% 8% (< 2 yrs) 40% (> 65 yrs)	Blood cultures Piemonte vs. Puglia 760 per 100 000 vs. 139 per 100 000	(115)
Netherlands, 2000	1990-1999	Nationwide	All	SPB 5094 SPM 1959		SPM 15%-17%	SPB per 1 000 blood cultures 3.1 vs 2.0	(116)
Norway, 2004	1995-2001	Nationwide	All	4624	19-20		Incidence increased ten-fold, blood culture rate, two-fold over 20 yrs	(89)
Sweden, 2001	1981-1995	Göteborg area	All	876 cases 904 episodes	IPI increase 5.3-10.3	15%	84% ≥ 1 underlying disease	(88)
Sweden, 1998	1981-1996	Southern Sweden (Malmö) Population 420 000	All	560	15.2	19% > 65 yrs 1981-1984 17% 1993-1996 33% < 65 yrs 21% → 11%		(117)
Sweden, 1997	1990-1995	Nationwide	All	SPB 1990 449 1995 1155			SPM (CSF cultures) unchanged 1990-1995	(118)

Country, publication year	Time period	Region	Age (years)	No. of cases	Annual incidence per 100 000		CFP (%)	Remarks	Reference
					IPI	SPB/SPM			
Italy, 2005	2001	Population in Piemonte 4.3 million, and in Puglia, 4.1 million	All	Piemonte 135 Puglia 24	Piemonte 3.1 Puglia 0.6	26% 8% (< 2 yrs) 40% (> 65 yrs)	Blood cultures Piemonte vs. Puglia 760 per 100 000 vs. 139 per 100 000	(115)	
									SPB per 1 000 blood cultures 3.1 vs 2.0
Netherlands, 2000	1990- 1999	Nationwide	All	SPB 5094 SPM 1959		SPM 15%-17%		(116)	
Norway, 2004	1995- 2001	Nationwide	All	4624	19-20		Incidence increased ten-fold, blood culture rate, two-fold over 20 yrs	(89)	
Sweden, 2001	1981- 1995	Göteborg area	All	876 cases 904 episodes	IPI increase 5.3-10.3	15%	84% ≥ 1 underlying disease	(88)	
Sweden, 1998	1981- 1996	Southern Sweden (Malmö) Population 420 000	All	560	15.2	19% > 65 yrs 1981-1984 17% 1993-1996 33% < 65 yrs 21% → 11%		(117)	
Sweden, 1997	1990- 1995	Nationwide	All	SPB 1990 449 1995 1155		SPB 1990 5 1995 15.0	SPM (CSF cultures) unchanged 1990-1995	(118)	

Aborigines (96) and many Native American populations have a higher incidence of IPI in children under two years (97-99).

2.1.5 Mortality

Before the era of serum therapy and antibiotic treatment, mortality due to IPI was higher than 80% (100). Following the introduction of penicillin, the case-fatality rate dropped radically, but despite appropriate treatment and modern intensive care, has remained between 7% and 36% during the past few decades (101). Among young children, CFPs are generally less than 2% in developed countries. In the USA, IPI accounts for more deaths than any other vaccine-preventable bacterial infection (102, 103). Almost half of these deaths occurred in persons aged 65 years or older, and 48.1% in persons aged 18-64 years (66). Pneumonia is the most common cause of IPI-related mortality, and the elderly are more likely to have pneumonia rather than primary bacteremia. This may, at least partly, explain why IPI-related mortality among elderly increases with age (104).

In publications from the last ten years, overall IPI-related mortality has ranged between 6% and 27.8% (Table 1). The CFP varies considerably depending on age-group, underlying medical conditions, type of infection (SPB vs. SPM) and the time-point at which CFP is defined. The highest case fatality have occurred among persons of advanced age and with underlying diseases (104), particularly cirrhosis and alcohol abuse (11). Case fatality also varies significantly by geographic region (104) (Table 1). These differences most likely reflect variations in underlying conditions, hospitalization, and blood culturing practices (104, 105). Among non-elderly adults, the CFP is 2.2 times higher when the IPI case has an underlying condition for which PPV23 is recommended (10). The CFP of SPM varies between 15% and 25% (Table 1).

2.1.6 Invasive pneumococcal disease in Finland

In Finland, three previous nationwide studies have been conducted on the incidence of IPI, of which only one included all age-groups, and the remaining two, children (Table 2). In the late 1970s, the incidence of SPB and SPM was 2.7 and 0.6 per 100 000, respectively, among persons of all ages (122). In this study, *S. pneumoniae* was the fourth (7.8%) most common cause of bacteremia, and 36% of SPB cases occurred among children between one month and four years. Among Finnish adults from three different geographical areas (Southern, Central and Northern Finland), the overall annual incidence of IPI was 9.1 per 100 000, but the incidence rose from 27.1 through 35.8 to 44.5 per 100 000 among those aged 65 years or older, 75 years or older, and 85 years or older, respectively (85). The incidence of SPB and SPM was 8.2 and 0.9 per 100 000.

The incidence of IPI in a nationwide laboratory-based surveillance among Finnish children was 8.9, 24.2, and 45.3 per 100 000 among those under 16 years, under five years, and under two years, respectively (59). In the catchment area of the Tampere University Hospital, the incidence of bacteremic pneumococcal infections among children under 16 years was 10.5 per 100 000, and among those under two years, 53 per 100 000 during the ten-year period 1983-1992 (123). In a nationwide and population-based case-control study among children under 16 years, daycare center or family daycare attendance and a history of frequent otitis media associated with a higher risk for IPI among children under two years (124).

Three Finnish studies report the outcome of IPI. Among children under 15 years, the CFP was about 1% (59). Researchers studied pneumococcal bacteremia among adult patients admitted to the Helsinki University Central Hospital during two periods (55). The overall CFP was 21%, and the rate showed a small decrease from 28% in the 1970s to 17% in the late 1980s. The most common underlying factors were alcohol abuse, cardiovascular diseases, and COPD. In a study from the Turku University Central Hospital, the CFP was 34% among adult patients with SPB (56). Of those patients, 70% had at least one chronic underlying disease and 31% were classified as alcohol abusers.

Jokinen (125) studied the incidence and etiology of pneumonia in Eastern Finland. The overall incidence of pneumonia was 13 per 1000, and in 19% of microbiologically verified cases, the causative agent was *S. pneumoniae*. Among persons aged 60 years or older in a municipality in Eastern Finland, pneumococcal pneumonia was serologically diagnosed in 40% of all pneumonia episodes, thus corresponding to an incidence of 7.0 per 1000 person-years (126). The overall

pneumonia-related mortality rate among the elderly was 8.7 per 1000 person-years. If the initial pneumonia episode was pneumococcal, the subsequent mortality was three times higher than among other elderly inhabitants of the same area. In a study among children under 15 years in four municipalities in Eastern Finland, 28% of pneumonias were caused by *S.pneumoniae* (43).

2.2 Factors influencing the risk of invasive pneumococcal infections

2.2.1 Host factors

Being under 2 or 65 years or older is a well recognized risk factor for IPI. Compared to adolescent, the incidence can be as much as 50 times higher (99). The increased risk of disease among children under two years seems to be related to an immature immunologic response to the polysaccharide capsule and to the high prevalence of colonization (128). Among the elderly, higher rates of underlying medical conditions and age-related immune dysfunction contribute to the increased risk for IPI (129). On the other hand, Sims et al. (130) have shown that age is also independently associated with the risk for pneumococcal infections even when controlling for other risk factors. Several studies overrepresented the rates of IPI among males (10, 74, 75, 79, 131), and in a case-control study with immunocompetent non-elderly adults, male gender was an independent risk factor for invasive infection (76). Underlying conditions such as smoking and alcoholism are more common among males, which may also explain the predominance of males (33).

Many underlying medical conditions are believed to increase the risk for and severity of IPI. Even if the strength of the evidence documenting the risk associated with each condition varies, these conditions are considered indications for PPV23 in many countries, including Finland (Appendix 1). In population-based studies, the rate of IPI among patients with various immunocompromising conditions varies from 33 to 547 per 100 000, and is highest among those with hematological malignancy. In immunocompetent patients (persons with diabetes mellitus, chronic pulmonary disease, and cardiac failure) rates vary less (range, 12-47 per 100 000). These studies reported higher rates for solid cancer (216 to 300 per 100 000), chronic pulmonary disease (63 to 503 per 100 000) and HIV (423 to 2031 per 100 000) (11, 75, 132).

Different pathophysiological mechanisms may explain increased susceptibility to *S. pneumoniae* and severe disease manifestations among persons with underlying disorders. Children and adults with functional and anatomic asplenia are at markedly increased risk for bacteremia, which is also associated with high fatality (133-137). Splenic dysfunction leads to the impaired clearance of encapsulated bacteria from the bloodstream (138), and persons with sickle-cell anemia are at particularly high risk (139). Congestive heart failure, but not ischemic heart disease, is associated

Table 2. Summary of studies on invasive pneumococcal infections (IPI) in Finland

Study population, publication year	Study period	Setting	Age (years)	No. of cases	Annual incidence per 100 000	CFP (%)	Remarks	Reference
Nationwide, 1982	1976-1980	LBS	All	695	SPB 2.7 SPM 0.6	NA		(122)
Nationwide, 1992	1985-1989	LBS	≤ 15	452	< 16 yrs 8.9 < 5 yrs 24.2 < 2 yrs 45.3	NA	SPB with no focus 69% pneumonia 15% meningitis 11% IPI risk factors: < 2 yrs: daycare center, family care, frequent otitis ≥ 2 yrs: siblings under school-age	(59)
Nationwide, 1995	1986-1989	LBS Case-control study	≤ 15	149	NA	NA	95% coverage of PPV23 serotypes	(124)
Three geographical regions (Helsinki, Tampere, Oulu), 1997	1983-1992	LBS	≥ 16	959	IPI 9.1 SPB 8.2 SPM 0.9	NA		(85)
Municipality in Eastern Finland, 1997	1982-1985	Vaccine study (PPV14, influenza). Pneumococcal pneumonia	≥ 60	2837	Overall pneumococcal CAP 5300	Overall pneumonia - related mortality 8.7 per 1000 person-years	Pneumonia-related mortality accounted for 17% of total mortality. Pneumococcal pneumonia accounted for three-fold higher mortality than did other causes of pneumonia	(127)
4 municipalities in Eastern Finland, 1998	1981-1982	Prospective, population-based. Serology of pneumonias	< 15	133	NA	NA	28% of pneumonias caused by pneumococcus Study population 47 000	(43)
Eastern Finland, 4 municipalities, 1991	1981-1982	Prospective, population-based. Radiology, autopsy and serology of pneumonias	All	871	Overall pneumonia: 1300	Overall CFP, all pneumonias: 8% < 15 yrs 0.5% 15-59 yrs 3% ≥ 60 yrs male 21% female 14%	One or more pathogen identified in 258 patients: 19% pneumococcus in all age groups < 5 yrs 17% 5-14 yrs 26% 15-59 yrs 14% ≥ 60 yrs 20% Hospital-acquired pneumonia: 30% pneumococcus	(125)

Study population, publication year	Study period	Setting	Age (years)	No. of cases	Annual incidence per 100 000	CFP (%)	Remarks	Reference
Tertiary care hospital, 1992	1976-1979 1986-1989	Retrospective LBS and chart review	≥ 15	159	NA	21% 1) period 28% 2) period 17%		(55)
Tertiary care hospital, 1995	1983-1992	LBS	< 16	NA	10.5 < 2 yrs 53	NA	Increasing incidence (per 100 000): 1993 < 16 yrs 20 < 2 yrs 20 1994 < 16 yrs 30 < 2 yrs 110	(123)
Tertiary care hospital, 1996	1985-1994	LBS of SPB	Adults	94	NA	34%	Mortality higher than in previous studies from Scandinavia	(56)

CAP, community-acquired pneumonia; CFP, case-fatality proportion; LBS, laboratory-based surveillance; NA, not available; PPV14, 14-valent pneumococcal polysaccharide vaccine; SPB, *Streptococcus pneumoniae* bacteremia; SPM, *Streptococcus pneumoniae* meningitis

with both all-cause pneumonia and IPI. The precise mechanism remains unknown, however (140, 141). Diabetes mellitus is associated with decreased immunity, risk for metabolic derangement, and angiopathy followed by cardiovascular and renal dysfunction (142-145). In two recent population-based studies in Denmark, the risk for pneumococcal bacteremia was higher among young adults and patients with no other coexisting comorbidity. Diabetic patients appeared to have no higher case fatality than did nondiabetic patients (109, 146). The risk of IPI is especially high in persons with chronic lung diseases, such as COPD and emphysema, probably due to poor ciliary function (75). The effect of alcoholism is multifactorial and includes lifestyle-related issues such as cold exposure, malnutrition, and cigarette smoking, as well as suppression of the gag reflex and the impaired function of neutrophils (147-152). Some population-based studies list about one third of patients with IPI as alcoholics (142, 143, 153). Both alcohol- and non-alcohol-related liver disease is related to a higher risk for severe pneumococcal infections; persons with cirrhosis suffer a particularly high fatality rate (75, 153, 154).

