TECHNICAL REPORT

Generic protocol on enhanced surveillance for invasive pneumococcal disease at the EU/EEA level

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This report was commissioned by the European Centre for Disease Prevention and Control (ECDC), coordinated by Edoardo Colzani and produced by Camelia Savulescu, Germaine Hanquet, Marta Valenciano and Alain Moren of Epiconcept for the SpIDnet project team.

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Contents

Tables

Abbreviations and glossary

Ag	Antigen, in the context of this paper referring to laboratory method to detect *S. pneumoniae* antigen
Antimicrobial susceptibility	In this context, used as the ability of a microorganism to resist the action of an antimicrobial agent, according to clinical breakpoints of the standards used
Completeness of data	Proportion of all cases with no missing variable or information
CSF	Cerebrospinal fluid
DD	Disk diffusion, a method for antimicrobial susceptibility testing
ECDC	European Centre for Disease Prevention and Control, Stockholm, Sweden
EU/EEA	European Union/European Economic Area
EUCAST	European Committee on Antimicrobial Susceptibility Testing
ICD	International Classification of Diseases, used as discharge diagnostic codes or for coding causes of death. The ninth or 10th revisions are currently used in most countries.
IPD	Invasive pneumococcal disease, defined as isolation of *Streptococcus pneumoniae* or detection of *Streptococcus pneumoniae* nucleic acid or antigen from normally sterile fluid
ICU	Intensive care unit
Lab	Hospital laboratory
MIC	Minimum inhibitory concentration, the lowest concentration of an antimicrobial that inhibits the visible growth of a microorganism after overnight incubation
NA	Not applicable (in context of IPD ECDC case definition)
PCR	Polymerase chain reaction
PCV	Pneumococcal conjugate vaccine
PCV7	7-valent pneumococcal conjugate vaccine
PCV10	10-valent pneumococcal conjugate vaccine
PCV13	13-valent pneumococcal conjugate vaccine
PPSV23	23-valent pneumococcal polysaccharide vaccine
Sentinel surveillance system	Surveillance system that involves collecting data from sample of reporting sites
Sensitivity (of surveillance system)	Proportion of cases reported by surveillance system out of total number of cases meeting same case definition in entire population. Also called degree of ascertainment or exhaustiveness of surveillance system
Surveillance site	In the context of this paper, surveillance system (in country or region) that collaborates with EU/EEA project
Surveillance unit	Hospital/laboratory reporting cases to surveillance site included in EU/EEA project
TESSy	The European Surveillance System
Vaccination coverage	Proportion of the eligible population which is effectively vaccinated. Vaccination coverage should be defined by schedule (number of doses or complete schedule)
VE	Vaccine effectiveness, defined as measure of direct effect of vaccination against target disease when used under field conditions

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1 Executive summary

The first pneumococcal conjugate vaccine (PCV) was licensed in 2001. European Union/European Economic Area (EU/EEA) Member States have progressively introduced PCVs in their national immunisation plans. Monitoring the performance of these vaccines in field conditions represents a high priority. Many Member States have set up or reinforced surveillance systems to collect data to assess the health benefits of PCVs in reducing the burden of invasive pneumococcal disease (IPD) in all age groups.

Between 2012 and 2014, the European Centre for Disease Prevention and Control (ECDC) funded SpIDnet, a pilot project on 'assessing the impact of vaccination with the conjugate vaccines on the epidemiology of the invasive pneumococcal disease in Europe' It aimed to set up active IPD surveillance in children under five years of age to monitor the impact of PCV programmes and improve the comparability of IPD data across Europe. In 2014, ECDC funded the 'SpIDnet complementary activities' project to collect additional surveillance data in all age groups.

The current SpIDnet generic protocol takes into account the lessons learned during the pilot project and proposes a uniform approach for active IPD surveillance in children and enhanced surveillance in other age groups. Public health authorities can adapt the generic protocol to meet their specific needs. The document covers the description of the public health importance of IPD and rationale for surveillance, surveillance objectives, case identification, data collection, monitoring indicators and feedback and supervision.

This protocol covers neither the specific studies to measure the impact of vaccination programmes and PCV effectiveness nor the evaluation of surveillance systems. Specific protocols are developed for these aspects under the SpIDnet project and are available upon request.

According to local needs and surveillance capacity, surveillance sites are invited to use these documents by developing specific surveillance protocols with the ultimate goal of strengthening IPD surveillance systems and improving comparability of indicators in the EU/EEA.

2 Background

Streptococcus pneumoniae is a Gram-positive diplococcus bacterium causing a wide spectrum of illnesses from otitis media to meningitis and represents a major public health problem worldwide. IPD is defined as the isolation of *S. pneumoniae* or detection of *S. pneumoniae* nucleic acid or antigen from a normally sterile fluid [1] and may present as meningitis, bacteraemic pneumonia, bacteraemia without focus, septic shock and, less frequently, arthritis, pericarditis or peritonitis. *S. pneumoniae* is commonly found in nasopharyngeal carriage, particularly among young children, who represent the main reservoir of pneumococci and source of transmission to new hosts. Carriage plays an important role in the epidemiology of pneumococcus, as recent acquisition of *S. pneumoniae* is thought to precede episodes of pneumococcal disease. More than 90 serotypes of *S. pneumoniae* have been identified according to their polysaccharide capsular type showing different virulence and extent of drug resistance. Some of them share many serological properties (i.e. cross-reactive antibodies) and are thus included in the same serogroup (e.g. serotypes 9N and 9V).

