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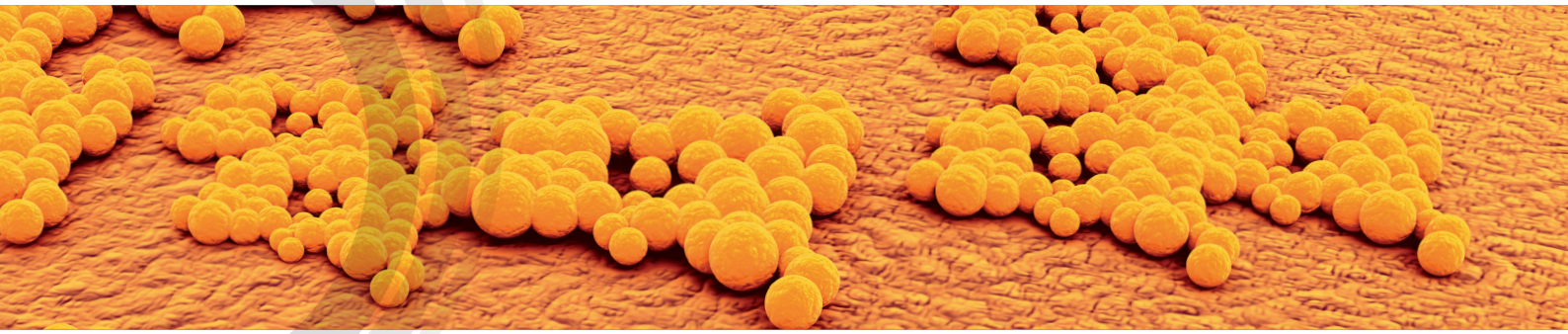

Surveillance of invasive pneumococcal disease in Europe

2010

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ECDC SURVEILLANCE REPORT

Surveillance of invasive pneumococcal disease in Europe, 2010

This report of the European Centre for Disease Prevention and Control (ECDC) was coordinated and written by Adoración Navarro Torné.

Contributing authors
Lucia Pastore Celentano, Andrew J Amato Gauci, Ole Heuer and Frantiska Hruba.

Data analysis
Adoración Navarro Torné and Marta Busana.

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Abbreviations

CAP	Community-acquired pneumonia
CFR	Case fatality rate
CSF	Cerebrospinal fluid
CTX	Cefotaxime
DSN	Dedicated Surveillance Network
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EQA	External Quality Assessment
ERY	Erythromycin
EUCAST	European Committee on Antimicrobial Susceptibility Testing
EU-IBIS Network	European Invasive Bacterial Infections Surveillance
HPA	Health Protection Agency, London
IPD	Invasive pneumococcal disease
MIC	Minimum inhibitory concentration
MS	Member States
PBP	Penicillin-binding protein
PCV7	Hepta-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PEN	Penicillin
PPV23	Pneumococcal polysaccharide vaccine
SIR	Susceptible, Intermediate, Resistant classification (antimicrobial susceptibility to erythromycin, penicillin and cefotaxime)
SXT	Sulfamethoxazole/trimetoprim
TESSy	The European Surveillance System
VPD	Vaccine preventable diseases

Executive summary

In 2010, a new enhanced surveillance system for IPD was established in the European Union, coordinated by ECDC, and this report describes the results of the first year of data collection (2010 data).

The main aim of this report is to provide information on the epidemiological trends and morbidity caused by the circulating *S. pneumoniae* serotypes, antimicrobial susceptibility and certain other epidemiological features of IPD.

Surveillance systems covering IPD across Europe are heterogeneous. Surveillance of IPD is compulsory for the majority of the Member States but voluntary in Belgium, Cyprus, France, Hungary and Spain. For most countries it is comprehensive and there are sentinel systems in two Member States. IPD surveillance differs widely across Europe due to the heterogeneity of reporting systems, case definitions applied, laboratory methods and disparities in blood-culturing practices to detect cases [1,2].

As at August 2010, hepta-valent pneumococcal conjugate vaccine (PCV7) was available in 24 Member States, the 10-valent pneumococcal conjugate vaccine (PCV10) was used in 16 and the 13-valent pneumococcal conjugate vaccine (PCV13) in 21 (VENICE II)[1]. In 2010, four Member States moved to a higher valent vaccine (PCV13) and three more in 2011. In 2010, Finland implemented universal vaccination with PCV10 (country communication) and Bulgaria introduced a mandatory immunisation with PCV10 (3+1 doses) (country communication).

In 2010, 21 565 cases of IPD were reported in 26 EU/EEA countries. ECDC actively encouraged Member States to apply EU 2008 case definition and thus, only confirmed cases were analysed. Of 26 EU/EEA countries reporting IPD cases, 18 applied EU 2008 case definition, one country applied EU 2002 case definition and two applied other (unspecified) case definitions. For the other countries the case definition was unknown.

Overall, data completeness was good for age, gender, specimen, serotype, antimicrobial susceptibility to penicillin (as categories: susceptible S, intermediate I, and resistant R) and typing method. Data quality was less complete for clinical presentation, outcome, vaccination status, vaccination type and minimum inhibitory concentration (MIC). The major findings of the EU surveillance are summarised below:

- The highest notification rates are among children under one year (18.54 per 100 000) and adults of 65 years or above (15.59 per 100 000).
- Notification rates ranged from 0.28 per 100 000 population (Lithuania) to 17.35 (Denmark). Nordic countries (Denmark, Finland, Norway and Sweden) presented the highest notification rates together with Belgium. However, these figures should be interpreted cautiously due to the heterogeneity of surveillance systems and variations in representativeness across Europe.
- Case fatality rate (CFR) varied substantially within the EU/EEA countries from 0% to 26.9%.These figures should also be interpreted with caution since missing information for the variable 'outcome' was 79.5%. The timeframe for follow-up also differs from country to country.
- Meningitis was the most common clinical presentation reported among children under one year.
- Pneumonia/septicaemia was the most frequent presentation for all other age groups. These results should also be interpreted with caution due to the incompleteness of data for the variable and differences in surveillance systems.
- The ten most frequently reported serotypes in children under five years were (in order of frequency): 19A, 1, 7F, 14, 3, 6B, 19F, 22F, 12F and 5.
- The ten most frequently reported serotypes in age groups above 15 years were (in order of frequency): 1, 19A, 7F, 14, 3, 19F, 12F, 6B, 5 and 22F.
- The theoretical vaccine preventable proportion of cases using PCV7, PCV10 and PCV13 in children under five years was 19.2%, 46.1% and 73.1% respectively.
- The theoretical vaccine preventable proportion of cases using PCV7, PCV10 and PCV13 in age groups above 15 years was 17.9%, 36.2% and 56.9% respectively.
- The most frequently reported serotypes causing IPD not covered by conjugate vaccines were 22F, 8, 12F and 9N. These serotypes were mainly reported in age groups above 15 years and are theoretically covered by the pneumococcal polysaccharide vaccine (PPV23).
- The cases showed a clear, seasonal distribution with a noticeable rise during the winter months, mainly reported among those aged 15+ years.
- Erythromycin was the antibiotic with the highest non-susceptibility (intermediate + resistant) proportion (17.6%) followed by penicillin (8.9%).
- Multidrug-resistance (defined as resistance to three or more antibiotic classes) to penicillin, erythromycin and cefotaxime was reported in serotypes 1, 14, 19A, 19F and 23F.
- In general, the proportion of non-susceptibility (intermediate + resistant) to penicillin and/or erythromycin was higher in southern and eastern European countries and in Finland.

Despite issues with heterogeneity of data, this new surveillance at EU level offers significant added value, thanks to experts' efforts in most Member States, the widespread use of the EU 2008 case definition and the relatively satisfactory data quality overall.

[1] VENICE II. Available at: http://venice.cineca.org/VENICE_Survey_PNC_1_2012-02-24.pdf

1. Introduction

1.1 Invasive pneumococcal disease surveillance

1.1.1 Invasive pneumococcal disease

Invasive pneumococcal disease (IPD) is an acute and serious illness caused by *Streptococcus pneumoniae*. Invasive disease may lead to severe syndromes including meningitis, septicaemia, pneumonia/empyema, and bacteraemia among others, and may result in serious sequelae and permanent impairment [3,4]. Children are at major risk [5] as are immune-compromised patients and the elderly. The WHO estimates that more than 1.6 million people die of pneumococcal disease annually and that about half of these deaths are in children under five years of age [5]. Of the 93 different serotypes characterised, only 20 to 30 of them are responsible for the majority of invasive pneumococcal diseases worldwide.

Despite its frequency and severity, pneumococcal disease can be prevented by vaccination. A 23-valent pneumococcal polysaccharide vaccine based on the main serotypes causing IPD was licensed in 1983. The first pneumococcal conjugate vaccine was licensed in the United States in 2000. In Europe, the vaccine was licensed in 2001 and has been in use ever since. This vaccine (PCV7)[2] includes purified capsular polysaccharide of seven frequent and important serotypes. A variety of studies have shown the conjugate vaccine to be safe and effective. The introduction of the vaccine has markedly decreased the incidence of IPD caused by serotypes included in the vaccine [6,7]. Moreover, the vaccination of infants has resulted in 'herd immunity' by reducing nasopharyngeal carriage [8,9] and transmission of the bacterium. As an indirect effect, the vaccination of infants has decreased pneumococcal morbidity and mortality among the elderly [10]. New conjugate vaccines have been marketed in Europe, the 10-valent pneumococcal conjugate vaccine (PCV10)[3] in March 2009 and the 13-valent conjugate vaccine (PCV13)[4] in December 2009, the latter having recently been authorised for adults over 50 years. The polysaccharide vaccine (PPV23) is indicated for use in children of two years and above in risk groups and for the elderly.

S. pneumoniae is a common commensal of the upper respiratory tract [11] and through colonisation it can be a cause of local and invasive infection. In general, community-acquired respiratory infections, and those caused by *S. pneumoniae* in particular, are the main clinical entities for prescription of antimicrobial agents in young children. Antimicrobial use and abuse is one of the main causes for the emergence of antimicrobial resistance in respiratory pathogens. Individuals that carry (nasopharyngeal colonisation) and hence potentially transmit resistant pneumococci are also at higher risk of developing invasive pneumococcal disease caused by resistant strains [12].

1.1.2 An overview of invasive bacterial disease surveillance projects in Europe

From 1999 to 2007, the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) ran a Dedicated Surveillance Network (DSN) in Europe for the surveillance of invasive bacterial diseases caused by *Neisseria meningitidis* and *Haemophilus influenzae*. The network was successfully coordinated by the Health Protection Agency (HPA) in London and the project was funded by DG SANCO. The surveillance of IPD was not covered by the EU-IBIS network.

In October 2007, coordination of the EU IBD surveillance activities was transferred to ECDC.

After the transition, the establishment of the EU enhanced surveillance for IPD was identified as one of the top priorities, by both Member States' representatives and ECDC, and pneumococcal disease was highlighted as an important public health threat in Europe.

As a first step, in 2007–2008, ECDC sponsored a project aiming to describe the surveillance systems for IPD in Europe [2], map national laboratory performance, and collect information on vaccination policies and schedules in Member States to find common elements for creating the EU system. The project took into account the knowledge acquired from another EU funded project, Pneumococcal Disease in Europe (Pnc-EURO), which was established to determine the epidemiology of *Streptococcus pneumoniae* in a variety of European countries prior to the large-scale introduction of the new pneumococcal conjugate vaccine PCV7 [1].

During 2012, another ECDC funded project, the Vaccine European New Integrated Collaboration Effort (VENICE II)[5] has been collecting information on vaccination policies and the impact of pneumococcal vaccination programmes.

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[2] Product characteristics of PCV7 available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000323/WC500041563.pdf

[3] Product characteristics of PCV10 available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000973/WC500054346.pdf

[4] Product characteristics of PCV13 available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001104/WC500057247.pdf

[5] VENICE II. Available at: http://venice.cineca.org/

Vaccination schedules in European countries have been regularly updated and published by the EUVAC.NET (now transferred to ECDC)[6].

Furthermore, the European Antimicrobial Resistance Surveillance Network (EARS-Net, former EARSS)[7] has also been collecting and analysing data on the antimicrobial resistance of *S. pneumoniae* since 1998.

EARS-Net is a network of national surveillance systems providing European reference data on antimicrobial resistance for public health purposes. EARS-Net is the largest publicly funded system for surveillance of antimicrobial resistance in Europe. The coordination of EARS-Net was transferred from the Dutch National Institute of Public Health and the Environment (RIVM) to ECDC in January 2010.

1.1.3 ECDC IPD surveillance networks

The various projects funded by ECDC reveal the heterogeneity of IPD surveillance across Europe. This variability relates to the surveillance systems; case definition applied; laboratory methods for diagnosis and characterisation of *S. pneumoniae* and healthcare and medical practices, especially as regards blood culturing.

Following agreement with the Member States, ECDC established a European invasive pneumococcal disease network in November 2010. European surveillance for IPD has now been integrated into existing structures and the network of invasive bacterial diseases.

Member States' nominated experts (both epidemiologists and microbiologists) collaborate with ECDC to improve IPD surveillance by collecting and reporting comparable, good-quality data.

External Quality Assessment Schemes (EQAs) and training are coordinated by ECDC in the EU and outsourced to the IPD network of laboratory experts in Member States. The main goal is to strengthen and harmonise the laboratory capacities in Member States while reinforcing the collaboration between laboratories and public health institutes in Europe.

Prior to this initiative, ECDC had been collecting data on invasive pneumococcal disease in TESSy since 2006 as part of the basic surveillance for all EU-notifiable diseases. The results of the analysis are published on a regular basis in the Annual Epidemiological Report (AER)[8].

When the enhanced surveillance systems began operating, information on laboratory characterisation of the isolates, clinical presentation and vaccination status were added to the core set of variables. Data are now collected on an annual basis.

In parallel, information on IPD antimicrobial resistance and serotype distribution is available through the European Antimicrobial Resistance Surveillance Network (EARS-Net) for 27 Member States. Antimicrobial susceptibility test results are collected by national surveillance networks from clinical laboratories in the participating countries. At present, around 900 public health laboratories serving approximately 1 400 hospitals are reporting data to EARS-Net. These participating hospitals and laboratories provide services to an estimated population of 100 million European citizens. The national surveillance networks upload their data to The European Surveillance System (TESSy) at ECDC on an annual basis. External quality assessment (EQA) and protocols on testing methods to improve the consistency and quality of the data are funded by ECDC.

1.1.4 Objectives of invasive pneumococcal disease surveillance

Specific objectives for the passive surveillance for IPD were:

- To determine age-specific notification rates in EU/EEA countries
- To collect information on clinical presentation and outcome of the disease
- To establish a baseline for monitoring IPD trends and seasonality
- To monitor circulating serotypes of *S. pneumoniae* in order to detect emerging strains and serotype replacement in the EU
- To track antimicrobial resistance in pneumococcal isolates within the EU.

[6] EUVAC-Net. Available at: http://ecdc.europa.eu/en/activities/surveillance/euvac/Pages/index.aspx

[7] EARS-Net. Available at: http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx

[8] Annual Epidemiological Report. Available at:

http://ecdc.europa.eu/en/publications/Publications/1111_SUR_Annual_Epidemiological_Report_on_Communicable_Diseases_in_Europe.pdf

2. Methods: Data collection and presentation

2.1 Reporting of invasive pneumococcal disease data in TESSy

The competent bodies[9] for surveillance in the Member States have designated national contact points for IPD surveillance who work together with ECDC on the reporting of IPD data to TESSy. National data are uploaded directly by the reporting country into the appropriate database. A set of validation rules was designed together with the variables of the dataset. The validation rules facilitate verification of data by an automated procedure. This verification of data during the uploading process enables countries to check their files before submission, thus improving the quality of data.

It was agreed that IPD data reporting to ECDC would initially be done on a yearly basis.

Along with the data collection, countries were asked to provide a description of their national surveillance systems. A table containing this information is included in the report (see Annex, Tables A1 and A2) and this acts as a guide to interpreting national data.

The system allows the reporting of aggregate data, although case-based reporting is favoured by ECDC.

The IPD dataset consists of a core group of variables common to all diseases combined with an enhanced dataset specific for IPD (see Annex, Table A4).

2.2 Implementation of EU case definitions

The official 2008 EU case definition for IPD should be applied to data reported to ECDC since 1 January 2009. Full sets of published case definitions have been made available[10]. Member States were encouraged to apply 2008 EU definition for the collection of 2010 data. Network members agreed that only confirmed cases of invasive pneumococcal disease should be reported.

Case definition for invasive pneumococcal disease

Clinical criteria

Not relevant for surveillance purposes

Laboratory criteria

At least one of the following three:

- Isolation of *Streptococcus pneumoniae* from a normally sterile site
- Detection of *Streptococcus pneumoniae* nucleic acid from a normally sterile site
- Detection of *Streptococcus pneumoniae* antigen from a normally sterile site

Epidemiological criteria

NA

Case classification

- *Possible case:* NA
- *Probable case:* NA
- *Confirmed case:* Any person meeting the laboratory criteria for case confirmation.

