Enhanced surveillance for Invasive Pneumococcal Disease in Norway

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The revised SpIDnet Norway protocol is based on the generic SpIDnet II protocol and amended to include extended analyses on Norwegian data in Norway (SpIDnet Norway). The SpIDnet II protocol has been approved and will last until Oct 2019. We apply for changes to the generic protocol for SpIDnet Norway.

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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 have set up or reinforced surveillance systems to collect data to assess the health benefits of PCV vaccination in reducing the burden of invasive pneumococcal disease (IPD) in all age groups up to 64 years of age. The age group 65 years and older are covered by another complementary study. The I-MOVE+ study

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". The study aimed 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) that aimed at enhancing IPD surveillance in all age groups under 65 years.

The SpIDnet Norway protocol has been approved by REK previously. However, we have updated the protocol and apply for additional changes; extended end date for the study and approval to link MSIS with data from The National Registry for date of death. The generic SpIDnet2 protocol encourages partner countries to use the generic protocol to develop site-specific protocols with the ultimate goal to strengthen the IPD surveillance systems and improve the comparability of indicators in the EU/EEA. SpIDnet Norway aims to determine the impact of the pneumococcal conjugate vaccination programme on the invasive pneumococcal disease (IPD) burden among different medical risk groups. In SpIDnet Norway we cover all IPD cases reported to MSIs in 2009-2017. Furthermore, SpIDnet Norway aims to determine whether the population falling ill and the clinical presentation of IPD has changed during the study period.

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 - PPV23) and pneumococcal conjugate vaccines (PCVs). PPV23 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. Currently, PCV13 is licensed for 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 for the prevention of invasive disease and pneumonia caused by *S. 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 EU 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).

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

PPV23	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F, 33F

Country specific background

In Norway, PCV7 was introduced in the childhood immunisation programme in July 2006. Immunisation is provided free of charge at healthy baby clinics in a 2+1 schedule with doses administered at 3, 5 and 12 months of age. In April 2011, PCV7 was replaced with PCV13. Immunisations administered in the childhood immunisation programme are mandatorily recorded in the national immunisation registry (SYSVAK), and the vaccine uptake for the complete schedule is approximately 92%.

PPV23 has been available in Norway since 1983. In 1996 a recommendation for use of PPV23 for risk groups and elderly (age ≥ 65 years) was published by the Norwegian Institute of Public Health (NIPH) [1]. The recommendations were substantially revised in 2013 [2]. The revision included a new description of risk groups, recommendation for revaccination, recommendation for when to perform antibody measurement, and recommendation to use PCV13 for immunisation of the groups with the highest risk for IPD. Pneumococcal vaccination to elderly and risk groups are not reimbursed as a rule, although individuals with certain immunodeficiency conditions can have the costs reimbursed. Immunisations to elderly and risk groups are administered by medical specialists, GPs or at municipal health clinics. Immunisations can be voluntarily recorded in SYSVAK, but presumably the majority of these immunisations are not entered in the database. The uptake of PPV23 in risk groups and the elderly has been estimated by sales statistics. In the past decade, approximately 27,000 doses have been distributed annually, and an estimated 15-25% of risk groups are immunized.

Surveillance of IPD is performed by NIPH, using the European case definition. Cases are notified by laboratories and clinicians to the Surveillance System for Communicable Diseases (MSIS). Notification from the clinician is missing for up to 25% of notified cases. Isolates of *S. pneumoniae* are forwarded to the National Reference Laboratory (NRL) at NIPH for serotyping and antimicrobial susceptibility testing. Isolates are received from more than 95% of notified cases. Data from MSIS, SYSVAK, National registry and NRL can be linked by the unique 11-digit personal identification number.

The population-wide impact of the introduction of PCV7 and the subsequent switch to PCV13 in the childhood immunization program in Norway has been described in cohort studies focusing on the direct and indirect effect, and on antimicrobial resistance [3-6]. The impact of pneumococcal

carriage has been assessed in cross-sectional studies [7-9]. One study has investigated the impact of the indirect effect on iatrogenically-immunosuppressed individuals [10], but studies on the impact in other medical risk groups are lacking.

Rationale for IPD active surveillance

IPD is a severe and frequent disease. Now that PCV vaccines have been introduced, post-licensure surveillance is crucial to assess the impact of these vaccines on the epidemiology of pneumococcal disease; to identify risk factors for vaccine failure; and to collect evidence of serotype replacement following the introduction of the vaccines. It also questioned whether characteristics of the IPD population changes in terms of comorbidities and clinical presentation following the change in the serotype distribution.