Two major groups of vaccines are currently available to protect against *S. pneumoniae*: polysaccharide vaccine (23-valent vaccine - PPSV23) and PCVs. PPSV23 was licensed in 1983 and is generally recommended for use in the elderly, adults and children ≥2 years with underlying medical conditions (risk groups) following national recommendations. PCVs (PCV7, PCV10 and PCV13) cover the 7, 10 and 13 serotypes most frequently causing IPD in developed countries during the pre-vaccine era (Table 1). PCVs were licensed in the EU in 2001 (PCV7) and 2009 (PCV10 and PCV13) for use in children under five years of age, with PCV10 and PCV13 progressively replacing PCV7 [2,3]. PCV13 was approved to prevent IPD in adults in 2011, and children up to 17 years in 2012 and for adults to prevent pneumonia in 2015. Currently, PCV13 is licensed for the prevention of invasive disease, pneumonia and acute otitis media caused by *S. pneumoniae* in infants, children and adolescents from 6 weeks to 17 years of age, as well as invasive disease and pneumonia caused by *S. pneumoniae* in adults ≥18 years of age.

PCV10 and PCV13 were approved on the basis of immunogenicity data. Currently, 25 of 31 EU/EEA Member States have PCV included in their infant immunisation schedule, but vaccination policies vary widely across Member States in terms of vaccine (PCV 10/13), dose schedule (2+1 or 3+1 doses) and target groups (risk groups only or universal vaccination in children). PCV13 vaccination in the elderly has been introduced in certain EU/EEA countries, alone or in combination with PPSV23 [4].

Medical practices, detection of IPD cases and IPD surveillance also differ widely across countries. Published data on surveillance systems show variations in reporting methods, case definitions, laboratory methods and disparities in blood-culturing practices to detect cases [5].

Table 1: *S. pneumoniae* serotypes included in different vaccines

Vaccine	Serotypes
PCV7	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10	PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and 1, 5, 7F
PCV13	PCV10 serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F) and 3, 6A, 19A
PPSV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

2.1 Country-specific background

Each surveillance site provides a brief description of:

- the public health importance of IPD for the country/region (number of cases, incidence, mortality, case-fatality); and
- vaccination programmes (vaccines available, history of vaccination introduction by vaccine, recommendations for vaccination (current and changes over time), schedules, vaccination coverage, any published evaluation of impact or effectiveness).

2.2 Rationale for active IPD surveillance at the EU/EEA level and in EU Member States

IPD is a severe and frequent disease. Since PCVs have been introduced in most EU countries, post-licensure surveillance is crucial to assess the impact of these vaccines on the epidemiology of pneumococcal disease in Member States, compare the effectiveness of different vaccination schedules, identify risk factors for vaccine failure and collect evidence of serotype replacement following the introduction of vaccines.

According to Decisions 1082/2013/EU and 2000/96/EC, IPD is included in the priority list of diseases under surveillance at the EU level [1]. EU surveillance of IPD is important to provide comparable data on IPD at the EU level, measure the effectiveness and impact of PCVs at a supra-national level, including its indirect effect, monitor circulating strains and detect emerging serotypes representing new health threats and changing targets in the EU. In addition, IPD surveillance at the EU level is a unique opportunity to assess the serotype-specific effectiveness of PCV on additional serotypes (for which clinical protection is uncertain) and compare the effectiveness and impact of different vaccine policies (schedules/vaccines) as individual country studies may lack the statistical power for responding to these research questions [6]. This allows ECDC to produce scientific guidance to inform policymaking related to PCVs in the EU.

Trends in diagnostic procedures (e.g. blood culturing), under-reporting (suboptimal sensitivity of the surveillance systems) and missing data (mainly on clinical data and vaccination status) represent the main challenges of many IPD surveillance systems and may influence the results of impact and effectiveness studies based on surveillance data.

In particular, an active surveillance system collecting a minimum set of variables in a similar way in different EU countries may achieve and improve surveillance objectives by:

- improving reporting and completeness of data collected
- taking into account trends in diagnostic procedures
- improving the comparability of the data at the EU level; and
- allowing pooling of certain data for meaningful results at the EU level.

Each surveillance site provides additional rationale for active surveillance in the specific context.

2.3 Objectives

The aim is to enhance the existing IPD surveillance system in all age groups in order to:

- estimate the incidence rate and mortality due to IPD in children and adults
- provide systematic monitoring of circulating *S. pneumoniae* serotypes to detect emerging strains and serotype replacement
- measure the vaccine effectiveness of the pneumococcal vaccines
- evaluate the impact of PCVs in terms of the disease burden of vaccine and non-vaccine strains; and
- monitor antimicrobial non-susceptibility in pneumococcal isolates.

