

## SURVEILLANCE REPORT

Annual Epidemiological Report for 2015

# Haemophilus influenzae

### Key facts

- In 2015, 3 162 confirmed cases of invasive *Haemophilus influenzae* (*H. influenzae*) disease were reported by 30 EU/EEA Member States to ECDC.
- The notification rate was 0.7 cases per 100 000 population and has steadily increased between 2011 and 2015.
- Age-specific rates were highest in infants below one year of age (4.5 cases per 100 000 population) and people aged 65 years or older (1.9 cases per 100 000 population).
- The *H. influenzae* serotype b (Hib) vaccination has led to a progressive and sustained reduction of serotype b infections. In 2015, 4% of cases with a known serotype were caused by serotype b, 58% of which were aged 25 years and over.
- Non-capsulated strains caused the majority of cases in all age groups, and 82% of all cases for which serotyping results were available.
- Serotype f caused 9% of cases overall and 69% of cases among non-b capsulated serotypes (serotypes a, c, d, e and f).
- The changing epidemiology of invasive *H. influenzae* disease should be carefully monitored.
- Disease surveillance should include all age groups, serotypes and clinical presentations.

### Methods

This report is based on data for 2015 retrieved from The European Surveillance System (TESSy) on 26 October 2016. TESSy is a system for the collection, analysis and dissemination of data on communicable diseases. EU Member States and EEA countries contribute to the system by uploading their infectious disease surveillance data at regular intervals.

For a detailed description of methods used to produce this report, please refer to the *Methods* chapter [1].

An overview of the national surveillance systems is available online [2].

Additional data on *H. influenzae* are accessible from ECDC's online *Surveillance atlas of infectious diseases* [3].

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Suggested citation: European Centre for Disease Prevention and Control. *Haemophilus influenzae*. In: ECDC. Annual epidemiological report for 2015. Stockholm: ECDC; 2017.

Stockholm, November 2017

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ECDC has coordinated the surveillance of invasive *H. influenzae* disease at the European level since the transfer of EU-IBIS (European Union Invasive Bacterial Infections Surveillance Network) to ECDC in 2007.

Thirty EU/EEA Member States report data on invasive *H. influenzae* disease to ECDC. All Member States report data using the EU case definition (Commission Implementing Decision 2012/506/EU of 8 August 2012 of the European Parliament and of the Council) or use a case definition that is compatible with the EU case definition for confirmed cases. The majority of Member States report data from comprehensive, passive surveillance systems with national coverage. Belgium, France and Spain report data from sentinel surveillance systems.

## Epidemiology

In 2015, 3 162 confirmed cases of invasive *H. influenzae* disease were reported in 30 countries (Table 1, Figure 1). No confirmed cases were reported by Croatia, Cyprus, Luxembourg or Malta. Liechtenstein does not report data (Table 1). In 2015, the overall confirmed case notification rate was 0.7 cases per 100 000 population, with the highest rates reported by Sweden (2.3 cases per 100 000 population), Norway (1.9) and Denmark (1.6) (Table 1, Figure 2). The notification rate of invasive *H. influenzae* in EU/EEA countries has increased consistently between 2011 and 2015, a trend observed across several countries, notably Austria, Denmark, Germany and Italy.