S. pneumoniae is the most common pathogen to infect persons with hematological malignancies (multiple myeloma, leukemia and lymphoma) before chemotherapy and hospitalization tip the balance toward gram-negative infections (38, 155). Pneumococcus is the leading cause of community-acquired pneumonia and bacteremia in patients with HIV infection and increases the risk for IPI as much as 10- to 100-fold over that of the general population (7, 156-158). Some researchers have even suggested that bacteremic pneumococcal pneumonia and unusual pneumococcal infections in young adults should trigger a search for HIV infection (159, 160). After the introduction of highly active antiretroviral therapy (HAART) in the mid-1990s, the incidence of IPI dropped by 50% among persons living with AIDS (161). Mortality among HIV patients with IPI seems to be no higher than among non-HIV infected patients, which may stem from the fact that a majority of the patients are young, with no other underlying conditions, and are monitored closely by medical care (33). In a multicenter study, however, mortality at 14 days was significantly higher among those with lower CD4 counts (162).

2.2.2 Socioeconomic factors and living conditions

Pneumococcal infection disproportionately affects persons of lower socioeconomic status (75, 79). Studies in the USA suggest the association may be confounded by over-representation of blacks among low-income IPI cases. A study in metropolitan Atlanta, however, showed that the difference in rates of invasive disease between

blacks and whites decreased in areas with higher incomes, and rates were nearly the same at the highest income levels (163). In a case-control study by Nuorti et al. (76), low household income was not significantly associated with the risk for illness, but a low level of education proved to be a strong independent risk factor after controlling for confounding factors.

Overcrowding is also a risk factor for sporadic IPI and outbreaks of invasive disease in both institutional and non-institutional settings. Studies from different countries show that daycare attendance is strongly associated with increased risk for IPI (124, 164-166). Within-family colonization, particularly after the age of six months, may cause clusters of illnesses stemming from the same serotype of *S. pneumoniae* (36, 167).

2.3 Chronic pulmonary diseases and invasive pneumococcal infections

Chronic obstructive pulmonary diseases are established risk factors for invasive pneumococcal infections (19), but asthma without systemic corticosteroid use is currently not considered an indication of PPV23 in Finland and many other countries (20, 168) (Appendix 1). Asthma prevalence continues to rise globally (169, 170). An estimated 4.4% of Finnish adults have asthma and the prevalence has risen since the 1960s (171, 172). Available information regarding whether asthma is associated with increased risk for IPI is limited and somewhat inconsistent (173, 174). A recent study of persons aged 2-49 years enrolled in the Medicaid program in one US state, where cases of IPI were identified through active population-based surveillance, suggested that asthma moderately increased one's risk for IPI (OR 2.4, 95% CI 1.9-3.1) (173) (Table 3). However, another recent study of mostly older adults (average age over 50 years) used administrative data from the U.S. Veteran's Administration Healthcare system and found that persons with COPD were at greater risk for hospitalization for pneumococcal pneumonia than were control subjects, but persons with asthma were not (174). A retrospective study (1964-1983) in Rochester, NY (USA), which included both IPI and pneumococcal pneumonia and controlled for high-risk conditions for IPI and smoking exposure, showed that serious pneumococcal disease was associated with a history of asthma among all ages (OR 2.4, 95% CI 0.9-6.6) and among adults (OR 6.7, 95% CI 1.6-27.3) (175). The population-attributable risk (PAR) in adults of this study was 17%, and in a study by Talbot et al., was calculated to be 11% in adults (173). The PAR for all combined vaccine-eligible (Advisory Committee on Immunization Practices (176)) conditions in adults was 24%, suggesting that at a population level, asthma

status alone disproportionately increases the burden of serious pneumococcal disease (175). A study in Scotland reported a case-fatality rate of 3.3% among IPI patients with asthma (11).

A group of persons with asthma can be heterogeneous depending on factors such as the intensity and type of medication (immunosuppression) and the need for hospitalization. In one study, Talbot et al. (173) defined asthma as either high or low risk. High-risk patients were those who required at least one of the following: 1) admission to hospital or emergency department, 2) the use of intensive therapy for acute asthma attacks, or 3) long-term corticosteroid use or the dispensing of three or more prescriptions for β -agonists within the year prior to enrollment in the study. The annual incidence of IPI was nearly two-fold higher (4.2 vs. 2.3 per 10 000 persons) among patients with high-risk asthma than among those with low-risk asthma.

With asthma, several pathological alterations in the airways could explain the higher risk for IPI. The mucociliary clearance of the bronchi is impaired due to the abnormal production of sputum and to airway obstruction (177). These abnormalities can serve as a focus for viral infections, which could in turn develop into invasive bacterial infections (178-181). Long-term immunosuppressive treatment of asthma with corticosteroids may be associated with higher risk for pneumococcal disease (19). Other studies have also published information suggesting differences in innate and acquired immunity between asthmatic and nonasthmatic subjects (177, 182-187).

Table 3. Summary of studies on asthma as a risk factor for invasive pneumococcal infections (IPI)

Country, publication year	Time period	Study design	Age (years)	No. of cases	Annual incidence per 100 000 per proportion of asthma cases	Definition and remarks	Reference
USA, 2008	1964-1983	Population-based, retrospective case-control	All	174 cases 348 controls	IPI incidence 4.7 Asthma incidence in general population 238	Serious pneumococcal disease (IPI) and pneumococcal pneumonia Adjusted OR for asthma 6.7	(175)
USA, 2000	1995-1996	Population-based, case-control	18-64	228 cases 301 controls		Study objective: smoking and risk of IPI. OR 2.5 when unadjusted, not significant when adjusted for other risk factors OR 2.4 for IPI among asthma cases	(188)
USA, 2005	1995-2002	Population-based, nested case-control	2-49	635 cases 6350 controls	IPI incidence among cases with: 1) High-risk asthma 42 2) Low-risk asthma 23 3) No asthma 12		(173)
USA, 2007	1997-2002	Case-control	Adults	16 074 COPD 2746 asthma		Veterans Health Administration PPV23 vaccination study OR for COPD 3.87, OR for asthma 0.3	(174)
Scotland, 2003	1999-2001	Population-based Laboratory-record linkage	All	1715	Chronic pulmonary disease (COPD, emphysema) 276 Asthma 192		(11)
USA, 2006	2001-2003	Population-based, case series study	≥ 18	1878	IPI cases lacking vaccine indication: asthma 18-49 yrs 9% 50-64 yrs 7% 18-64 yrs 8%	ABC, Vaccine-preventable IPI cases with asthma, 0.3-0.4% of all cases; Asthma, 11% of all cases; 38% of vaccinated cases; 86% of cases with current vaccine indication COPD, 26% of all cases; 44% of vaccinated case patients	(20)

ABC, Active Bacterial Core Surveillance (USA); COPD, chronic obstructive pulmonary disease; OR, odds ratio; PPV23, 23-valent pneumococcal polysaccharide vaccine

2.4 Nosocomial invasive pneumococcal infections

The role of *S. pneumoniae* in healthcare-associated infections remains poorly defined (21, 22). Institutional outbreaks of multidrug-resistant *S. pneumoniae* have been reported, and the prevalence of antimicrobial-resistant strains may be higher in older adults living in long-term care facilities (23-26). Invasive pneumococcal disease is an important cause of illness and death in older adults living in long-term care facilities, thus emphasizing the need for better prevention efforts through immunization (28). The epidemiology of nosocomial pneumococcal bacteremia (NPB) has previously been studied primarily in single hospitals, which may not be representative of all healthcare facilities serving the population (189-197), and none of these studies was population based. In previous studies, the proportion of SPB among nosocomial hospitalized patients varies. Recent studies in Europe report lower proportions (10%-14%) (194-197) of SPB among such patients, unlike studies in the USA, which report higher such proportions, as do previous reports from Spain (25%-29%) (190, 192) (Table 4). Reasons for these differences may stem from differences in the populations under study, small numbers of cases from individual hospitals (189-195), and the case definitions used, as well as from admission criteria and the culture sampling policy. NPB has previously been associated with severe underlying conditions, including neoplasia, COPD, heart failure, and cirrhosis (197). As with community-associated pneumococcal bacteremia (CAPB), NPB is detected predominately during the fall and winter (193). In addition, NPB presents as pneumonia as frequently as does CAPB. However, substantially greater proportions of patients with NPB may have extrapulmonary symptoms, such as gastrointestinal complaints.

NPB is associated with a higher mortality rate than is CAPB (197). This is unsurprising, because NPB occurs primarily in critically ill patients with severe underlying diseases. Several studies have reported relatively high case-fatality proportions, ranging from 38% to 76% (189, 190, 194).

Table 4. Summary of studies on nosocomial bacteremias (NPB) in Europe and Northern America

Country, publication year	Time period	Setting	No. of NPB	Prevalence of NPB (%)	Definition	Remarks	Reference
Spain, 1986	5 yrs		23	41		57% malignancy	(190)
Spain, 1992	22 months	1 teaching hospital	35	25		CFP 74% (NPB) vs. 45% (CAPB)	(198)
Spain, 2000	1989-1996	1 teaching hospital	21	14	CDC	All age groups, 20% malignancy, 18% HIV	(194)
Spain, 2002	1988-2000	1 teaching hospital	39	10	≥ 48 h	Adults, 17% malignancy	(195)
Spain, 2005	1995-2002	2 teaching hospitals	108	11	≥ 72 h	CFP 38% (NPB) vs. 18% (CAPB)	(197)
France, 2003	1997	Several hospitals	90	10	> 72 h	Age ≥ 14 yrs, 15% malignancy	(196)
USA, 1981	3.5 yrs		37	59		CFP 46%, 27% within 7 days	(189)
USA, 1987	66 months	1 veterans center	36	41		Adults and children, CFP 21% within 1 month	(191)
USA, 1999	1984-1994	1 teaching hospital	37	27	> 72 h	CFP 76% (NPB) vs. 27% (CAPB)	(193)

CAPB, community-acquired pneumococcal bacteremia; CDC, Centers for Disease Control and Prevention (USA); CFP, case-fatality proportion

2.5 Prevention

Pneumococcal infections constitute a considerable global disease burden, and the need to prevent these infections by means of vaccination is obvious. The year 1911 saw the first large-scale vaccine trial of a crude whole-cell pneumococcal vaccine (5). The first hexavalent type-specific polysaccharide vaccines were marketed in 1946, but interest in these was low, probably due to the arrival of penicillin. In 1977, the first commercially available 14-valent pneumococcal polysaccharide vaccine was licensed in the USA and was replaced in 1983 by a reformulated 23-valent vaccine.

The poor immunogenicity of polysaccharide vaccines in children under two years led to the development of second generation vaccines in which capsular polysaccharides are conjugated to one of several different proteins (199).

2.5.1 Pneumococcal polysaccharide vaccine

PPV23 contains 25 µg of each included, purified capsular polysaccharide antigen of *S. pneumoniae* (serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F). The 23 capsular types in the vaccine represent approximately 90% of all serotypes that cause invasive disease (33, 200-202).

In the USA and in most European countries, PPV23 is recommended for persons at risk for pneumococcal infections due to age, immunosuppression, and defined comorbidities (Appendix 1). In Finland, the vaccine coverage among persons at risk is very low: only about 3% (203), compared to 63.4% among those 65 years or older in the USA (204).

The protective efficacy of PPV23 in adults against IPI seems scientifically overwhelming, ranging from 56% to 81% in case-control studies (13-15, 17) and 40% to 70% in meta-analyses and observational studies (205-209). Two randomized, controlled studies among the elderly have indicated a protective efficacy of 60-80% (210, 211).

