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Generic protocol on Enhanced surveillance for Invasive Pneumococcal Disease at the EU/EEA level

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Contents

Glossary

Term or abbreviation	Definition
Ab	Antibiotic or antimicrobial, referring to the drugs used for antimicrobial susceptibility testing
Ag	Antigen, referring to the laboratory method to detect *S. pneumoniae* antigen
Antimicrobial susceptibility	In this context, used as the capacity of antibiotic/antimicrobial treatment to successfully inhibit the bacterial growing, according to clinical breakpoints of the standards used
Antimicrobial non-susceptibility	Intermediate susceptibility or resistance to an antimicrobial as defined by the standards used
CDC	Centres for Disease Control and Prevention, Atlanta, US
CLSI	Clinical and Laboratory Standards Institute, international standards that describe the methods and clinical breakpoints for antimicrobial susceptibility testing
Completeness of data	The proportion of all cases with no missing variable or information
Comprehensive surveillance system	A population-based surveillance system implying notifications from all possible reporting units
Coverage of the surveillance system	The proportion of the population effectively under surveillance compared to the total population of the country
CSF	Cerebrospinal fluid
DD	Disk diffusion, a method for antimicrobial susceptibility testing
EARS-net	European Antimicrobial Resistance Surveillance Network
EC	European Commission
ECDC	European Centre for Disease Prevention and Control, Stockholm, Sweden
EU/EEA	European Union/European Economic Area
EUCAST	European Committee on Antimicrobial Susceptibility Testing, European standards for antimicrobial susceptibility testing (http://www.srga.org/Eucastwt/eucastdefinitions.htm)
GP	General Practitioner
ICD	International Statistical Classification of Diseases and Related Health Problems, used as discharge diagnostic codes or for coding causes of death. The 9th or 10th revision are currently used in most countries
Impact of a vaccination programme	The measure of the effects of a specific vaccination programme in a specific population, which include indirect, total and overall effect against the target disease
IPD	Invasive pneumococcal disease, defined as isolation of *Streptococcus pneumoniae* or the detection of *Streptococcus pneumoniae* nucleic acid or antigen from a normally sterile fluid
ICU	Intensive Care Unit
LAB	Laboratory, here used to refer to the hospital laboratory

Term or abbreviation	Definition
MIC	Minimum inhibitory concentration, a method for antimicrobial susceptibility testing
MLST	Multilocus sequence typing
MS	Member States of the European Union or European Economic Area (30 countries)
NA	Not applicable (in the context of IPD ECDC case definition)
NIP	National Immunisation Plan
NRC	National Reference Centre
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
PPV23	23-valent pneumococcal polysaccharide vaccine
Sentinel surveillance system	A surveillance system that involves collecting data from a sample of reporting sites
Sensitivity (of the surveillance system)	The proportion of cases reported by the surveillance system out of the total number of cases meeting the same case definition in the entire population. Also called the degree of ascertainment or the exhaustiveness of the surveillance system
Surveillance site	Surveillance system (in a country or a region) that collaborate to the EU/EEA project.
Surveillance unit	Hospital/laboratory reporting cases to a surveillance site included in the EU/EEA project
TESSy	The European Surveillance System (http://ecdc.europa.eu/en/activities/surveillance/tessy/pages/tessy.aspx)
Sp	*Streptococcus pneumoniae*
Vaccination coverage	The proportion of the eligible population which is effectively vaccinated. Vaccine coverage should be defined by schedule (number of doses or complete schedule)
Vaccination registry	Electronic database where vaccination data are recorded. It usually includes patient unique identifier; age; sex; vaccine type; vaccination date; vaccine brand/ manufacturer; vaccine lot number
VE	Vaccine effectiveness, defined as the measure of the direct effect of vaccination against target disease when used under field conditions

1 Preface

Since its licensure in 2001, European Union/European Economic Area (EU/EEA) member states have progressively introduced pneumococcal conjugate vaccines (PCV) in their national immunisation plans since 2006. Monitoring the performance of these vaccines in field conditions represents a high priority. Therefore many member states set up or reinforced surveillance systems to collect data to assess the health benefits of PCV vaccination in reducing the burden of invasive pneumococcal diseases (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" aiming at setting up an active IPD surveillance in children under five years to monitor the impact of PCV vaccination programmes and to improve comparability of IPD data across Europe. In 2014, ECDC funded "SpIDnet Complementary activities" project to collect surveillance data in all age groups. The SpIDnet2 project aims at enhancing IPD surveillance in all age groups.