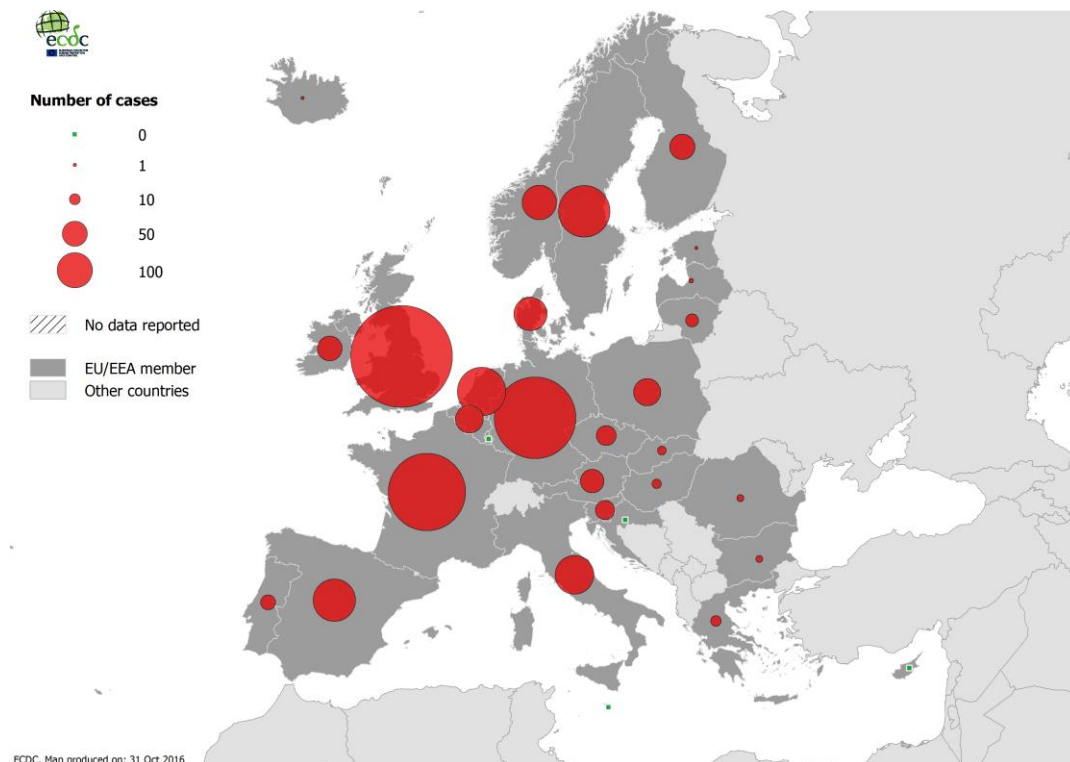
**Table 1. Cases of invasive *Haemophilus influenzae* disease: number and rate per 100 000 population, EU/EEA, 2011–2015**