The protective role of PPV23 against other forms of pneumococcal infections than IPI is more controversial. Several studies have failed to demonstrate a significant protective effect of PPV23 against non-bacteremic pneumococcal pneumonia, all-cause pneumonia, and pneumonia mortality (206, 212, 213). On the contrary, a three-year prospective cohort study of all elderly in Stockholm showed a strong indication that pneumococcal vaccination was effective not only in

the prevention of invasive pneumococcal disease, but also of pneumonia overall, although to a low degree (214, 215). Other studies have demonstrated the efficacy of pneumococcal vaccination in preventing pneumococcal pneumonia and reducing the risk of death due to pneumonia (205), as well as in decreasing the patient's length of stay in hospital (216).

In most immunocompromised patients, with the exception of patients having had a splenectomy, PPV23 seems to have poor efficacy (201). Nevertheless, given the data demonstrating the safety, low cost, and efficacy of PPV23, the use of the vaccine in the elderly and individuals at high risk for severe pneumococcal infections is considered cost effective (217-219).

2.5.2 Pneumococcal conjugate vaccine

PCV7 contains the purified capsular polysaccharides 4, 6B, 9V, 14, 18C, 19F, and 23F of *S. pneumoniae*. A 10-valent pneumococcal conjugate vaccine (PCV10) also includes 1, 5, and 7F, whereas serotypes 3, 6A, and 19A are added to the 13-valent vaccine (PCV13). PCV7 was licensed in 2000 in the USA and in 2001 in the E.U. Before the introduction of PCV7, serogroups in the vaccine were responsible for almost 90% of IPI in young children in the USA and Canada, and for at least 60% in all other regions but Asia, where coverage was 43% (220).

After the introduction of PCV7 in the USA, the rate of IPI was 69% lower among those under two years, but the rate among adults did also decline. In addition, the vaccine reduced disease caused by drug-resistant strains (221). A study in Atlanta showed that the overall incidence of IPI dropped from 30.2 to 13.2 per 100 000 following the large-scale introduction of PCV7 (222). A recent meta-analysis demonstrated that PCV7 prevents not only IPI resulting from *S. pneumoniae* vaccine types with more than 90% efficacy, but also radiologically verified pneumonia in children under two years (223).

Although the experience from the continued effectiveness of PCV7 in the USA is encouraging, some researchers have expressed concern about the replacement of vaccine serotypes with non-vaccine serotypes. In a study conducted by the CDC (ABC surveillance), the annual incidence of disease due to nonvaccine serotypes increased from an average of 16.3 cases per 100 000 population during prevaccine years to 19.9 cases per 100 000 population in 2004 among children under five years, and from 27.0 cases per 100 000 population during prevaccine years to 29.8 cases per 100 000 population in 2004 among adults 65 years or older. Significant rises in the incidence of disease due to serotypes 3, 15, 19A, 22F, and 33F during this period

were observed among both children and the elderly (224). Pelton et al. reported that serotype 19A has emerged as the most frequent cause of IPI in Massachusetts, and a multi-drug resistant sequence type of 19A has become an important cause of invasive disease (225).

New conjugate vaccines are currently in development that will incorporate additional serotypes, but this is probably only a short-term solution to the replacement phenomenon. A vaccine based on one or more antigens common to all serotypes would prove a better solution to this problem (226).

2.5.3 Other strategies

In a meta-analysis of influenza vaccine among elderly persons, the efficacy of preventing all-cause pneumonia was 50% (95% CI, 28%-56%) (227). Among persons developing pneumonia or other pulmonary complications during the influenza A (H3N2) Hong Kong pandemic, pneumococcus was the most commonly identified bacterial pathogen (228, 229). In experimental studies, adults infected with influenza A virus appear to have increased susceptibility to colonization of the nasopharynx by *S. pneumoniae* (230, 231). In a study in Stockholm, Christenson et al. found influenza vaccination to have a 58% protective efficacy against IPI among the elderly, although the number of patients was too small to obtain statistical significance (33, 214).

Cigarette smoking is a risk factor for IPI. In a community-based case-control study of immunocompetent persons aged 18-64 years, the population-attributable risk (PAR) was 51% for cigarette smoking, 17% for passive smoking, and 14% for chronic illness (76). After controlling for gender, race, chronic illnesses, level of education, and exposure to children, IPIs were associated with cigarette smoking (OR 4.1, 95% CI, 2.4-7.3) and passive smoking (OR 2.5, 95% CI, 1.2-5.1). Dose-response relations were determined for the current number of cigarettes smoked daily, pack-years of smoking, and time since quitting. The risk returned to baseline after ten years. Among HIV-infected adults in San Francisco during the pre-HAART era, cigarette smoking was nearly twice as common among those with IPI as among controls after controlling for CD4 lymphocyte count, race, vaccination history, and contact with children (128, 232). In a recent study evaluating nasopharyngeal cultures taken before and 12-15 months after cessation of smoking, the high number of pathogens (including *S. pneumoniae*) and low number of interfering organisms revert to normal after complete cessation of smoking (233). Nuorti et al. estimated that if the prevalence of cigarette smoking in the USA could be reduced from the

current 25% to 15%, the incidence of IPI among nonelderly adults would potentially decrease by approximately 18% (76).

As noted previously, heavy alcohol consumption can be frequent among otherwise healthy persons with pneumococcal infections (75, 153). Among certain native populations in particular, alcoholism is the predominate risk factor for IPI (152). In Finland, a representative sample of the adult population estimates the prevalence of hazardous drinking at 5.8%, and that it is more prevalent among men than among women (8.5% vs. 3.1%) (234).

3 AIMS OF THE STUDY

The purpose of this study was to provide comprehensive baseline information on the epidemiology of invasive pneumococcal infections (IPI) in Finland before the introduction of routine childhood immunization with pneumococcal conjugate vaccines. Linking population-based national surveillance data collected during the eight-year study period (1995-2002) with data available in multiple national healthcare registries and other databases enabled us to define the pneumococcal disease burden, including the incidence, established and new risk factors (such as asthma), clinical outcomes, and the contribution of healthcare-associated pneumococcal infections to the overall disease burden. The findings of the study highlight the multiple missed opportunities for preventing pneumococcal infections in Finland, where the use of pneumococcal vaccines has thus far been suboptimal, as well as the need for developing comprehensive prevention strategies to address this major public health problem.

The specific objectives were:

1. To evaluate regional variation and trends in IPI in Finland and to correlate regional pneumococcal bacteremia and meningitis rates with blood and cerebrospinal fluid (CSF) culture sampling rates in a population-based cohort study. To evaluate the serotype distribution and vaccine coverage of currently available and new potential pneumococcal vaccines (I).
2. To assess the risk of IPI and all-cause mortality among persons with and without underlying medical conditions that are considered indications of 23-valent pneumococcal polysaccharide vaccine (PPV23) by linking data on IPI to national healthcare registries and vital statistics (II).
3. To evaluate the association of chronic pulmonary disease, particularly asthma, and IPI among persons aged 18-49 years in a population-based case-control study (III).
4. To study the characteristics, risk factors, and outcome of patients with nosocomial pneumococcal bacteremia (NPB) in a population-based cohort study (IV).

4 MATERIALS AND METHODS

4.1 Surveillance of invasive pneumococcal infections in Finland

In Finland (1995-2002: population 5.2 million), the national healthcare system is organized into 20 geographically and administratively defined healthcare districts (HCD) with catchment populations ranging from 68 000 to 1.4 million. Since 1995, all Finnish clinical microbiology laboratories have been required to notify bacterial isolations from blood and CSF, including *S. pneumoniae*, to the National Infectious Disease Register (NIDR) at the National Public Health Institute (KTL). Most laboratory reporting is currently done electronically. With each notification, the following information is transmitted to NIDR: date and type of specimen, date of birth, gender, and place of treatment. Using this information and a time interval of three months, possible multiple positive culture results or notifications concerning the same patient are merged into a single case either by a notifying laboratory or after the notification is received in the NIDR database. Data from this population-based laboratory surveillance system formed the basis for data collection for all of the studies presented.

4.2 Study population and case definitions

A case of invasive IPI (I-IV) was defined as an illness in which *S. pneumoniae* was isolated from blood or CSF or both during 1995-2002 and reported to the NIDR. Of a total of 4611 IPI episodes identified from primary diagnostic laboratory, only the first episode of each case-patient was included in the analysis ($n = 4357$); recurrent episodes and those lacking identifying information were excluded. Cases with *S. pneumoniae* bacteremias (SPBs) were defined as the isolation of *S pneumoniae* from blood only; cases with *S. pneumoaniae* meningitis (SPMs) included those in which *S. pneumoniae* was isolated from CSF with or without SPB within seven days of each other.

For the evaluation of the burden of NPB (IV), data on IPI patients' hospitalizations obtained seven or fewer days prior to the first positive blood culture specimen for *S. pneumoniae* were retrieved from the National Hospital Discharge Register (HILMO) by using each case-patient's unique national identity code for database linkage. Information on hospitalizations was available for 4217 (96.8%) of IPI case-patients, of which 3973 were bacteremias. Pneumococcal bacteremia was defined as nosocomial if the first positive blood culture was obtained more than two

days after admission, or if the patient had been hospitalized for more than two days during the seven days prior to the first positive blood culture.

4.3 Controls (III)

For each case, ten controls matched on age (same year of birth if possible, otherwise ± 1 year), gender, and place of residence were randomly selected from the Population Information System.

4.4 Definitions and ascertainment of underlying medical conditions (II-IV)

To obtain information on comorbidities and underlying conditions for which PPV23 is recommended (Appendix 1), we linked the IPI surveillance database to the following national population-based registries using the date of the first positive specimen for *S. pneumoniae* and the patient's unique national identity code: the Cancer Registry (diagnosis of hematological and non-hematological malignancy within one year or five years prior to the specimen date), NIDR (HIV infection), National Social Insurance Institution (KELA), and HILMO. Each HILMO record includes each patient's identifying information, admission and discharge dates, healthcare provider, type of service, medical specialty, place (home or institution) from which he or she was transferred to the facility, and data on surgical procedures and discharge diagnoses. Data were coded according to the International Classification of Diseases (ICD) 9th or 10th Revision (since 1996). The presence of the following chronic underlying diseases was defined as a KELA record indicating entitlement for reimbursement of medication expenses related to diabetes mellitus, chronic pulmonary disease (COPD and asthma), congenital or acquired immunodeficiency, rheumatic and other autoimmune diseases requiring immunosuppressive therapy, solid organ and bone marrow transplantation, cardiac failure, and renal failure. Alcohol-related diseases (ARDs), chronic liver diseases, diseases of the spleen, and CSF leakage were defined as a record in HILMO with one or more ICD discharge diagnoses within one year prior to the first positive specimen date (Appendix 2).

In the population-based case-control study (III), patients with chronic pulmonary disease were identified among those entitled to special reimbursement of medication expenses for asthma or COPD in the KELA database or who had a record of being hospitalized for these conditions during the 12 months prior to the IPI episode

registered in the HILMO database. The criteria for KELA reimbursement include a physician's certificate indicating the diagnosis and severity of the disease, including lung function tests and the need for drug treatment lasting at least six months. In the KELA database, asthma and COPD share the same reimbursement group code and cannot be separated. Because of restrictions on persons aged 50 years or younger, we considered all such individuals as having medicated asthma and no COPD. A total of 190 (8.6%) cases with asthma or COPD or both, and 702 (3.2%) controls were identified in the KELA database. Persons at low risk for asthma (LRA) were defined as those meeting the KELA reimbursement criteria for asthma or COPD or both, but with no record of hospitalization for these conditions in the 12 months prior to the IPI episode. High-risk asthma (HRA) was defined as at least one hospitalization with an ICD-9 or ICD-10 coded primary diagnosis (Appendix 2) for this condition in the previous 12 months.

4.5 Clinical outcome of pneumococcal infection (II-IV)

The vital status (possible date of death) at 7, 28, and 90 days from the first positive culture of *S. pneumoniae* for each case-patient was determined from the National Population Information System by use of the national identity codes.

4.6 Blood and cerebrospinal fluid activity (I)

Information about the annual numbers of blood culture and CSF sets processed during the study period were obtained through a survey of all clinical microbiology laboratories that had reported any bacterial isolation from blood or CSF to the NIDR during 1995-2002. International guidelines require that the blood specimen collection method include obtaining blood in two pairs of aerobic and anaerobic bottles (approximately 10 ml and 5 ml per bottle for adults and children, respectively) from two different sites (235). Blood and CSF culturing rates were expressed as the number of culture sets processed per 100 000 population, and the yield of SPB or SPM as cases per 1000 blood or CSF cultures. One HCD was excluded from the analysis because the laboratory data on isolations of *S. pneumoniae* from blood were incomplete.