The current SpIDnet2 generic protocol, takes into account the lessons learnt during the pilot project and proposes a uniform approach for active IPD surveillance in children and enhanced surveillance in the 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, the surveillance objectives, case identification, data collection, monitoring indicators and feedback and supervision.

Please note that this protocol covers neither the specific studies to measure the impact of vaccination programmes and PCV vaccine effectiveness nor the evaluation of the surveillance systems. Specific protocols will be developed for these aspects under the SpIDnet2 project and will be made available along the project.

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

2 Background

Streptococcus pneumoniae is a Gram-positive diplococcus bacterium causing a wide spectrum of illness from otitis media to meningitis, representing a major public health problem worldwide. Invasive pneumococcal disease (IPD) is defined as the isolation of *S. pneumoniae* or the detection of *S. pneumoniae* nucleic acid or antigen from a normally sterile fluid and may present as meningitis, bacteraemic pneumonia, bacteraemia without focus, septic shock, and less frequently arthritis or peritonitis. *S. pneumoniae* is commonly found in nasopharyngeal carriage, particularly among young children, who form the main reservoir of pneumococci and their transmission to new hosts. Carriage thus plays an important role in the epidemiology of pneumococcus, as recent acquisition of *S. pneumoniae* is thought to precede episodes of pneumococcal disease.

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

PCV10 and PCV13 were approved on the basis of immunogenicity data. Currently 25 out of 31 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). The introduction of the PCV13 vaccination in the elderly is still under evaluation in many EU/European Economic Area (EEA) countries.

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.

Table 1: *Streptococcus 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 to provide a brief description of:*
  - Public health importance of IPD for the country/region (number of cases, incidence, mortality, case-fatality, etc)
  - Vaccination programme (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 IPD active surveillance at EU/EEA level and in the EU MS

IPD is a severe and frequent disease. Now that PCV vaccines 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; to compare the effectiveness of different vaccination schedules; to identify risk factors for vaccine failure; and to collect evidence of serotype replacement following the introduction of the vaccines.

According to the EC/2119/98 decision, IPD is included in the priority list of diseases under surveillance at EU level. EU surveillance of IPD is important to provide comparable data on IPD at EU level, measure the effectiveness and impact of PCV 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 to compare the effectiveness and impact of different vaccine policies (schedules / vaccines) as individual countries lack the power for responding to these research questions. This will allow the ECDC to produce guidance for PCV policy 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;
- allowing pooling of some data for meaningful results at the EU level.

► *Each surveillance site to provide additional rationale for the active surveillance in the specific context.*

2.3 Objectives

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 conjugate vaccines;
- Evaluate the impact of pneumococcal conjugate vaccines in terms of the disease burden of vaccine and non-vaccine strains;
- Monitor antimicrobial non-susceptibility in pneumococcal isolates.

► *Each surveillance site to adapt the above objectives to the IPD active surveillance in the country/region.*

2.4 Methods

2.4.1 Population under surveillance

The study population will consist of persons living in the catchment area of the data source used to identify cases (i.e. hospitals´, laboratories' catchment areas). All age groups will be included to allow the assessment of the indirect effect of PCV vaccines in the age groups not targeted for vaccination.

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

Each site will assess and describe where the population under surveillance seek healthcare services to ensure that all laboratories and hospitals notifying the cases are contacted to detect any missing case.

► *Each surveillance site to state the population under surveillance. The population under surveillance will include all ages.*

2.4.2 Type of surveillance system

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

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

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

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

► *Each surveillance site to briefly describe the existing surveillance system and the changes necessary 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 to provide the estimated sensitivity of the current surveillance system and its coverage.*

2.4.3 Selection of surveillance units

Minimum criteria for surveillance units (hospital/laboratory) selection:

- Known denominator 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
- Accessibility of patients with IPD
- Willingness to participate in the surveillance system

Description of the surveillance units included in the surveillance system.