[9] The ECDC founding Regulation states that in its relations with the Member States ECDC shall cooperate with the competent bodies operating in its technical field, particularly in the area of surveillance [Regulation (EC) No 851/2004 of the European Parliament and of the Council, Art. 3, Par. 2. Available at: http://ecdc.europa.eu/en/aboutus/Key%20Documents/0404_KD_Regulation_establishing_ECDC.pdf]

[10] See Commission Decision of 28 April 2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council: Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:159:0046:0090:EN:PDF

2.3 Data collection 2010

In 2011, data using the EU enhanced invasive pneumococcal disease dataset were reported to TESSy for the first time. The collection of 2010 data took place between 4 July and 10 September 2011.

The majority of the data were collected in a case-based format. Only one country reported aggregate data.

Member States submitted data gathered from a range of the following data sources:

- Enhanced surveillance with integrated epidemiological and laboratory data, submitted by a reconciled notification/laboratory data source. The laboratory and epidemiological data is integrated at the national surveillance institute, with laboratory data coming mainly from the national reference laboratory (although in some countries data are also submitted by peripheral laboratories) and data from the notification system.
- Data collected from two parallel data sources, the notification system and the laboratory system, without it being possible to reconcile the two datasets at national level.
- Data coming from the national notification system or from the laboratory system only (no multiple data sources available at national level).

Due to the diversity among national surveillance systems, it was considered important that the countries updated the available information on case definition used, data sources available in the country and characteristics of surveillance systems (i.e. universal versus sentinel, active versus passive, etc.)

2.4 Data analysis

IPD surveillance data were uploaded, validated and approved in TESSy by the Member State contact points. A verification report produced by TESSy provides an overview of the completeness of data by country. Once the data were submitted, EU individual datasets were validated.

ECDC asked the national experts about potential duplication of data or surveillance restricted to certain age groups. Potential overlapping of the two data sources available at national level was reported by Czech Republic and France, although the extent was difficult to determine. Therefore the following criteria were applied:

- For Czech Republic, only data submitted from the data source 'Laboratory surveillance of invasive pneumococcal infections' (CZ-NRL-STR, combined notification-laboratory data) were considered for the analysis in this report.
- For France, the total number of cases was calculated considering only data reported by the data source 'Community invasive infections hospitalised' (FR-EPIBAC[11], notification data). Data uploaded from FR-PNEUMO-NRL (combined notification-laboratory data) data source were taken into account for the analysis of the enhanced variables (clinical presentation, specimen, serotype, and antimicrobial susceptibility data). France IPD surveillance relies on a sentinel network of hospital laboratories, covering at least 75% of acute care activity and the French metropolitan population (the coverage proportion was 75.3% in 2010). Incidence rates are estimated using the population covered by the participating hospitals as denominator.
- In the Netherlands, IPD is only notifiable for children up to five years of age, and only cases within this age group were reported. Therefore denominators were considered accordingly.

This report includes the total number of reported confirmed cases of IPD and a description of epidemiological and laboratory variables with appropriate completeness. Data are presented with the 'date used for statistics'[12] as the preferred date.

Case Fatality Rate (CFR) was calculated as follows:

$$CFR = \frac{Number\ reported\ as\ dead}{Number\ reported\ as\ dead + Number\ reported\ as\ alive}$$

Cases with the variable 'outcome' reported as 'unknown' or with a missing value were not taken into account in the denominator. There is no common definition of the point in time at which a fatal outcome is determined. This may add variation to the outcome figures throughout Europe. Acknowledging the differences in IPD surveillance systems and reporting across Europe, CFR was calculated on a country basis. Serotype-specific case fatality rate was calculated following the same rule. Consequently only cases with known outcomes were considered.

[11] Surveillance des infections invasives à *Haemophilus influenzae*, *Listeria monocytogenes*, *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Streptococcus agalactiae* (B) et *Streptococcus pyogenes* (A) en France métropolitaine.

[12] 'Date used for statistics' defined as the reference date used for standard reports that is compared to the reporting period. The date used for statistics can be any date that the reporting country finds applicable – e.g. date of notification, date of diagnosis or other.

Member States were asked to provide minimum inhibitory concentration (MIC) and interpretation of antimicrobial susceptibility testing expressed as susceptible (S), intermediate (I) and resistant (R), according to the standards and protocols used for antimicrobial susceptibility testing at national level. However, some countries submitted data on MIC but not on SIR and conversely, other countries only reported SIR but not MIC. Therefore, data were analysed and presented separately as SIR and MIC. Completeness was higher for SIR data than for MIC data. Since information was lacking on national standards and methods for antimicrobial susceptibility testing, MIC data are presented in a standard format to be interpreted according to the standards used at national level. As a reference we adopted EUCAST breakpoints. Statistical analysis was performed using STATA® 11.0 (StataCorp, USA).

2.5 Laboratory methods

For a range of clinical and diagnostic reasons it is difficult to determine the true burden of pneumococcal disease (e.g. methods are not accurate enough to diagnose mucosal infections such as sinusitis and otitis media). Occult pneumococcal bacteraemia is difficult to assess. Therefore, present diagnostic tools are only sensitive enough for the most severe presentations of invasive pneumococcal disease.

Confirmation of an IPD case implies the isolation and/or detection of nucleic acid and/or detection of *Streptococcus pneumoniae* antigens at a normally sterile site.

2.5.1 Serotyping methods

In Europe, a variety of laboratory methods are used to serotype strains, such as Quellung, Pneumotest®, slide agglutination, latex agglutination, co-agglutination, multiplex PCR, and gel diffusion.

Quellung reaction is an immunological reaction in which antibodies bind to the capsule of certain capsulated microorganisms. The antibody reaction allows these species to be visualised under a contrast phase microscope. If the reaction is positive, the capsule becomes opaque and appears to enlarge. Quellung is the German word for swelling and describes the microscopic appearance of pneumococcal or other bacterial capsules after their polysaccharide antigen has combined with a specific antibody. The antibody usually comes from serum taken from an immunised laboratory animal (usually rabbit for pneumococcus). As a result of this combination and the precipitation of the large, complex molecule formed, the capsule appears to swell because of increased surface tension, and its outlines become clearly delineated.

When specific anti-pneumococcal antibodies, as such or coupled to latex particles or staphylococci via protein A, are mixed with pneumococci of the corresponding capsular type, an agglutination reaction occurs. This agglutination is visible to the naked eye. This is the principle of slide agglutination, latex agglutination and co-agglutination methods.

Pneumotest® is a commercial application of the latex slide agglutination method (Statens Serum Institut, Denmark).

Multiplex PCR is a molecular method based on the amplification of specific DNA sequences. It enables causative microorganisms and/or serotype specific genes to be identified with a high degree of sensitivity and specificity.

Gel diffusion is a simple precipitation assay that consists of evaluating the precipitin reaction in a clear gel, seen when an antigen placed in a hole in the gel (usually agarose) diffuses evenly into the medium. An obvious ring forms where the antigen meets the antibody. In the case of pneumococci, specific antisera against capsular antigens are used, allowing the identification and serotyping of a particular pneumococcal strain

2.5.2 Antimicrobial susceptibility testing methods

The antimicrobial gradient diffusion method is based on the principle of establishing an antimicrobial concentration gradient in an agar medium as a means of determining susceptibility. The Etest® is a commercial version. It employs thin plastic test strips impregnated with a dried antibiotic concentration gradient and marked on the upper surface with a concentration scale. After overnight incubation, the tests are read by viewing the strips from the top of the plate. The MIC is determined by the intersection of the lower part of the ellipse-shaped growth inhibition area with the test strip [13].

The broth dilution method procedure involves preparing two-fold dilutions of antibiotics in a liquid growth medium dispensed in test tubes. The lowest concentration of antibiotic that prevented growth represents the minimal inhibitory concentration (MIC). This method can be done on a 'miniature' (broth microdilution) scale using microtiter plates [13].

The use of instrumentation can standardise the reading of end points and often produces susceptibility test results more quickly than manual readings because sensitive optical systems enable the detection of subtle changes in bacterial growth [13].

Antimicrobial susceptibility testing was reported by the countries as MIC (see Section 3.3.2) and some countries also reported category (susceptible S, intermediate I or resistant R) according to national standards and protocols. A separate analysis is provided in order to facilitate comprehension.

3. Results

3.1 Case definition applied and data source

All Member States apart from Bulgaria (aggregated data) reported case-based data. EU 2008 case definition was applied by 18 Member States, one country applied EU 2002 case definition, while two used the 'Other' (unspecified) case definition. For five countries the case definition was unknown.

With regard to population coverage, at national level France applies a correction factor of 1.61904 to estimate the total number of cases in its national reports (the correction factor has not been applied for this analysis). Greece has a surveillance system with national coverage for meningitis only. The population coverage is not national for Spain and therefore, the notification rate needs to be interpreted cautiously. The true notification rate for Spain is probably higher than reported here due to the data submitted not being completely representative. There is no unique surveillance system in the UK. The Netherlands did not report adult cases of IPD (all reported cases were under five years of age).

All countries but three reported data from a unique data source (Cyprus, Czech Republic and France submitted data from two different data sources).

According to the data source profiles uploaded by countries, 18 countries had a reconciled notification/laboratory surveillance system (this means that laboratory data and epidemiological and/or vaccination information are collected and filed together on a case-by-case basis at national level), six countries only had laboratory-based surveillance systems and two countries only presented data from the notification system.

3.2 Quality and completeness of reporting

In 2010, 21 565 confirmed cases of invasive pneumococcal disease (IPD) were reported by 26 countries, namely Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, and United Kingdom. Germany, Liechtenstein, Luxembourg and Portugal did not report data on IPD in 2010.

Data on serotypes were reported by 22 countries: Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Malta, Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, and United Kingdom.

Data on antimicrobial susceptibility were submitted by 21 countries: Austria, Belgium, Cyprus, Denmark, Estonia, Finland, France, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, Norway, Poland, Romania, Slovakia, Slovenia, Spain, and United Kingdom.

All cases considered for inclusion in the analysis were laboratory-confirmed cases.

All countries reported case-based data except Bulgaria, which submitted aggregated data.

Data on age, age month, gender and classification were almost complete. Information on the variable specimen was also nearly complete (1.3% missing) (Table 3.1).

Data on vaccination status represented less than 10% of the total reported cases.

Completeness on serotype (53.3% missing) and test method for serotyping (56.6% missing) were very similar, indicating that the serotyping method is known for almost all cases of serotype reported.

Minimum inhibitory concentration (MIC) data were reported in approximately 20–25% of the total reported cases. The method for determining MIC was reported in approximately 53% of the reported results for MIC (the three antibiotics pooled).

Antimicrobial resistance data expressed as susceptible (S), intermediate (I) and resistant(R) was more complete than when expressed as MIC, especially for penicillin (40.8%) and erythromycin (37.0%).

Table 3.1 Quality of 2010 data. Distribution of known, unknown, not applicable and blank responses per variable for all reported cases of IPD by country, EU/EEA countries* (n=22 667)

Variable**	Known		UNK		Blank		Overall missing
	n	%	n	%	n	%	%
Age	22 601	99.7	0	0	66.0	0.3	0.3
AgeMonth	1 471	100	0	0	21 196	93.5	93.5
Classification	22 666	100	1	0	0	0	0
Clinical Presentation	8 449	37.3	14 169	62.5	49	0.2	62.7
Gender	22 598	99.7	69	0.3	0	0	0.3
Outcome	4 638	20.5	17 101	75.4	928	4.1	79.5
VaccStatus	1 979	8.7	20 639	91.1	49	0.2	91.3
VaccType	1 919	8.5	7 521	33.2	389	1.7	91.5
Serotype	10 585	46.7	4 839	21.3	7 243	32.0	53.3
Specimen	22 370	98.7	268	1.2	29	0.1	1.3
ResultMICSign_CTX	5 240	23.1	0	0	17 427	76.9	76.9
ResultMICSign_ERY	3 953	17.4	0	0	18 714	82.6	82.6
ResultMICSign_PEN	5 244	23.1	0	0	17 423	76.9	76.9
ResultMICValueCTX	5 252	23.2	0	0	17 415	76.8	76.8
ResultMICValueERY	4 031	17.8	0	0	18 636	82.2	82.2
ResultMICValuePEN	5 384	23.8	0	0	17 283	76.2	76.2
SIR_PEN	9 247	40.8	879	3.9	12 541	55.3	59.2
SIR_CTX	6 186	27.3	998	4.4	15 483	68.3	72.7
SIR_ERY	8 382	37.0	929	4.1	13 350	58.9	63.0
TestMethodMIC	7 730	34.1	107	0.5	14 830	65.4	65.9
TestMethodTyping1	9 880	43.4	84	0.4	7 367	32.3	56.6

*Only CZ-NRL-STR data source for Czech Republic; data from FR-EPIBAC and FR-PNEUMO-NRL for France

** Variables defined in the dataset used for the 2010 IPD data collection. See Annex (Table A4)

3.3 Laboratory methods reported

3.3.1 Laboratory methods for serotyping

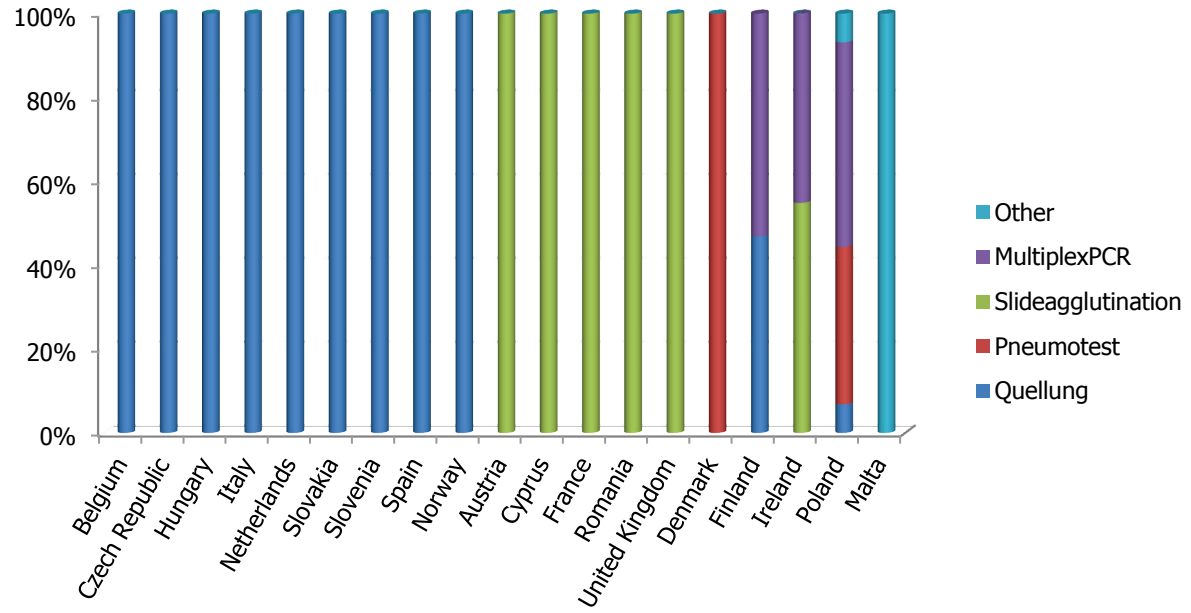
According to the data, Quellung is the preferred technique for serotyping in Europe and was in 62% of all cases for which serotype was reported. This was followed by slide agglutination and Pneumotest®.

Of the 9 946 cases for which information on serotype was available, the test method was reported in 9 880 (99.3%) cases.

Some cases were reported to the serogroup level (i.e. serogroup 19, serogroup 7). This may indicate that the countries reporting to this level did not have information available to characterise to the serotype level.

Figure 3.1 presents the distribution of serotyping methods by country. Finland, Ireland and Poland used two or more methods for serotyping pneumococcal strains.