4.7 Serotyping and antimicrobial susceptibility (I, III-IV)

As described previously, *Streptococcus pneumoniae* isolates sent to the reference laboratory at KTL as a part of national surveillance during 1995-2002 were serotyped using pneumococcal antisera (236). Pneumococcal serotypes were grouped as follows: PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), 10-valent PCV serotypes (adding serotypes 1, 5, and 7F), 13-valent PCV serotypes (adding serotypes 3, 6A, and 19A), PPV23 serotypes (1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, and 33F), and all other serotypes/groups. From 1995 to 1999, serogroups 10, 11, 12, 15, 17, and 33 remained untested for type level, and since 2000, serogroups 11, 12, and 15 have been tested for type level. As described previously, antimicrobial susceptibility testing was performed using Clinical and Standard Laboratory Institute methods (237).

4.8 Calculation of incidence rates and statistical analyses

For the study of trends and geographical variation in IPI in Finland (I), population data from Statistics Finland for 1995-2002 served as denominators to calculate age- and gender-specific incidence rates as well as rates of blood and CSF culturing. Average annualized incidence rates during the surveillance period were calculated by using the total number of cases and population during 1995-2002. To evaluate secular trends, age- and gender-specific rates were calculated for each 12-month period from January 1995 to December 2002. Blood and CSF culturing rates were expressed as the number of culture sets processed per 100 000 population, and the yield of SPB or SPM as cases per 1000 blood or CSF cultures. Poisson regression models served to assess whether observed changes in annual incidence rates over time were statistically significant. The chi-squared test and chi-squared test for trends served to assess statistical significance in cross-tabulated data. $P < 0.05$ were considered significant. The Spearman correlation coefficient and P values were calculated for the relationship between regional rates of SPB and SPM as well as between rates of blood and CSF cultures processed, respectively.

In the study of IPI and all-cause mortality among persons with and without chronic medical conditions (II), the population at risk in person-years for disease specific categories was obtained from corresponding national healthcare registries. Male-to-female rate ratios with 95% confidence intervals (CI) were also calculated.

Categorical variables were analyzed with the χ^2 test or with Fisher's exact test. Continuous variables were analyzed with the Mann-Whitney U test. $P < 0.05$ was considered statistically significant.

For the population-based case-control study of chronic pulmonary diseases and the risk of IPI (III), data from KELA on the total number of persons entitled to reimbursement for chronic lung disease medications during 1995-2002 served as the denominator to calculate the average annualized incidence of IPI among persons with chronic lung disease. To identify independent factors associated with IPI and to control for confounding, we used a conditional logistic regression model. Chronic lung disease was the main variable of interest and the covariates included appear in Appendix 1. The likelihood ratio test served to assess the significance of each covariate. Matched Odds Ratios (mOR) and 95% CIs were calculated to compare risk factor characteristics between cases and controls. Adjusted population attributable risks (PAR) for the independent risk factors in the model were calculated as described previously (238).

In the study of NPB (IV), we calculated average annualized incidence rates during the surveillance period by using population data from Statistics Finland and the total number of patient-days from HILMO during 1995-2002 as denominators. The χ^2 test or Fisher's exact test served to assess statistical significance for categorical variables, and the Mann-Whitney *U* test for continuous variables. $P < 0.05$ was considered statistically significant. Relative risks (RR) and 95% CIs were calculated to compare patient and disease characteristics between NPBs and community-acquired pneumococcal bacteremias (CAPBs); the RRs were adjusted by multivariable logarithmic binomial regression. Univariate and multivariable logistic regression served to assess the association of patient and disease characteristics with the outcome of death within 28 days (all-cause mortality). To estimate the hazard ratio of progression to death while adjusting for covariates, we used the Cox proportional hazard regression model in which age was treated as a continuous variable.

4.9 Ethical aspects

Research use of data from population-based registries was authorized by the Ministry of Social Affairs and Health, the Finnish Data Protection Authority, and the National Research and Development Center for Welfare and Health. Because the studies were exclusively laboratory- and register-based, no ethics committee approval was required.

5 RESULTS

5.1 Overall rates of invasive pneumococcal infections (I)

During 1995-2002, a total of 4357 cases of IPI were identified (average annualized incidence, 10.6 cases per 100 000 population). The median age of the IPI cases was 52.6 years (range, 0-98 years) and 2536 (58.2%) were males; 4106 (94.2%) were SPBs (median age, 53.1 years; proportion males, 58.3%) and 251 SPMs (median age, 47.9 years; males 56.6%).

The overall annualized incidence of SPB was 9.9 cases per 100 000 population, and was higher for males than for females. Rates were highest at extremes of age (Table 5a, 5b) and increased by age in adult age groups. In children aged one year, the rate of bacteremia was more than twice as high as for children aged less than one year. The overall annualized SPM incidence was 0.6 cases per 100 000 population. The annualized rate of meningitis was highest among children aged under one year (3.9 per 100 000 population), nearly twice the rate among one-year-olds (Table 6a, 6b). Rates of meningitis did not differ by gender.

Table 5a. Annual incidence of *Streptococcus pneumoniae* bacteremia in males by age, Finland, 1995-2002

Age group (years)	Annual incidence in males (cases per 100 000)									Change	
	1995	1996	1997	1998	1999	2000	2001	2002	1995-2002	(%) ^a	P value
< 1	21.8	16.2	30.0	27.6	27.3	30.9	31.5	24.6	26.1	38.0	0.4
1	42.4	62.2	41.8	53.2	34.5	68.1	58.2	76.8	54.4	50.2	0.1
2-4	12.0	12.0	15.3	8.3	10.7	13.3	15.8	17.1	13.0	37.0	0.3
5-17	1.9	3.3	3.5	2.5	3.0	3.2	2.3	2.4	2.7	-6.1	0.8
18-34	4.5	3.9	6.2	5.7	8.6	4.8	7.6	4.8	5.7	32.3	0.1
35-49	8.7	8.8	12.5	13.5	12.6	12.4	10.1	12.4	11.3	26.9	0.06
50-64	10.6	12.3	15.6	15.4	13.2	16.4	14.8	17.7	14.6	41.9	0.08
65-74	16.6	26.5	29.8	22.2	20.0	23.9	22.1	22.9	23.0	0.0	1.0
> 75	32.0	25.8	45.0	41.5	41.0	43.2	38.7	31.1	37.4	9.5	0.6
All	9.0	10.1	13.2	12.4	12.2	13.0	12.3	12.8	11.9	29.6	< 0.001

^a Poisson trend: $(\exp^{(\text{time coefficient} \cdot 7)} - 1) \cdot 100$

Table 5b. Annual incidence of *Streptococcus pneumoniae* bacteremia in females by age, Finland, 1995-2002

Age group (years)	Annual incidence in females (cases per 100,000)									Change	
	1995	1996	1997	1998	1999	2000	2001	2002	1995-2002	(%) ^a	P value
< 1	19.3	6.8	17.2	21.6	10.7	47.4	14.6	11.2	18.1	49.0	0.4
1	47.0	29.2	60.9	51.5	53.8	49.7	50.8	51.0	49.0	20.8	0.5
2-4	12.4	8.3	11.6	6.5	11.1	11.5	16.4	19.1	12.1	85.2	0.06
5-17	1.2	3.2	1.5	0.5	1.2	1.5	2.2	2.7	1.7	35.1	0.5
18-34	2.1	2.3	3.2	2.9	3.8	3.1	4.4	3.9	3.2	86.5	0.02
35-49	1.5	3.2	7.0	5.0	5.4	6.3	8.4	5.7	5.3	139.9	< 0.001
50-64	7.1	6.4	6.8	8.3	8.4	8.4	10.3	9.5	8.2	52.2	0.02
65-74	15.5	10.4	12.4	14.2	13.9	11.5	16.4	17.2	13.9	26.0	0.2
> 75	16.2	18.7	26.5	28.0	25.3	23.6	30.6	23.1	24.1	38.0	0.03
All	6.1	6.0	8.3	8.0	8.2	8.3	10.5	9.2	8.1	58.7	< 0.001

^a Poisson trend: $(\exp^{(\text{time coefficient} \cdot 7)} - 1) \cdot 100$

5.2. Temporal trends and geographic variation in rates of invasive pneumococcal infection (I)

The overall annual IPI rate during the study period increased significantly from 8.2 to 11.5 cases per 100 000 population (35.1%, Poisson trend, $P < 0.001$). Most of this increase stemmed from an increase in SPB rates, particularly among persons aged 2-4, 18-64, and more than 75 years. No significant trend was observed for SPM (Tables 6a, 6b).

The overall annualized incidence of IPI varied from 7.9 to 15.1 per 100 000 population among different HCDs. Geographical variation was observed in both SPB rates and SPM rates.

During the study period, a total of 1 319 222 blood culture sets and 46 907 CSF culture sets were processed in 30 microbiology laboratories. The annual national blood culturing rate increased between 1995 and 2002 (29.6%, Poisson trend, $P < 0.001$); no significant change occurred in annual CSF culture rates. The higher incidence of SPB was significantly associated with the higher blood culturing intensity in HCD (Spearman rank correlation coefficient 0.55, $P = 0.015$).

However, we found no correlation between the incidence of SPM in HCD and CSF culturing intensity (Spearman rank correlation coefficient 0.36, $P= 0.12$). In addition, a statistically significant association arose between the increase in incidence of SPB and blood culture rates over time during the study period (Spearman rank correlation coefficient 0.81, $P= 0.015$).

Table 6a. Annual incidence of *Streptococcus pneumoniae* meningitis in males by age, Finland, 1995-2002

Age group (years)	Annual incidence in males (cases per 100,000)								Change		
	1995	1996	1997	1998	1999	2000	2001	2002	1995-2002	(%) ^a	P value
< 1	3.1	3.2	3.3	0.0	10.3	3.4	0.0	3.5	3.4	-5.4	1.0
1	0.0	0.0	0.0	6.7	3.5	3.4	3.4	0.0	2.1	193.9	0.4
2-4	1.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	-100	1.0
5-17	0.5	0.7	0.5	0.0	0.2	0.0	0.0	0.0	0.2	-97.1	0.02
18-34	0.7	0.5	0.3	0.2	0.0	0.4	0.9	0.0	0.4	-50.3	0.4
35-49	0.3	1.5	0.8	1.0	1.0	1.0	1.0	0.5	0.9	0.0	1.0
50-64	1.0	1.4	0.9	1.7	0.6	1.2	0.8	1.4	1.1	-5.4	0.9
65-74	1.1	1.1	0.0	0.5	0.0	1.0	0.5	1.0	0.7	-7.4	0.9
> 75	2.2	1.1	1.1	1.0	1.0	0.9	0.0	0.9	1.0	-71.6	0.3
All	0.7	1.0	0.6	0.8	0.6	0.8	0.7	0.6	0.7	-29.5	0.2

^a Poisson trend: $(\exp^{(\text{time coefficient} \cdot 7)} - 1) \cdot 100$

Table 6b. Annual incidence of *Streptococcus pneumoniae* meningitis in females by age, Finland, 1995-2002

Age group (years)	Annual incidence in females (cases per 100,000)									Change	
	1995	1996	1997	1998	1999	2000	2001	2002	1995-2002	(%) ^a	P value
< 1	16.3	6.8	0.0	0.0	7.1	0.0	0.0	3.7	4.4	-92.8	0.03
1	9.4	0.0	0.0	0.0	0.0	0.0	3.6	3.6	2.2	-65.7	0.5
2-4	0.0	0.0	2.1	1.1	1.1	0.0	0.0	1.2	0.7	34.2	0.8
5-17	0.5	0.2	0.0	0.0	0.2	0.2	0.0	0.3	0.2	-59.5	0.5
18-34	0.4	0.4	0.2	0.0	0.2	0.0	0.0	0.0	0.1	-97.2	0.04
35-49	0.2	0.3	0.7	0.3	0.4	0.2	0.9	0.5	0.4	108.5	0.3
50-64	0.7	0.9	0.7	0.6	1.4	0.6	1.0	0.8	0.8	11.9	0.8
65-74	0.4	1.2	1.6	0.8	1.2	0.8	0.8	0.0	0.9	-47.1	0.4
> 75	0.5	0.9	0.0	0.5	0.0	0.4	0.4	0.8	0.4	20.8	0.9
All	0.7	0.6	0.5	0.3	0.6	0.3	0.5	0.5	0.5	-29.5	0.2

^aPoisson trend: $(\exp^{(\text{time coefficient} \cdot 7)} - 1) \cdot 100$

5.3 Influence of underlying medical conditions (II-III)

Overall, 2302 (52.8%) of the 4357 cases presented at least one underlying condition, including age 65 years or older, for which PPV23 is recommended. Among working-age patients aged 18-64 years, however, only 799 (36.1%) had a current indication of PPV23. Of patients aged 18-49 and 50-64 years, 372 (29.0%) and 427 (45.7%), respectively, exhibited a condition for which PPV23 is currently recommended. Among those of working-age, ARDs, chronic pulmonary disease, and diabetes mellitus were the most common vaccine indications, whereas chronic pulmonary disease, cardiac failure, and diabetes mellitus were the most common among elderly patients (Table 7). Persons aged 18-64 years accounted for 96.0% of cases with ARDs. The highest rates of IPI occurred in patients with hematological malignancy and organ or bone marrow transplantation.