In Norway, an enhanced surveillance system will allow the study of:

- The various vaccination effects: direct, indirect, overall, total effect
- Replacement of circulating vaccine strains by non-vaccine strains
- Changes in clinical profile (overall and by serotype) and in disease severity
- Changes in the prevalence of underlying medical conditions among IPD cases

Objectives

- To estimate the incidence rate and mortality due to IPD in children and adults;
- To describe the changes in the serotype distribution and possible changes in the clinical characteristics of the IPD cases has occurred during the seven years since the switch from PCV7 to PCV13.

And by:

- Serotype category (all serotypes, vaccine serotypes (PCV7, PCV10 non7, PCV13non10, PPV23nonPCV13), vaccine-related and non-vaccine serotypes;

  (See Table 1 – Serotypes contained in different pneumococcal vaccines)

- Clinical manifestation;
- Comorbidity risk-groups

Methods

Study population

The study population will consist of inhabitants in Norway aged < 65 years. Yearly updates on the population denominator available from Statistics Norway (www.ssb.no) will be used. Furthermore, aggregated data from the Norwegian Patient Registry (NPR) about the size of the different risk groups will be applied for.

Case identification

The cases will be individuals younger than 65 years who are notified with invasive pneumococcal disease to MSIS in the years 2009-2017. In Norway, cases of IPD are notified to the Norwegian Surveillance System for Communicable Diseases (MSIS). This is a comprehensive, mandatory, laboratory-based surveillance system, where IPD cases are notified both by the laboratory and the clinician. The passive laboratory-based surveillance in Norway has been on-going for decades and is well-established. The sensitivity of this system is believed to be very high.

In NPR hospital discharge diagnoses (ICD-10) are recorded. As part of the study, we will link information from NPR with information from MSIS to improve and complete clinical information provided by the notifying physicians and to define medical risk groups. Furthermore, we will link information on date of death from the National Registry and vaccine history from the National Immunization Register (SYSVAK).

Outcomes

IPD Definition

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

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

The case definition of IPD in MSIS complies with the European Commission 2008 case definition for confirmed cases of IPD. A strict definition of vaccine serotypes has been used in Norway, including the serotypes targeted by the respective vaccines but not cross-reacting serotypes.

Identification of *S. pneumoniae* nucleic acid in a normally sterile material is included in the case definition in Norway. However, the gene targets or PCR methods used by diagnostic laboratories in Norway have not been standardised and described in detail. For culture-negative specimens, confirmative analyses will be attempted at NIPH, including sequencing of the capsular gene *wzh*.

Case identification

The surveillance of IPD in Norway is laboratory based. A copy of the report form is automatically generated from electronic laboratory logs in diagnostic laboratories when *S. pneumoniae* is identified in a normally sterile site material. This copy is sent to MSIS.

Isolates are forwarded to the national reference laboratory. Results from the reference laboratory are submitted electronically to MSIS.

Outcome classification

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

1. serotypes
2. clinical manifestations and comorbidity risk groups
3. 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: PCV7-serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) and PCV13-serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, 19A)
- PPV serotypes: the 23 serotypes included in the PPV vaccine
- Non-vaccine serotypes: all the other serotypes
- 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
  - Arthritis

- Bacteraemia without known focus of infection
- Other: Empyema, peritonitis, pericarditis, other clinical pictures

3. Classification of IPD by outcome

30-day survival

Data

Data sources

The following data sources will be used in this study (see also attachment 2):

- Infectious diseases surveillance system (MSIS)
- Hospital discharge database (NPR)
- Immunisation registry (SYSVAK)
- National registry
- Data on vaccine history gathered during SpIDnet 2

Denominators

- Census data by age groups
- Aggregated data of NPR on the size of the risk groups

Data collection

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

- Demographic data: age in months/years, gender
- Hospitalisation data: admission and discharge dates, clinical manifestation (list – see attachment 1), outcome (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
- Vaccination data: type of vaccine (PCV7/13 and/or PPV23), number of doses, dates of administration (each dose for PCV, the last dose for PPV23)
- Underlying conditions; list – see attachment 1

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
- Hospitalisation data: clinical manifestation (list – see attachment 1), outcome (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
- Vaccination data (if available): type of vaccine (PCV7/13 and/or PPV23), number of doses, dates of administration (each dose for PCV, the last dose for PPV23).
- Underlying conditions - see attachment 1

Analysis plan

IPD cases will be described by time period, age group, serotype categories, clinical presentation, co-morbidities and outcome.

