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# European enhanced surveillance of invasive pneumococcal disease in 2010: Data from 26 European countries in the post-heptavalent conjugate vaccine era

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ABSTRACT

*Streptococcus pneumoniae* is a leading cause of severe infectious diseases worldwide. This paper presents the results from the first European invasive pneumococcal disease (IPD) enhanced surveillance where additional and valuable data were reported and analysed. Following its authorisation in Europe in 2001 for use in children aged between two months and five years, the heptavalent pneumococcal conjugate vaccine (PCV7) was progressively introduced in the European Union (EU)/European Economic Area (EEA) countries, albeit with different schemes and policies. In mid-2010 European countries started to switch to a higher valency vaccine (PCV10/PCV13), still without a significant impact by the time of this surveillance. Therefore, this surveillance provides an overview of baseline data from the transition period between the introduction of PCV7 and the implementation of PCV10/PCV13.

In 2010, 26 EU/EEA countries reported 21 565 cases of IPD to The European Surveillance System (TESSy) applying the EU 2008 case definition. Serotype was determined in 9 946/21 565 (46.1%) cases. The most common serotypes were 19A, 1, 7F, 3, 14, 22F, 8, 4, 12F and 19F, accounting for 5 949/9 946 (59.8%) of the serotyped isolates. Data on antimicrobial susceptibility testing (AST) in the form of minimum inhibitory concentrations (MIC) were submitted for penicillin 5 384/21 565 (25.0%), erythromycin 4 031/21 565 (18.7%) and cefotaxime 5 252/21 565 (24.4%). Non-susceptibility to erythromycin was highest at 17.6% followed by penicillin at 8.9%.

PCV7 serotype coverage among children <5 years in Europe, was 19.2%; for the same age group, the serotype coverage for PCV10 and PCV13 were 46.1% and 73.1%, respectively.

In the era of pneumococcal conjugate vaccines, the monitoring of changing trends in antimicrobial resistance and serotype distribution are essential in assessing the impact of vaccines and antibiotic use control programmes across European countries.



## 1. Introduction

*Streptococcus pneumoniae* infections are a major public health threat and cause high morbidity and mortality worldwide especially among children under 5 years and amongst the elderly [1,2]. It is the leading cause of bloodstream infection (BSI), meningitis, upper respiratory tract infections and otitis media [2]. It is the most frequent causative agent of community acquired pneumonia (CAP), resulting in high case-fatality ratios (CFR) [3].

*S. pneumoniae* is surrounded by a polysaccharide capsule that protects the bacterium from phagocitosis and intracellular killing and therefore is an important virulence factor [4]. Based on differences in the capsule and recognition by different specific antibodies, 93 serotypes with different invasiveness and mortality potential have been identified [5,6].

Different medical practices [7] and country differences in reporting and surveillance systems of IPD may well explain the large variation of IPD notification rates from 0.4 to 20 cases per 100 000 population per year [8] between European countries that have been reported previously [9].

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[1] See Appendix A.

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The introduction of PCV7 targeting children less than 5 years of age has proven highly successful in reducing invasive and mucosal disease caused by the vaccine serotypes and in decreasing antibiotic resistance associated with vaccine serotypes [10]. An additional benefit of the PCV is the decrease in nasopharyngeal carriage of vaccine serotypes that confers a degree of herd immunity in the population [11]. Nevertheless, this success may be partially offset by an increase in non-vaccine serotypes [12,13]. Furthermore, antimicrobial resistance has emerged and spreads in these non-vaccine serotypes [14].

In response, new pneumococcal conjugate vaccines (PCV10, PCV13) that include additional serotypes have been licensed and EU/EEA countries started introducing them gradually since 2010. The impact of pneumococcal conjugated vaccines and the burden of pneumococcal infections should be closely monitored and better quality data should be analysed in order to assess vaccine strategies throughout Europe. Moreover, it may prove useful to indicate where new expanded valency vaccines should be developed in response to serotype replacement observed after the implementation of PCV7 and as expected for PCV13 [15]. Here we report on the results from an analysis of data from the first enhanced surveillance programme for IPD set up by the European Centre for Disease Prevention and Control (ECDC) in collaboration with the EU/EEA Member States in order to assess the burden of IPD and the prevalence of the different serotypes across Europe.