Of the 1282 total IPI cases aged 18-49 years, all were included in the case-control study. Overall, 359 (28.0%) case-patients (compared with 743 (5.8%) of control-subjects) presented an underlying medical condition for which PPV23 is recommended. Of these case-patients, 77 (6.0%) LRA (compared with 302 (2.4%) of the controls), 14 (1.1%) case-patients, and 12 (0.1%) of the controls had HRA (Table 8). The incidence of IPI among persons aged 18-49 years with LRA was 18.2 per 100 000 annually. Only four (0.3%) case-patients and none of the controls had

Table 7. Risk of invasive *Streptococcus pneumoniae* infection (IPI) associated with selected underlying conditions, Finland, 1995-2002

Underlying condition ^a	Number of IPI cases by age group (years)					All (%) N = 4357	Population at risk (person-years)	Rate/100 000/year	95% CI	Case fatality proportion at day 7/28/90
	< 18 N = 733	18-64 N = 2216	≥ 65 N = 1408							
Chronic pulmonary disease ^b	44	190	260	494 (11.3)	1 435 000	34.4	31.4-37.4	8/12/15		
Cardiac failure	13	51	287	351 (8.1)	746 000	47.1	42.2-52.0	16/24/30		
Diabetes mellitus	3	140	186	329 (7.5)	1 014 000	32.5	29.0-36.0	13/19/23		
Type 1 diabetes ^c	3	16	0	19 (0.4)	158 000	12.0	6.6-17.4	5/5/5		
Immunodeficiency or rheumatic diseases	4	128	138	270 (6.2)	779 000	34.7	30.5-38.9	14/19/22		
Alcohol-related diseases	0	241	10	251 (5.8)	1 117 000 ^d	21.9 ^e	19.1-24.6	21/28/33		
Non-hematological malignancy	2	46	58	106 (2.4)	208 000	50.9	41.2-60.6	22/29/41		
< 1 year since diagnosis	13	92	139	244 (5.6)	730 000	33.4	29.2-37.6	16/24/33		
< 5 years since diagnosis	5	25	26	56 (1.3)	10 000	547.2	398.9-685.5	14/16/25		
Hematological malignancy	23	68	72	163 (3.7)	38 000	434.5	367.8-501.2	10/13/21		
< 1 year since diagnosis	5	26	3	34 (0.8)	21 000	163.7	108.7-218.7	3/6/9		
< 5 years since diagnosis	1	15	8	24 (0.6)	27 000	88.6	53.1-124.1	8/13/17		
Organ or bone marrow transplantation	0	15	5	20 (0.5)	NA			15/30/35		
Chronic renal failure	0	10	0	10 (0.2)	8000	129.7	49.3-210.1	10/20/30		
Chronic liver disease										
HIV infection										

^a Patient may have more than one underlying condition; ^b chronic obstructive pulmonary disease (COPD) or bronchial asthma or both; ^c diabetes mellitus diagnosed at age < 30 years and insulin treatment; ^d extrapolation based on the 12-month prevalence of persons with alcohol use disorders from a representative sample of Finland's adult (≥ 30 years) population (239); ^e IPI cases with alcohol-related diseases aged ≥ 30 years (n = 245), CI, confidence interval

Table 8. Association of chronic pulmonary disease with invasive pneumococcal infection among persons aged 18-49 years - a conditional logistic regression model

Variable	Case-patients (N = 1282)	Controls (N = 12 785)	mOR	95% CI	P value	PAR	95% CI
Chronic pulmonary disease-no. (%)							
High-risk asthma	14 (1.1)	12 (0.1)	12.3	5.4-28.0	< 0.001	0.010	0.035-0.017
Low-risk asthma	77 (6.0)	302 (2.4)	2.8	2.1-3.6	< 0.001	0.039	0.023-0.055
Hospitalization for COPD	4 (0.3)	0 (0.0)	NA	NA	NA	NA	NA
Other underlying medical conditions – no. (%)							
Chronic liver disease	9 (0.7)	1 (< 0.1)	96.6	10.6-883.9	< 0.001	0.0069	0.0016-0.012
Hematological malignancy	25 (2.0)	5 (< 0.1)	56.0	20.0-157.0	< 0.001	0.019	0.010-0.028
Diseases of spleen	2 (0.2)	1 (< 0.1)	35.6	3.0-428.5	< 0.005	0.0015	0.00-0.0040
Alcohol-related diseases	151 (11.8)	72 (0.6)	27.2	19.9-37.3	< 0.001	0.11	0.092-0.13
HIV infection	10 (0.8)	7 (0.1)	14.3	5.3-38.5	< 0.001	0.0073	0.0018-0.013
Non-hematological malignancy	11 (0.9)	23 (0.2)	5.1	2.4-10.9	< 0.001	0.0069	0.0016-0.013
Organ or bone marrow transplantation	13 (1.0)	13 (0.1)	2.9	1.0-8.8	0.059	0.0067	0.00-0.015
Cardiac failure	8 (0.6)	13 (0.1)	2.8	1.0-8.2	0.059	0.004	0.00-0.010
Immunodeficiency or rheumatic diseases	56 (4.4)	190 (1.5)	3.1	2.3-4.4	< 0.001	0.030	0.017-0.044
Diabetes mellitus	45 (3.5)	148 (1.2)	2.3	1.6-3.5	< 0.001	0.020	0.0076-0.034

mOR, matched odds ratio; CI, confidence interval; PAR, population-attributable risk; NA, not available

a record of hospitalization for COPD in the previous 12 months. Of the 77 patients with LRA, ten (13.0%) presented one or more additional conditions for which PPV23 is recommended. No patients with HRA exhibited other conditions. In a conditional logistic regression model adjusted for other risk factors, case-patients were more likely than controls to have HRA and LRA. The adjusted population-attributable risks (PARs) for HRA and LRA were 0.010 (95%CI, 0.0035-0.017) and 0.039 (95%CI, 0.023-0.055), respectively.

5.4 Burden of nosocomial pneumococcal bacteremia (IV)

During the study period, 387 patients with NPB were identified (43-53 cases per year), representing approximately 9.7% of the 3973 hospitalized SPB cases (range by year, 8-14%). The average annualized NPB incidence rate was 0.9 cases per 100 000 population (range by year, 0.8-1.0; range by tertiary care region, 0.7-1.2) and 0.66 cases per 100 000 patient-days (range by year, 0.60-0.73; range by tertiary care region, 0.49-0.95).

Many characteristics of patients with NPB differed from those with CAPB in univariate analysis (Table 9). Patients with NPB were significantly older than patients with CAPB (median age, 67.3 vs. 51.6 years; $P < 0.001$). Of the patients with NPB, 229 (59.2%) presented at least one underlying condition (other than age 65 or older) for which PPV23 is currently recommended, compared with 1241 (34.6%) of the 3586 patients with CAPB ($P < 0.001$). This difference was due to significantly greater proportions of chronic pulmonary disease, cardiac failure, diabetes mellitus, ARD, non-hematological and hematological malignancies, and immunodeficiency or rheumatic diseases among patients with NPB. Among the 152 NPB cases aged 16-64 years, 113 (74.3%) had at least one underlying condition for which PPV23 is recommended. Characteristics independently associated with higher risk for NPB in the logarithmic binominal regression model included male gender, increasing age, malignancies, chronic liver disease, ARD, and chronic pulmonary disease.

Table 9. Comparison of characteristics for patients with nosocomial and community-associated pneumococcal bacteremia, Finland, 1995-2002

Characteristic	No. (%) of patients			RR (95% CI)	P value	Adjusted RR (95% CI)
	NPB	CAPB				
Age group						
< 16 years	20 (5.2)	599 (16.7)	reference			
16-64 years	152 (39.3)	1859 (51.8)	2.34 (1.48-3.70)	< 0.001	2.01 (1.27-3.18)	
> 64 years	215 (55.6)	1128 (31.5)	4.95 (3.16-7.76)	< 0.001	4.51 (2.89-7.05)	
Gender						
Male	241 (62.3)	2081 (58.0)	1.17 (0.97-1.43)	0.12	1.28 (1.05-1.55)	
Female	146 (37.7)	1505 (42.0)	reference			
Underlying condition ^a						
Chronic pulmonary disease	67 (17.3)	405 (11.3)	1.55 (1.22-1.98)	0.001	1.28 (1.01-1.64)	
Cardiac failure	56 (14.5)	288 (8.0)	1.78 (1.38-2.32)	< 0.001	-	
Diabetes mellitus	45 (11.6)	272 (7.6)	1.52 (1.14-2.03)	0.007	-	
Immunodeficiency or rheumatic diseases	38 (9.8)	213 (5.9)	1.61 (1.18-2.20)	0.004	-	
Non-hematologic malignancy	37 (9.6)	64 (1.8)	4.05 (3.08-5.34)	< 0.001	2.60 (2.02-3.36)	
Alcohol-related disease	33 (8.5)	209 (5.8)	1.44 (1.03-2.00)	0.05	1.83 (1.29-2.60)	
Hematologic malignancy	26 (6.7)	29 (0.8)	5.13 (3.82-6.90)	< 0.001	3.77 (2.76-5.13)	
Chronic liver disease	5 (1.3)	14 (0.4)	2.72 (1.28-5.82)	0.03	2.77 (1.29-5.94)	
Organ/bone marrow transplantation	4 (1.0)	28 (0.8)	1.29 (0.51-3.23)	0.55	-	
Chronic renal failure	2 (0.5)	21 (0.6)	0.89 (0.24-3.37)	1.00	-	
≥ 1 underlying condition	229 (59.2)	1241 (34.6)	2.31 (1.82-2.93)	< 0.001	Not adjusted	

^a Patient may have more than one underlying condition; NPB, nosocomial pneumococcal bacteremia; CAPB, community-associated pneumococcal bacteremia; RR, relative risk; CI, confidence interval

5.5 Clinical outcome of invasive pneumococcal infections

Of the total 4357 IPI cases, 202 (4.6%) died on the day of admission, 373 (8.6%) died within one week, and 536 (12.3%) within 28 days. An additional 130 cases died between 29 and 90 days after the first blood- and/or CSF-culture positive for *S. pneumoniae*. During hospitalization for IPI, 437 (10.0%) cases died. The in-hospital case-fatality proportions (CFPs) at 7, 28, and 90 days were 7.9%, 10.2%, and 10.7%, respectively. Of all the deaths during the first month, persons aged 18-49 and 50-64 years accounted for 124 (23.1%) and 130 (24.2%), respectively; CFPs in these groups were 9.7% and 13.9%, respectively. The CFPs at 7, 28, and 90 days were similar for both genders among those aged 18-49 years, but significantly higher in men than in women among those aged 50-64 years at 28 and 90 days (16.8% vs. 9.0% and 21.4% vs. 12.4%; $P < 0.01$ for both comparisons). The CFPs at days 28 and 90 were significantly higher for meningitis than for bacteremia ($P < 0.02$).