► *Each surveillance site to briefly describe how they can assure this minimum criteria for surveillance units selection.*

2.4.4 Outcomes

- **IPD Definition**

The EC 2012 case definition should be used to report IPD cases[1] :

PNEUMOCOCCAL INVASIVE DISEASE(S) (*Streptococcus pneumoniae*)

Clinical criteria

Not relevant for surveillance purposes

Laboratory criteria

At least one of the following three:

- Isolation of S. pneumoniae from a normally sterile site
- Detection of S. pneumoniae nucleic acid from a normally sterile site
- 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

Any person meeting the laboratory criteria

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

- **Case identification**

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

- Laboratory results: regular checks of laboratory results logs and retrieve of individual data from medical history of the patient and vaccination data from the available sources (i.e. link with the vaccination registries or GP records, etc.)
- Admission for above-mentioned clinical syndromes: regular checks of admission/emergency departments logs and follow up of the patient for clinical/laboratory diagnosis
- Regular reminders will be sent to laboratories and hospitals to report all diagnosed cases.

► *Each surveillance site to state how the case identification is done and frequency of contact with the data sources. In any case, the individual data collection will require a link between the clinical data, laboratory data and vaccination data.*

[1] European Commission, COMMISSION IMPLEMENTING DECISION of 8 August 2012 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 (notified under document C(2012) 5538) http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2012:262:0001:0057:EN:PDF

- **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 could be done at the hospital laboratory or at the 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:
    - penicillin, macrolide, cephalosporin *(other classes of antimicrobials if tested)*
    - methods used: MIC, DD, etest
    - clinical breakpoints used (standards: ideally EUCAST).
    -

► *Each surveillance site to specify at what level antimicrobial susceptibility testing is performed, the antimicrobials tested and methods used (their sensitivity and specificity if available). At the European level, MIC by antimicrobial will be reported (see table 2 at the end of the document). If other methods used in the country, the surveillance site should state the specific method, the clinical breakpoints for each antimicrobial tested and the reference/standard used.*

- **Outcome classification**

The main outcome of this surveillance is IPD, as defined according to above case definition. This outcome will be further classified by:

1. serotypes
2. clinical manifestations
3. antimicrobial susceptibility
4. severity

1. Classification of IPD by serotype

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

- All type
- Vaccine serotypes: according to the vaccine used, the 7, 10, 13 serotypes targeted by the respective 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 will not include serotypes for which cross-protection was not demonstrated, e.g. 19A and 6C will not be included in the evaluation of PCV7)
- PPV serotypes: the 23 serotypes included in the PPV vaccine
- Non-vaccine serotypes: all the other serotypes according to the vaccine used (i.e. non vaccine and non vaccine-related)
- Serotype specific.

2. 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
- Other: arthritis, peritonitis, pericarditis, others [to be specified]

3. Classification of IPD by antimicrobial susceptibility

MIC by antimicrobial will be reported at European level from each surveillance site (see above). Classification according to EUCAST will be used for comparisons among surveillance sites.

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

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/ GP records
- Population data source

► *Each surveillance site to describe 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 to provide the population data. In case the hospital catchment area population is used as denominator, the methods of determining the population covered by the participating hospital should also be described as well as its potential limitations.*

- **Data collection**

Individual data collection should be assured for all IPD cases included in the surveillance system. The minimum set of data that will be 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 at 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, Erythromycin, Cephalosporin
- Vaccination data: type of vaccine (PCV7/10/13 and/or PPV23), number of doses, dates of administration (each dose for PCV, the last dose for PPV23)
- Underlying conditions (according to the country recommendations for vaccination of risk groups)
- Current season influenza vaccination.

The minimum set of data that will be collected for each IPD case in the age groups 5-64 years includes:

- Demographic data: age in years, gender, residence in the hospital/laboratory catchment area, reporting site
- Hospitalisation data: clinical manifestation, outcome (alive, intra-hospital death or death at 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, Erythromycin, Cephalosporin
- Vaccination data (if available): type of vaccine (PCV7/10/13 and/or PPV23), number of doses, dates of administration (each dose for PCV, the last dose for PPV23)
- Underlying conditions (according to the country recommendations for vaccination of risk groups)
- Influenza vaccination.