Figure 3.1 Percentage of reported serotyping test methods used among cases reported as IPD by country, EU/EEA countries, 2010 (n=9 880)

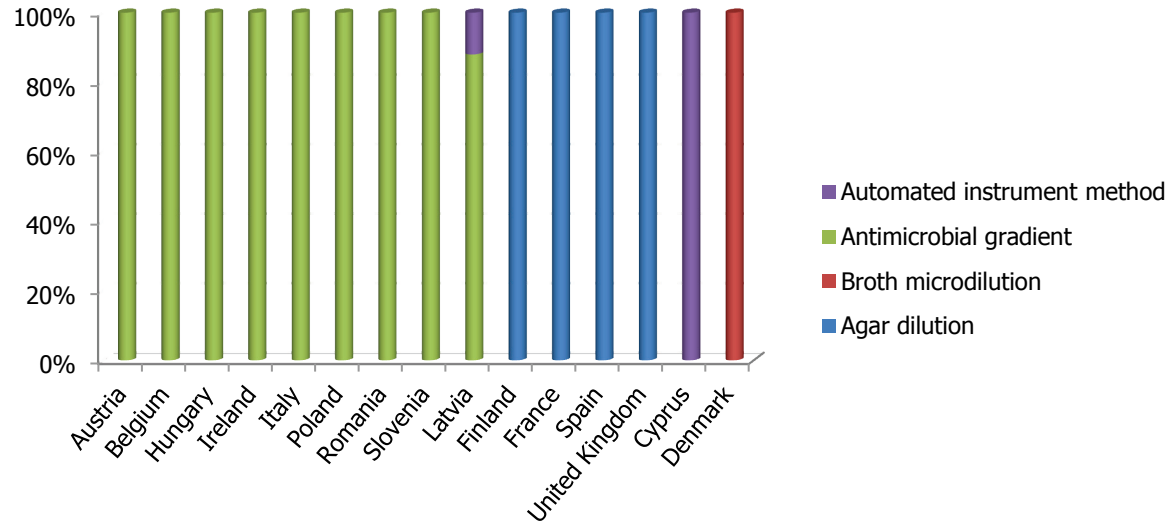


3.3.2 Laboratory methods for antimicrobial susceptibility testing

Member States reported antimicrobial susceptibility testing results expressed as minimum inhibitory concentration (MIC). Countries that reported data on antimicrobial susceptibility as MIC were: Austria, Belgium, Cyprus, Denmark, Spain, Finland, France (for penicillin and cefotaxime), Hungary, Ireland, Italy, Lithuania (only for penicillin), Latvia, Poland (for penicillin and cefotaxime), Romania and Slovenia. Belgium, France, Slovenia and Spain reported the MIC test method for all the cases where MIC was reported (Figure 3.2). Data were reported for penicillin (n=5 384), erythromycin (n=4 031), and cefotaxime (n=5 252).

The test method for MIC is reported in 53% of the cases including information on MIC (pooling the three antibiotics together). Antimicrobial gradient is the preferred method for determining MIC among the countries reporting this method. This method represented 60% of all cases for which MIC was reported. The method is preferred in nine out of 15 countries reporting MIC data. Most of the countries applied a single method for determining MIC.

Figure 3.2 Percentage of reported MIC test methods used among cases reported as IPD by country, EU/EEA countries, 2010 (n=7 730)



4. Descriptive analyses

4.1 Number of cases

In 2010, 21 565 confirmed cases of invasive pneumococcal disease (IPD) were reported to TESSy by the EU/EEA countries.

Notification rates ranged from 17.35 per 100 000 (Denmark) to 0.28 (Lithuania). The Nordic countries (Denmark, Finland, Norway and Sweden) presented the highest notification rates, together with Belgium. This statement needs to be interpreted cautiously due to the diversity of surveillance systems and variations in the completeness/representativeness of their data across Europe (Table 4.1).

Table 4.1 Number of reported and notification rates of IPD cases in EU/EEA countries, 2010 (n=21 565)

Country	Number of reported cases (N)	Notification rate (cases per 100 000)
Austria	325	3.88
Belgium	1 851	17.08
Bulgaria[a]	26	0.34
Cyprus	23	2.86
Czech Republic	300	2.86
Denmark	960	17.35
Estonia	14	1.05
Finland	836	15.62
France[b]	5 117	10.80
Greece[c]	38	0.34
Hungary	107	1.06
Ireland	304	8.19
Italy	854	1.30
Latvia	16	0.67
Lithuania	9	0.28
Malta	11	2.68
Netherlands[d]	55	4.92
Poland	333	0.89
Romania	80	0.38
Slovakia	18	0.34
Slovenia	224	10.73
Spain[e]	2 212	4.74
Sweden	1 456	14.82
United Kingdom[f]	5 616	9.00
EU total	**20 785**	**5.09**
Iceland	32	11.50
Norway	748	16.18
Total	**21 565**	**5.22**

a Aggregated reporting

b France: no national coverage for IPD (see Methods)

c National coverage only for meningitis

d Netherlands reports data on IPD only for children up to five years. Notification rate was calculated accordingly.

e No national coverage of this surveillance for Spain. Notification rate needs to be interpreted with caution. Notification rate for Spain is probably higher due to the incompleteness of the data submitted.

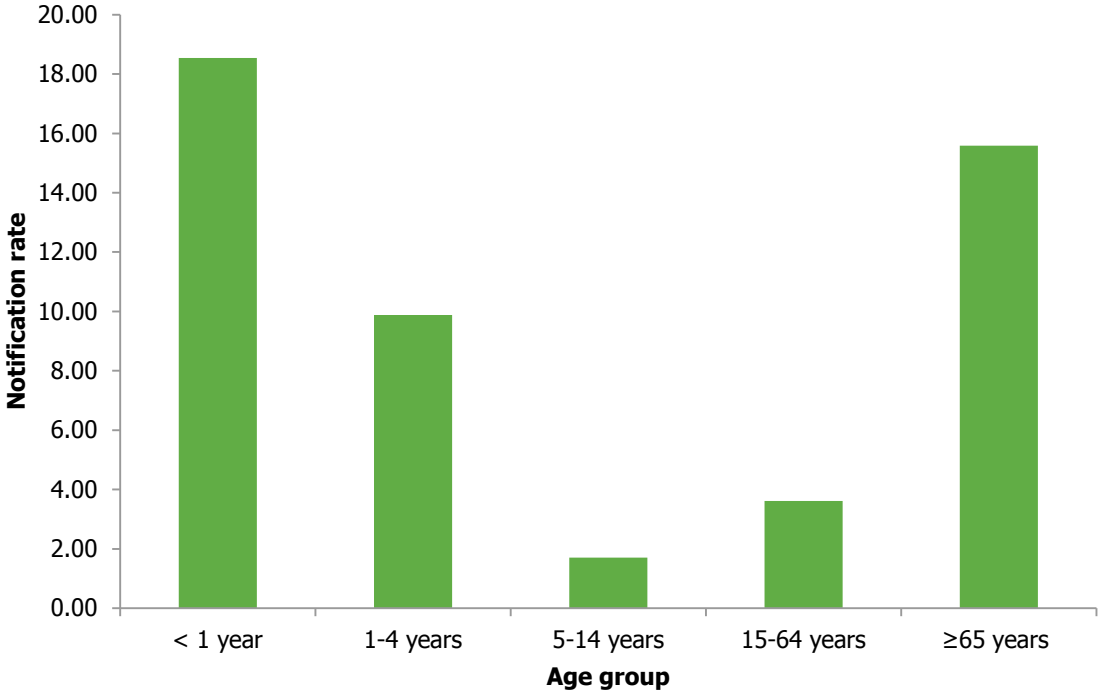
f There is no unique surveillance system in the UK. Data are representative (as submitted by England and Wales, Scotland and Northern Ireland), however surveillance systems might not be identical.

4.2 Age and gender

Of the 21 473 reported cases for which age information was provided, 45% (n=9 727) concerned people aged 65 years or older, 42% (n=9036) concerned adults aged 15 to 64 years and 13% (n=2 710) concerned children 0 to 14 years of age. In the latter group, children aged one to four years accounted for the highest proportion of cases (7%, n=1 444) (Table 4.2).

The highest notification rates were reported among children under one year (18.54 per 100 000) followed by adults aged 65 years or above (15.59 per 100 000) (Figure 4.1).

Figure 4.1 Notification rate (cases per 100 000 population) of reported IPD cases by age group, EU/EEA countries, 2010 (n=21 473)



For the Netherlands 50.9% of the cases reported concerned infants under one year of age and 47.3% concerned children aged one to four years. Adult cases were not reported since IPD is only notifiable at national level for children up to the age of five years. Slovenia (20.5%), Slovakia (22.3%), Greece (21.1%), Romania (25.1%) and Poland (24.1%) reported a significant number of cases in the under-five age group. Cyprus (20%) was the country that reported the highest number of cases in the age group five to 14 years. Estonia and Malta did not report cases among children.

Table 4.2 Distribution by age group* of reported IPD cases by country, EU/EEA countries, 2010 (n=21 473)

Country	< 1 year		1-4 years		5-14 years		15-64 years		≥65 years		Total (N)
	N	%	n	%	n	%	n	%	n	%	N
Austria	10	3.1	23	7.1	7	2.2	133	40.9	152	46.8	325
Belgium	118	6.5	187	10.3	67	3.7	659	36.3	784	43.2	1 815
Bulgaria**											
Cyprus	1	5.0	2	10.0	4	20.0	5	25.0	8	40.0	20
Czech Republic	6	2.0	16	5.3	10	3.3	139	46.3	129	43.0	300
Denmark	20	2.1	22	2.3	15	1.6	402	41.9	501	52.2	960
Estonia	0	0.0	0	0.0	0	0.0	11	78.6	3	21.4	14
Finland	20	2.4	82	9.8	13	1.6	417	49.9	304	36.4	836
France	176	3.4	262	5.1	139	2.7	2 126	41.5	2 414	47.2	5 117
Greece	2	5.3	6	15.8	4	10.5	18	47.4	8	21.1	38
Hungary	3	2.8	15	14.0	3	2.8	52	48.6	34	31.8	107
Ireland	16	5.3	19	6.3	3	1.0	116	38.2	150	49.3	304
Italy	29	3.4	58	6.8	28	3.3	323	38.0	413	48.5	851
Latvia	0	0.0	2	13.3	0	0.0	11	73.3	2	13.3	15
Lithuania	0	0.0	1	11.1	1	11.1	5	55.6	2	22.2	9
Malta	0	0.0	0	0.0	0	0.0	6	54.5	5	45.5	11
Netherlands	28	50.9	26	47.3	1	1.8	0	0.0	0	0.0	55
Poland	29	8.7	51	15.4	25	7.5	170	51.2	57	17.2	332
Romania	9	11.3	11	13.8	10	12.5	39	48.8	11	13.8	80
Slovakia	1	5.6	3	16.7	1	5.6	10	55.6	3	16.7	18
Slovenia	7	3.1	39	17.4	2	0.9	85	37.9	91	40.6	224
Spain	107	4.8	231	10.4	72	3.3	865	39.1	937	42.4	2 212
Sweden	18	1.2	33	2.3	13	0.9	575	39.5	817	56.1	1 456
United Kingdom	81	1.4	332	5.9	139	2.5	2 544	45.5	2 498	44.7	5 594
EU total	681	3.3	1 421	6.9	557	2.7	8 711	42.0	9 323	45.1	**20 693**
Iceland	2	6.3	2	6.3	1	3.1	13	40.6	14	43.8	32
Norway	15	2.0	21	2.8	10	1.3	312	41.7	390	52.1	748
Total	698	3.3	1 444	6.7	568	2.6	9 036	42.1	9 727	45.3	**21 473**

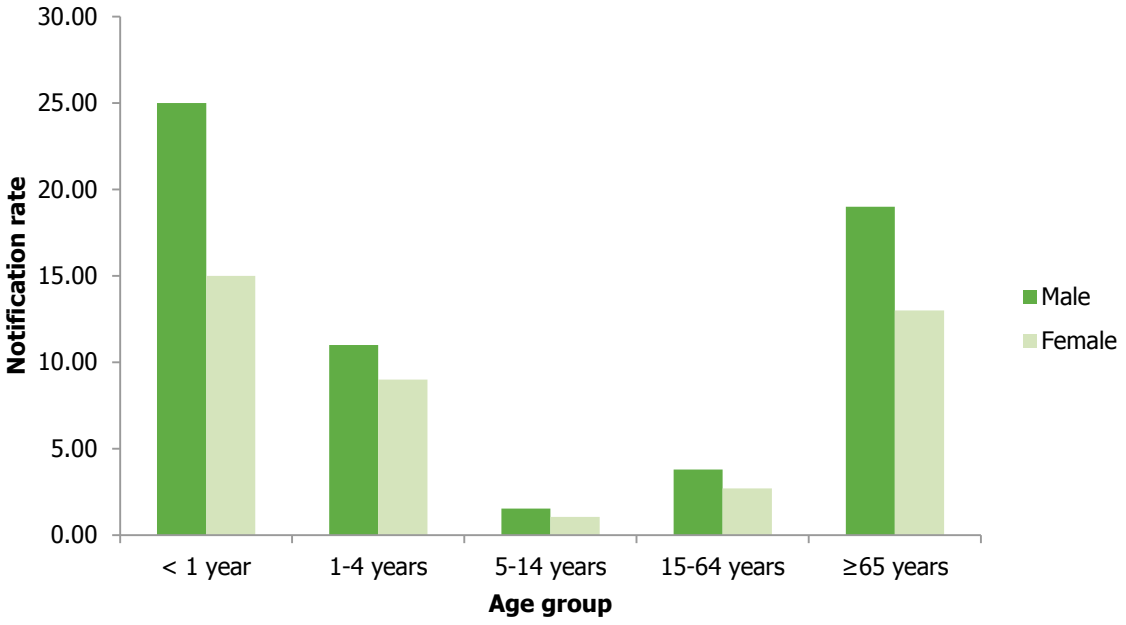
*Overall, age was missing for 66 cases

**Bulgaria reported aggregated data (26 cases)

Of the 21 496 reported cases where gender information was specified, 55% (n=11 798) were male and 45% (n=9 698) were female, corresponding to a 1.22:1 male/female ratio.

As regards the distribution of notification rates among genders (Figure 4.2), male predominance was more evident in children under one year and adults over 65 years. Males showed slightly higher rates than females for all other age groups.

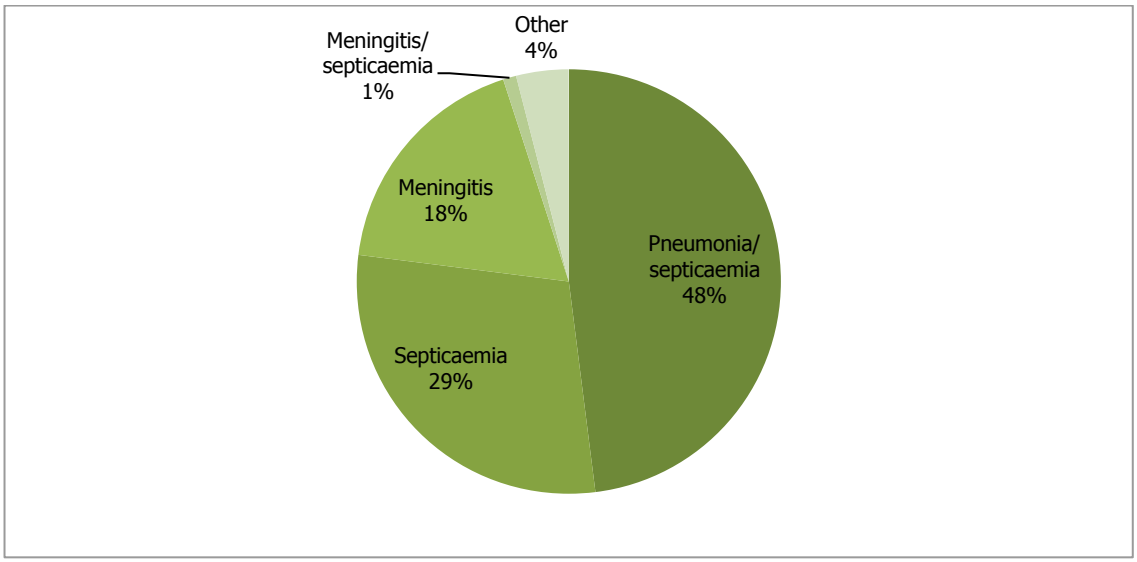
Figure 4.2 Notification rate (cases per 100 000 population) of reported IPD cases by age group and gender, EU/EEA countries, 2010 (n=21 496)



4.3 Clinical presentation

Of the 7 948 cases for which the clinical presentation was known (62.7% missing), pneumonia/septicaemia was the most frequent clinical presentation accounting for 48% of all cases, followed by septicaemia accounting for 29% (Figure 4.3).

Figure 4.3 Distribution by clinical presentation of reported IPD cases, 2010 (n=7 948)



Meningitis was the only clinical presentation reported by France. Of all cases with known clinical presentation by country, meningitis was the most common clinical presentation for the Netherlands (42%), Poland (40%), Romania (89%) and Slovakia (61%) (Table 4.3).

Table 4.3 Distribution of reported IPD cases by clinical presentation and by country, EU/EEA countries, 2010 (n=7 948)

Country	Meningitis/ septicaemia		Meningitis		Septicaemia		Pneumonia/ septicaemia		Other		Total
	n	%	n	%	n	%	n	%	n	%	N
Austria	21	6.5	28	8.6	154	47.4	118	36.3	4	1.2	325
Belgium	5	0.6	86	10.2	73	8.6	682	80.6	0	0.0	846
Cyprus	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	1
Czech Republic	6	2.0	38	12.7	110	36.7	146	48.7	0	0.0	300
Denmark	0	0.0	67	7.0	893	93.0	0	0.0	0	0.0	960
Estonia	0	0.0	4	28.6	10	71.4	0	0.0	0	0.0	14
France	0	0.0	409	100.0	0	0.0	0	0.0	0	0.0	409
Hungary	0	0.0	29	31.5	23	25.0	3	3.3	37	40.2	92
Ireland	8	6.3	15	11.7	34	26.6	64	50.0	7	5.5	128
Italy*	0	0.0	307	36.1	301	35.4	243	28.6	0	0.0	851
Latvia	1	6.3	6	37.5	4	25.0	5	31.3	0	0.0	16
Lithuania	0	0.0	0	0.0	8	88.9	0	0.0	1	11.1	9
Malta	0	0.0	0	0.0	0	0.0	0	0.0	11	100.0	11
Netherlands	0	0.0	22	41.5	15	28.3	6	11.3	10	18.9	53
Poland	43	12.9	132	39.6	96	28.8	17	5.1	45	13.5	333
Romania	0	0.0	66	89.2	2	2.7	0	0.0	6	8.1	74
Slovakia	2	11.1	11	61.1	5	27.8	0	0.0	0	0.0	18
Slovenia	0	0.0	6	6.5	20	21.5	55	59.1	12	12.9	93
Spain	0	0.0	189	8.5	0	0.0	2 023	91.5	0	0.0	2 212
UK	2	0.3	34	4.4	427	55.2	165	21.3	145	18.8	773
EU total	88	1.2	1 449	19.3	2 176	28.9	3 527	46.9	278	3.7	**7 518**
Norway	16	3.7	19	4.4	93	21.6	251	58.4	51	11.9	430
Total	104	1.3	1 468	18.5	2 269	28.5	3 778	47.5	329	4.1	**7 948**

*Italy does not follow this classification. All cases of meningitis/septicaemia were classified as meningitis by the country.