The highest CFPs at 28 days occurred among persons with non-hematological malignancy, ARD, and cardiac failure (Table 7). Of those cases aged 18-64 years who died on the day of culture or during the first week, the median ages were 50.2 and 48.7 years, respectively; the most common underlying medical conditions were ARDs, diabetes, and immunodeficiency/rheumatic diseases in both groups. Of the fatal cases among persons aged 18-49 years and 50-64 years, 61 (49.2%) and 76 (58.5%), respectively, exhibited an underlying condition considered an indication of PPV23. The CFP for patients aged 18-64 years with a vaccine indication was 17.1%, compared with 8.5% for patients with no such indication (relative risk (RR), 2.1; 95%CI, 1.6-2.6). Of the case-patients with LRA in the case-control study, seven (9.1%) died within 28 days. All but one death occurred within seven days; no cases with HRA died.

Of the NPB cases, 121 (31.3%) died within 90 days of the first positive blood culture. Of these deaths, 67 (55.4%) occurred within 7 days, and 92 (76.0%) within 28 days; 88 (72.7%) were aged 65 years or older. The overall CFPs at 7, 28, and 90 days were significantly higher in NPB than in CAPB cases (17.3% vs. 7.6%, 23.8% vs. 10.8%, and 31.3% vs. 13.4%, respectively; $P < 0.001$ for all comparisons). In males, CFPs were nearly 1.5 times higher than in females, and were almost twice as high among the elderly as among patients aged 16-64 years (Table 10). CFPs were highest among patients with non-hematological malignancies, cardiac failure, ARDs, hematological malignancies, and immunodeficiency or rheumatic diseases. Factors significantly associated with death within 28 days of positive blood culture (all-cause mortality) in univariate analyses included increasing age and cardiac failure. After adjusting for age and gender in the multivariable logistic regression model, patient characteristics that independently predicted death within 28 days

included immunodeficiency or rheumatic diseases ($P= 0.004$) and ARDs ($P= 0.014$). To evaluate the outcome of all-cause mortality after NPB, we used a Cox proportional hazard regression model. In addition to the variables identified in multivariable logistic regression, non-hematological and hematological malignancies independently increased the risk (hazard) of death.

Table 10. Characteristics associated with death in patients with nosocomial pneumococcal bacteremia, Finland, 1995-2002

Characteristic	Deaths (case fatality proportion, %)		
	At day 7	At day 28	At day 90
Age group			
< 16 years	0 (0)	0 (0)	0 (0)
16-64 years	18 (11.8)	23 (15.1)	33 (21.7)
> 64 years	49 (22.8)	69 (32.1)	88 (40.9)
All	67 (17.3)	92 (23.8)	121 (31.3)
Gender			
Male	47 (19.5)	65 (27.0)	86 (35.7)
Female	20 (13.7)	27 (18.5)	35 (24.0)
Underlying condition ^a			
Chronic pulmonary disease	14 (20.9)	21 (31.3)	24 (35.8)
Cardiac failure	15 (26.8)	20 (35.7)	25 (44.6)
Diabetes mellitus	9 (20.0)	13 (28.9)	16 (35.6)
Immunodeficiency/rheumatic diseases	10 (26.3)	14 (36.8)	16 (42.1)
Non-hematologic malignancy	11 (29.7)	13 (35.1)	19 (51.4)
Alcohol-related disease	9 (27.3)	11 (33.3)	14 (42.4)
Hematologic malignancy	7 (26.9)	8 (30.8)	11 (42.3)
Chronic liver disease	1 (20.0)	1 (20.0)	2 (40.0)
Organ/bone marrow transplantation	0 (0)	0 (0)	0 (0)
Chronic renal failure	0 (0)	0 (0)	0 (0)
≥ 1 underlying condition	48 (71.6)	66 (71.7)	85 (70.2)

^aPatient may have more than one underlying condition

5.6 Pneumococcal serotypes and the proportion of potentially vaccine-preventable infections (I, III-IV)

We serotyped a total of 4056 (93.1%) *S. pneumoniae* isolates from patients with IPI and estimated the proportion of potentially vaccine-preventable pneumococcal infections with currently available and investigational vaccines.

1) PPV23

Of all pneumococcal isolates, 3395 (83.7 %) were serotypes/serogroups included in PPV23; 1806 (88.9%) were among nonelderly adults aged 18-64 years, and 1110 (86.0%) were among patients aged 65 years or older (Table 11b). In the case-control study (III), 1056 (82.4%) of the isolates were serotyped, and PPV23 coverage was 92.9% among patients with chronic lung disease. In the NPB study (IV), a total of 319 (82.4%) *S. pneumoniae* isolates were available for serotyping. Of the pneumococcal isolates, 228 (71.5%) were serotypes included in PPV23.

2) PCV7

The serotypes included in PCV7 accounted for 2131 (52.5%) of all pneumococcal isolates available for serotyping. Of the 573 pneumococcal isolates among children under the age of five, 400 (69.8%) were serotypes included in PCV7. The serotype coverage was highest among children aged one to four years (74.1%); among those aged two to eleven months, serotype coverage was 59.0% (Table 11a). In adult age groups, serotype coverage was 48.2% and 51.6% among IPI cases aged 18-64 years and 65 or older, respectively. Among cases with chronic pulmonary disease (III), 44 (54.3%) of the isolates were serotypes included in PCV7, and 147 (46.1%) in the study of nosocomial pneumococcal bacteremia (IV).

3) 10-valent and 13-valent pneumococcal conjugate vaccines (PCV10 and PCV13)

The serotypes included in PCV10 and PCV13 accounted for 2524 (62.2%) and 3156 (77.8%) of all serotyped isolates of *S. pneumoniae*, respectively (Tables 11a and 11b). Among those groups aged 5, 18-64 and 65 years or older, serotype coverage was 75.9% vs. 91.3%, 60.4% vs. 74.8%, and 57.4% vs. 75.9%, respectively. Among cases with chronic pulmonary disease (III), serotype coverage for PCV10 was 72.8%, and for PCV13, 79.0%.

Table 11a. The most common serotypes of *S. pneumoniae* in invasive infections among children, Finland, 1995-2002

Individual serotype ^a	Number of isolates among children (%)									
	< 1 year		1 year		2-4 years		5-17 years		Total	
6B	22	(15.2)	56	(23.0)	36	(19.5)	10	(6.2)	124	(16.9)
14	18	(12.4)	59	(24.3)	31	(16.8)	10	(6.2)	118	(16.1)
19A	21	(14.5)	18	(7.4)	15	(8.1)	4	(2.5)	58	(7.9)
18C	7	(4.8)	17	(7.0)	17	(9.2)	16	(9.9)	57	(7.8)
7F	14	(9.7)	9	(3.7)	8	(4.3)	25	(15.5)	56	(7.6)
23F	12	(8.3)	18	(7.4)	12	(6.5)	13	(8.1)	55	(7.5)
19F	11	(7.6)	20	(8.2)	15	(8.1)	8	(5.0)	54	(7.4)
4	6	(4.1)	8	(3.3)	14	(7.6)	19	(11.8)	47	(6.4)
6A	7	(4.8)	10	(4.1)	11	(5.9)	6	(3.7)	34	(4.6)
9V	7	(4.8)	7	(2.9)	7	(3.8)	11	(6.8)	32	(4.4)
Other	20	(13.8)	21	(8.6)	19	(10.3)	39	(24.2)	99	(13.5)
serotypes/groups										
All serotypes	145	(19.8)	243	(33.1)	185	(25.2)	161	(21.9)	734	(18.1)
Serotypes included in vaccines										
7-valent	83	(57.2)	185	(76.1)	132	(71.3)	87	(54.0)	487	(66.3)
10-valent	97	(66.9)	194	(79.8)	144	(77.8)	121	(75.2)	556	(75.7)
13-valent	127	(87.6)	225	(92.6)	171	(92.4)	135	(83.9)	658	(89.6)

^aAll serotypes constituting at least 2% of all cases are listed individually

Table 11b. The most common serotypes of *S. pneumoniae* in invasive infections among adults, Finland, 1995-2002

Individual serotype ^a	Number of isolates (%) among adults											
	18-34 years		35-49 years		50-64 years		65-74 years		≥ 75 years		Total	
4	90	(22.9)	140	(18.3)	120	(13.7)	77	(12.8)	66	(9.6)	493	(14.8)
14	42	(10.7)	73	(9.5)	106	(12.1)	60	(10.0)	94	(13.6)	375	(11.3)
3	14	(3.6)	90	(11.7)	94	(10.8)	70	(11.6)	62	(9.0)	330	(9.9)
7F	75	(19.1)	72	(9.4)	62	(7.1)	37	(6.2)	34	(4.9)	280	(8.4)
23F	21	(5.3)	29	(3.8)	56	(6.4)	52	(8.7)	68	(9.9)	226	(6.8)
9V	34	(8.7)	54	(7.0)	44	(5.0)	29	(4.8)	30	(4.4)	191	(5.7)
6B	8	(2.0)	22	(2.9)	39	(4.5)	26	(4.3)	47	(6.8)	142	(4.3)
19F	6	(1.5)	13	(1.7)	29	(3.3)	35	(5.8)	47	(6.8)	130	(3.9)
22F	15	(3.8)	24	(3.1)	39	(4.5)	18	(3.0)	33	(4.8)	129	(3.9)
6A	4	(1.0)	15	(2.0)	34	(3.9)	21	(3.5)	34	(4.9)	108	(3.3)
9N	8	(2.0)	20	(2.6)	35	(4.0)	16	(2.7)	24	(3.5)	103	(3.1)
8	9	(2.3)	39	(5.1)	24	(2.7)	14	(2.3)	9	(1.3)	95	(2.9)
19A	10	(2.5)	13	(1.7)	18	(2.1)	25	(4.2)	26	(3.8)	92	(2.8)
18C	9	(2.3)	17	(2.2)	27	(3.1)	16	(2.7)	18	(2.6)	87	(2.6)
Other	48	(12.2)	145	(18.9)	146	(16.7)	105	(17.5)	97	(14.1)	541	(16.3)
serotypes/groups												
All serotypes	393	(11.8)	766	(23.1)	873	(26.3)	601	(18.1)	689	(20.7)	3322	(81.9)
Serotypes included in vaccines												
7-valent	210	(53.4)	348	(45.4)	421	(48.2)	295	(49.1)	370	(53.7)	1644	(49.5)
10-valent	298	(75.8)	439	(57.3)	490	(56.1)	336	(55.9)	405	(58.8)	1968	(59.2)
13-valent	326	(83.0)	557	(72.7)	636	(72.9)	452	(75.2)	527	(76.5)	2498	(75.2)
23-valent ^b	370	(94.1)	675	(88.1)	761	(87.2)	512	(85.2)	598	(86.8)	2916	(87.8)
23-valent ^c	359	(91.3)	636	(83.0)	707	(81.0)	485	(80.7)	565	(82.0)	2752	(82.8)

^a All serotypes constituting at least 2% of all cases are listed individually; ^b all serogroups included in the PPV23 vaccine; ^c excluding serogroups 10, 11, 12, 15, 17, and 33, none of which were serotyped

5.7 Antimicrobial susceptibility

Antimicrobial susceptibility testing results were available for 138 (35.7%) nosocomial *S. pneumoniae* isolates: six isolates (4.3%) were resistant to erythromycin, and five (3.6%) were intermediately resistant to penicillin; no patients with a nonsusceptible isolate died within 28 days.

6 DISCUSSION

The studies in this thesis provide baseline data on the epidemiological characteristics of IPIs from eight years of population-based surveillance in Finland. The surveillance system in Finland offers nationwide and comprehensive data on IPI. Linking IPI data collected with data available in national healthcare registries as well as other databases enabled us to more accurately define the pneumococcal disease burden and to identify the most important risk factors. This information is of particular interest as public health authorities in Finland prepare for the introduction of routine childhood immunization with pneumococcal conjugate vaccines, which will likely occur in 2010. This new key information contributed by the original studies includes documenting an increase by one third in the incidence of IPI during the study period and showing that these temporal and regional increases were associated with higher blood culturing rates (I). This indicates that the true incidence of SPB in Finland is likely higher than previously estimated; confirming the substantial burden of IPI among non-elderly adults without established underlying medical conditions that are indications for PPV23; two-thirds of IPIs and one half of fatal cases occurred in persons without a recognized PPV23 indication (II); providing confirmatory evidence for recent findings in other studies that both HRA and LRA are independent risk factors for IPI (III); and, for the first time, we quantify the impact of healthcare-associated pneumococcal bacteremia from nationwide surveillance data, thus documenting that mortality was more than double that of CAPB (IV). This thesis also discusses the public health policy implications of these findings.