| Country        | 2011            |            | 2012            |            | 2013            |            | 2014            |            | National coverage | Reported cases | 2015        |            |            |
|----------------|-----------------|------------|-----------------|------------|-----------------|------------|-----------------|------------|-------------------|----------------|-------------|------------|------------|
|                | Confirmed cases |            | Confirmed cases |            | Confirmed cases |            | Confirmed cases |            |                   |                | Number      | Rate       | ASR        |
|                | Number          | Rate       | Number          | Rate       | Number          | Rate       | Number          | Rate       |                   |                |             |            |            |
| Austria        | 3               | 0.0        | 6               | 0.1        | 25              | 0.3        | 28              | 0.3        | Y                 | 45             | 45          | 0.5        | 0.5        |
| Belgium        | 96              | -          | 78              | -          | 67              | -          | 56              | -          | N                 | 64             | 64          | -          | -          |
| Bulgaria       | 2               | 0.0        | 3               | 0.0        | 1               | 0.0        | 2               | 0.0        | Y                 | 4              | 4           | 0.1        | 0.1        |
| Croatia        | .               | .          | 2               | 0.0        | 4               | 0.1        | 1               | 0.0        | Y                 | 0              | 0           | 0.0        | 0.0        |
| Cyprus         | 9               | 1.1        | 8               | 0.9        | 2               | 0.2        | 1               | 0.1        | Y                 | 0              | 0           | 0.0        | 0.0        |
| Czech Republic | 15              | 0.1        | 11              | 0.1        | 22              | 0.2        | 19              | 0.2        | Y                 | 32             | 32          | 0.3        | 0.3        |
| Denmark        | 47              | 0.8        | 65              | 1.2        | 69              | 1.2        | 82              | 1.5        | Y                 | 90             | 90          | 1.6        | 1.5        |
| Estonia        | 2               | 0.2        | 3               | 0.2        | 2               | 0.2        | 4               | 0.3        | Y                 | 1              | 1           | 0.1        | 0.1        |
| Finland        | 66              | 1.2        | 81              | 1.5        | 48              | 0.9        | 59              | 1.1        | Y                 | 52             | 52          | 1.0        | 0.9        |
| France         | 492             | 1.0        | 491             | 1.0        | 489             | 1.0        | 453             | 0.9        | 72%               | 490            | 490         | 1.0        | 1.0        |
| Germany        | 267             | 0.3        | 321             | 0.4        | 415             | 0.5        | 458             | 0.6        | Y                 | 549            | 542         | 0.7        | 0.6        |
| Greece         | 7               | 0.1        | 6               | 0.1        | 9               | 0.1        | 6               | 0.1        | Y                 | 10             | 10          | 0.1        | 0.1        |
| Hungary        | 8               | 0.1        | 4               | 0.0        | 2               | 0.0        | 7               | 0.1        | Y                 | 8              | 8           | 0.1        | 0.1        |
| Ireland        | 44              | 1.0        | 41              | 0.9        | 41              | 0.9        | 61              | 1.3        | Y                 | 51             | 51          | 1.1        | 1.1        |
| Italy          | 36              | 0.1        | 60              | 0.1        | 78              | 0.1        | 101             | 0.2        | Y                 | 123            | 123         | 0.2        | 0.2        |
| Latvia         | 0               | 0.0        | 1               | 0.0        | 0               | 0.0        | 1               | 0.0        | Y                 | 2              | 2           | 0.1        | 0.1        |
| Lithuania      | 2               | 0.1        | 3               | 0.1        | 2               | 0.1        | 2               | 0.1        | Y                 | 14             | 14          | 0.5        | 0.4        |
| Luxembourg     | 0               | 0.0        | .               | .          | .               | .          | .               | .          | Y                 | 0              | 0           | 0.0        | 0.0        |
| Malta          | 0               | 0.0        | 5               | 1.2        | 0               | 0.0        | 0               | 0.0        | Y                 | 0              | 0           | 0.0        | 0.0        |
| Netherlands    | 137             | 0.8        | 135             | 0.8        | 159             | 0.9        | 160             | 1.0        | Y                 | 195            | 195         | 1.2        | 1.1        |
| Poland         | 22              | 0.1        | 35              | 0.1        | 25              | 0.1        | 41              | 0.1        | Y                 | 62             | 62          | 0.2        | 0.2        |
| Portugal       | 23              | 0.2        | 45              | 0.4        | 28              | 0.3        | 40              | 0.4        | Y                 | 22             | 18          | 0.2        | 0.2        |
| Romania        | 10              | 0.0        | 9               | 0.0        | 5               | 0.0        | 2               | 0.0        | Y                 | 4              | 4           | 0.0        | 0.0        |
| Slovakia       | 0               | 0.0        | 3               | 0.1        | 5               | 0.1        | 4               | 0.1        | Y                 | 7              | 7           | 0.1        | 0.1        |
| Slovenia       | 22              | 1.1        | 18              | 0.9        | 16              | 0.8        | 15              | 0.7        | Y                 | 31             | 31          | 1.5        | 1.5        |
| Spain          | 115             | 0.5        | 87              | 0.4        | 90              | 0.4        | 130             | 0.6        | 50%               | 147            | 147         | 0.6        | 0.6        |
| Sweden         | 203             | 2.2        | 214             | 2.3        | 196             | 2.1        | 204             | 2.1        | Y                 | 221            | 221         | 2.3        | 2.1        |
| United Kingdom | 739             | 1.2        | 726             | 1.1        | 715             | 1.1        | 787             | 1.2        | Y                 | 850            | 850         | 1.3        | 1.3        |
| <b>EU</b>      | <b>2367</b>     | <b>0.5</b> | <b>2461</b>     | <b>0.5</b> | <b>2515</b>     | <b>0.6</b> | <b>2724</b>     | <b>0.6</b> | .                 | <b>3074</b>    | <b>3063</b> | <b>0.7</b> | <b>0.6</b> |
| Iceland        | 2               | 0.6        | 0               | 0.0        | 0               | 0.0        | 4               | 1.2        | Y                 | 1              | 1           | 0.3        | 0.4        |
| Liechtenstein  | .               | .          | .               | .          | .               | .          | .               | .          | .                 | .              | .           | .          | .          |
| Norway         | 85              | 1.7        | 78              | 1.6        | 86              | 1.7        | 71              | 1.4        | Y                 | 98             | 98          | 1.9        | 1.9        |
| <b>EU/EEA</b>  | <b>2454</b>     | <b>0.5</b> | <b>2539</b>     | <b>0.5</b> | <b>2601</b>     | <b>0.6</b> | <b>2799</b>     | <b>0.6</b> | .                 | <b>3173</b>    | <b>3162</b> | <b>0.7</b> | <b>0.6</b> |

Source: Country reports. Legend: Y = yes, N = no, . = no data reported, ASR: age-standardised rate, - = no notification rate calculated.