Meningitis was the most common clinical presentation among children under one year of age.

Pneumonia/septicaemia was the most frequent clinical presentation for all other age groups except among those aged 15–64 years. In this age group, meningitis/septicaemia was the most common clinical presentation (Table 4.4).

Among all cases reporting meningitis as a clinical presentation, the 0–14 years age group accounted for 27%, 15–64 years accounted for 21%, and those aged ≥ 65 years accounted for 12%. These differences were statistically significant ($p<0.0001$, Pearson's chi-squared) (Table 4.4).

Table 4.4 Distribution of reported IPD cases by clinical presentation and by age group, EU/EEA countries, 2010 (n=7 921)

Age group	Clinical presentation										
	Meningitis		Septicaemia		Pneumonia/ Septicaemia		Meningitis/ septicaemia		Other		Total
	n	%	n	%	n	%	n	%	n	%	
<1 year	189	42	107	24	132	29	14	3	10	2	452
1-4 yrs	121	17	148	21	378	54	16	2	33	5	696
5-14 yrs	77	28	51	18	138	49	4	1	9	3	279
15-64 yrs	675	21	879	27	1 461	45	49	2	152	5	3 216
≥ 65 yrs	398	12	1 075	33	1 659	51	21	1	125	4	3 278
Total	1 460	18	2 260	29	3 768	48	104	1	329	4	7 921

4.4 Case fatality rate

Twenty countries reported data on outcome but the completeness for this variable differed widely from country to country. Cyprus, Denmark, Lithuania and Malta reported no deaths.

The case fatality rate ranged from 0% for Cyprus, Denmark, Lithuania and Malta to 26.9% for Hungary (Table 4.5).

Data on CFR should be interpreted with caution because data for the variable 'outcome' was significantly incomplete (overall missing 79.5%) and there was uncertainty regarding the denominator. Moreover, in Europe there is no common approach to the follow-up time or end-point for a fatal outcome.

Table 4.5 Case fatality rate due to IPD in EU/EEA countries*, 2010 (n=4 596)

Country	No. of cases	No. of cases with known outcome	No. of deaths	CFR (%)	Confidence Interval (%)
Austria	325	218	16	7.3	4.3 - 11.7
Belgium	1 851	1 255	67	5.3	4.2 - 6.7
Cyprus	23	11	0	0.0	0.0 - 28.5
Czech Republic	300	247	44	17.8	13.3 - 23.2
Denmark	960	35	0	0.0	0.0 - 10.0
Estonia	14	14	1	7.1	0.2 - 33.9
Greece	38	32	4	12.5	3.5 - 29.0
Hungary	107	26	7	26.9	11.6 - 47.8
Ireland	304	93	5	5.4	1.8 - 12.1
Italy	854	605	101	16.7	13.8 - 19.9
Latvia	16	15	1	6.7	0.2 - 32.0
Lithuania	9	8	0	0.0	0.0 - 36.9
Malta	11	11	0	0.0	0.0 - 28.5
Netherlands	55	54	5	9.3	3.1 - 20.3
Norway	748	373	44	11.8	8.7 - 15.5
Poland	333	333	65	19.5	15.4 - 24.2
Romania	80	80	12	15.0	8.0 - 24.7
Slovenia	224	224	6	2.7	1.0 - 5.7
Slovakia	18	16	1	6.3	0.2 - 30.2
United Kingdom	5 616	946	71	7.5	5.9 - 9.4

*Outcome not reported by Finland, France, Iceland, Spain or Sweden.

4.5 Reported vaccination status

Vaccination status was known in only 8.7% of the reported cases. Of the 1 979 cases for which vaccination status was reported, only 345 (17.4%) were fully vaccinated, 4.2% partially vaccinated[13] and 78.3% unvaccinated, according to the respective national schedules (Table 4.6).

Table 4.6 Distribution of reported IPD cases by vaccination status and country, EU/EEA countries, 2010 (n= 1 979)

Country	Fully vaccinated		Partly vaccinated		Unvaccinated		Total
	n	%	n	%	n	%	n
Austria	6	19.4	1	3.2	24	77.4	31
Belgium	171	32.3	15	2.8	343	64.8	529
Cyprus	0	0.0	0	0.0	7	100.0	7
Denmark	14	48.3	3	10.3	12	41.4	29
Estonia	0	0.0	0	0.0	8	100.0	8
Ireland	27	39.1	10	14.5	32	46.4	69
Italy	43	14.8	0	0.0	248	85.2	291
Lithuania	0	0.0	0	0.0	3	100.0	3
Netherlands	38	73.1	5	9.6	9	17.3	52
Poland	2	0.6	6	1.8	325	97.6	333
Romania	0	0.0	0	0.0	2	100.0	2
Slovakia	1	5.6	0	0.0	17	94.4	18
Sweden	10	2.8	10	2.8	340	94.4	360
UK	6	18.8	20	62.5	6	18.8	32
Norway	27	12.6	14	6.5	174	80.9	215
Total	345	17.4	84	4.2	1 550	78.3	**1 979**

Table 4.7 shows IPD cases that were fully vaccinated with PCV7, as reported by the countries. PCV10 alone (PCV7 serotypes + 1, 5,7F) would have covered 65 cases in the under-fives age group. PCV13 alone (PCV7 + 1, 3, 5, 6A, 7F, 19A) would have covered 112 cases in the under-fives age group.

Table 4.7 Distribution of IPD cases in PCV7 fully vaccinated* cases, by PCV10 and PCV13 specific serotypes and age group, EU/EEA countries, 2010 (n=130)

Serotype	< 1 year	1-4 years	5-14 years	15-64 years	≥65 years	Total
1	1	29	8	2	1	41
3	1	2	0	0	2	5
5	4	11	1	0	0	16
6A	3	0	0	1	0	4
7F	5	15	0	0	0	20
19A	21	20	0	2	1	44
Total	35	77	9	5	4	**130**

*PCV7 fully vaccinated as reported by Member States.

[13] Partly vaccinated signifies those that did not complete a vaccination series in accordance with their age and national vaccination schedules. This criterion is set by every country.

4.6 Specimens

Blood isolates accounted for 91% (n=15 654) of the total number of cases for which the specimen was reported (n=17 253).

Table 4.8 Distribution of specimens among reported IPD cases by specimen type and country, EU/EEA countries, 2010 (n=17 253)

Country	Blood		CSF		Total
	n	%	n	%	n
Austria	281	90.1	31	9.9	312
Belgium	1 779	96.1	72	3.9	1 851
Cyprus	14	87.5	2	12.5	16
Czech Republic	264	88.0	36	12.0	300
Denmark	893	93.0	67	7.0	960
Estonia	6	85.7	1	14.3	7
Finland	833	99.6	3	0.4	836
France	718	63.7	409	36.3	1 127
Greece	0	0.0	17	100.0	17
Hungary	78	72.9	29	27.1	107
Ireland	263	95.6	12	4.4	275
Italy	563	66.2	288	33.8	851
Latvia	10	62.5	6	37.5	16
Lithuania	4	100.0	0	0.0	4
Malta	11	100.0	0	0.0	11
Netherlands	30	56.6	23	43.4	53
Poland	125	60.7	81	39.3	206
Romania	6	8.3	66	91.7	72
Slovakia	6	33.3	12	66.7	18
Slovenia	202	90.2	22	9.8	224
Spain	2 023	91.5	189	8.5	2 212
Sweden	1 367	95.6	63	4.4	1 430
United Kingdom	5 445	97.7	131	2.3	5 576
EU Total	14 921	90.5	1 560	9.5	**16 481**
Iceland	31	96.9	1	3.1	32
Norway	702	94.9	38	5.1	740
Total	15 654	90.7	1 599	9.3	**17 253**

Most of the blood isolates were reported to have been taken from persons aged over 15 years (Table 4.9). Children under one year showed the highest CSF/blood ratio (28.2%) followed by the 5–14 year age group (19.1%).

Table 4.9 Distribution of specimens among reported IPD cases by specimen type and age* group, EU/EEA countries, 2010 (n=17191)

Speci-men	<1 year			1–4 yrs			5–14 yrs			15–64 yrs			≥ 65 yrs			Total
	n	%	CSF/ Blood ratio	n	%	CSF/ Blood ratio	n	%	CSF/ Blood ratio	n	%	CSF/ Blood ratio	n	%	CSF/ Blood ratio	
Blood	929	78		655	89		412	84		6 422	89		7 180	94		15 598
CSF	259	22	28.2%	80	11	12.4%	79	16	19.1%	755	11	12.4%	420	6	6.4%	1 593
Total	1 188			735			491			7 177			7 600			17 191

* 62 missing cases with missing age

4.7 Serotype distribution

4.7.1 Most common serotypes

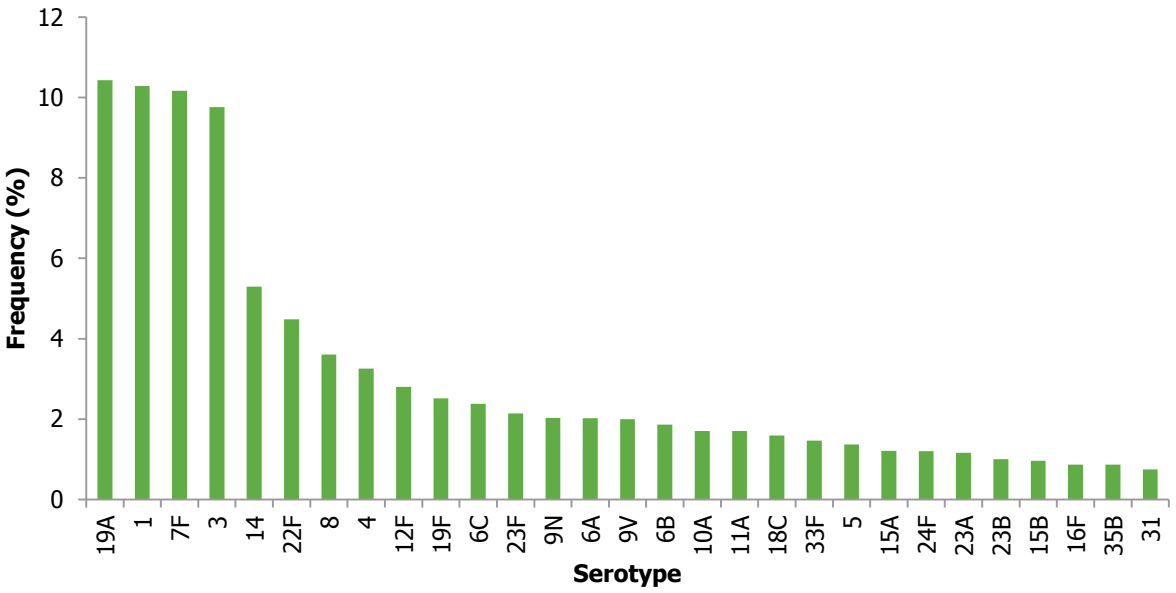
Of the 21 565 reported confirmed cases of invasive pneumococcal disease, only 9 946 (46.1%) had included information on the isolate serotype. Of these, the ten most common serotypes were 19A, 1, 7F, 3, 14, 22F, 8, 4, 12F and 19F, accounting for 59.8% (n=5 949/9 946) of the typed isolates reported (Figure 4.4 and Table 4.10).

The most prevalent serotypes were 19A (n=991), serotype 1 (n=978) and serotype 7F (n=966) that accounted for 10.0%, 9.8% and 7.7% respectively of the total number of serotyped reported cases.

Twenty isolates were non-typeable (NTYP).

One isolate of serotype 6D was reported.

Figure 4.4 Distribution of reported IPD cases by serotype, EU/EEA countries, 2010 (n=9946)



It is interesting to note that serotypes 14, 4 and 19F (included in PCV7) occur in significant numbers in Europe. These serotypes were a particularly frequent occurrence in Finland and Spain (mainly serotype 14) (Table 4.10). Further information is presented in the discussion section

Table 4.10 Distribution of reported IPD cases by serotype and country, EU/EEA countries, 2010 (n=9946*)

Country	Serotype 19A**		Serotype 1@		Serotype 7F~		Serotype 3#		Serotype 14&		Serotype 22F^		Serotype 8^		Serotype 4$		Serotype 12F^		Serotype 19F£		Other	
	n	%	n	%	N	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Austria	22	8	14	5	19	7	44	15	25	9	9	3	5	2	13	5	3	1	14	5	120	42
Belgium	124	7	279	15	108	6	124	7	35	2	32	2	56	3	28	2	50	3	4	0	1 011	55
Cyprus	0	0	4	40	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6	60
Czech Republic	8	3	42	14	18	6	51	17	16	5	5	2	5	2	16	5	3	1	9	3	121	41
Denmark	72	8	170	18	89	9	73	8	22	2	56	6	57	6	48	5	39	4	15	2	319	33
Finland	31	4	1	0	49	6	77	10	147	18	46	6	5	1	73	9	2	0	49	6	317	40
France	168	15	93	8	163	14	79	7	25	2	36	3	21	2	6	1	80	7	30	3	426	38
Greece	2	8	1	4	0	0	4	17	0	0	0	0	0	0	0	0	0	0	0	0	17	71
Hungary	9	8	1	1	3	3	36	34	1	1	1	1	1	1	4	4	1	1	2	2	48	45
Ireland	18	7	7	3	21	9	12	5	13	5	19	8	23	9	9	4	7	3	8	3	109	44
Italy	26	9	42	15	35	13	40	14	13	5	9	3	7	3	8	3	3	1	8	3	85	31
Lithuania	0	0	0	0	0	0	0	0	1	33	0	0	0	0	0	0	0	0	0	0	2	67
Malta	0	0	0	0	0	0	1	14	1	14	0	0	2	29	0	0	0	0	0	0	3	43
Netherlands	11	24	6	13	4	9	2	4	0	0	0	0	3	7	0	0	0	0	0	0	19	42
Poland	9	4	11	5	5	2	21	10	28	14	3	1	5	2	10	5	6	3	22	11	85	41
Romania	0	0	5	24	2	10	4	19	0	0	0	0	0	0	0	0	0	0	4	19	6	29
Slovenia	18	8	16	7	14	6	35	16	32	14	3	1	3	1	12	5	0	0	5	2	86	38
Spain	321	15	169	8	244	11	238	11	119	5	82	4	86	4	49	2	60	3	49	2	795	36
UK	71	14	63	13	88	18	36	7	5	1	36	7	45	9	1	0	10	2	5	1	137	28
Iceland	2	6	1	3	1	3	2	6	4	13	0	0	0	0	2	6	0	0	4	13	16	50
Norway	79	11	53	7	103	14	49	7	16	2	89	12	19	3	30	4	2	0	11	2	268	37
Total	**991**		**978**		**966**		**928**		**503**		**426**		**343**		**309**		**266**		**239**		**3 996**	

**Serotype 19A protected against by the 13-valent vaccine and PPV23

@Serotype 1 protected against by 10- and 13-valent vaccines and PPV23

~ Serotype 7F protected against by 10- and 13-valent vaccines and PPV23

£Serotype 19F protected against by the 7-, 10- and 13-valent vaccines & PPV23

#Serotype 3 protected against by the 13-valent vaccine and PPV23

&Serotype 14 protected against by the 7-, 10- and 13-valent vaccines & PPV23

$Serotype 4 protected against by the 7-, 10- & 13-valent vaccines & PPV23

^Serotype protected against by the PPV23

*9 946 cases with reported serotype

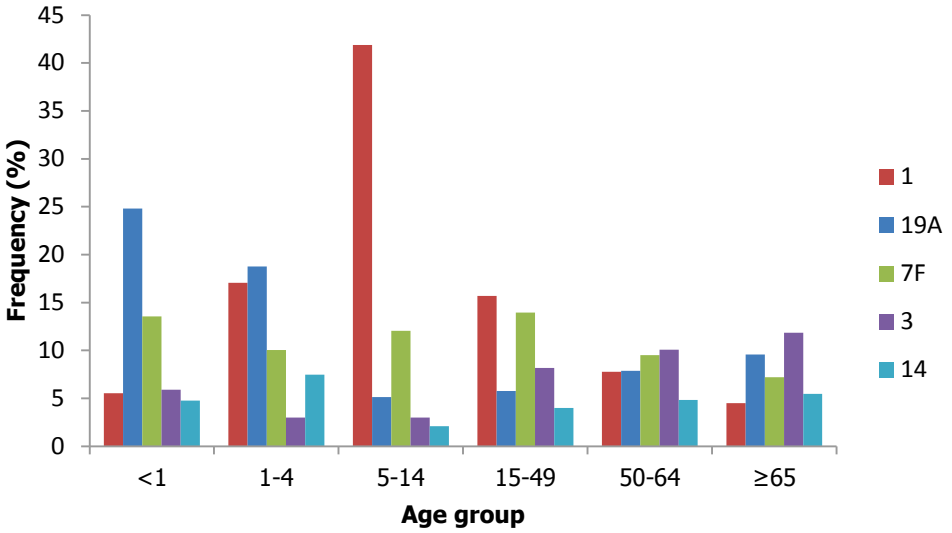
4.7.2 Serotype and age

Of the 5 927 cases for which serotype and age were reported, serotypes 19A and 7F were the most common reported in children under one year of age. In children of one to four years, serotypes 19A and 1 were the most frequently reported, while serotypes 1 and 7F were the most frequently reported for the 5–14 year age group. Among adults, serotypes 1 and 7F were predominant and in the oldest age group serotypes 19A and 3.