6.1 Overall rates of invasive pneumococcal infections in Finland (I)

The overall rates of IPI in Finland during the study period were similar to those of previous reports from other European countries (8, 9, 240, 241) and from California, USA (70). Consistent with other reports, this study also shows a bimodal age-related variation in the incidence of IPI, with small children and persons aged 65 years and older suffering the highest rates. Previous reports have also described differences in incidence by gender (6, 8, 9, 70, 85). However, the incidence of invasive infections among infants under two in our study and in other European studies is significantly lower than reported rates from studies in the USA before the introduction of pneumococcal conjugate vaccine (8, 10, 90). This study provides evidence that these

differences in disease rates may at least partly stem from differences in blood culturing rates, diagnostic and admission practices – particularly the practice of outpatient blood culturing – and the treatment of young children with occult bacteremia in the USA. According to clinical practice guidelines in Finland, blood cultures are obtained only if the child with febrile illness is hospitalized. Interestingly, no comparative data are available about the relation of blood culturing rates and SPB in children from the USA. A significant increase in the annual rate of IPI during the study period was detected among both genders and was attributed to an increase in the rate of bacteremia over time among both. As we calculated rates for calendar years, some of the year-to-year variation in rates may be related to the well-documented seasonality of pneumococcal disease and to variations in the incidence of respiratory virus circulation, including seasonal influenza and respiratory syncytial virus (128, 242, 243).

The incidence of SPM was highest in children under one year, and the age-specific rates were similar to those found in other studies from developed countries (119, 244). In contrast to the SPB rate, the rate of SPM remained relatively constant during the study period. Similarly, increasing trends in the rates of bacteremia and largely stable SPM rates have been reported from Denmark during 1989-1994, Sweden, Norway, the UK, Scotland, and South Carolina, USA (79, 87-89, 119) conceivably because the diagnostic practice for meningitis may vary less than for pneumonia and bacteremia. In contrast, decreasing observed rates of SPB were reported from Denmark during 1995-1999 (90).

6.2 Temporal trends and geographical variation in invasive pneumococcal infection rates (I)

Previous reports from England and Wales (8, 9) and from South Carolina, USA, (79) also suggested that higher rates of blood culture sampling were associated with a higher incidence of pneumococcal infections. In Sweden, however, no increase in IPI incidence was correlated with an increase in blood culture sampling rates (241). Our data indicate that the regional variation and secular rise in the incidence of SPB were associated with blood culture sampling rates. Although the introduction of electronic laboratory reporting during the study period has improved the timeliness and thoroughness of surveillance data, the change from mail to electronic reporting showed no correlation with an observed increase in bloodstream infections in Finland (83).

6.3 Influence of underlying medical conditions (II)

In our study, almost two-thirds of IPI cases among working-age adults exhibited none of the underlying conditions for which PPV23 is recommended. This proportion is substantially higher than that previously reported from the USA (41%) (10, 245), but few comparable data are available from European countries. As in previous studies, ARD was the most frequent (10.9%) underlying condition in the working-age group (246). The incidence of IPI among persons with ARD in our study, however, was lower (21.9) than estimates from the USA and Scotland, ranging from 62.0 to 483.4 per 100 000 population in previous population-based studies (11, 75, 132). Because of the lower baseline incidence in Finland, however, difficulties in defining the population at risk for ARD, as well as evaluating the accuracy and representativeness of the denominator data used in these studies, interpretation of the observed differences is complex. Our estimated denominator for ARD was an extrapolation based on the 12-month prevalence of persons with alcohol use disorders from a representative sample of the Finnish adult (30 years or older) population (239).

Among patients with various immunocompromising conditions, the rate of IPI varied from 33.4 to 547.2 per 100 000, and was highest among those with hematological malignancy. Among immunocompetent patients (persons with diabetes mellitus, chronic pulmonary disease, and cardiac failure), rates showed less variation (range, 12.0-47.1 per 100 000). Previous population-based studies from the USA and Scotland reported higher rates for solid cancer (216.1 to 300.4 per 100 000), chronic pulmonary disease (62.9 to 503.0 per 100 000), and HIV (422.9 to 2031.4 per 100 000) (11, 75, 132), likely due to differences in population composition, databases, definitions, sources of denominator data, and the accuracy and thoroughness in identifying the diagnoses of underlying conditions in IPI patients. Previous studies have included malignancies at any point in time (11, 132), whereas we restricted those diagnosed less than five or one year, respectively, before the IPI episode. For chronic pulmonary diseases, some studies incorporated only COPD and emphysema cases (75, 132), but we included asthma as well. The relatively low rate of IPI among persons infected with HIV in Finland may reflect easier access to antiretroviral therapy, early antibiotic treatment without blood cultures, and the use of prophylactic antibiotics among those with low CD4⁺ T cell counts.

Of the national registries we used to define the co-morbidities for IPI cases and to acquire population-based denominators, the Finnish Cancer Registry has almost 100% coverage (247, 248), and the comprehensiveness of hospital discharge data has been validated previously (249-252).

This is the second study in which persons with asthma were found to be at increased risk of IPI. The observations in our study are in agreement with those of a previous study (173) in which persons with mostly high-risk asthma were at a 2.4-fold higher risk for IPI than did controls. The group of persons with asthma was heterogeneous, depending on factors such as the intensity and type of medication (immunosuppression) and the need for hospitalization. We defined HRA and COPD as at least one hospitalization for asthma or COPD during the 12 months prior to the IPI episode, whereas Talbot et al. (173) considered hospitalization optional in their definition of HRA, in which they defined asthma as either high- or low-risk. High-risk patients were those who required at least one of the following: admission to a hospital or emergency department, intensive therapy for acute asthma attacks, long-term corticosteroids, or the dispensing of three or more prescriptions for β -agonists in the year prior to enrolment in the study. The annual incidence of IPI was nearly two-fold (4.2 vs. 2.3 per 10 000 persons) higher among patients with HRA than among those with LRA. In our study, the difference in risk for IPI was even more pronounced between the two groups with different severeness and consequent medication. The ascertainment of asthma in the study by Talbot et al. (173) differed somewhat from ours, thus possibly resulting in our categorization of a higher number of evere cases of asthma or COPD in the group of high-risk patients.

The selection of age groups differs between studies that address asthma and IPI. We restricted our study to non-elderly working-aged adults due to the difficulties in defining and diagnosing asthma in children. Not including children could explain the higher risk for IPI among cases with asthma in our study that that reported in Talbot et al. (173), which included subjects 2-49 years of age. The studybase also differed: our study was nationwide, population-based, and unselected, whereas that of Talbot et al. comprised primarily persons of low socioeconomic status enrolled in a Medicaid (TennCare) program. Consequently, the results may not be fully applicable to the entire US population. The risk of underestimating the incidence of HIV infection is more obvious in a population with a high prevalence of HIV because the HIV infection often goes undetected until a known HIV-related illness develops (7, 253).

6.4 Burden of nosocomial pneumococcal bacteremia (IV)

The study of NPB provides a comprehensive, population-based evaluation of the burden of NPB, highlighting how its characteristics differ from those of CAPB. Our estimates from national laboratory-based surveillance are representative of the entire population of Finland. The standard case definition minimized selection bias due to different case mixes, and provides accurate rates for comparison over time and

place. The registry-based design enabled the use of accurate denominators for NPB rates (i.e., total hospital patient-days) and differentiation between traditional nosocomial and healthcare-associated cases. Although annual rates of NPB per 100 000 population and patient-days during the study period varied little, rates varied in different tertiary care regions, possibly reflecting small numbers of cases or local disease clusters.

The proportion of SPBs among hospitalized nosocomial patients varied from 7.5% to 13.9% annually. This proportion is smaller than that previously reported from Spain (25%-41%) (190, 192) and the USA (27%-59%) (189, 191, 193), but similar to that in a report from France (10%) (196) and in recent reports from Spain (10%-14%) (194, 195, 197). The reasons for these differences may stem not only from differences in study populations, the small numbers of cases from individual hospitals (189-195), and the case definitions used, but also from admission criteria and differences in blood culture sampling practices among pneumonia patients between those who are hospitalized and those who are outpatients.

The definitions used in previous reports for the nosocomial acquisition of disease also varied; some included episodes that manifested 48 or more hours after hospitalization (195), whereas others used a longer, 72-hour cut-off point (193, 196, 197). In addition to the episodes in which the index blood culture was obtained more than two days after hospitalization, our analysis also included those that may have been associated with a previous admission in the same or other healthcare setting within a seven-day period. These potentially healthcare-associated infections accounted for about one-third of nosocomial SPBs, and patient characteristics in the two groups were similar. The median period of hospitalization before the index blood culture (eight days) is consistent with that of previous reports, thus indicating that NPB tends to occur after a relatively prolonged period of hospitalization (195, 197).

Patients with NPB had significantly more chronic pulmonary diseases, cardiac failure, diabetes mellitus, ARD, malignancies, and immunodeficiency or rheumatic disease than did patients with CAPB. Previous research has associated NPB with severe underlying conditions, including neoplasia, COPD, heart failure, and cirrhosis (197). A case-control study design in elderly veterans found that diagnoses of respiratory or hematological malignancy, anemia, COPD, and coronary artery disease on admission to the hospital were independent clinical predictors of NPB (193).

6.5 Clinical outcome of invasive pneumococcal infections (II, IV)

By linking surveillance data to national vital statistics, we were able to estimate all-cause mortality up to three months following an episode of IPI. Although the CFP

was 8.6% during the first week, mortality at one month among patients with various underlying conditions ranged from about 5% to 30% and increased in most groups up to three months after the first positive culture, probably reflecting both the severity of the underlying illness and the effects of long-term sequelae (100). Overall mortality was highest for non-hematological malignancy, chronic liver disease, ARDs, cardiac failure, and HIV infection. Our findings are consistent with those of two previous population-based studies on IPI and pneumococcal bacteremic pneumonia in which case-fatality among persons with underlying medical conditions ranged from 3.3% to 13.4% (11) and from 5.8% to 33.9% (104), respectively. In both studies, the highest mortality rate was observed among persons with cirrhosis and alcohol abuse, coronary artery disease/congestive heart failure, and non-hematological malignancies. Definitions used to assess IPI-associated mortality vary: some studies evaluate all-cause mortality (193-196), whereas others evaluate only mortality directly attributable to IPI (197). Differences in healthcare delivery systems and in the length of hospital stay can influence the analysis of vital status at discharge (i.e., in-hospital mortality).

All-cause mortality was significantly higher in NPB than in CAPB cases. The risk of death increased with age, being 34% among persons aged 65 years or older, and nearly 1.5 times higher among males than among females. Our time-dependent model showed that, in addition to age, male gender, and malignancies, risk of death was independently associated with immunodeficiency or rheumatic diseases and ARDs. Previous studies on NPB have reported much higher CFPs, ranging from 38% to 76% (189, 190, 194). This may stem from differences in the study populations, as some included only adults (193, 194, 197) or elderly males (191). In some studies, up to 57% of NPB cases suffered malignancies (190), likely reflecting a selection bias in hospital-based case-ascertainment. Our data indicate that in studies evaluating the clinical outcome of pneumococcal infections, mortality rates should be stratified according to nosocomial and community-associated cases.

6.6 Pneumococcal serotypes and the proportion of potentially vaccine-preventable infections (I, III, IV)

Our data indicate that some 70% and 52% of invasive pneumococcal infections among children under 5 and persons 65 years and older, respectively, stemmed from serotypes included in currently available PCV7. About 86% of the serotypes/groups of pneumococcal isolates from patients aged 65 years and older were those included in PPV23. Among children aged five or younger, 75.9% and 91.3% were serotypes included in PCV10 and PCV13, respectively. In the USA, routine childhood pneumococcal conjugate vaccine immunization has resulted in

dramatic reductions in rates of pneumococcal-related diseases and in major changes in the epidemiology of pneumococcal infections in children and adults (221). More than 70% of the serotypes of the pneumococcal isolates from NPB patients were those included in PPV23, and 74% of NPB patients aged 16-64 years presented at least one underlying condition for which PPV23 is currently recommended. In Finland, PCV7 is not currently included in the national childhood immunization program, and despite national recommendations, the uptake of PPV23 among persons aged 65 years and older as well as among those with high-risk conditions is extremely low (203).