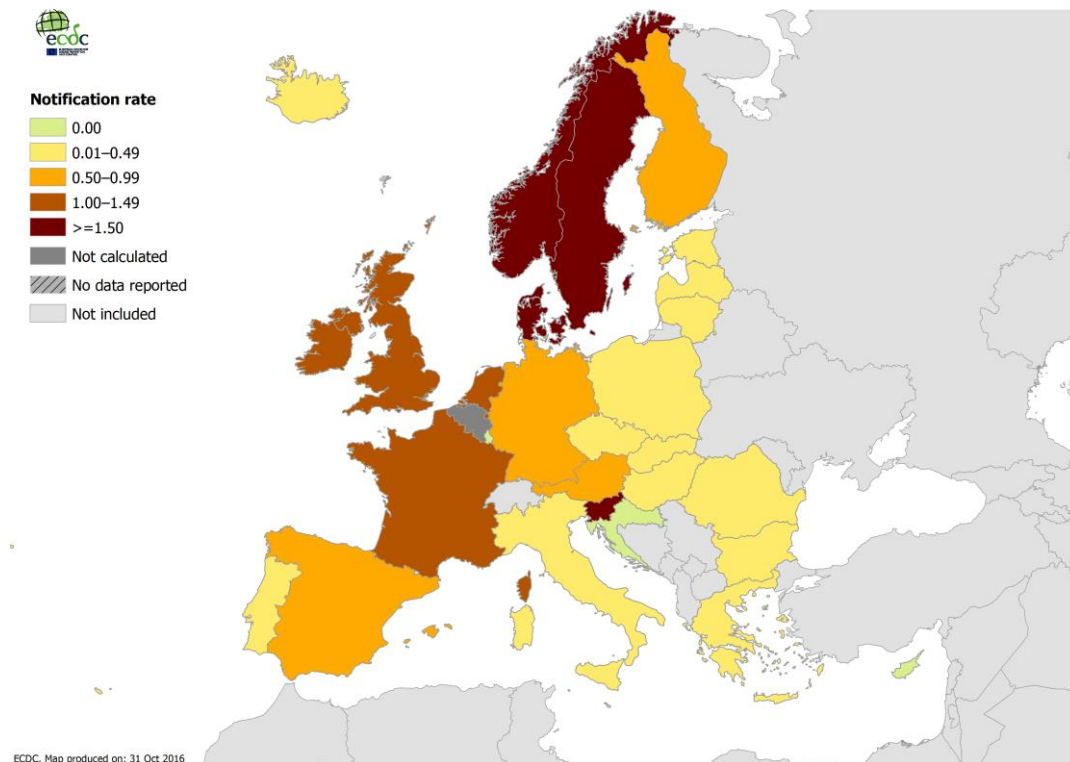
The national coverage in France is calculated based on the entire French population when in fact the surveillance system only collects data from metropolitan France. The coverage of the surveillance system shown for France is therefore underestimated.

**Figure 1. Distribution of confirmed cases of invasive *Haemophilus influenzae* disease, by country, EU/EEA, 2015**



Source: Country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

**Figure 2. Distribution of confirmed cases of invasive *Haemophilus influenzae* disease per 100 000 population, by country, EU/EEA, 2015**



Source: Country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

## Age and gender distribution

In 2015, invasive *H. influenzae* disease was predominantly reported in infants and the elderly, with a notification rate of 4.5 confirmed cases per 100 000 population in children under one year of age, and 1.9 confirmed cases per 100 000 population in adults aged 65 years or over (Figure 3). For both age groups, higher rates were observed in males than in females. The overall notification rate was 0.7 cases per 100 000 population for males and 0.7 for females, with a male-to-female ratio of 1:1.

**Figure 3. Rate per 100 000 of confirmed cases of invasive *Haemophilus influenzae* disease in the EU/EEA, by age and gender, 2015**