It is noteworthy that serotypes 19A, 7F, 3 and 1 are the most prevalent serotypes in children under 15 years and these are not covered by PCV7 (Figure 4.5).

Serotypes 3 and 8 were predominant (Table 4.10 and Figure 4.5) in older age groups (over 15 years of age) as described elsewhere [12,13].

Figure 4.5 Distribution of reported IPD cases by 'top five' serotype and age group, EU/EEA countries, 2010 (n=4 348*)



4.7.3 Serotype and gender

Serotypes 7F and 3 were the most common in the male group, whereas serotypes 19A and 1 were the most frequent among females. However, as expected [14], these differences were not statistically significant.

Table 4.11 Distribution of reported IPD cases by 'top ten' serotype and gender, EU/EEA countries, 2010 (n=5 924*)

Serotype	Male		Female	
	n	%	n	%
1	511	15	459	18
3	543	16	385	15
4	190	6	118	5
7F	558	17	402	16
8	199	6	142	6
12F	153	5	112	4
14	270	8	232	9
19A	519	15	466	18
19F	151	5	88	3
22F	257	8	169	7
Total	**3 351**		**2 573**	

*Overall 25 missing cases for gender: serotypes 1 (n=8), 19A (n=6), 7F (n=6), 8 (n=2), 4 (n=1), 12F (n=1) and 14 (n=1)

4.7.4 Serotype and clinical presentation

Serotype information was missing in 53.3% of the reported cases for which clinical presentation was known. Serotype 1 was the most frequent serotype reported among cases with pneumonia/septicaemia (n=413) as clinical presentation, followed by serotypes 19A, 7F and 3 (Table 4.12).

Similarly, serotype 19A was the most frequent serotype reported among cases with meningitis as clinical presentation (n=112), followed by serotypes 3 and 7F.

Table 4.12 Distribution of reported IPD cases by 'top ten' serotype and clinical presentation, EU/EEA countries, 2010 (n=4 176*)

Serotype	Meningitis		Septicaemia		Pneumonia/ septicaemia		Meningitis/ septicaemia		Other	
	n	%	n	%	n	%	n	%	n	%
1	31	6	257	20	413	18	0	0	12	12
3	103	20	166	13	376	17	4	10	28	28
4	13	2	72	6	93	4	2	5	7	7
7F	97	18	216	17	374	17	5	13	14	14
8	23	4	101	8	144	6	2	5	3	3
12F	50	9	57	4	76	3	4	10	2	2
14	24	5	67	5	167	7	5	13	9	9
19A	112	21	194	15	410	18	5	13	15	15
19F	46	9	40	3	58	3	5	13	3	3
22F	28	5	107	8	123	6	7	18	6	6
Total	527		1 277		2 234		39		99	

4.7.5 Serotype and mortality

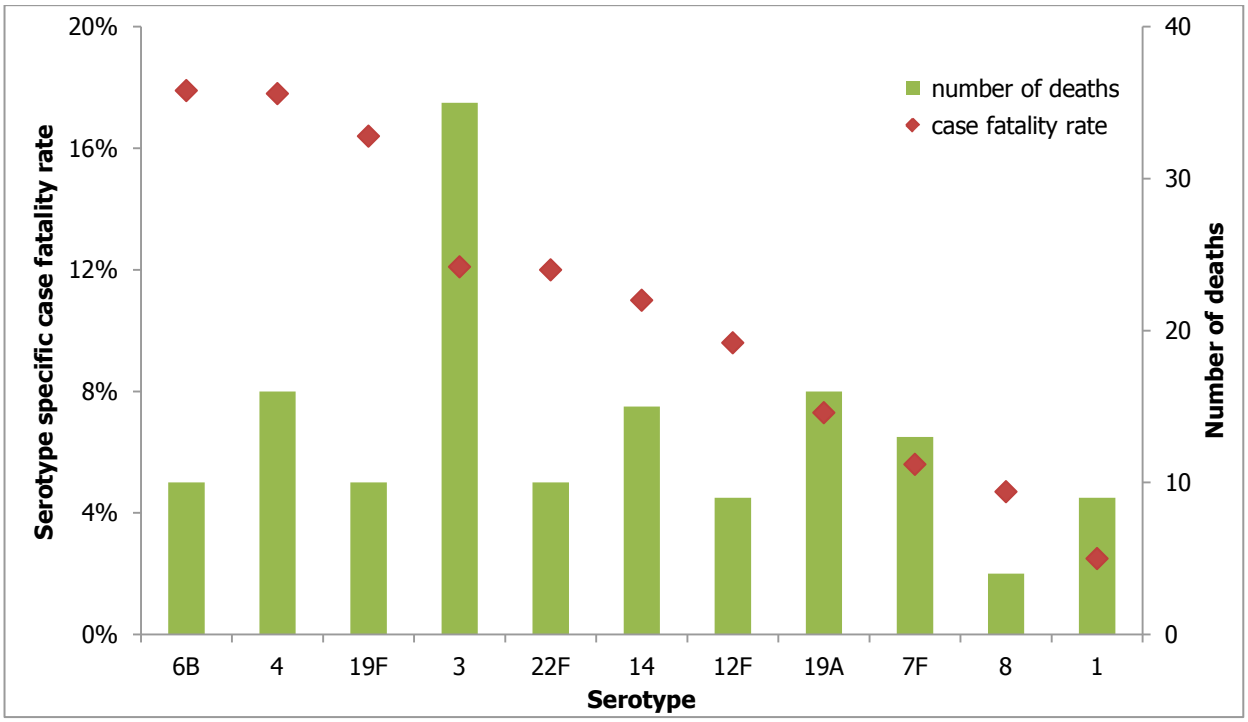
Of 450 reported deaths, 58.7% had serotype data available (n=264).

Serotype 3 accounted for the majority of reported deaths (n=35), followed by serotype 19A and 4 (n=16 each), serotype 14 (n=15) and 7F (n=13) (Figure 4.6).

Among the ten most frequent serotypes, serotype 6B (17.9%) presented the highest serotype-specific case fatality rate followed by serotype 4 (17.8%), serotype 19F (16.4%) and serotype 3 (12.1%). It is worth mentioning that these four serotypes are covered by at least one of all the licensed vaccines (PCV7, PCV10, PCV13 and PPV23).

These serotypes occur mainly in the adult population (over 15 years) with almost equal distribution across age groups 15-64 and ≥ 65 years.

Figure 4.6 Distribution of reported IPD case death(n=147*) and case–fatality rate by serotype, EU/EEA countries, 2010



4.7.6 Serotype and conjugate vaccines

Among those aged under 15 years, the most frequent serotype was 19A (3.2%, n=315), only covered by PCV13. This was followed by serotype 1 (3.2%, n=321) covered by PCV10 and PCV13; serotype 7F (2.0%, n=201) covered by PCV10 and PCV13 and serotype 14 (1.0%, n=99) covered by PCV7, PCV10 and PCV13 (Table 4.13).

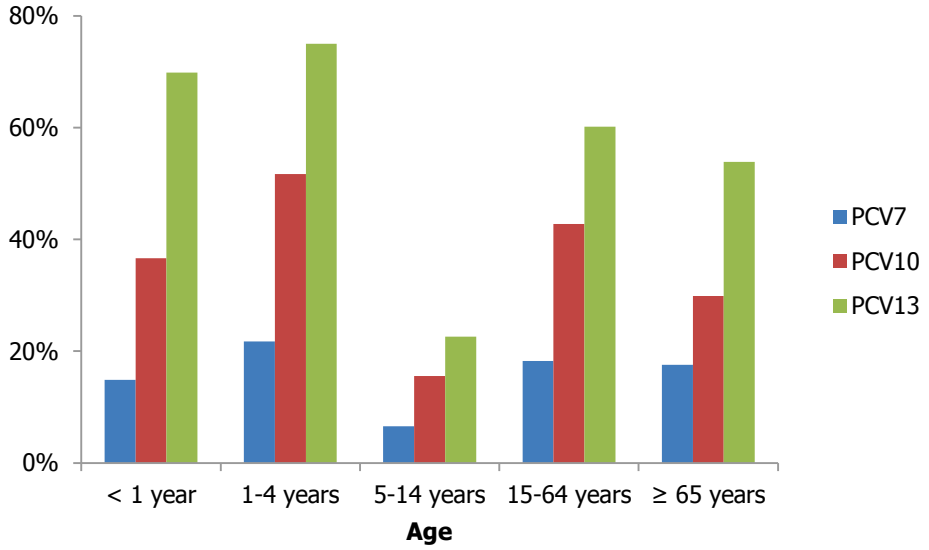
If all age groups are taken into account, the sequence of most frequent serotypes was 19A (10.0%, n=991), 1 (9.8%, n=978), 7F (9.7%, n=966), 3 (9.3%, n=928) – covered only by PCV13, and 14 (5.1%, n=503).

Table 4.13 Distribution of reported IPD disease cases by serotype and age group for the three licensed PCV, EU/EEA countries, 2010 (n=9 946*)

PCV7 serotypes	PCV10 serotypes	PCV13 serotypes	Number and % of cases			
			< 15 years		All age groups	
			n	%	N	%
4	4	4	14	0.1	309	3.1
6B	6B	6B	55	0.6	177	1.8
9V	9V	9V	17	0.2	190	1.9
14	14	14	99	1.0	503	5.1
18C	18C	18C	37	0.4	151	1.5
19F	19F	19F	61	0.6	239	2.4
23F	23F	23F	32	0.3	203	2.0
	1	1	321	3.2	978	9.8
	5	5	50	0.5	130	1.3
	7F	7F	201	2.0	966	9.7
		3	68	0.7	928	9.3
		6A	31	0.3	192	1.9
		19A	315	3.2	991	10.0

Figure 4.7 suggests that PCV13 could have potentially prevented more than 60% of the cases occurring in children under one year. Overall, the potential coverage of PCV13 is higher than 50% in all age groups except for 5–14years. This age group accounts for the lowest notification rates and the smallest total number of cases.

Figure 4.7 Percentage of cases covered by PCV type and age group, EU/EEA countries, 2010 (n=9 946)



Among the non-PCV serotypes, serotype 22F (n=426) accounted for 4.28%, serotype 8 (n=343) 3.45%, serotype 12F (n=266) 2.67% and serotype 6C (n=226) 2.27% of serotyped isolates. Serotype 9N (n=193) accounted for 1.94% (Table 4.14).

Table 4.14 Distribution of IPD cases by non-PCV serotype and age group, EU/EEA countries, 2010 (n=9946*)

Non-PCV serotypes	Number of cases			
	< 15 years		All age groups	
	n	%	n	%
2	1	0.01	2	0.02
6	-	-	51	0.51
6C	16	0.16	226	2.27
6D	-	-	1	0.01
7	-	-	119	1.20
7B	-	-	11	0.11
7C	-	-	4	0.04
8	14	0.14	343	3.45
9	-	-	41	0.41
9A	1	0.01	8	0.08
9L	-	-	2	0.02
9N	9	0.09	193	1.94
10	1	-	25	0.25
10A	29	0.29	162	1.63
10B	1	0.01	6	0.06
10F	-	-	4	0.04
11	-	-	13	0.13
11A	9	0.09	162	1.63
11B	-	-	4	0.04
11D	-	-	5	0.05
11F	-	-	6	0.06
12	-	-	103	1.04
12A	-	-	2	0.02
12B	-	-	4	0.04
12F	56	0.56	266	2.67
13	-	-	11	0.11
15	1	0.01	31	0.31
15A	26	0.26	115	1.16
15B	28	0.28	91	0.91
15B/C	1	0.01	1	0.01
15C	13	0.13	56	0.56
15F	-	-	3	0.03
16	-	-	8	0.08
16F	6	0.06	82	0.82
17	-	-	10	0.10
17A	-	-	1	0.01
17F	6	0.06	55	0.55
18	-	-	9	0.09
18A	-	-	6	0.06
18B	-	-	3	0.03
18F	-	-	3	0.03
19	3	0.03	145	1.46
20	2	-	66	0.66
21	7	0.07	19	0.19
22	-	-	77	0.77
22A	1	0.01	1	0.01
22F	31	0.31	426	4.28
23	-	-	25	0.25

Non-PCV serotypes	Number of cases			
	< 15 years		All age groups	
	n	%	n	%
23A	7	0.07	110	1.11
23B	26	0.26	95	0.96
24	2	0.02	22	0.22
24A	3	0.03	5	0.05
24B	2	0.02	2	0.02
24F	47	0.47	114	1.15
25	-	-	2	0.02
25A	7	0.07	13	0.13
25F	-	-	2	0.02
27	2	0.02	2	0.02
28	-	-	1	0.01
28A	-	-	2	0.02
28F	-	-	3	0.03
29	2	0.02	28	0.28
31	2	0.02	71	0.71
32	-	-	1	0.01
33	5	0.05	41	0.41
33A	1	0.01	1	0.01
33F	29	0.29	139	1.40
34	1	0.01	28	0.28
35	3	0.03	27	0.27
35A	-	-	1	0.01
35B	11	0.11	82	0.82
35C	-	-	6	0.06
35F	5	0.05	67	0.67
36	-	-	1	0.01
37	3	0.03	7	0.07
38	10	0.10	59	0.59
39	1	0.01	2	0.02
40	-	-	1	0.01
NTYP	20	0.20	44	0.44
O	-	-	3	0.03
Total	**451**	**4.5**	**3 989**	**40.1**

*Number of cases with reported serotype (n=9 946)

4.7.7 Serotype and polysaccharide vaccine

Among adults (15–64 years), 32.1% of the reported cases would have been covered, and among those aged over 65 years 29.9% of the reported cases (Table 4.15).

Table 4.15 Distribution of IPD cases by PPV23 and age group, EU/EEA countries, 2010 (n=9 946*)

PPV23 serotypes	Number of cases					
	15–64 years		≥ 65 years		All age groups	
	n	%	n	%	n	%
1	460	4.6	187	1.9	978	9.8
2	1	0.0	-	-	2	0.0
3	366	3.7	493	5.0	928	9.3
4	177	1.8	118	1.2	309	3.1
5	53	0.5	26	0.3	130	1.3
6B	51	0.5	71	0.7	177	1.8
7F	463	4.7	299	3.0	966	9.7
8	188	1.9	140	1.4	343	3.4
9N	96	1.0	88	0.9	193	1.9
9V	87	0.9	86	0.9	190	1.9
14	177	1.8	227	2.3	503	5.1
20	39	0.4	25	0.3	66	0.7
10A	63	0.6	69	0.7	162	1.6
11A	67	0.7	86	0.9	162	1.6
12F	132	1.3	77	0.8	266	2.7
15B	30	0.3	33	0.3	91	0.9
17F	22	0.2	27	0.3	55	0.6
18C	66	0.7	48	0.5	151	1.5
19A	274	2.8	398	4.0	991	10.0
19F	84	0.8	94	0.9	239	2.4
22F	167	1.7	226	2.3	426	4.3
23F	86	0.9	85	0.9	203	2.0
33F	41	0.4	68	0.7	139	1.4

4.8 Seasonality

During 2010, the distribution of IPD cases followed a seasonal pattern (as observed in previous years) with a clear increase during the winter months, peaking in December. This sequence was observed both for the total number of cases and for the 'top ten' serotypes (Figures 4.8 and 4.9).