Each surveillance site adapts the above objectives to IPD active surveillance in the country/region.

2.4 Methods

2.4.1 Population under surveillance

The study population consists of persons living in the catchment area of the data source used to identify cases (i.e. hospital and laboratory catchment areas). All age groups are included to allow the assessment of the indirect effect of PCV vaccines in the age groups not targeted for vaccination.

Each site precisely estimates the population of the catchment area. Special attention is given to match both the denominator and numerator data of the surveillance population to enable the correct calculation of incidence rates.

Each site assesses and describes where the population under surveillance seeks healthcare services to ensure that all laboratories and hospitals notifying the cases are contacted to detect any missing cases.

Each surveillance site states the population under surveillance and how this was estimated (data sources, method and time of population estimation, potential limitations). The population under surveillance includes all ages.

2.4.2 Type of surveillance system

The proposed surveillance system is an active system for children under five years of age and enhanced in the surveillance of other age groups.

Each surveillance site states the type of surveillance by age groups included. This should be reflected in the description of case finding and timelines for active data collection.

The surveillance system should be built on the existing surveillance systems that may be:

- sentinel or comprehensive
- mandatory or voluntary; or
- laboratory-based or hospital-based.

Each surveillance site briefly describes the existing surveillance system and the necessary changes to improve the capture of cases in the catchment areas (if not already in place). These changes should also be reflected in the surveillance methods below.

If the current IPD surveillance system was ever evaluated, surveillance sites would provide the estimated sensitivity of the current surveillance system and its coverage.

2.4.3 Selection of surveillance units

T minimum criteria for surveillance unit (hospital/laboratory) selection include:

- known denominators in the catchment area
- individual data collection for the minimum set of variables included by age groups
- surveillance of (services provided for) all IPD clinical manifestations
- diagnostic (X-ray) and laboratory (isolation/PCR/Ag detection) facilities
- access to care for patients with IPD; and
- willingness to participate in the surveillance system.

A description of the surveillance units is included in the surveillance system.

Each surveillance site briefly describes how they can ensure this minimum criteria for surveillance unit selection.

2.4.4 Outcomes

IPD definition

The EC 2012 case definition should be used to report IPD cases (1):

Pneumococcal invasive disease(s) (*S. pneumoniae*)

Clinical criteria

Clinical criteria are not relevant for surveillance purposes.

Laboratory criteria

At least one of the following three criteria must be met:

- Isolation of *S. pneumoniae* from a normally sterile site
- Detection of *S. pneumoniae* nucleic acid from a normally sterile site; and
- Detection of *S. pneumoniae* antigen from a normally sterile site.

Epidemiological criteria

NA

Case classification

A. Possible case

NA

B. Probable case

NA

C. Confirmed case

A confirmed case is any person meeting the laboratory criteria.

Each surveillance site states the case definition currently used and compliance with the 2012 EC case definition above. For PCR tests, each surveillance site describes criteria to consider a true positive result (e.g. detection of two specific pneumococcal genes: ply and an additional capsular gene or lyt and an additional capsular gene should be used).

Case identification

Depending on the surveillance settings (laboratory- or hospital-based), the starting point for IPD case identification includes:

- laboratory results: regular checks of laboratory results logs and retrieval of individual data from medical history of the patient and vaccination data from the available sources (i.e. link with the vaccination registries or medical records)
- admission for specific clinical syndromes compatible with an IPD (see page 12, outcome classification): regular checks of admission/emergency departments logs and follow up of the patient for clinical/laboratory diagnosis; and
- regular reminders are sent to laboratories and hospitals to report all diagnosed cases.

Each surveillance site states how case identification is done and the frequency of contact with data sources. In any case, individual data collection requires a link between clinical, laboratory and vaccination data.

Laboratory confirmation, serotyping and antimicrobial susceptibility testing

To comply with the IPD case definition, laboratory confirmation through culture, PCR or Ag detection could be used for diagnosis. The specific objectives of the surveillance system also require serotyping and antimicrobial susceptibility testing.

- Isolation and identification/ PCR or Ag detection can be done at the hospital or reference laboratory.
- Serotyping of isolates is usually done at the reference laboratory using capsular reaction testing (Quellung test), gel diffusion with type-specific antisera or PCR.
- Antimicrobial susceptibility testing should be done for all isolates:
  - Antibiotics to be included: penicillin, macrolide, cephalosporin *(other classes of antimicrobials if tested)*
  - Methods to be used: MIC, DD, Etest
  - Clinical breakpoints to be used (standards: preferentially European Committee on Antimicrobial Susceptibility Testing (EUCAST)).

Each surveillance site specifies at what level antimicrobial susceptibility testing is performed, the antimicrobials tested and methods used (and their sensitivity and specificity if available). At the European level, minimum inhibitory concentration (MIC) by antimicrobial are reported (Table 2). If other methods are used in the country, the surveillance site should state the specific method, clinical breakpoints for each antimicrobial tested and reference/standard used.