The (disease-, age group- and vaccine-specific) incidences of IPD will be calculated by dividing the number of cases by the size of the subgroups in the Norwegian population and will be presented per 100,000 inhabitants.

We will categorise cases into medical risk groups using ICD-10 codes. We include ICD-10 codes for co-morbidity only if registered within the last two years before the date of diagnosis. In Norway, hospital discharge data are only available on individual level for registry linkage since 2008. For IPD-cases reported in 2009, we included all available data from January 2008 up to the date of testing. Those with no registered medical risk condition in the two years prior to the sampling date will be assumed not to have a medical risk condition. We include ICD-10 codes for clinical presentation only if registered 30 days before or after the date of the IPD diagnosis. Relevant ICD-10 codes are presented in full in attachment 1, table 1 a-c.

The impact is computed as:

- the reduction in the number of cases in the post-PCV13 period compared with the reference period, expressed as absolute numbers or percentage change in the number of cases;
- the reduction in the cumulative incidence or rate in the post-PCV13 period compared with the reference period, expressed as rate/risk difference;
- the relative reduction in the incidence proportion or rate during the post-PCV13 period, expressed as the annual change in incidence rate ratio with the corresponding 95% CI.

- A change in the serotype distribution and vaccine-type / non-vaccine type IPD incidence
- A change in the incidence and proportion of the different clinical presentations (meningitis, invasive pneumonia, bacteraemia without focus, pyogenic arthritis and others) and fatality
- A change in the prevalence of comorbidities in the population falling ill

The impact will be analysed separately for the different comorbidity groups.

On the basis of estimates of pneumococcal vaccination uptake among individuals < 65 years of age, we can describe:

- an overall effect: the measure of impact in the age group ≤65 years of age in a population where a proportion of people in this age group and the paediatric age group is vaccinated compared with the same population before the introduction of the vaccination programmes;
- indirect effect: the measure of impact of infant conjugate vaccination programme among persons < 5 years and 5-64 years of age compared to the same population before the introduction of the infant vaccination programme;

Ethical considerations

Measures to ensure confidentiality will be implemented according to the current legislations.

Electronic databases will be transferred using secure channels at the superior levels.

The legal framework for public health surveillance in Norway is regulated by the Law on communicable diseases (Smittevernloven) and the MSIS regulation.

The study has received ethical clearance from the Committee of Research Ethics in Norway. We will apply for a change in the obtained ethical clearance for SpIDnet Norway for the following amendments:

- Extension of study end date from Oct 19.2019 to Dec 31 2021 for SPIDnet Norway. This will only include data management and data analysis in Norway. The European SpIDnet II project will be finalized Oct 19. 2019 as previously planned

- Linkage with date of death from the National Registry

References

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10. Steens, A., et al., *Indirect effects of pneumococcal childhood vaccination in individuals treated with immunosuppressants in ambulatory care: a case-cohort study.* Clinical Infectious Diseases, 2018.

Attachments

Attachment 1. Invasive pneumococcal disease (IPD) – Linkage of NPR data for research.

ICD-10 codes to identify clinical manifestation and underlying medical risk conditions for individuals notified to MSIS with IPD in 2009-2017

We ask for ICD-10 codes for individuals notified to MSIS with IPD from 2009-2017 and who has been registered with ICD-10 codes in NPR that are among the codes listed in Table 1a-c and 2. A list with the 11 digit personal identification number and the date of diagnosis from MSIS will be submitted from MSIS to NPR.

Table 1a-c: The extraction of data in Table 1a-c can be limited to ICD-10 codes registered in NPR 30 days prior to and until 30 days after the date of IPD diagnosis in MSIS

Tabell 2: The extraction of data in Table 2 can be limited to ICD-10 codes registered in NPR two years (24 months) prior to the date of IPD diagnosis in MSIS. For individuals notified to MSIS with IPD in 2009, the observation time will be less than two full years (case based data for linkage is only available in NPR from 2008).