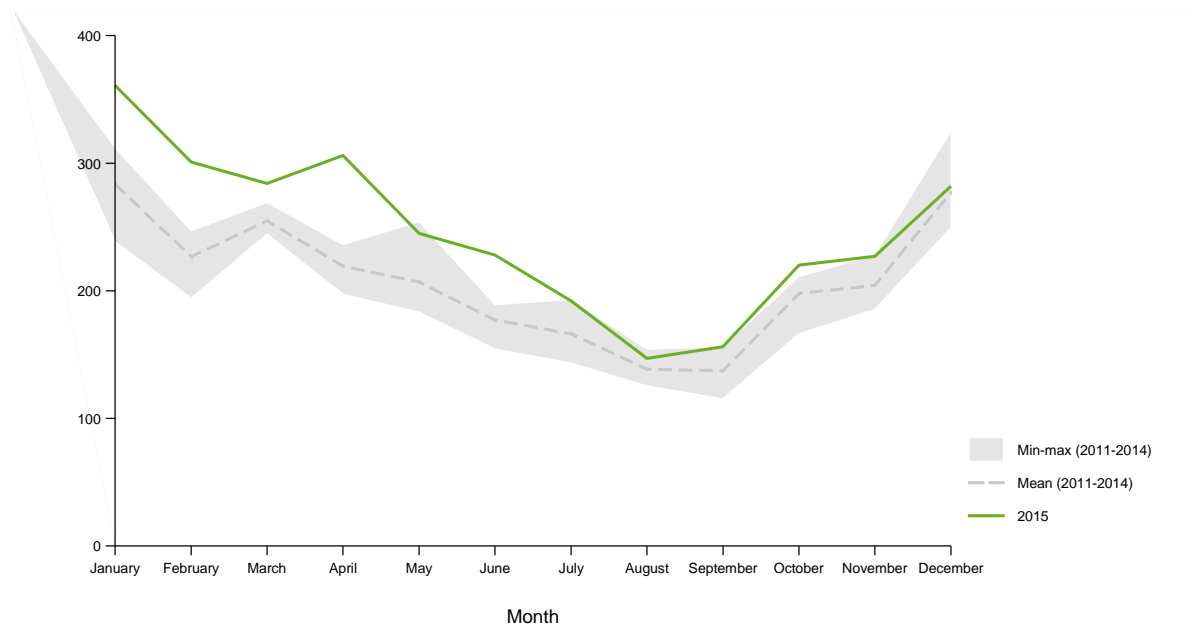


Source: Country reports from Austria, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

## Seasonality

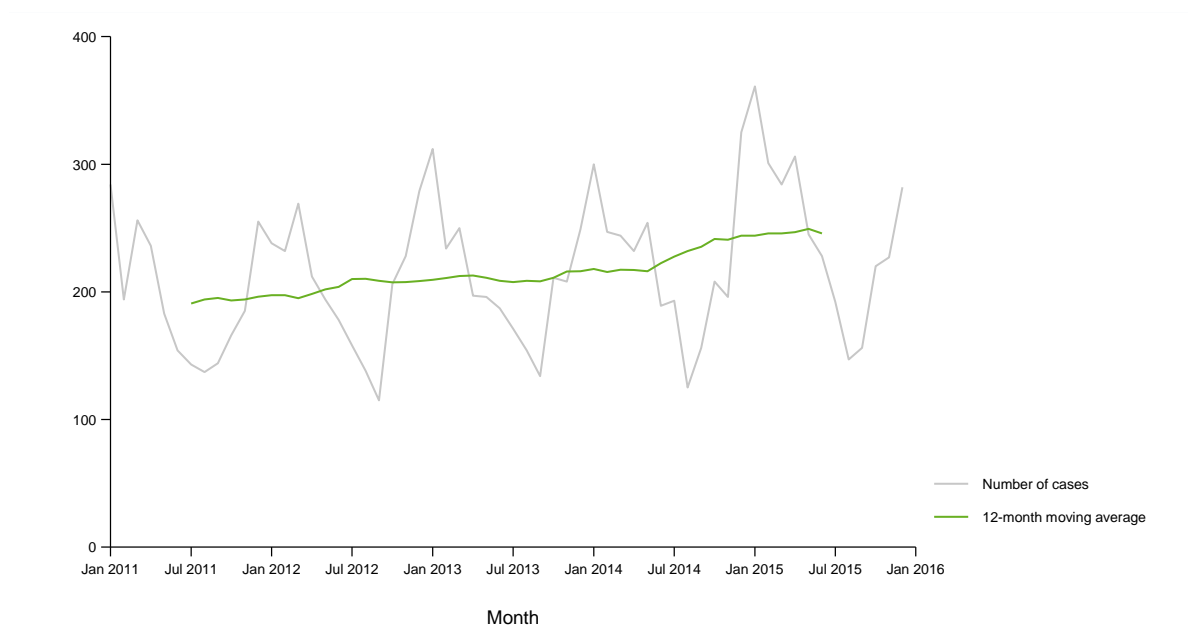
The distribution of invasive *H. influenzae* cases by month follows a seasonal pattern, with the highest number of reported cases in the winter months, followed by a steady decrease until August and an increasing trend towards the end of the year. Compared with previous years, a higher number of cases were observed in the first half of 2015 (Figure 4). Figure 5 shows an increasing trend in the number of cases reported from 2011–2015.