Outcome classification

The main outcome of this surveillance is IPD, as defined according to the above case definition. This outcome is further classified by serotypes, clinical manifestations, antimicrobial susceptibility and severity.

Classification of IPD by serotype

According to the serotyping results and the vaccine used in the surveillance site, cases are classified by serotype categories:

- All types
- Vaccine serotypes: according to the vaccine used, the 7, 10 and 13 serotypes targeted by the respective conjugate vaccines
- Vaccine related serotypes: the serotypes from the same serogroups as the vaccine serotypes for which cross-protection was demonstrated or assumed. (The serotypes included in this category should be clearly stated. This category does not include serotypes for which cross-protection was not demonstrated, e.g. 19A and 6C are not included in the evaluation of PCV7)
- PPSV serotypes: the 23 serotypes included in the PPSV vaccine
- Non-vaccine serotypes: all the other serotypes according to the vaccine used (i.e. non vaccine and non vaccine-related); and
- Serotype-specific.

Classification of IPD by clinical manifestations

The following clinical manifestations of IPD are included in the surveillance and should be specified for each IPD case:

- Meningitis
- Bacteraemic pneumonia
- Empyema
- Bacteraemia without known focus of infection
- Septic shock
- Others (arthritis, peritonitis, pericarditis).

Classification of IPD by antimicrobial susceptibility

MIC by antimicrobial is reported at the European level from each surveillance site. Classification according to EUCAST is used for comparisons among surveillance sites.

Classification of IPD by severity

Severity is defined as intra-hospital death or death after 30 days of an IPD episode. Other indicators of IPD severity such as clinical manifestation as meningitis, length of hospital stay of more than 14 days and intensive care unit (ICU) admission are measured.

Each surveillance site to describe the outcomes used for IPD surveillance, taking into account classification by serotyping, clinical manifestation, antimicrobial susceptibility testing and severity.

2.4.5 Data

Data sources

The following data sources should be considered according to the settings:

- laboratory databases/results logs
- hospital admission logs/discharge databases
- vaccination data: vaccination cards/vaccine registries/well-baby clinics/medical records; and
- population data source.

Each surveillance site describes the sources for data collection or the possibility of linking the available databases.

Denominators

- Census data by age groups
- Hospital catchment area population data by age group

Each surveillance site provides population data. In case the population from the hospital/laboratory catchment area is used as the denominator, the methods of determining the population covered by the participating surveillance unit (hospital, laboratory) should also be described as well as its potential limitations.

Data collection

Individual data collection should be ensured for all IPD cases included in the surveillance system. The minimum set of data that is collected for each IPD case in the age groups <5 years and ≥65 years includes:

- demographic data: age in months/years (ideally date of birth if not considered personal information), gender, residence in the hospital/laboratory catchment area, reporting site
- hospitalisation data: admission and discharge dates, clinical manifestation, need for ICU care, outcome (alive, intra-hospital death or death within 30 days after the disease onset/diagnosis)
- laboratory data: sterile site that tested positive, method of isolation or detection (tests used), date of isolation, result of serotyping and tests used, MIC of antimicrobial susceptibility testing for penicillin, macrolide, cephalosporin
- vaccination data: type of vaccine (PCV7/10/13 and/or PPSV23), number of doses, dates of administration (each dose for PCV, the last dose for PPSV23)
- underlying conditions (according to the country recommendations for vaccination of risk groups); and
- current season influenza vaccination status.

The minimum set of data that is collected for each IPD case in the age group 5–64 years includes:

- demographic data: age, gender, residence in hospital/laboratory catchment area, reporting site
- hospitalisation data: clinical manifestation, outcome (alive, intra-hospital death or death within 30 days after disease onset/diagnosis)
- laboratory data: site, date of isolation, method of isolation or detection, result of serotyping and tests used, MIC of antimicrobial susceptibility testing for penicillin, macrolide, cephalosporin
- vaccination data (if available): type of vaccine (PCV7/10/13 and/or PPSV23), number of doses, dates of administration (each dose for PCV, the last dose for PPSV23)
- underlying conditions (according to country recommendations for vaccination of risk groups)
- current seasonal influenza vaccination status.

Each surveillance site states if the minimum set of data for individual data collection can be collected and fills in Table 2.

Additional data collection is desirable but not compulsory:

- Member of vulnerable group (to be specified)
- Day (group) care attendance
- Influenza positive test within 10 days before admission
- Other risk factors for IPD (to be specified).

Each surveillance site specifies the additional variables collected (if any) and includes them in Table 2.

Additional information at the hospital/laboratory level or population level that could be used for interpretation of data comprises:

- the number of hospitalisations of any cause (for the age groups under surveillance)
- the number of deaths of any cause (for the age groups under surveillance)
- the number of cultures performed in the age groups included (blood and cerebrospinal fluid (CSF) cultures)
- changes in clinical practices over time that may affect diagnosis and characterisation of pneumococcus
- changes in laboratory methods over time related to the diagnosis and characterisation of pneumococcus; and
- changes in reporting/surveillance system over time (e.g. age groups and clinical syndromes covered)

Each surveillance site lists additional information to be collected.