## 2. Materials and methods

### 2.1. Scope

Twenty-six European countries participated in the surveillance for IPD from 1st January to 31st December 2010 inclusive, namely Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, The Netherlands, Norway, Poland, Romania, Slovakia, Slovenia, Spain, Sweden, and the United Kingdom. This corresponded to approximately 82% of the total population of EU/EEA countries in 2010. A case of IPD was defined, in accordance with the EU 2008 case definition [16], as the isolation of *S. pneumoniae* or detection of *S. pneumoniae* nucleic acid or antigen from a normally sterile site of a patient.

### 2.2. Surveillance systems and case definitions

Notification of IPD is mandatory in 19 European countries: Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, Hungary, Iceland, Ireland, Latvia, Lithuania, Malta, The Netherlands, Norway, Poland, Slovakia, Slovenia, Spain and Sweden. It is voluntary in 5 countries: Belgium, France, Germany, Italy, and the United Kingdom [17]. Cyprus and France have a sentinel surveillance system while all other countries operate a comprehensive surveillance system [17]. The official EU 2008 [16] case definition for IPD was applied in 18 countries. Bulgaria applied the EU 2002 case definition [18], whereas the United Kingdom and Denmark applied other non-specified case definitions. All countries reported case-based data with the exception of Bulgaria that submitted aggregated data.

### 2.3. Vaccination programmes

PCV7 (including serotypes 4, 6B, 9V, 14, 18C, 19F, 23F) received marketing authorisation in the EU in 2001. Since then it was gradually introduced in almost all EU/EEA countries though under different schemes and policies (Table 1). PCV10 (PCV7 serotypes plus 1, 5, 7F) and PCV13 (PCV10 plus 3, 6A, 19A) were licensed and EU/EEA countries started their implementation in mid-2010. Thus, it is highly unlikely that the vaccine change impacted this surveillance.

### 2.4. Data sources

ECDC experts in collaboration with European national experts developed an additional set of variables. EU/EEA countries reported to TESSy[2] these enhanced data on IPD for the first time in 2010.

### 2.5. Laboratory methods

In Europe, serotyping of pneumococcal strains is performed by various laboratory methods: Quellung, Pneumotest-Latex®, slide agglutination, multiplex PCR, coagglutination and gel diffusion. *Quellung* (62.0%) was the preferred technique for serotyping in Europe, followed by slide agglutination (21%) and Pneumotest-Latex® (11.0%). Serotype data were reported by Austria, Belgium, Cyprus, Czech Republic, Denmark, Finland, France, Hungary, Ireland, Italy, Malta, The Netherlands, Poland, Romania, Slovakia, Slovenia, Spain, the United Kingdom and Norway.

Fifteen countries reported data on MIC: Austria, Belgium, Cyprus, Denmark, Finland, France, Hungary, Ireland, Italy, Latvia, Poland, Romania, Slovenia, Spain and the United Kingdom. As an indication in the European Antimicrobial Resistance Surveillance Network (EARS-Net) report[3] for 2010, 66% of reporting laboratories in Europe used Clinical and Laboratory Standards Institute (CLSI)[4] standards whereas 29% applied the European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines.[5] According to these guidelines we considered as non-susceptible to penicillin isolates with MIC $\geq$0.12 mg/L, which is considered the cut-off value for meningeal isolates and the most used for surveillance studies. Antimicrobial gradient was the preferred method for AST of *S. pneumoniae* in most reporting European countries (60%), followed by agar dilution.

### 2.6. Data quality

Data were uploaded, validated and approved in TESSy by the countries. Individual datasets were further manually checked, validated and cleaned for inconsistencies, double reporting and impossible values.

### 2.7. Data analysis

Data comparisons were performed using the Pearson $\chi^2$ test as appropriate. The notification rate was defined as the number of laboratory confirmed cases of IPD per 100 000 inhabitants. Population data for denominators were retrieved from the European Statistics (EUROSTAT) website.[6] STATA® 11.0 software was used to perform statistical tests and analysis.

## 3. Results

### 3.1. Epidemiology

In 2010, 21 565 cases of IPD were reported by 26 EU/EEA countries. Notification rates ranged from 0.3 in Lithuania to 17.4

[2] For more on this platform go to: http://ecdc.europa.eu/en/activities/surveillance/TESSy/Pages/TESSy.aspx.
[3] EARS-Net report 2010 data, http://www.ecdc.europa.eu/en/publications/Publications/1111_SUR_AMR_data.pdf.
[4] CLSI standards, http://www.clsi.org/standards/.
[5] EUCAST guidelines, http://www.eucast.org/.
[6] EUROSTAT, http://epp.eurostat.ec.europa.eu/portal/page/portal/eurostat/home/.

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