Figure 4.8 Distribution of reported IPD cases by month, EU/EEA countries, 2010 (n=21 209)

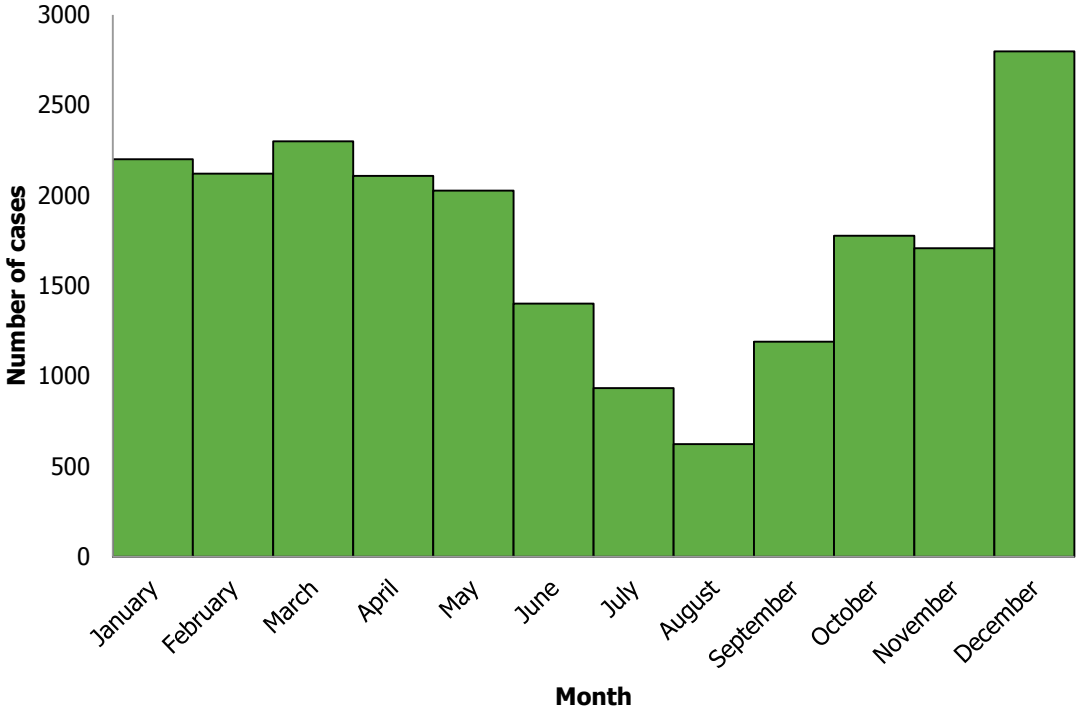
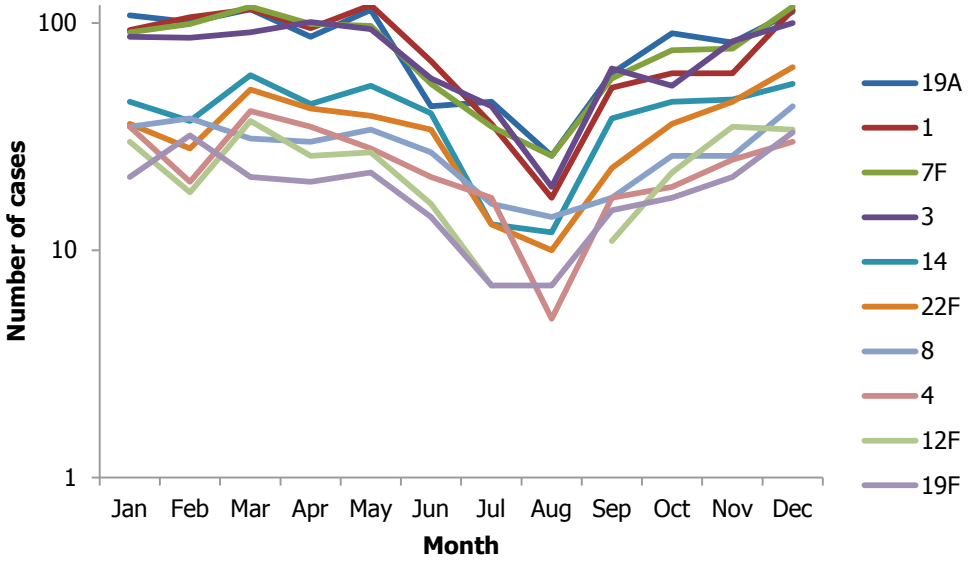
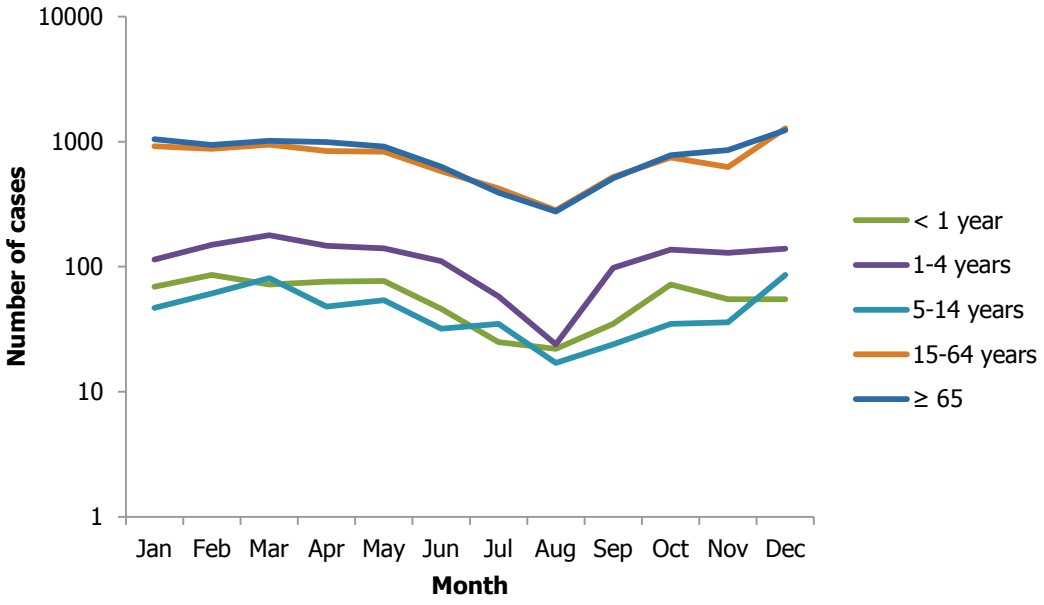


Figure 4.9 Distribution of reported IPD cases by 'top ten' serotype and by month, EU/EEA countries, 2010 (n=5 949)



According to the log scale graph above, data show that invasive pneumococcal disease is more common in winter than during the summer months (Figure 4.9). This distribution is slightly more pronounced for adults (age groups 15–64 and ≥ 65 years), as seen in the log scale graph below (Figure 4.10).

Figure 4.10 Distribution of reported IPD cases by month and age group, EU/EEA countries, 2010 (n=21120)



4.9 Antimicrobial resistance

Table 4.16 summarises the distribution of resistance among cases of invasive pneumococcal disease.

Table 4.16 Distribution of reported IPD cases by SIR (Susceptible, Intermediate or Resistant) scale (PEN, ERY, CTX) and country, EU/EEA countries, 2010 (PEN n=9 247, ERY n=8 382, CTX n=6 186)

Antibiotic	Penicillin				Erythromycin				Cefotaxime*			
	%			n	%			n	%			n
Country	S	I	R	Total	S	I	R	Total	S	I	R	Total
Austria	92.2	5.5	2.4	255	87.5	0.0	12.5	255	99.6	0.4	0.0	255
Belgium	99.6	0.0	0.4	1 847	75.0	0.1	24.9	1 847	99.9	0.1	0.1	1 846
Cyprus	63.6	9.1	27.3	11	45.5	9.1	45.5	11	90.9	0.0	9.1	11
Denmark	51.4	47.1	1.4	70	42.9	1.4	55.7	70	97.1	2.9	0.0	70
Estonia	100.0	0.0	0.0	6	66.7	0.0	33.3	3	100.0	0.0	0.0	4
Finland	76.8	19.6	3.7	792	71.8	0.0	28.2	792	95.7	4.0	0.3	792
France	72.5	27.3	0.2	1 127	70.0	0.5	29.5	1 127	94.8	5.1	0.2	1 127
Hungary	97.0	0.0	3.0	101	78.5	0.0	21.5	93	98.7	0.0	1.3	79
Ireland	84.6	11.0	4.5	246	87.4	0.0	12.6	246	90.7	8.9	0.4	246
Italy	84.9	5.7	9.4	106	70.8	0.0	29.2	106	-	-	-	-
Latvia	87.5	6.3	6.3	16	87.5	0.0	12.5	16	100.0	0.0	0.0	13
Malta	72.7	9.1	18.2	11	72.7	0.0	27.3	11	100.0	0.0	0.0	11
Poland	78.9	3.9	17.2	204	62.2	0.0	37.8	196	91.2	6.4	2.5	204
Romania	57.1	9.5	33.3	21	61.9	0.0	38.1	21	76.2	9.5	14.3	21
Slovakia	83.3	0.0	16.7	12	75.0	0.0	25.0	4	100.0	0.0	0.0	6
Slovenia	83.5	0.0	16.5	224	81.7	0.0	18.3	224	95.5	4.5	0.0	224
UK	97.3	1.7	1.0	4 198	95.3	0.3	4.4	3 360	99.2	0.5	0.3	1 277

*In Finland, instead of cefotaxime, susceptibility to ceftriaxone was determined

4.9.1 Resistance to penicillin

Seventeen countries (Table 4.16 and Figure 4.11) reported 9 247 cases with information on resistance to penicillin. In total, 91.1 %(n=8420) of these cases were described as susceptible (S), 6.8% (n=629) as intermediate (I) and 2.1% (n= 198) as resistant (R) to penicillin.

Regarding non-susceptibility (understood as intermediate + resistant), two countries presented <1%, two countries between 1 and 5%, one country 5–10%, seven countries 10–25% and five countries 25–50% (Table 4.16).

Cyprus (27.3%) reported the highest percentage of resistance (R), followed by Romania (33.3%).

4.9.2 Resistance to erythromycin

Seventeen countries (Table 4.16 and Figure 4.11) reported 8 382 cases with information on resistance to erythromycin of which 82.5% (n=6911) were described as susceptible (S), 0.3% (n=21) intermediate (I) and 17.3% (n= 1450) resistant (R) to erythromycin.

Regarding non-susceptibility, no countries presented <1%, one country fell within the 1–5% category, no countries within the 5–10% category, seven countries had 10–25% and nine countries presented 25–50% (Table 4.16)

Denmark reported the highest percentage of resistance (R) (55.7%), followed by Cyprus (45.5%). Nevertheless, data from Denmark need to be interpreted with caution since Denmark did not report susceptibility data for all isolates. This high percentage of resistance is most likely due to a reporting artefact.

4.9.3 Resistance to cefotaxime

Sixteen countries (Table 4.16 and Figure 4.11) reported 6 186 cases of which 97.3% (n=6 020) were susceptible (S), 2.4% (n=146) intermediate (I) and 0.3 % (n= 20) resistant (R) to cefotaxime.

As regards non-susceptibility, seven countries presented <1%, four countries between 1-5%, four countries between 5-10%, one country between 10-25% and zero countries between 25-50% (Table 4.16).

Romania reported the highest percentage of resistance (R) (14.3%), followed by Cyprus (9.1%).

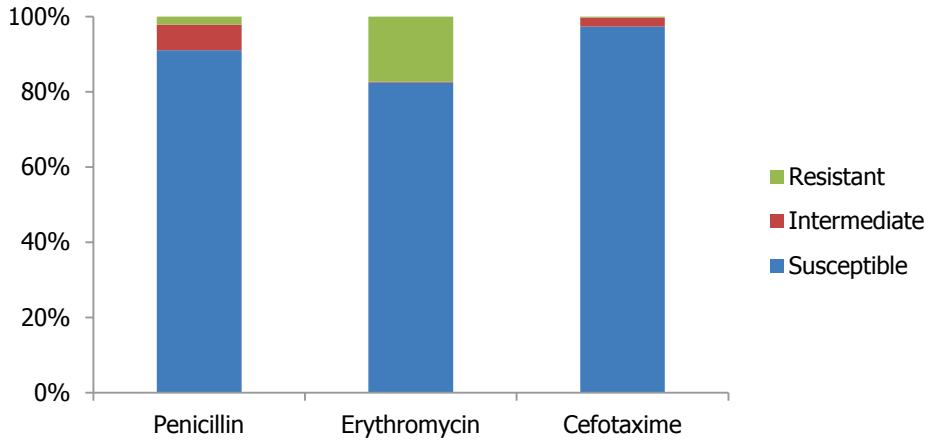
Countries in Southern and Eastern Europe reported the highest proportion of non-susceptibility of *S. pneumoniae* to penicillin and/or erythromycin. However, in the northern countries Finland is an exception for penicillin (non-susceptibility 23.3%) and erythromycin (non-susceptibility 28.2%) and Denmark for erythromycin (non-susceptibility 57.1%) and penicillin (non-susceptibility 48.5%, intermediate 47.1%). However, as mentioned above, it is likely that this high non-susceptibility pattern for Denmark is due to incomplete reporting of susceptible isolates.

Figure 4.11 clearly shows of the three antibiotics tested erythromycin demonstrates the highest percentage of resistance. Penicillin was the antibiotic with the greatest intermediate resistance.

The overall percentage of non-susceptibility was 17.6% for erythromycin, 8.9% for penicillin and 2.7% for cefotaxime.

Overall, resistance to erythromycin is predominant in Europe with sixteen countries reporting a proportion of non-susceptibility above 10%.

Figure 4.11 Distribution of reported IPD cases by SIR scale (PEN, ERY, CTX), EU/EEA countries, 2010 (PEN n=9 247, ERY n=8 382, CTX n=6 186)



4.9.4 Resistance and serotype

Of the total number of serotyped isolates for which antimicrobial susceptibility information was provided (n=1 475), 1 307 were reported with resistance (R) to erythromycin, 152 to penicillin and 16 to cefotaxime.

Simultaneous resistance to penicillin, erythromycin and cefotaxime (multidrug-resistance) was observed in serotypes 19A, 14, 1, 19F, and 23F (Table 4.17).

Dual resistance to penicillin and erythromycin was reported in serotypes 19F, 19A, 14, 15A, 6A, 6B, 9V, 23A, 23F, 1 and 24A.

Resistance to erythromycin alone was reported for serotypes 6C, 33F, 24F, 11A, 9N, and 15C.

Serotype 1 usually remains susceptible to penicillin [16], although resistance to erythromycin (macrolides) has been published. In this surveillance exercise, resistance to penicillin in serotype 1 was reported, however only for very few isolates (n=3).

Table 4.17 Distribution of reported IPD cases by serotype and antimicrobial resistance, EU/EEA countries, 2010 (PEN n=152, ERY n=1307, CTX n=16)

	Penicillin R		Erythromycin R		Cefotaxime R	
Serotype	n	%	n	%	N	%
19A@	22	14.5	267	20.4	3	18.8
14&	37	24.3	244	18.7	2	12.5
1$	3	2.0	156	11.9	1	6.3
19	1	0.7	87	6.7	1	6.3
19F&	24	15.8	75	5.7	5	31.3
6B&	20	13.2	73	5.6	2	12.5
15A	5	3.3	58	4.4	-	-
6A*	4	2.6	35	2.7	-	-
9V&	7	4.6	32	2.4	-	-
6C	-	-	31	2.4	-	-
23F&	15	9.9	28	2.1	1	6.3
33F#	-	-	27	2.1	-	-
24F	-	-	21	1.6	-	-
33	-	-	19	1.5	-	-
15	1	0.7	18	1.4	-	-
6	-	-	16	1.2	-	-
3*	2	1.3	14	1.1	1	6.3
11A#	-	-	11	0.8	-	-
9N#	-	-	9	0.7	-	-
35B	1	0.7	8	0.6	-	-
15B#	1	0.7	6	0.5	-	-

	Penicillin R		Erythromycin R		Cefotaxime R	
Serotype	n	%	n	%	N	%
15C	-	-	6	0.5	-	-
23	-	-	6	0.5	-	-
9	-	-	5	0.4	-	-
23A	1	0.7	5	0.4	-	-
7F[$]	-	-	4	0.3	-	-
9A	-	-	4	0.3	-	-
10A[#]	-	-	3	0.2	-	-
12	-	-	3	0.2	-	-
18C[&]	-	-	3	0.2	-	-
24	-	-	3	0.2	-	-
35C	-	-	3	0.2	-	-
38	-	-	3	0.2	-	-
4[#]	2	1.3	2	0.2	-	-
7	-	-	2	0.2	-	-
8[#]	-	-	2	0.2	-	-
10	-	-	2	0.2	-	-
11	-	-	2	0.2	-	-
12F[#]	-	-	2	0.2	-	-
22F[#]	1	0.7	2	0.2	-	-
2[#]	-	-	1	0.1	-	-
12B	-	-	1	0.1	-	-
17	-	-	1	0.1	-	-
23B	1	0.7	1	0.1	-	-
24A	1	0.7	1	0.1	-	-
24B	-	-	1	0.1	-	-
33A	-	-	1	0.1	-	-
35	-	-	1	0.1	-	-
35F	1	0.7	1	0.1	-	-
O	-	-	1	0.1	-	-
5[$]	1	0.7	-	-	-	-
NTYP	1	0.7	-	-	-	-
Total	152	-	1 307	-	16	-

[@] serotype protected against by the 13-valent PCV and PPV23

[#] serotype protected against by the PPV23

[&] serotype protected against by the 7, 10, and 13-valent PCV and PPV23

*percentage referred to the total number of cases with reported serotype and antimicrobial susceptibility (reported as R) within each antibiotic.