Data checking and transmission

Data are checked to identify outliers and implausible or missing information at the country/regional level. Data should be completed (if missing) or validated (at request) against the data source as much as possible.

The transfer of data from surveillance units to central level within the country is done according to site-specific legislation regarding medical data protection. Secured data transmission from site level to SpIDnet coordination is organised using EpiFiles (a platform for secure data transfer developed by coordination hub).

Each surveillance site describes data checking and data management.

Analysis plan

Data descriptions and the calculation of the surveillance indicators should be included in an analysis plan. This should include a brief description of surveillance data, data checking, description of each variable and calculation of specific indicators. Examples of these indicators include:

- incidence rate of confirmed hospitalised IPD overall, serotype-specific IPD (all, vaccine, vaccine-related and non-vaccine types, serotype-specific), IPD clinical presentations and IPD susceptibility to a specific antibiotic/antimicrobial. These incidences are subsequently presented by age, sex, and underlying conditions.

- distribution of serotypes by clinical presentation
- number of IPD deaths/total number of IPD overall and by clinical presentation, serotypes
- distribution of isolates by antimicrobial susceptibility (according to EUCAST)
- number of severe cases (see definition page 12) and their description in case reports
- number of clusters of severe cases and specific serotypes; and
- indicators based on vaccine status: number/description of vaccine failures

Each surveillance site develops an analysis plan presenting the descriptive analysis and analysis by indicators.

2.4.6 Surveillance responsibilities, reporting and information flow

Levels of responsibilities

- Hospital/laboratory level (surveillance unit)
- Intermediate level (regional level)
- National level: national institute/national reference laboratory
- EU level

Reporting

- Level
  - In the country: contact of surveillance site personnel with surveillance units
  - At the EU level: data transfer according to established mechanisms
- Frequency of reporting
  - monthly, quarterly, annually
- Forms: case-based/laboratory (lab) forms
  - Web-based forms for data transmission.

Each surveillance site describes the responsibilities by level and frequency of reporting. Whenever possible, a TESSy-compatible format should be used.

2.4.7 Monitoring and evaluation (depends on type of system)

The system is monitored through process indicators (examples):

- number of reminders sent to data sources
- number and proportion of notified IPD cases fully documented
- number and proportion of IPD cases reported with complete information collected for each variable; and
- percentage of cases with isolates collected and sent to the reference laboratory for serotyping, antimicrobial susceptibility testing.

Each surveillance site establishes a minimum set of indicators that is used for ongoing monitoring the performance of enhanced surveillance.

Evaluation of surveillance system performance should be done regularly according to a specific evaluation protocol developed in accordance with published general guidelines. The following attributes are assessed with priority:

- Sensitivity of the system. Possible methods are:
  - comparison with other data sources (e.g. comparison of hospital logs with lab logs in the participating sites)
  - capture-recapture analysis; and
  - other methods (e.g. regression methods).
- Completeness
  - Percentage of missing data by each variable
  - Percentage of missing priority variables (age, clinical manifestations, vaccination variables).

Each surveillance site evaluates its system using a protocol for active IPD surveillance system evaluation prepared in advance.

2.4.8 Feedback and supervision

Each surveillance site establishes a mechanism for regular feedback to surveillance units. An annual report is prepared and presented during annual meetings at the EU level to exchange results and lessons learned.

The coordination team organises periodic teleconferences and/or technical workshops to facilitate decision-making and exchanges among partners.

Each surveillance site briefly describes feedback to the surveillance units and dissemination of site-specific results.

2.5 Ethical considerations

This enhanced surveillance system is included among surveillance activities in the countries/regions where it is implemented. Ensuring confidentiality in the data flow and ethical approval of this activity is done according to current legislation in the country/region.

In line with local legislation, paper forms are stored in secure locked cabinets at the surveillance unit, regional and central levels and access to these cabinets is restricted to essential surveillance personnel and surveillance coordinators. Electronic databases will be transferred using secure channels at the superior levels.

Each surveillance site obtains ethical approval and ensure confidentiality according to specific legislation.

2.6 Studies on vaccination impact and vaccine effectiveness

Surveillance data will be used for measuring vaccination programme impact and PCV/PPSV vaccine effectiveness. These studies will be conducted according to specific protocols.

Generic protocols for vaccination programme impact and PCV/PPSV vaccine effectiveness will be updated.