► *Each surveillance site to state if the minimum set of data for individual data collection could be collected and fill in the table 2 (end of the document).*

Additional data collection is desirable but not compulsory:

- Vulnerable population groups (to be specified)
- Group care attendance
- Influenza positive test 10 days before admission
- Other risk factors, specify

► *Each surveillance site to specify the additional variables collected (if any) and include them in the table 2 (presented at the end of the document).*

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

- Number of hospitalisations of any cause (for the age groups under surveillance)
- Number of deaths of any cause (for the age groups under surveillance)
- Number of cultures performed in the age groups included (mainly blood cultures)
- Changes in clinical practices over time
- Changes in laboratory methods over time
- Changes in reporting/surveillance system over time (e.g. age groups and clinical syndromes covered)

► *Each surveillance site to list the additional information to be collected.*

- **Data checking and transmission**

Data will be checked to find outliers, implausible or missing information at country/regional level. As much as possible, data should be completed or validated against the data source.
The transfer of data from the surveillance units to central level will be done according to site-specific legislation regarding medical data protection. Secured data transmission from the site level to SpIDnet2 coordination will be organised using EpiFiles (a platform for secure data transfer developed by EpiConcept).

► *Each surveillance site to describe data checking and data management.*

- **Analysis plan**

Data description and the calculation of the surveillance indicators should be included in an analysis plan. This should include a brief description of the 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, IPD serotypes (all types, vaccine types, vaccine related types, non-vaccine types, serotype specific), IPD clinical presentations, IPD susceptibility to a specific antibiotic/antimicrobial. These incidences will be subsequently presented by age, sex, 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 (empyema, septic shock, ICU admitted cases): described in case reports
- Number of clusters of severe cases and specific serotypes
- Indicators based on vaccine status: number/description of vaccine failures

► *Each surveillance site to develop 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/lab forms
    - Web-based forms for data transmission

► *Each surveillance site to describe the responsibilities by level and the frequency of reporting. Whenever possible, a TESSy compatible format should be used.*

2.4.7 Monitoring and evaluation (depends on the type of the system)

The system will be 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
- Percentage of cases with isolates collected and sent to the reference laboratory for serotyping, antimicrobial susceptibility testing

► *Each surveillance site to establish a minimum set of indicators that will be used for ongoing monitoring the performance of enhanced surveillance.*

Evaluation of the surveillance system performance should be done regularly according to a specific evaluation protocol developed in accordance with published general guidelines. The following attributes will be 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
  - Other methods (e.g. regression methods)
- Completeness
  - Percentage of missing by each variable
  - Percentage of missing priority variables (age, clinical manifestations, vaccination variables)

► *Each surveillance site to evaluate its system using a protocol for active IPD surveillance system evaluation prepared in advance.*

2.4.8 Feedback and supervision

Each surveillance site will establish a mechanism for regular feedback to the surveillance units. An annual report will be prepared and presented during annual meetings at EU level to exchange results and lessons learnt.

The co-ordination team will organise periodic teleconferences and/or technical workshops to facilitate the decision making and the exchange among the partners.

► *Each surveillance site to briefly describe the feedback to the surveillance units and dissemination of the site specific results.*

2.5 Ethical considerations

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

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

► *Each surveillance site to obtain the ethical approval and to assure the confidentiality according to the specific legislation.*

2.6 Studies on vaccination impact and vaccine effectiveness

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

► *Generic protocols for vaccination programme impact and PCV/PPV 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 the case is notified the first time to the site level	
residence		Residence in the catchment area	Numeric	0-no 1-yes 9-unknown	Residence in the catchment area of the surveillance unit reporting to the system	
ageyears		Age of the case in years	Numeric	###	Age of patient in years as reported at the 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 the site level in years at time of hospital admission for children<2years	
sex		Gender	Code	0-female 1-male 9-unknown	Gender of the reported case	
dateadm		Date of the admission in the hospital	Date	dd/mm/yyyy	Date when the case was admitted to the hospital	
datedis		Date of the discharge from the hospital	Date	dd/mm/yyyy	Date when the case was discharged from the 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 the 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-pneumonia* *3-empyema* *4-bacteremia* *5-septic shock* *8-other, specify* *9-not known*	*Clinical manifestation of the 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	A case presenting with lab confirmed pneumococcal meningitis	
pneumonia		Bacteremic pneumococcal pneumonia	Code	0-no 1-yes 9-unknown	A case presenting with lab confirmed pneumococcal pneumonia	
empyema		Pneumococcal empyema	Code	0-no 1-yes 9-unknown	A case presenting with lab confirmed pneumococcal empyema	
bacteremia		Bacteremia without known focus of infection	Code	0-no 1-yes 9-unknown	A 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	A case presenting with clinician diagnosed septic shock regardless focus of infection	
arthritis		Pneumococcal Arthritis	Code	0-no 1-yes 9-unknown	A case presenting with lab confirmed pneumococcal arthritis	
otherclin		Other clinical entities	Text	String20	Other clinical entities of the IPD case	Please specify other clinical entity for the IPD cases