**Figure 4. Seasonal distribution of confirmed cases of invasive *Haemophilus influenzae* disease, EU/EEA, 2015 compared with 2011–2014**



Source: Country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

**Figure 5. Distribution of cases of invasive *Haemophilus influenzae* disease, by month, EU/EEA, 2011–2015**



Source: Country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, the United Kingdom.

## Serotype

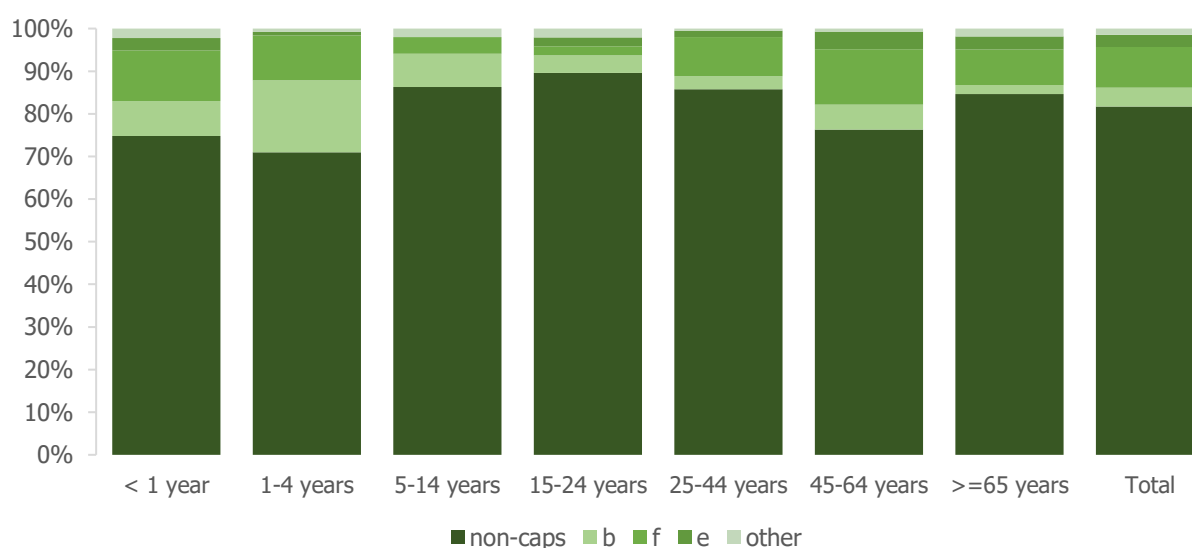
Of the 3 162 reported confirmed cases of invasive *H. influenzae* disease, 2 015 (64%), reported by 23 Member States, had a known serotyping result. Of these 2 015 cases, 82% (n=1 647) were non-capsulated (non-typeable). Non-capsulated strains were the most common cause of infection in all age groups (Figure 6). The majority of invasive non-capsulated strains were observed among cases 65 years of age or over (Figure 7). Serotype b (Hib)

caused 4% (n=90) of cases in 2015. Among cases of Hib invasive *H. influenzae* disease, 58% were aged 25 years or over (Figure 7).

Among non-b capsulated serotypes (serotypes a, c, d, e, f and those reported as 'non-b', n=278), serotype f was the most commonly reported serotype (69%, n=191) and the second most common cause of invasive *H. influenzae* disease overall (9%). Serotype e contributed to 21% (n=58) of non-b capsulated infections and 3% of all cases. The majority of cases of serotypes e and f infection were in persons aged 45 years and over (Figure 7). Six cases of serotype a, one case of serotype c, and one case of serotype d were reported. For 21 cases, the serotype reported was 'non-b'.

Among 18 Member States that consistently reported serotype data from 2011 to 2015 a consistent upward trend in non-capsulated strains was observed, with a 38% increase in the notification rate per 100 000 (2011: 0.29, n=1 128; 2015: 0.40, n=1 610). No consistent increasing trends were observed among other serotypes (Figure 8).