[$] serotype protected against by the 10 and 13-valent PCV and PPV23

4.9.5 Minimum inhibitory concentration (MIC)

Overall penicillin MIC was ≤ 0.06 mg/L for 75.6% of isolates, 0.125 < MIC ≤ 2mg/L for 23.3% and MIC > 2mg/L for 1.12%. High-level resistance to penicillin (MIC ≥ 8mg/L) was reported in only 0.1% (n=6) of isolates with reported MIC for penicillin (n=5 244). High-level resistance to penicillin was related to serotypes 14, 19A, 19F and 23F (Table 4.18).

Erythromycin MIC was ≤0.25 mg/L for 70.9% of the isolates with this information, 0.25 < MIC ≤ 0.5 mg/L for 5.4% of the isolates and MIC> 0.5 mg/L for 23.7 % of the isolates. High-level resistance to erythromycin (MIC ≥ 32 mg/L) was reported in 19.9% (n=777) of isolates with reported MIC for erythromycin (n=3912). High-level resistance to erythromycin was related mainly to serotypes 19A, 14, 6B, 19F, 6C, 24F, 23A, and 33F (Table 4.18).

Cefotaxime susceptibility proportions were 91.3% of the isolates with this information for MIC ≤ 0.5mg/L, 8.4% of the isolates for 1 mg/L < MIC ≤ 2 mg/L and 0.3% of these isolates for MIC > 2 mg/L. High-level resistance to cefotaxime (MIC ≥ 4 mg/L) was reported in only 0.3% (n=16) of isolates with reported MIC for cefotaxime (n=5240). High-level resistance to cefotaxime was related to serotypes 14, 19A and 19F (Table 4.18).

Table 4.18 Distribution of reported IPD cases by antibiotic and MIC, EU/EEA countries, 2010 (PEN n=5244, ERY n=3912, CTX n=5340)

MIC	Penicillin		Erythromycin		Cefotaxime	
	n	%	n	%	n	%
0.03	3 428	65.4	6	0.2	3 645	69.6
0.06	534	10.2	52	1.3	288	5.5
0.125	240	4.6	2 715	69.4	352	6.7
0.25	184	3.5	212	5.4	197	3.8
0.5	190	3.6	1	0.0	302	5.8
1	340	6.5	9	0.2	365	7.0
2	270	5.1	4	0.1	75	1.4
4	52	1.0	7	0.2	9	0.2
8	5	0.1	66	1.7	3	0.1
16	1	0.02	63	1.6	2	0.04
32	-	-	78	2.0	-	-
64	-	-	66	1.7	-	-
>64	-	-	633	16.2	2	0.04
Total	**5 244**		**3 912**		**5 240**	

Table 4.18 presents data on MIC. According to EUCAST breakpoints, 75.6% of cases that reported MIC for penicillin were susceptible if the clinical presentation was meningitis and 24.4% would be considered resistant (MIC > 0.06 mg/L).

In total, 23.7% of reported cases were resistant to erythromycin (MIC > 0.5 mg/L) and 0.38% resistant to cefotaxime (MIC > 2mg/L).

Explanatory note to aid interpretation of Table 4.18:

- Intervals defined as MIC are greater than the previous interval and smaller or equal to the upper limit of that interval. For example, within the 0.125 category of penicillin, all reported cases with 0.06 < MIC ≤ 0.125 are included. The cases in this category represent 4.6 % of all cases with reported MIC for penicillin.
- Information on particular guidelines used to determine MIC was not reported. Therefore, the table should be interpreted according to EUCAST breakpoints[14] for *S. pneumoniae* as follows:
  - Benzylpenicillin (infections other than meningitis) S ≤ 0.06 mg/L, R > 2 mg/L
  - Benzylpenicillin (meningitis) S ≤ 0.06 mg/L, R > 0.06 mg/L
  - Erythromycin S ≤ 0.25 mg/L, R > 0.5 mg/L
  - Cefotaxime S ≤ 0.5 mg/L, R > 2 mg/L.

4.9.6 Resistance and clinical presentation

Of the 699 cases of reported resistance with known clinical presentation, 592 presented resistance to erythromycin, 94 to penicillin and 13 to cefotaxime.

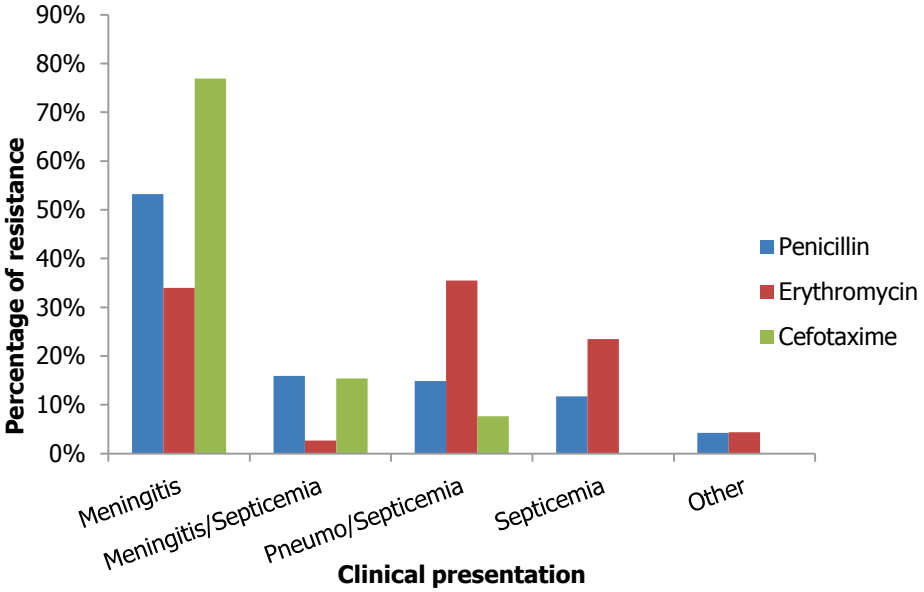
Within the different clinical presentations, penicillin (53%) and cefotaxime (77%) presented the highest proportion of resistance in meningitis (Figure 6.12).

Erythromycin (35%) presented the highest proportion of resistance in pneumonia/septicaemia compared to other clinical presentations.

Meningitis presented a greater proportion (0.05%, n=3) of high-level penicillin resistance (MIC ≥ 8mg/L) than non-meningitis clinical presentations. However, this statement needs to be interpreted cautiously given the small number of isolates (n=6) with high-level resistance to penicillin.

[14] http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Disk_test_documents/EUCAST_breakpoints_v_2.0_111130.pdf

Figure 4.12 Distribution of resistance for reported IPD cases by antibiotic and clinical presentation and total, EU/EEA countries, 2010 (PEN n=94, ERY n=592, CTX n=13)



4.9.7 *S. pneumoniae* results from EARS-Net compared with IPD antimicrobial susceptibility data

The Member States reported similar data for *S. pneumoniae* to the EARS-Net antimicrobial resistance surveillance database and to the IPD enhanced surveillance (see Annex, Table A5). For most countries, antimicrobial susceptibility testing results reported to EARS-Net correspond with the data reported to the IPD enhanced surveillance, despite some differences in the sources of these data. However, for a few countries (Estonia, Latvia and Malta) there seem to be more significant differences in antimicrobial susceptibility testing results. In most cases, the reporting from these countries is based on a small number of cases (n<20) and thus, confidence intervals are too large to allow appropriate comparisons. Denmark reports a larger number of cases. However, Denmark did not report complete susceptibility data for all isolates to the IPD enhanced surveillance, meaning that its results were biased towards a higher rate of non-susceptibility.

5. Discussion

This report represents the first enhanced surveillance report for invasive pneumococcal disease in Europe.

Despite the limitations of the data, the analysis reveals some interesting epidemiological points with an important public health perspective.

In 2010, 21 565 confirmed cases of invasive pneumococcal disease were reported in Europe. The highest notification rates were among children under one year (18.54 per 100 000) and adults of 65 years and over (15.59 per 100 000). This pattern, which has been seen in European data since 2006 as well as in other parts of the world [14, 16-19], supports the recommendations for targeting these age groups for vaccination.

The most frequent clinical presentation was bacteraemic pneumonia, accounting for 48% of cases. Once again, in accordance with similar findings published elsewhere [20-22], *S. pneumoniae* is considered to be the leading bacterial cause of pneumonia and is reported as a major cause of hospital admissions for children and adults [22,23].

The case-fatality rate varies markedly from 0% (Cyprus, Denmark, Lithuania and Malta did not report deaths) to 26.9% (Hungary). However, these figures should be interpreted cautiously due to the incompleteness of the variable 'outcome' (79.5% missing). Moreover, there may be a certain degree of ascertainment bias (under-reporting of 'alives'), giving inaccurate results. There may be other reasons for the variation across countries, such as time-point at which the fatal outcome is defined, healthcare and health-seeking behaviour, underlying disease, level of antimicrobial resistance, age group, clinical presentation and/or predominance of different serotypes. Furthermore, there is evidence that pneumococcal invasiveness does not necessarily mean lethality. Low invasive serotypes usually account for higher case-fatality rates [24,25].

The most prevalent serotypes reported to cause IPD were 19A, 1, 7F and 3. These four serotypes are most prevalent in children under 15 years. None of these serotypes are covered by PCV7 although they are included in PCV13. Therefore, on the basis of serotype coverage alone, these results appear to support the decision to shift to a higher valent vaccine.

PPV23 is currently recommended for children in risk groups from the age of two years and for adults. PCV13 was recently authorised for use in adults over 50 years. Serotypes 22F, 8, 12F and 9N occur in a significant number (n=1 228, 12.3%), predominantly in the adult population and are only covered by PPV23. In light of this finding, given that the four serotypes are not covered by PCV13, and on the basis of serotype coverage alone, the data suggest that PPV23 continues to be relevant for the vaccination of adults in risk groups, since PCV13 would not cover this important percentage of reported serotypes.

When taking all age groups into consideration, 17.8% (n=1 772) of all cases with reported serotype (n=9 946) would have been covered by PCV7 alone, 38.7% (n=3 832) would have been covered by PCV10 alone and 60.0% (n=5 938) would have been covered by PCV13 alone. PCV13-specific serotypes (1, 5, 7F, 3, 6A and 19A) would have covered 42.2% (n=4 166) of all cases with reported serotype (Table 4.13).

Serotype 6C was reported in 2.27% of cases for which information on serotype was available, mainly in adults aged 15 years and over. The increased prevalence in nasopharyngeal carriage of serotype 6C in certain settings after vaccination has been discussed elsewhere [26]. Currently serotype 6C is not covered by any of the licensed vaccines. However, there is evidence that PCV13 has the potential to confer cross-protection against serotypes not directly covered by the vaccine, namely serotypes 6C and 7A [27,28]. This finding also supports the idea of introducing PCV13 into national vaccination schemes, since PCV13 contains serotype 6A. Moreover, serotype 6C has been reported as being resistant to macrolides in this surveillance exercise.

Among the most frequent serotypes, serotype 3 accounted for the highest number of deaths (n=35). This serotype has been associated with low invasive potential but has caused more severe disease and increased mortality [10], as has serotype 6B. Serotype 6B accounts for the highest serotype-specific fatality rate (17.9%), despite being included in PCV7. One reason might be that serotype 6B is strongly associated with resistance [29,30]. In this surveillance, a number of serotype 6B isolates have been reported as resistant to both penicillin and erythromycin. Nevertheless, this information should be interpreted with caution due to the small number of cases for which serotype and death was known (n=264). Moreover, there are other factors involved, such as capsule type or presence of virulence determinants.

Pneumococcal vaccination is currently carried out in 29 EU/EEA countries (VENICE II). A considerable number (n=1 051, 10.6%) of the serotypes 4, 14 and 19F, included in all three PCVs, have been reported across Europe, especially in Finland and Spain. In both countries PCV7 was introduced to the private market in 2001 but it was never incorporated into the routine childhood immunisation programme in either country, except in the Autonomous Region of Madrid in Spain, and hence the estimated PCV7 vaccination coverage has been low (less than 1% in Finnish children [31]). Between February 2009 and August 2010, over 30 000 Finnish children were immunised with PCV10 in a large, nationwide effectiveness trial (FinIP) [32] that was followed by the introduction of PCV10 into the national immunisation programme in Finland in September 2010 [31].The preliminary results seem to be positive:

according to the 2011 surveillance data, there has been a reduction of over 80% in IPD occurrence among infants aged six to eleven months compared to the 2004–2008 period, prior to the PCV10 vaccination campaign [31]. Madrid replaced PCV7 with PCV13 in June 2010. Recent publications show a reduction in the incidence of invasive pneumococcal disease for PCV13 or PCV10 serotypes in certain countries that have moved to PCV13 [33] or PCV10, as seen in Finland.

Serotypes 3 (9.3%, n=928; included in PCV13 and PPV23) and 8 (3.4%, n=343; included in PPV23) were significantly represented and predominant in adults, as described elsewhere [12,13]. Close monitoring of these serotypes is recommended to detect a shift to younger ages and thus, serotype replacement. This finding also supports the recommendation that adults should be vaccinated with PCV13 or PPV23.

One of the major challenges of pneumococcal surveillance is assessing the impact of the vaccine by inducing serotype replacement (defined as the reduction of serotypes included in the vaccines and the rise of non-vaccine serotypes instead). This phenomenon has been widely described [34-38]. Unfortunately, discussion of this issue is premature after only one year of surveillance. Furthermore, there is a need to increase data collection on vaccine coverage at national and sub-national level to allow a more accurate interpretation of surveillance data. Nevertheless, the findings of the 2010 data analysis may constitute a baseline for future studies and comparisons.

Invasive pneumococcal diseases display a seasonal pattern which is even more evident in older age groups. There may be a number of factors involved including co-infection with respiratory viruses (influenza, syncytial respiratory virus, etc.) or temperature and environmental conditions [39-43]. A stronger commitment on recommendations for vaccines in the older age group may be required (influenza, PCV13 and PPV23 vaccines).

Non-susceptibility has been reported, especially to macrolides (erythromycin), and certain serotypes present non-susceptibility to penicillin, erythromycin and cefotaxime. Therefore, not only resistant but multidrug-resistant (resistance to three or more antimicrobial classes) serotypes have been reported.

Erythromycin is the antibiotic that presented the highest level of non-susceptibility (17.6%), followed by penicillin (8.9%).

Simultaneous resistance to penicillin, erythromycin and cefotaxime (multidrug-resistance) was observed in serotypes 19A, 14, 1, 19F, and 23F. Serotypes 19A, 14, 19F and 23F, are considered to be the most antimicrobial resistant [29,30]. High-level resistance to penicillin, erythromycin and cefotaxime was found in serotypes 14, 19A and 19F.

Although there are no major discrepancies in the antimicrobial susceptibility testing results for EARS-Net and IPD surveillance, the variation could be explained by differences in the surveillance systems (laboratory-based with little national coverage in EARS-Net vs. mainly population-based surveillance systems with nationwide coverage for IPD surveillance). It could also be due to differences in case definition (only blood and CSF for EARS-Net whereas IPD surveillance collects data from all sterile sites). However, as explained above, one significant factor is that EARS-Net does not analyse data from countries that submit less than 20 isolates while IPD surveillance does not restrict the number of cases for analysis.

Overall, looking at trends in data published in the Annual Epidemiological Report[15], the notification rate for IPD decreased slowly from 2006 to 2009. An increase was observed in 2010 compared to 2009 (4.29%, n=14 273 vs. 5.22%, n=21 565). However, this increase should be interpreted with caution as there is a temporal association with the implementation of the ECDC IPD project in 2010, when new countries strengthened or introduced IPD surveillance and coincidental changes in the surveillance systems, all of which could have had an impact on the reporting.

[15] Available at:

http://ecdc.europa.eu/en/publications/Publications/1111_SUR_Annual_Epidemiological_Report_on_Communicable_Diseases_in_Europe.pdf

6. Limitations and strengths

Although the major strength of this report is that it includes a large number of participants (26 EU/EEA countries), figures should be interpreted cautiously due to the differing characteristics and comprehensiveness of the national surveillance systems in terms of coverage and representativeness (see Annex, Table A1).

The widespread use of the EU 2008 case definition for IPD is an asset as it allowed only laboratory-confirmed cases to be reported.

The added value of the IPD surveillance from a European perspective is that it has enabled IPD data to be pooled at supranational level. The aim is to provide comprehensive baseline information on the epidemiology of IPD in EU/EEA countries to determine the burden of the disease at European level. This will in turn facilitate the prioritisation of policies, assessment of the impact of vaccination and the development of future vaccines. It will also enable data to be compared with other regions of the world.