6.7 Limitations

Although the major strength of our data is the nationwide and population-based surveillance design over multiple years, our study also has some limitations:

1) It is well known that ICD-coding in hospital discharge data may be incomplete and could be subject to misclassification. For this reason, we used hospital discharge data to identify only underlying conditions (ARD, chronic liver diseases, diseases of the spleen, and CSF leakage) for which data were unavailable in the two other registries that use standardized criteria and definitions. The standardized reimbursement criteria for underlying conditions in KELA's database may, however, have excluded mild cases of certain underlying conditions such as COPD, asthma, and diabetes mellitus type 2.

2) In the LRA group, we were unable to distinguish between asthma and COPD. On the other hand, our study population comprised non-elderly working-age persons where the proportion of COPD cases is likely to be extremely low.

3) In study III, we did not have precise information about the medication of the case-patients and controls. Based on KELA data between 1997 and 2002, 91.2% of all patients entitled to special reimbursement of medication expenses for asthma or COPD or both (i.e., the LRA group) received medication containing inhalation or oral steroids, and 16.9%, oral steroids. We can assume that the use of oral corticosteroids among LRA patients in the present study was significantly lower, since 15.3% of all cases with asthma were HRA.

4) We had no information on the patients' smoking habits, as some of the associations we found that were at higher risk for IPI (e.g. ARDs and COPD) may be confounded by smoking. About half of invasive pneumococcal diseases in immunocompetent non-elderly adults were previously attributed to cigarette smoking (76). In a previous case-control study of the risk of cigarette smoking on the development of IPI (76), asthma was associated with an increased odds ratio of

2.5 for IPI before, but not after, adjustment for other risk factors such as smoking and socioeconomic status.

5) Information about the PPV23 vaccination status of the IPI cases was unavailable in laboratory-based surveillance. However, PPV23 is little used in Finland. Consequently, one can reasonably assume that disease rates in our study population represent a pre-vaccination baseline.

6) Due to the registry-based study design, our analysis of the clinical outcome lacked chart review data to assess the effect of the severity of illness indicators on IPI-related mortality. Information on some underlying conditions may also have been missing.

7) The denominator data for persons with comorbidities were available only in aggregated form and allowed no estimation of age-specific rates in various groups of patients with comorbidities.

8) Data on the numbers of blood and CSF cultures performed at clinical microbiology laboratories were available only in aggregate form and allowed no evaluation of possible age- and gender-specific differences or of secular trends in blood and CSF culturing rates. Clinical practices and protocols for culture sampling may differ by age, particularly among the elderly, and may reflect population groups at increasing risk (8).

9) Information about the incidence of and serotypes causing IPI is restricted to the years 1995-2002. Some studies have recently reported data reflecting the current situation (254). From 2003 to 2006, the incidence of IPI has remained at around 14 per 100 000 population. During 1995-2006, a seasonal pattern and constancy in the composition of majority serotypes has prevailed with the fluctuation in rank order of prevalent serotypes among children under two. In other age groups, the proportion of PCV7 and PCV10 serotypes has significantly increased.

6.8 Summary

The findings of this study establish a baseline for the epidemiological characteristics of IPI in Finland and provide new information about developments in the epidemiology of IPI. The main results of the study are summarized below.

I The annual incidence of IPI increased by one-third during the study period. Most of this increase stemmed from an increase in pneumococcal bacteremia rates. Temporal increases and higher regional IPI rates were

significantly associated with higher blood culturing rates. This indicates that the true incidence of SPB in Finland may be higher than previously estimated, and that blood culture rates should be taken into account when evaluating surveillance data and the impact of vaccination programs. About 89% and 86% of the serotypes/groups of pneumococcal isolates from nonelderly adults and patients aged 65 years and older, respectively, were included in PPV23. Some 70%, 48%, and 52% of IPIs among children under five, nonelderly adults, and persons aged 65 years and older, respectively, resulted from serotypes included in PCV7. The serotype coverage of currently available pneumococcal vaccines is high, and is even higher with investigational conjugate vaccines. The use of pneumococcal vaccines has been suboptimal, thus emphasizing the need for comprehensive prevention strategies.

- II** The patient groups with the highest rates of IPI differed from those at the highest risk of death (e.g., patients with ARDs had a mortality rate similar to that of patients with non-hematological malignancies). In addition to young children and the elderly, the burden of IPI is also substantial among working-age persons without high-risk conditions. In the general population of non-elderly adults, two-thirds of invasive infections and one-half of fatal cases occur in persons with no recognized PPV23 indication. The current vaccine indications fail to address a significant proportion of the disease burden among nonelderly adults.
- III** Data in our study indicate that both HRA and LRA are independent risk factors for IPI among nonelderly adults. The risk among persons with a recent hospitalization for asthma was 4.4 times as high as among those with other chronic pulmonary diseases. About 90% of the serotypes of the pneumococcal isolates from patients in this age group are included in PPV23, and some 50% in the PCV7, respectively. Not only are persons with HRA requiring hospitalization and immunosuppressive therapy at significantly increased risk, but so are those with LRA. The results of our study support other recently published findings that asthma is an independent risk factor for IPI.
- IV** About 10% of all SPBs were healthcare-associated, and mortality among patients with NPB was more than twice as high as among patients with CAPB. Most patients with nosocomial disease had underlying conditions for which PPV23 is recommended, thus emphasizing the importance of strengthening prevention efforts in these patient groups. This is the first time the impact of healthcare-

associated pneumococcal bacteremia has been quantified from nationwide surveillance data.

6.9 Opportunities for prevention

Our results confirmed the appropriateness of current PPV23 indications for underlying medical conditions while at the same time highlighting multiple missed opportunities for their prevention. Because of the considerable disease burden and high mortality among nonelderly adults with no current vaccine indication, reaching this group of patients through prevention strategies is a priority.

One proposed strategy includes lowering the recommended age for PPV23 vaccination to include all persons aged 50 years and older, which could result in a moderately higher number of IPI cases prevented than with the current high-risk indications (20, 255). However, given the increasing risk for IPI and mortality with age, and the unknown duration of protection after primary immunization, the optimal timing and frequency of revaccination with PPV23 must be determined before this strategy can be implemented. Currently, no data are available on the clinical effectiveness of revaccination, and serological studies suggest that antibody responses may be lower after revaccination than after primary vaccination (256-258). Routine childhood immunization with PCV7 remains to be introduced in Finland. However, increasing evidence has been accumulating about the substantial indirect benefits of childhood PCV7 immunization in reducing rates of adult pneumococcal disease in the USA and elsewhere (259, 260). There is also evidence from the USA that the all-cause rate for pneumonia has decreased significantly in the age-groups under two years and 18-39 years (261-263). The serotypes included in PCV7 cause approximately 50% of IPI in Finnish adults, a proportion similar to that in the USA before PCV7 introduction. Therefore, introducing routine childhood immunization in Finland could provide an opportunity to substantially reduce the disease burden among difficult-to-reach groups of working-age adults with no PPV23 indications (263).

Our study supports recently published evidence that asthma is an independent risk factor for IPI. Further, PPV23 serotype coverage of IPI cases aged 18-49 years with chronic pulmonary disease, mainly asthma, was about 90%. We recommend that asthma be considered for inclusion in the list of conditions for which PPV23 is recommended to prevent IPI and community-acquired pneumonia (264, 265).

Because a substantial proportion of NPB in Finland stems from conjugate vaccine serotypes, a childhood immunization program could also offer the potential to reduce NPB indirectly. Targeting persons with chronic conditions for the

administration of PPV23 remains an established strategy for reaching those at highest risk for invasive infection.

An additional prevention strategy addressing this major public health problem would be campaigns and other actions aimed at reducing cigarette smoking. A case control study from the USA (188) estimated that if the prevalence of cigarette smoking could be reduced from 25% to 15%, the incidence of IPI among nonelderly adults would potentially decrease by approximately 18%.

Heavy alcohol use is also a distinct risk factor for IPI, and its mortality rate is significant. Political decisions aimed at reducing total alcohol consumption in society, as well as campaigns targeting alcoholics with PPV23, could reduce the burden of IPI in this patient group. Raising clinical awareness of IPI among alcoholics in order to improve both diagnostics and treatment is also important.

6.10 Future directions

Although PPV23 is an established tool in the prevention of IPI in adults, this vaccine has several limitations, such as poor antibody responses in immunocompromized persons, limited duration of protection – especially among the elderly, poor immunogenicity of several antigens, and the lack of impact on pneumococcal carriage. Because the aging population and the growing number of persons at greater risk for IPI due to immunosuppressive medication increases the public health impact of IPI, the demand for more efficient prevention strategies is considerable.

Following the introduction of PCV7 in the USA, population-based data have shown not only a large, rapid decline in overall and vaccine-type IPI in children under two years, but also reductions in vaccine-type disease among unvaccinated children and adults, as well as drops in the frequency of antibiotic-resistant infections (266). In Finland, public health authorities are preparing for the introduction of routine childhood immunization with pneumococcal conjugate vaccines, which is likely to occur in 2010 (267). Estimates indicate that the introduction of routine childhood immunization with PCV7 would prevent 3 cases of meningitis, 80 cases of pneumococcal bacteremia, 190 cases of pneumonia, 9600 cases of acute otitis media, and 1.2 deaths annually among children under five. Considering the indirect effects of the vaccine in the population of adults and children under five and calculating with a herd effect of 20%, an additional 100 cases of IPI and 19 deaths would be prevented. Postulating that PCV7 reduces in-patient pneumonia cases by 4%, 800 cases of pneumococcal pneumonia and 5 pneumonia-related deaths could be prevented among those over five.

New conjugate vaccines that will incorporate additional serotypes are in development, but this is probably no long-term solution to the replacement of vaccine serotypes. A vaccine based on pneumococcal proteins common to all serotypes and that contributes to pathogenesis is the current topic of interest among vaccine experts (226). The most promising and well-characterized vaccine candidates are pneumolysin, PspA, and PspC. Preliminary animal studies have demonstrated their potential to protect against infection with multiple serotypes or to prevent nasopharyngeal carriage or both (268, 269).

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9 APPENDIX

Appendix 1. Recommendations for the use of 23-valent pneumococcal polysaccharide vaccine in Finland

Immunocompetent persons aged ≥ 5 years

- Persons with cardiac failure, chronic pulmonary disease (chronic obstructive pulmonary disease, emphysema, but not asthma), diabetes mellitus, liver failure, renal failure, cerebrospinal fluid leakage, cochlear implants, and alcoholism
- Persons aged ≥ 65 years
- Persons residing in long-term care facilities

Immunocompromised persons aged ≥ 5 years

- Persons with functional or anatomic asplenia, HIV infection, lymphoma, multiple myeloma, nephrotic syndrome, congenital or acquired immunodeficiency (not agammaglobulinemia)
- Persons who received an organ or bone-marrow transplant
- Persons undergoing ongoing immunosuppressive chemotherapy (including systemic corticosteroids)

Appendix 2. ICD-9 and ICD-10 codes used in defining underlying conditions for data in the National Hospital Discharge database

Underlying condition	ICD-9 codes	ICD-10 codes
Alcohol-related diseases (Morbus Wernicke, mental, behavioral and neurological disorders due to alcohol use, hepatic and pancreatic disorders due to alcohol use, toxic effects of alcohol, maternal and fetal care due to alcohol abuse, rehabilitation and counseling due to alcohol abuse)	2651X; 2910A, 2911A, 2913A, 2918A, 2948X, 3039X, 3050A; 3318X; 3451A; 3575A; 3594A; 5710A, 5711A, 5712A, 5713X; 5770D, 5771B, 5771C; 5771D; 9800A, 9801A, 9802A, 9803A, 9808X, 9809X; 6554A; 7607A, E850A; V654A	E51.2; F10; G31.2; G40.51; G62.1; G72.1; K70; K86; T51; O35.4; P04.3; X45; Y91; Z50.2; Z71.4
Asthma bronchiale	4930A, 4930B, 4931A, 4931B, 4939A, 4939B	J45, J46
Cerebrospinal fluid leakage	3498A	G96.0
Chronic liver diseases (hepatic failure, cirrhosis of the liver and biliary ducts, portal hypertension, hepatorenal syndrome, and unspecified liver disease)	5709A, 5719X, 5739X; 5715A, 5716A, 5716X, 5719X; 5724A; 5739X	K72; K74; K76.7; K76.9
Chronic obstructive pulmonary disease (COPD)	4912B, 4960A	J44
Diseases of the spleen	2894A, 2895A	D73