Table 1a: Invasive pneumococcal disease (clinical)

ICD-10 Code	Diagnosis in Text
A40*, A41*	Streptococcal sepsis; other sepsis
A49*	Bacterial infection of unspecified site
G00*	Bacterial meningitis, not elsewhere classified
M00*	Pyogenic arthritis
I30.1	Infective pericarditis
B95.3	*S. pneumoniae* as the cause of diseases classified to other chapters
B95.5	Unspecified *Streptococcus* as the cause of diseases classified to other chapters

* including the 3 digits (e.g. A40.3).

Table 1b: Pneumococcal pneumonia

ICD-10 Code	Diagnosis in Text
J13	Pneumonia due to *S. pneumoniae*

Table 1c: All cause pneumonia

ICD-10 Code	Diagnosis in Text
J13	Bacterial pneumonia (specified)
J15.9	Bacterial pneumonia, unspecified
J18.0-18.2	Bronchopneumonia, unspecified; lobar pneumonia, unspecified; , hypostatic pneumonia, unspecified
J18.8-J18.9	Other pneumonia, organism unspecified; pneumonia, unspecified
J86*	Pyothorax (Incl. Empyema)

* including the 3 digits (e.g. A40.3).

Table 2: Underlying medical risk factors for invasive pneumococcal disease (comorbidities)

Risk conditions	Description	ICD-10 Code
Congenital/acquired immunodeficiency		D80-D89
Human immunodeficiency virus (HIV) disease		B20-B24
Chronic kidney disease		N18
Nephrotic syndrome		N04
Leukemia	Lymphoid and myeloid leukaemia; multiple myeloma	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	C81, C82, C83, C84, C85
Generalized malignancy (Metastatic solid tumors)	Malignant neoplasms of ill-defined, other secondary and unspecified sites	C76-C80
Other malignancies		C00-C75
Solid Organ Transplant	Transplanted organ and tissue status	Z94
Thalassemia, Sickle cell disorders, Other haemoglobinopathies,		D56, D57, D58.2, D73

Diseases of the spleen (including anatomical asplenia)		
Cerebrospinal fluid (CSF) leak		G96.0
Cochlear implant		Z96.2
Chronic heart disease	Chronic ischemic heart disease, Cardiomyopathy, Heart failure	I25, I42, I50
Chronic lung disease	Emphysema, Other COPD, Asthma	J43, J44, J45
Diabetes mellitus	Type 1 Diabetes, Type 2 Diabetes, Malnutrition-related diabetes, Other specified diabetes, Unspecified diabetes	E10, E11, E12, E13, E14
Alcoholism	Mental and behavioural 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,	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	K72, K73, K74, K76, K76.9, C22

Attachment 2 Overview of the included data and its data sources

Variable	Kind of data	Data source	Years included
Index date / year	Notification data, date of sampling of material for pneumococcal identification	MSIS	2009-2017

Demographic information of the IPD cases	Notification data	MSIS	2009-2017
Serotype	Laboratory data	Reference laboratory NIPH	2009-2017
Underlying medical risk conditions	Hospital discharge data, ICD-10 codes	NPR	2008-2017
Vaccination history	Registry data – registration of vaccinations in the childhood vaccination programme	SYSVAK	2008-2017
	Registry data (fully, partly or not vaccinated	MSIS	2009-2017
	Physicians – data from the generic I-MOVE+ study	Letter/phone calls	2015-2017
Clinical symptoms	Notification data (reported clinical symptoms or kind of specimen)	MSIS	2009-2017
	Hospital discharge data, ICD-10 codes	NPR	2009-2017
Outcome (30 days survival)	Registry data, date of death	National Registry	2009-2017

Attachment 3: MSIS variables included in the analysis

Variable from MSIS	Use in this study
Age in years	
Sex	
Date of testing	Used as index date
Material used for testing	Used in the definition of clinical picture
Method used for testing	To determine the proportion that has been cultured
Pneumococcal serotype	
Clinical picture	Combined with the ICD-10 codes (supplementary table 2) to define clinical picture
Outcome (healthy, still ill, died)	Intra hospital death
Vaccine history	Fully / partially / un-vaccinated

Attachment 4: data gathered under the generic SpIDnet II project that will be included for SpIDnet Norway

Date of each PPV23 dose	Used to define yes/no vaccinated with PPV23 the last 10 years, up to 14 days before the index date; used to define “vaccine failure”. 2015-2017
Date of each PCV dose Kind of PCV (PCV7/PCV10/PCV13)	Used to define yes/no vaccinated with PCV up to 14 days before the index date; used to define “vaccine failure”. 2015-2017