Table 2: List of variables, coding, definitions and data sources

Variable name	Site-specific variables	Variable label	Type	Values and coding	Definition	Comments
id		Case unique identifier			Case unique identifier	
siteid		Site identification	Unique ID	AA	Surveillance site identification	
datenotif		Date of notification	Date	dd/mm/yyyy	Date when case was notified for the first time to site level	
residence		Residence in the catchment area	Numeric	0: No 1: Yes 9: Unknown	Residence in catchment area of surveillance unit reporting to system	
ageyears		Age of the case in years	Numeric	###	Age of patient in years as reported at site level in years at time of hospital admission	
agemonths		Age of the case in months	Numeric	##	Age of patient in months as reported at site level in years at time of hospital admission for children <2 years	
sex		Gender	Code	0: Female 1: Male 9: Unknown	Gender of reported case	
dateadm		Date of the admission in the hospital	Date	dd/mm/yyyy	Date when case was admitted to hospital	
datedis		Date of the discharge from the hospital	Date	dd/mm/yyyy	Date when case was discharged from hospital	
outcome		Outcome	Code	0: Alive 1: Deceased 9: Unknown	Information on survival: alive, deceased, unknown	
datedeath		Date of death	Date	dd/mm/yyyy	Date of death of admitted patient (if outcome=1)	

Variable name	Site-specific variables	Variable label	Type	Values and coding	Definition	Comments
clinic		Clinical entity	Multiple choice	0: Unknown 1: Meningitis 2: Bacteraemic pneumonia 3: Empyema 4: Bacteraemia 5: Septic shock 8: Other, specify 9: Unknown	Clinical manifestation of IPD case	This multiple choice variable can be collected as such or each clinical entity can be entered separately using variables below. If clinic=8, variable 'otherclin' specifies other clinical entities of IPD not listed
meningitis		Pneumococcal meningitis	Code	0: No 1: Yes 9: Unknown	Case presenting with lab-confirmed pneumococcal meningitis	
pneumonia		Bacteraemic pneumococcal pneumonia	Code	0: No 1: Yes 9: Unknown	Case presenting with lab-confirmed pneumococcal pneumonia	
empyema		Pneumococcal empyema	Code	0: No 1: Yes 9: Unknown	Case presenting with lab-confirmed pneumococcal empyema	
bacteraemia		Bacteraemia without known focus of infection	Code	0: No 1: Yes 9: Unknown	Case presenting with lab-confirmed bacteraemia (blood stream infection) without known focus of infection	
septicsk		Pneumococcal septic shock	Code	0: No 1: Yes 9: Unknown	Case presenting with clinician-diagnosed septic shock regardless of focus of infection	
arthritis		Pneumococcal Arthritis	Code	0: No 1: Yes 9: Unknown	Case presenting with lab-confirmed pneumococcal arthritis	
otherclin		Other clinical entities	Text	string20	Other clinical entities of IPD case	Please specify other clinical entity for IPD cases
icuadm		Admission in the ICU	Code	0: No 1: Yes 9: Unknown	Lab-confirmed case that needed admission to ICU during pneumococcal episode	
datediag		Date of diagnosis	Date	dd/mm/yyyy	Date when diagnosis was made, should be same asidentification/confirmation of case	
fluid		Type of fluid tested positive	Multiple choice	0: None 1: CSF 2: Blood 3: Pleural 4: Articular 8: Other 9: Unknown	Fluid tested for IPD case	This multiple choice variable can be collected as such or each fluid can be entered separately using variables below. If fluid=8, variable (other fluid) specifies other positive sterile site fluids not listed

Variable name	Site-specific variables	Variable label	Type	Values and coding	Definition	Comments
lcr		Cerebrospinal fluid	Code	0: No 1: Yes 9: Unknown	Positive testing of CSF in case of meningitis	
blood		Blood culture	Code	0: No 1: Yes 9: Unknown	Positive testing of blood in any of invasive cases	
pleural		Pleural fluid	Code	0: No 1: Yes 9: Unknown	Positive testing of pleural fluid in case of pneumonia	
otherfluid		Other positive fluids	Text	String20	Other fluids that tested positive	
identif		Identification test performed	Multiple choice	0: Not done 1: Culture 2: PCR 3: Antigen 9: Unknown	Test performed for identification of IPD case	This multiple choice variable can be collected as such or separately as variables 30–32
culture		Culture performed	Code	0: No 1: Yes 9: Unknown	Culture performed on sterile site fluids	
pcridentif		PCR performed	Code	0: No 1: Yes 9: Unknown	PCR performed on sterile site fluids	
agidentif		Antigen detection	Code	0: No 1: Yes 9: Unknown	Ag detection performed on sterile site fluids	
serotype		Serotype identified	Text	string3 PEN: Pending NTP: Non-typeable UKN: Unknown	Serotype-identified	
serometh		Test performed for serotyping	Multiple choice	0: Not done 1: Quellung 2: PCR 3: Gel diffusion 8: Other 9: Unknown	Test performed for serotyping of *S. pneumoniae*	This multiple choice variable can be collected as such or separately as variables below. When serometh=8, variable 'seroother' specifies other methods used for serotyping
seroque		Serotyping using Quellung method	Code	0: No 1: Yes 9: Unknown	Serotyping using Quellung method	
seropcr		Serotyping using PCR	Code	0: No 1: Yes 9: Unknown	Serotyping using PCR	
serogel		Serotyping using gel diffusion with specific antisera	Code	0: No 1: Yes 9: Unknown	Serotype using gel diffusion with specific antisera	
seroother		Other methods used for serotyping	Text	string20		
micpeni		MIC to penicillin	Numeric	##.###	MIC to penicillin in µg/ml	If not tested, variable will be left blank
mic*[macrolide]*		MIC to macrolide	Numeric	##.##	MIC to macrolide in µg/ml [please specify macrolide used: erythromycin, azithromycin, clarithromycin, etc.]	If not tested, variable will be left blank