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
icuadm		Admission in the ICU	Code	0-no 1-yes 9-unknown	A lab confirmed case who needed admission in the ICU during the pneumococcal episode	
datediag		Date of diagnosis	Date	dd/mm/yyyy	Date when the diagnosis was made, should be the same with the identification/confirmation of the case	
fluid		*Type of fluid tested positive*	*Multiple choice*	*0-none* *1-LCR* *2-Blood* *3-Pleural* *4-Articular* *8-Other* *9-Not known*	*Fluid tested for the 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 (otherfluid) specifies other positive sterile site fluids not listed*
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 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-Not known*	*Test performed for identification of an IPD case*	*This multiple choice variable can be collected as such or separately as variables 30-32*

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
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-Not known*	*Test performed for serotyping of Streptococcus 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	

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
seroother		Other methods used for serotyping	Text	string20		
micpeni		MIC to penicillin	Numeric	##.###	MIC to penicillin in µg/ml	If not tested, the variable will be left blank
mic*[macrolid]*		MIC to macrolide	Numeric	##.##	MIC to macrolide in µg/ml [please specify the antimicrobial used: Erythromycin, Azithromycin, Clarithromycin, etc]	If not tested, the variable will be left blank
mic*[cepha]*		MIC to cephalosporin	Numeric	##.##	MIC to cephalosporin in µg/ml [please specify the antimicrobial used: Cefotaxime, Ceftriaxone, etc]	If not tested, the variable will be left blank
mic*[antimicrobial]*		MIC to antimicrobial	Numeric	##.##	MIC to different other antimicrobial tested	Please specify the 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 PCV	
brandpcv1		Dose 1 vaccine brand PCV	Code	0-no vacc 1-PCV13 2-PCV10 3-PCV7 8-other 9-unknown	Brand of first dose PCV	
dosepcv2		Dose 2 PCV	Code	0-no 1-yes 9-unknown	Second dose of vaccination with a PCV	

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
datepcv2		Date vaccination with second dose PCV	date	dd/mm/yyyy	Date of second dose PCV	
brandpcv2		Dose 2 vaccine brand PCV	Code	0-no vacc 1-PCV13 2-PCV10 3-PCV7 8-other 9-unknown	Brand of second dose PCV	
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 PCV	
brandpcv3		Dose 3 vaccine brand PCV	Code	0-no vacc 1-PCV13 2-PCV10 3-PCV7 8-other 9-unknown	Brand of third dose PCV	
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 PCV	
brandpcv4		Dose 4 vaccine brand PCV	Code	0-no vacc 1-PCV13 2-PCV10 3-PCV7 8-other 9-unknown	Brand of fourth dose PCV	

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
nbdoses		Number of doses	#		Number of doses PCV provided	
doseppv		PPV23 vaccination	Code	0-no 1-yes 9-unknown	Vaccination with PPV23	
dateppv		Date vaccination with PPV23	date	dd/mm/yyyy	Date of vaccination with PPV23	
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 a chronic cardiac disease: see table 3 for 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	

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
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 transplat	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 was diagnosed with diabetes mellitus type 1 or 2: see table 3 for ICD codes	

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
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	
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	
cohlear		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		Institutionalized persons for the elderly and disabled	Code	0-no 1-yes 9-unknown		
daycare		Day care attendance in children < 5y	Code	0-no 1-yes 9-unknown		

Variable name	Site specific variables	Variable label	Type	Values and coding	Definition	Comments
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*

► *Each surveillance site will include the name of the variables used in the site and add specific variables collected in addition to those from the table 2*

Table 3: Risk conditions for pneumococcal diseases and the 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 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 behavioral disorders due to use of alcohol, 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, NES, Chronic hepatitis, NES, Fibrosis and cirrhosis, Other diseases of liver, Malignancy of liver	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*
Institutionalized persons	Nursing homes and long-term facilities		*No specific ICD-10 codes*
Other ICD codes	**Site specific conditions included in the high-risk groups for pneumococcal infection**		