One positive aspect of the surveillance is that prior to its commencement, National Reference Laboratories undertook External Quality Assessment (EQA) schemes on identification, serotyping and antimicrobial susceptibility testing of *S. pneumoniae* and appropriate training to characterise *S. pneumoniae* isolates. These activities undoubtedly contributed to the improvement of European surveillance for IPD by increasing the specificity of IPD surveillance systems.

This surveillance report has several limitations. Surveillance of invasive pneumococcal disease varies across European countries. The differences relate to surveillance systems, healthcare systems, healthcare-seeking, diagnostics, laboratory methods and medical practices, especially concerning blood culturing. Surveillance systems for IPD differ in sensitivity, representativeness and specificity, making it difficult to compare data. Moreover, a certain degree of under-diagnosis and under-reporting is suspected.

The information on which the surveillance is based is paramount for interpretation of results. Despite the request for information on data sources and surveillance systems, there is a need for further updates on the comprehensiveness of the systems (i.e. surveillance focused in certain age groups or restricted to certain clinical presentations only).

Certain limitations in the laboratory capacity for serotyping are shown by the fact that some isolates have not been characterised to the serotype level but only up to serogroup (i.e. serogroup 7, 19, etc). However, some countries have been able to characterise recently described serotypes such as 6C and 6D. Serotype 11E was not reported, since it was not available within the coded value list for the variable serotype and was only referred to in terms of the lack of capacity to discriminate between serotype 11A and serotype 11E [44,45]. Characterisation of serotype 11E is not performed on a routine basis in Europe yet.

In order to complete the picture of IPD in Europe, it would be useful to have data on nasopharyngeal carriage of serotypes to assess herd immunity and potential serotype replacement. Moreover, information about outbreaks and serotypes responsible for epidemics might help to distinguish between secular trends and changes in the epidemiology of the pneumococcal disease. Unfortunately, it is not yet possible to collect such data.

Another limitation of this surveillance is the incompleteness and scarcity of information on certain variables, such as vaccination status and vaccine type, risk factors, outcome, serotype and antimicrobial resistance, making it impossible to evaluate vaccine effectiveness and vaccine impact by creating a sound baseline for the detection of serotype replacement in future editions. Unfortunately, due to insufficient data completeness, a deeper analysis in relation to vaccine type (assessing vaccine type usage) was impossible.

7. Conclusions and recommendations

Invasive pneumococcal disease is an important cause of morbidity and mortality much of which can be prevented by the use of appropriate vaccines. There is evidence of serotype replacement following the widespread use of PCV7. As shown in this report, some of the most predominant serotypes are not covered by PCV7, either in children or adults. Furthermore, some of the PCV10 and PCV13-specific serotypes exhibit antimicrobial resistance or multidrug-resistance. These findings (serotype replacement, antimicrobial resistance and evidence of reduced IPD incidence after introduction of PCV10 or PCV13) suggest that EU/EEA countries should seriously consider implementing immunisation schemes with available conjugate vaccines, taking into account the specific epidemiology of the disease in their country.

Systematic, good-quality surveillance of invasive pneumococcal disease is vital in order to monitor changes in the incidence, serotype distribution and antibiotic resistance of isolates following the introduction of vaccines.

Pneumococcal vaccination is not universal in all EU countries (VENICE II). The vaccine is not universally recommended across Europe and in some countries is only advised for risk groups. One consequence of this might be the continued circulation of serotypes that are already included in PCV7 (4, 14, and 19F), even in countries where PCV7 is implemented. Moreover, the economic crisis currently affecting many European countries might have an impact on the coverage of the vaccine in countries where its cost is not reimbursed. It would be advisable for EU/EEA countries to consider actively offering vaccination to tackle the severity of the disease and the current serotype distribution when designing their vaccination strategies.

The high notification rates in adults over 65 years and the increase in the number and severity of cases during the winter months, most likely related to co-infection with respiratory viruses, support the necessity for immunisation in the elderly (influenza and pneumococcal vaccines).

Although pneumococcal immunisation has decreased the frequency of antimicrobial resistant infections, vaccination is not the only option which needs to be addressed [46,47]. The prudent use of antimicrobials and strict clinical treatment policies are clearly also necessary to limit the emergence and spread of antimicrobial resistance within pneumococcal strains.

These findings support the continued monitoring of invasive pneumococcal disease in Europe and advocate improvement of surveillance to ensure high quality and comparable data across the EU/EEA countries. With regard to data completeness, more emphasis should be placed on improving information relating to serotype, antimicrobial susceptibility testing, severity of disease (clinical presentation and outcome) and vaccination parameters at national level. Vaccine coverage data would also aid the interpretation of the analysis.

There is also a need to further strengthen laboratory capacity and close collaboration between microbiologists and epidemiologists working on IPD throughout Europe. Together with Member States, ECDC advocates further harmonisation and standardisation of laboratory methods for IPD diagnostics through its different projects.

Furthermore, special studies, such as active epidemiologic surveillance, may be crucial to the prevention of under-reporting and other flaws in current passive systems [48].

In conclusion, the findings presented in this report stress the importance of standardised, reproducible, laboratory and clinically based, epidemiological surveillance across Europe.

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Annexes

Table A1 Description of the data sources for surveillance data on pneumococcal infections, reporting year 2010

						Data reported by					
Country	Data source	Legal character	Comprehen-sive	Active/Passive	Case-based/ Aggr.	Labs	Physicians	Hosp.	Others	Case def.	Nat. coverage
Austria	AT-Epidemiegesetz	Cp	Co	P	C	Y	Y	Y	Y	EU 2008	Y
Belgium	BE-REFLAB	V	Co	P	C	Y	N	N	N	Unknown	Y
Bulgaria	BG-NATIONAL_SURVEILLANCE	Cp	Co	P	A	Y	Y	Y	Y	EU 2002	Y
Cyprus	CY-NOTIFIED_DISEASES	Cp	Co	P	C	N	Y	N	N	EU 2008	Y
Cyprus	CY-LABNET	V	Se	A	C	Y	N	N	N	None	N
Czech Republic	CZ-EPIDAT	Cp	Co	A	C	Y	Y	Y	N		Y
Czech Republic	CZ-NRL-STR	Cp	Co	A	C	Y	Y	Y	N	EU 2008	Y
Denmark	DK-MIS	Cp	Co	P	C	N	Y	N	N	Other	Y
Estonia	EE-PNEUMOCOCC	Cp	Co	P	C	Y	Y	Y	Y	EU 2008	Y
Finland	FI-NIDR	Cp	Co	P	C	Y	N	N	Y		Y
France	FR-EPIBAC	V	Se	A	C	Y	N	Y	N	EU 2008	Y
France	FR-PNEUMO-NRL	V	Se	A	C	Y	N	N	N	EU 2008	Y
Greece	GR-Notification/Laboratory data	Cp	Co	P	C	Y	Y	Y	Y	EU 2008	Y
Hungary	HU-NRL_PNEU	V	Co	P	C	Y	N	N	N	EU 2008	Y
Iceland	IS-SUBJECT_TO_REGISTRATION	Cp	Co	P	C	Y	Y	Y	N	EU 2008	Y
Ireland	IE-PNEU	Cp	Co	P	C	Y	Y	Y	N	EU 2008	Y
Italy	IT-MENINGITIS	Cp	Co	P	C	N	Y	Y	N	EU 2008	Y
Latvia	LV-BSN	Cp	Co	P	C	Y	Y	Y	Y	EU 2008	Y
Lithuania	LT-COMMUNICABLE_DISEASES	Cp	Co	P	C	Y	Y	N	N		Y
Malta	MT-DISEASE_SURVEILLANCE	Cp	Co	P	C	Y	Y	Y	Y	EU 2008	Y
Netherlands	NL-OSIRIS	Cp	Co	P	C	Y	Y	N	N	EU 2008	Y
Norway	NO-MSIS_A	Cp	Co	P	C	Y	Y	Y	N		Y
Poland	PL-NATIONAL_SURVEILLANCE	Cp	Co	P	C	Y	Y	Y	N	EU 2008	Y
Romania	RO-RNSSy	Cp	Co	P	C	N	N	Y	N	EU 2008	Y
Slovakia	SK-EPIS	Cp	Co	A	C	Y	Y	Y	N	EU 2008	Y
Slovenia	SI-SURVIVAL	Cp	Co	P	C	Y	Y	Y	Y	EU 2008	Y
Spain	ES-NRL	V	O	P	C	Y	N	Y	N	-	-
Sweden	SE-SMINET	Cp	Co	P	C	Y	N	N	N	EU 2008	Y
United Kingdom	UK-PNEUMOCOCCAL	O	Co	P	C	Y	N	Y	Y	Other	Y

Cp: Compulsory, V: Voluntary, Co: Comprehensive, O: Other, Se: Sentinel, P: Passive, A: Active, C: Case-based, A: Aggregated, Y: Yes, N: No.

Table A2 Information on variables for enhanced surveillance collected by IPD surveillance systems (VENICE II* and country communication)

Country	Date of notification	Source of notification	Demographic variables	Date of onset of symptoms	Type of sample	Date of sampling	Laboratory test details	Type of IPD	Hospitalisation	Date of hospitalisation	Date of discharge	Underlying conditions	Vaccination status	Type of vaccine	Date of vaccine administration	Antibiotic resistance	Clinical outcome	Date of death	Serotyping	Molecular typing
Belgium (1)	√	√	√		√	√										√			√	
Belgium (2)	√	√	√	√	√	√	√	√	√	√		√	√	√	√		√		√	
Bulgaria									√											
Cyprus	√	√	√	√	√		√	√	√	√		√	√				√		√	
Czech Republic	√	√	√	√	√	√	√	√	√	√			√	√	√	√	√	√	√	√
Denmark	√	√	√	√	√	√		√	√	√		√	√			√	√	√	√	√
Estonia	√	√	√	√	√	√	√	√	√	√			√		√	√	√	√		
France	√	√	√		√	√	√	√	√							√			√	
Germany		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Hungary	√	√	√	√	√	√	√	√	√	√	√		√				√	√		
Iceland (1)	√	√	√		√	√	√	√								√	√		√	√
Iceland (2)	√	√	√	√	√	√	√	√	√							√	√	√	√	√
Ireland	√*	√*	√*	√*	√*	√*	√	√	√	√	√	√	√*	√	√	√	√	√	√*	√
Italy	√	√	√	√	√	√	√	√	√	√		√	√	√	√		√		√	
Latvia	√	√	√	√	√	√	√	√	√	√			√				√	√		
Lithuania	√	√	√	√				√	√	√		√	√		√		√	√		
The Netherlands	√	√	√		√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Norway	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Poland			√	√	√	√	√	√	√	√	√	√	√		√	√	√	√	√	√
Slovakia	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Slovenia	√	√	√	√	√	√		√	√	√	√		√	√	√	√	√		√	√
Spain	√	√	√	√	√		√	√	√								√		√	
Sweden	√	√	√	√	√	√	√						√			√			√	
UK (1)	√	√	√		√	√	√	√								√			√	
UK (2)	√	√	√	√	√	√	√	√								√			√	√

IE: For all children born since 2000 additional data has been routinely collected since 2008. For children and adults born before 2008 additional data has sometimes been collected since 2008. (*) indicates core notification data on all cases.

Table A3 Vaccination schedules (VENICE II and country communication)

Country	Date PCV first introduced	Vaccine given	Year PCV13	Immunisation schedule	1st d (m)	2nd d (m)	3rd d (m)	4th d (m)
Austria	July 2004	PCV10/PCV13		3+1 dose	3	5	7	12-24
Belgium	January 2005	PCV7	2011	2+1 dose	2	4	12	
Bulgaria	April 2010	PCV7/PCV10		3+1 dose/2+1 dose	2	3	4	12
Cyprus	August 2008	PCV10/PCV13		3+1 dose	2	4	6	12-15
Czech Republic	January 2010	PCV7/PCV10/PCV13		3+1 dose	2	4	6	18
Denmark	October 2007	PCV7/PCV13		2+1 dose	3	5	12	
Estonia		PCV7/PCV13		Not decided				
Finland	January 2009	PCV10		2+1 dose	3	5	12	
France	June 2006	PCV7/PCV13		2+1 dose	2	4	12	
Germany	July 2006	PCV10/PCV13		3+1 dose	2	3	4	11-14
Greece	January 2006	PCV7/PCV10/PCV13		3+1 dose	2	4	6	12-15
Hungary	October 2008	PCV7/PCV13	2010	2+1 dose	2	4	15	
Iceland	December 2006	PCV7/PCV10/PCV13		2+1 dose	3	5	12	
Ireland	October 2002	PCV7	2010	2+1 dose	2	6	12	
Italy	May 2005	PCV7/PCV10/PCV13		2+1 dose	3	5	11	
Latvia	January 2010	PCV7		3+1 dose	2	4	6	12-15
Lithuania		PCV7/PCV10		3+1 dose	2	4	6	24
Luxembourg	October 2004	PCV13		3+1 dose	2	3	4	12-15
Malta		PCV7/PCV10/PCV13		3+1 dose	2	4	13	None
Netherlands	June 2006	PCV7		3+1 dose	2	3	4	11
Norway	July 2006	PCV7	2011	2+1 dose	3	5	12	
Poland	May 2008	PCV7/ PCV13		3+1 dose/2+1 dose	NA	NA	NA	NA
Portugal	June 2010	PCV10/PCV13		2+1 dose	2	4	12-15	
Romania		PCV7/PCV10/PCV13	2011	3+1 dose	2	4	6	15-18
Slovakia	January 2006	PCV7/PCV13		2+1 dose	2	4	10	
Slovenia		PCV7/PCV10	2010	3+1 dose	2-3	4	6	24
Spain	June 2001	PCV7/PCV10/PCV13	2010	3+1 dose	2	4	6	15
Sweden	January 2009	PCV7/PCV10/PCV13		2+1 dose	3	5	12	
UK	September 2006	PCV7/PCV13		2+1 dose	2	4	13	

(m) = months

Table A4 Overview of enhanced set of variables for IPD surveillance

Technical fields	Laboratory variables
1. RecordID	22. DateOfSpecimen
2. RecordType	23. Specimen
3. RecordTypeVersion	24. Serotype
4. Subject	25. TestMethodTyping
5. Status	26. ResultMICValuePEN
6. DataSource	27. ResultMICValueERY
7. DateUsedForStatistics	28. ResultMICValueCTX
8. ReportingCountry	29. ResultMICSign_PEN
9. NRLData	30. ResultMICSign_ERY
Epidemiological variables	31. ResultMICSign_CTX
10. DateOfNotification	32. TestMethodMIC
11. PlaceOfNotification	33. SIR_PEN
12.PlaceOfResidence	34. SIR_ERY
13. Age	35. SIR_CTX
14. AgeMonth	
15. Gender	
16. DateOfDiagnosis	
17. Outcome	
18. Classification	
19. ClinicalPresentation	
20. VaccStatus	
21. VaccType	

Table A5 Overview of proportion of resistance in EARS-Net vs. IPD surveillance in 2010

Country	Penicillin R				Macrolide R			
	EARS-Net		IPD surveillance		EARS-Net		IPD surveillance	
	% R	N	% R	N*	% R	N	% R	N*
Austria	2.3	375	2.4	255	10.2	323	12.5	255
Belgium	0.4	1 797	0.4	1 847	24.7	1 797	24.9	1 847
Bulgaria	18.2	22	-	-	25.0	20	-	-
Cyprus	33.3	12	27.3	11	45.5	11	45.5	11
Czech Rep	0.0	288	-	-	5.9	288	-	-
Denmark	0.1	954	1.4	70	4.1	954	55.7	70
Estonia	1.6	64	0.0	6	2.2	45	33.3	3
Finland	1.3	611	3.7	792	27.0	607	28.2	792
France	0.2	1 127	0.2	1 127	29.5	1 127	29.5	1 127
Germany	0.3	354	-	-	8.6	359	-	-
Greece	-	-	-	-		-	-	-
Hungary	5.7	140	3.0	101	24.1	133	21.5	93
Iceland	2.7	37	-	-	10.8	37	-	-
Ireland	4.8	310	4.5	246	15.5	290	12.6	246
Italy	5.2	229	9.4	106	27.2	298	29.2	106
Latvia	5.4	37	6.3	16	5.3	38	12.5	16
Lithuania	7.7	39	-	-	0.0	35	-	-
Luxembourg	4.3	50	-	-	16.1	50	-	-
Malta	11.1	9	18.2	11	18.2	11	27.3	11
Netherlands	0.3	753		-	5.3	898	-	-
Norway	0.3	575	-	-	3.6	549	-	-
Poland	24.0	75	17.2	204	38.0	71	37.8	196
Portugal	14.7	156	-	-	21.8	156	-	-
Romania	30.8	13	33.3	21	27.3	11	38.1	21
Slovakia	-	-	16.7	12		-	18.3	4
Slovenia	0.4	232	16.5	224	17.2	232	25.0	224
Spain	29.8	862	-	-	25.4	862	-	-
Sweden	2.3	960	-	-	3.9	955	-	-
UK	0.7	1 336	1.0	4 198	4.4	1 289	4.4	3 360

*N: total number of isolates with antimicrobial susceptibility testing information, as categorised by the country (S, I, R)