Variable name	Site-specific variables	Variable label	Type	Values and coding	Definition	Comments
mic*[cepha]*		MIC to cephalosporin	Numeric	##.##	MIC to cephalosporin in µg/ml (please specify cephalosporin used: cefotaxime, ceftriaxone, etc.)	If not tested, variable will be left blank
mic*[antimicrobial]*		MIC to antimicrobial	Numeric	##.##	MIC to different other antimicrobial tested	Please specify antimicrobial using specific variables
dosepcv1		Dose 1 PCV	Code	0: No 1: Yes 9: Unknown	First dose of vaccination with a PCV	
datepcv1		Date of vaccination with first dose PCV	Date	dd/mm/yyyy	Date of first dose of PCV	
brandpcv1		Dose 1 vaccine type of PCV	Code	0: No vaccine 1: PCV13 2: PCV10 3: PCV7 8: Other 9: Unknown	Type of PCV at first dose	
dosepcv2		Dose 2 PCV	Code	0: No 1: Yes 9: Unknown	Second dose of vaccination with a PCV	
datepcv2		Date vaccination with second dose PCV	Date	dd/mm/yyyy	Date of second dose of PCV	
brandpcv2		Dose 2 vaccine type of PCV	Code	0: No vaccine 1: PCV13 2: PCV10 3: PCV7 8: Other 9: Unknown	Type of PCV at second dose	
dosepcv3		Dose 3 PCV	Code	0: No 1. Yes 9: Unknown	Third dose of vaccination with a PCV	
datepcv3		Date vaccination with third dose PCV	Date	dd/mm/yyyy	Date of third dose of PCV	
brandpcv3		Dose 3 vaccine type of PCV	Code	0: No vaccine 1: PCV13 2: PCV10 3: PCV7 8: Other 9: Unknown	Type of PCV at third dose	
dosepcv4		Dose 4 PCV	Code	0: No 1: Yes 9: Unknown	Fourth dose of vaccination with a PCV	
datepcv4		Date vaccination with fourth dose PCV	Date	dd/mm/yyyy	Date of fourth dose of PCV	
brandpcv4		Dose 4 vaccine type of PCV	Code	0: No vaccine 1: PCV13 2: PCV10 3: PCV7 8: Other 9: Unknown	Type of PCV at fourth dose	
nbdoses		Number of doses	#		Number of doses of PCV provided	
doseppv		PPSV23 vaccination	Code	0: No 1: Yes 9: Unknown	Vaccination with PPSV23	
dateppv		Date vaccination with PPSV23	Date	dd/mm/yyyy	Date of vaccination with PPSV23	

Variable name	Site-specific variables	Variable label	Type	Values and coding	Definition	Comments
nbdosesppv		Number of doses with PPSV23	Numeric	#	Number of doses of PPSV23 provided	
underdis		Underlying diseases	Code	0: No 1: Yes 9: Unknown	Presence of at least one underlying disease which represents high risk groups for getting IPD	This variable can be collected as such or by specifying conditions below
underdistype		Underlying diseases by immune status	Code	0: No 1: Immunocompetent 2: Immunocompromised 9: Unknown	Underlying diseases by immune status	For definitions, please refer to table 3
cardiovasc		Cardiovascular diseases	Code	0: No 1: Yes 9: Unknown	Patient was diagnosed with chronic cardiac disease: see table 3 for International Classification of Diseases (ICD) codes	
respdis		Respiratory diseases	Code	0: No 1: Yes 9: Unknown	Patient was diagnosed with a chronic respiratory disease or asthma: see table 3 for ICD codes	
rendis		Renal diseases	Code	0: No 1: Yes 9: Unknown	Patient was diagnosed with a chronic renal disease: see table 3 for ICD codes	
immunodef		Immunodeficiency	Code	0: No 1: Yes 9: Unknown	Patient was diagnosed with an acquired or congenital immunodeficiency: see table 3 for ICD codes	
hiv		Human immunodeficiency virus (HIV) disease	Code	0: No 1: Yes 9: Unknown	See table 3	
leukemia		Lymphoid and myeloid leukaemia; multiple myeloma	Code	0: No 1: Yes 9: Unknown	See table 3	
lymphoma		Hodgkin lymphoma, Follicular lymphoma, Non-follicular lymphoma, MatureT/NK-cell lymphoma, Other and unspecified types of non-Hodgkin lymphoma	Code	0: No 1: Yes 9: Unknown	See table 3	
transplant		Solid organ transplant	Code	0: No 1: Yes 9: Unknown	See table 3	
malignancy		Generalized malignancy	Code	0: No 1: Yes 9: Unknown	See table 3	
immunomed		Immunosuppressing medication	Code	0: No 1: Yes 9: Unknown	See table 3	
diabetes		Diabetes mellitus	Code	0: No 1: Yes 9: Unknown	Patient diagnosed with diabetes mellitus type 1 or 2: see table 3 for ICD codes	
asplenia		Asplenia or splenectomised	Code	0: No 1: Yes 9: Unknown	Patient with asplenia or splenectomy in the clinical history: see table 3 for ICD codes	