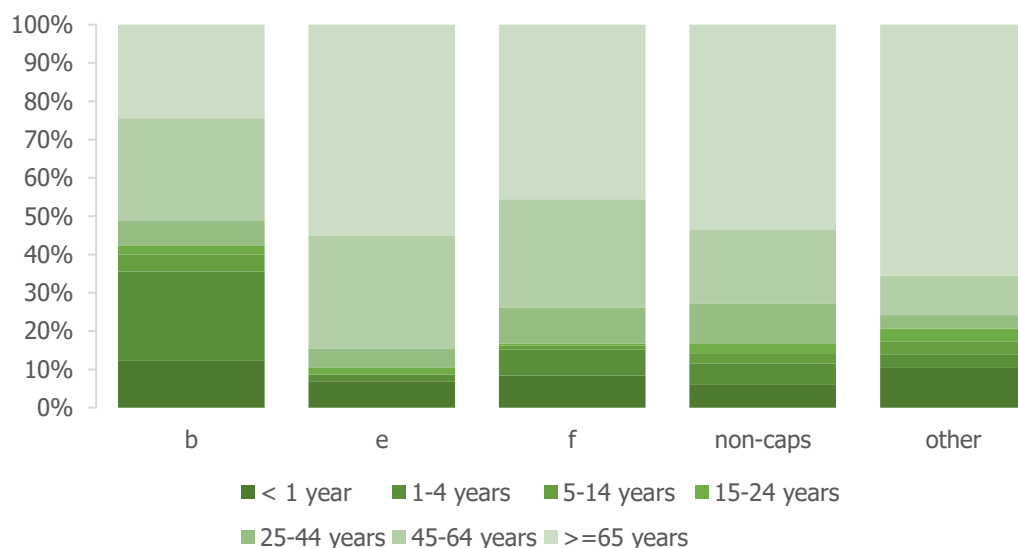
**Figure 6. Serotype distribution of confirmed cases of invasive *Haemophilus influenzae* disease, by age group, EU/EEA, 2015**



'Non-caps' refers to non-capsulated strains, 'other' refers to all cases reported as serotype a, c, d or 'non-b'.

Source: Country reports from Austria, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, United Kingdom.

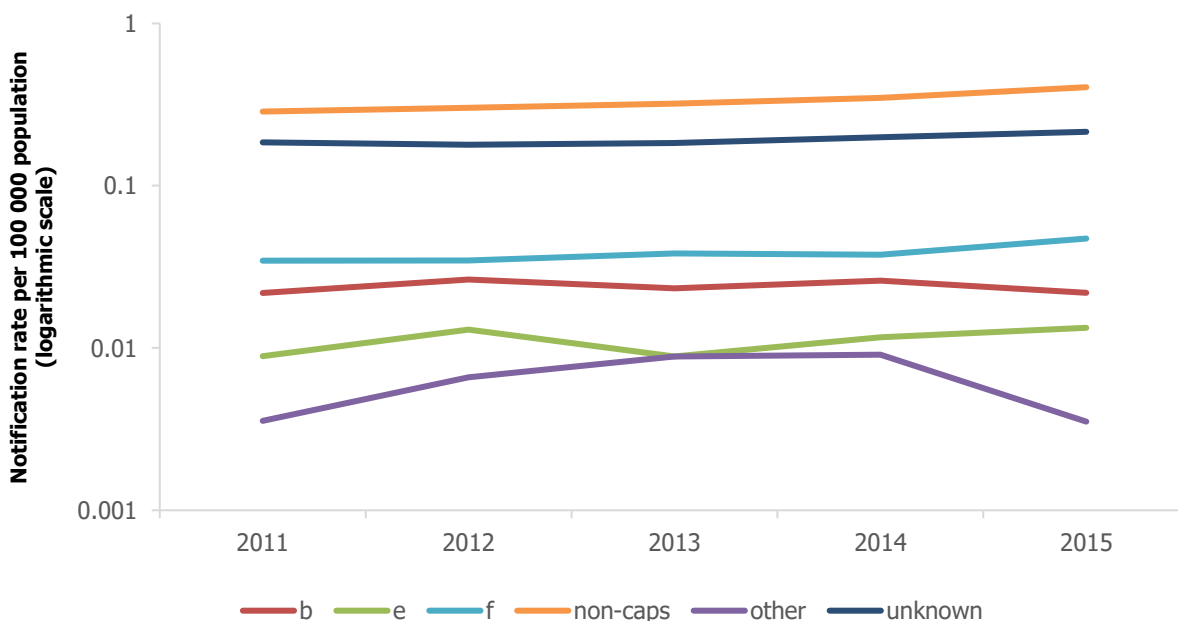
**Figure 7. Age group distribution of confirmed cases of invasive *Haemophilus influenzae* disease, by serotype, EU/EEA, 2015**



'Non-caps' refers to non-capsulated strains, 'other' refers to all cases reported as serotype a, c, d or 'non-b'.

Source: Country reports from Austria, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, Latvia, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, United Kingdom.