Variable name	Site-specific variables	Variable label	Type	Values and coding	Definition	Comments
sicklemia		Sickle cell disease	Code	0:No 1: Yes 9: Unknown	Patient with sickle cell disease in the clinical history: see table 3 for ICD codes	
csfleak		Cerebrospinal fluid (CSF) leak	Code	0: No 1: Yes 9: Unknown	See table 3	
cochlear		Cochlear implant	Code	0: No 1: Yes 9: Unknown	See table 3	
alcoholism		Alcoholism	Code	0: No 1: Yes 9: Unknown	See table 3	
liverdis		Liver chronic disease, including cirrhosis	Code	0: No 1: Yes 9: Unknown	See table 3	
smoking		Cigarette smoking	Code	0: No 1: Yes 9: Unknown	See table 3	
institutionalised		Institutionalised persons for the elderly and disabled	Code	0: No 1: Yes 9: Unknown		
daycare		Day care attendance in children < 5 years	Code	0: No 1: Yes 9: Unknown		
otherdis		Other underlying disease	Text	string20	Specify other underlying conditions included in the recommendation for PCV/PPV vaccination.	
fluvac		Influenza vaccination	Code	0: No 1: Yes 9: Unknown	Influenza vaccination in the previous season	
Other variables						Please include all other variables collected in the site specific surveillance system

#: Numerical value.

Each surveillance site will include the name of the variables used at the site and add specific variables collected in addition to those from Table 2.

Table 3: Risk conditions for pneumococcal diseases and corresponding ICD-9 and 10-codes

Risk conditions	Description	ICD-9 Code	ICD-10 Code
Immunocompromised persons			
Congenital/acquired immunodeficiency		135, 279	D80-D89
Human immunodeficiency virus (HIV) disease		042	B20-B24
Chronic kidney disease		585	N18
Nephrotic syndrome		581	N04
Leukemia	Lymphoid and myeloid leukemia; multiple myeloma	203 – 206 202.9	C91-C92, C93, C96.9 C90
Lymphoma	Hodgkin lymphoma, follicular lymphoma, non-follicular lymphoma, matureT/NK-cell lymphoma, other and unspecified types of non-Hodgkin lymphoma	200 - 202	C81, C82, C83, C84, C85
Generalized malignancy (Metastatic solid tumors)	Malignant neoplasms of ill-defined, other secondary and unspecified sites	195-199	C76-C80
Immunosuppressing medication			*No specific ICD-10 codes*
Solid organ transplant	Transplanted organ and tissue status	V42	Z94
Functional or anatomical asplenia			
Thalassemia, sickle cell disorders, other haemoglobinopathies, diseases of the spleen (including anatomical asplenia)		282, 289.4-5	D56, D57, D58.2, D73
Immunocompetent persons			
Cerebrospinal fluid (CSF) leak		349.81, 388.61	G96.0
Cochlear implant		431	Z96.2
Chronic heart disease	Chronic ischemic heart disease, cardiomyopathy, heart failure	412 – 414, 425, 428	I25, I42, I50
Chronic lung disease	Emphysema, other chronic obstructive pulmonary disease (COPD), asthma	492, 493	J43, J44, J45
Diabetes mellitus	Type 1 diabetes, type 2 diabetes, malnutrition-related diabetes, other specified diabetes, unspecified diabetes	250	E10, E11, E12, E13, E14
Alcoholism	Mental and behavioural disorders due to alcohol use, degeneration of nervous system due to alcohol, alcoholic polyneuropathy, alcoholic myopathy, alcoholic cardiomyopathy, alcoholic gastritis, alcoholic liver disease, alcohol-induced acute pancreatitis, alcohol-induced chronic pancreatitis, maternal care for suspected damage to fetus from alcohol	305, 281, 357.5, 425.5, 535.30-31, 571, 655	F10, G31.2*, G62.1, G72.1*, I42.6, K29.2, K70, K85.2*, K86.0*, O35.4
Chronic liver disease, cirrhosis	Hepatic failure, not elsewhere specified (NES), chronic hepatitis, NES, fibrosis and cirrhosis, other liver diseases, liver malignancy	155, 470 – 474 572.4, 573.9	K72, K73, K74, K76.7, K76.9, C22
Cigarette smoking	Tobacco use, mental disorders due to tobacco	300.51 292.89	Z72.0*, F17.2, F17.3*
Institutionalised persons	Nursing homes and long-term facilities		No specific ICD-10 codes
Other ICD codes	Site-specific conditions included in high-risk groups for pneumococcal infection		

2.7 Selected bibliography

2.7.1 Publications

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2.7.2 Presentations and posters

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