**Figure 8. Notification rate of confirmed cases of invasive *Haemophilus influenzae* disease, by serotype and year, EU/EEA, 2011–2015**



'Non-caps' refers to non-capsulated strains, 'other' refers to all cases reported as serotype a, c, d or 'non-b'.

Source: Country reports from the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, United Kingdom.

## Clinical presentation

The clinical presentation was known for 1 633 cases (52% of all cases) reported in 2015. Of these cases, septicaemia was reported in 854 cases (52%), pneumonia in 486 (30%) and meningitis in 160 (10%). Fifteen cases presented with both septicaemia and meningitis. Five cases of epiglottitis, five cases of cellulitis, and ten cases of septic arthritis/osteomyelitis were reported. For 98 cases, the clinical presentation was reported as 'other'.

Septicaemia was the most common clinical presentation across age groups and serotypes, except the one case of serotype c and cases reported with the serotype as 'non-b', for which pneumonia was the most common presentation.

## Outcome

The outcome was known for 1 594 (50%) of all cases. A total of 101 fatal cases was reported, a case fatality of 6% considering only cases with known outcome. Case fatality was highest among cases of non-capsulated strains (8%, n=73/970). No deaths due to Hib were reported in 2015. Eighty-seven percent (n=87) of deaths occurred in persons aged  $\geq 45$  years, and 74% of deaths (n=75) were in those  $\geq 65$  years.

## Discussion

In EU/EEA countries, cases of invasive *H. influenzae* disease are rare, with the greatest burden in infants and the elderly. The majority of cases is caused by infection with a non-capsulated strain. As in previous years, the disease was most commonly reported in the north of Europe. This observation is possibly due to better case ascertainment. The results should be interpreted with caution because the completeness of data for some variables, such as clinical presentation and outcome, was low. In addition, there is currently no common definition of fatal outcome due to invasive *H. influenzae* disease in Europe.

All EU/EEA Member States have made Hib vaccination part of their routine childhood immunisation schedule, and the sustained low number of Hib cases reported in all age groups highlights the success of this intervention. Indeed, serotype f is now the most common capsulated serotype observed in Europe and accounts for 9% of all cases, although the incidence of invasive disease caused by non-b encapsulated serotypes remains low in Europe. Before the introduction of Hib vaccination, invasive *H. influenzae* disease was predominantly caused by serotype b infections in healthy young children [4]. In 2015, the majority of Hib cases were observed in  $\geq 25$ -year-olds. While Hib vaccination has notably reduced the incidence of invasive Hib disease in all age groups, this reduction has been greatest in young children [5-8]. The majority of Hib cases now occur in older adults with underlying co-morbidities [8].

In the pre-vaccine era, non-capsulated *H. influenzae* was not a known common cause of invasive infection. However, it is now the leading cause of invasive *H. influenzae* disease in all age groups, particularly among groups who are more susceptible to infection, for example neonates, the elderly, and persons with underlying co-morbidities [9-12]. The number of non-capsulated cases reported has steadily increased over the past five years: an analysis of data in twelve European countries from 2007 to 2014 showed significant increasing trends in non-capsulated invasive *H. influenzae* disease among  $< \text{one-month-olds}$  and  $\geq 20$ -year-olds [12]. This may reflect a real increase in the incidence of disease, and factors such as increasing survival rates among persons more susceptible to infection and the increased use of immunosuppressive therapy may play a role [11]. The increase may also reflect changes and improvements in surveillance such as an increase in awareness among clinicians since Hib vaccine introduction, changing blood culture practices, and more accurate serotyping techniques [13-15].

Several studies have reported increasing trends in non-capsulated *H. influenzae* as well as in capsulated serotypes a, e and f, following the introduction of routine Hib vaccination [5, 12, 16-19]. Most studies, however, do not report evidence of strain replacement due to the introduction of routine Hib vaccination [6, 16, 18-20].

## Public health implications

The sustained success of Hib vaccination is evident. Maintaining high vaccination coverage in young children across Europe is essential to ensure the protection of all age groups against Hib.

The increasing recognition of non-capsulated *H. influenzae* as an important invasive pathogen shows the importance of the continuous monitoring of all strains, and more genetic typing studies of non-capsulated strains would be of benefit considering the genetic diversity of this pathogen. Also, all age groups, serotypes and clinical presentations should be included in routine surveillance systems for invasive *H. influenzae* disease in order to accurately assess changes in the epidemiology and develop preventative interventions.



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