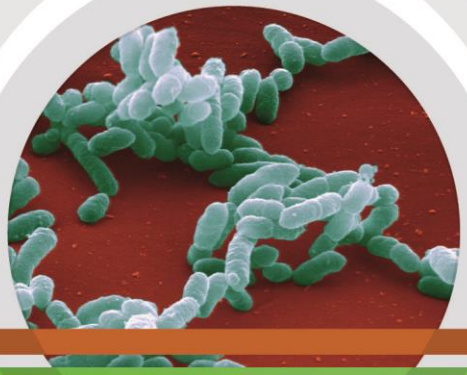


SURVEILLANCE REPORT

Annual Epidemiological Report for 2016

Haemophilus influenzae

Key facts

- In 2016, 3 379 confirmed cases of invasive *Haemophilus influenzae (H. influenzae)* disease were reported in the EU/EEA.
- The notification rate was 0.7 cases per 100 000 population, the same as in 2015. This plateau followed a steady increase between 2012 and 2015.
- Age-specific rates were highest in infants below one year of age (3.8 cases per 100 000 population), followed by people aged 65 years and over (1.9 cases per 100 000 population).
- Non-capsulated strains caused the majority of cases in all age groups and 78% of all cases for which serotyping results were available.
- Serotype f was the second-most common cause of invasive *H. influenzae* disease and accounted for 68% of cases among non-b capsulated serotypes (a, c, d, e and f).
- *H. influenzae* serotype b (Hib) vaccination has led to a progressive and sustained reduction of serotype b infections. In 2016, only 6% of cases with a known serotype were caused by serotype b, half of which were aged 25 years and over.
- 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 2016 retrieved from The European Surveillance System (TESSy) on 24 April 2018. TESSy is a system for the collection, analysis and dissemination of data on communicable diseases. 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].

A subset of the data used for this report is available through ECDC's online *Surveillance atlas of infectious diseases* [3].

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

Suggested citation: European Centre for Disease Prevention and Control. *Haemophilus influenzae*. In: ECDC. Annual epidemiological report for 2016. Stockholm: ECDC; 2018.

Stockholm, August 2018

In 2016, 29 EU/EEA Member States reported data on invasive *H. influenzae* disease to ECDC. All Member States reported 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 used a case definition that is compatible with the EU case definition for confirmed cases. The majority of Member States reported data from comprehensive passive surveillance systems with national coverage. Belgium, France and Spain reported data from sentinel surveillance systems [2]. Belgium reported aggregated data in 2016. Spain increased the estimated surveillance system coverage from 50% in 2015 and previous years to 85% in 2016.

Epidemiology

In 2016, 29 countries reported 3 379 confirmed cases of invasive *H. influenzae* disease in the EU/EEA (Table 1). France, Germany and the United Kingdom accounted for 59% of all confirmed cases in 2016. Estonia and Malta reported no cases, while Luxembourg did not report data in 2016 and Liechtenstein has never reported data on *H. influenzae* (Table 1). In 2016, the notification rate was 0.7 confirmed cases per 100 000 population in the EU/EEA, with the highest rates reported by Iceland (3.6 cases per 100 000 population), Denmark (1.9), Sweden (1.8) and Norway (1.6) (Table 1, Figure 1). The notification rate of invasive *H. influenzae* in the EU/EEA increased consistently between 2012 and 2015, but remained stable in 2016.

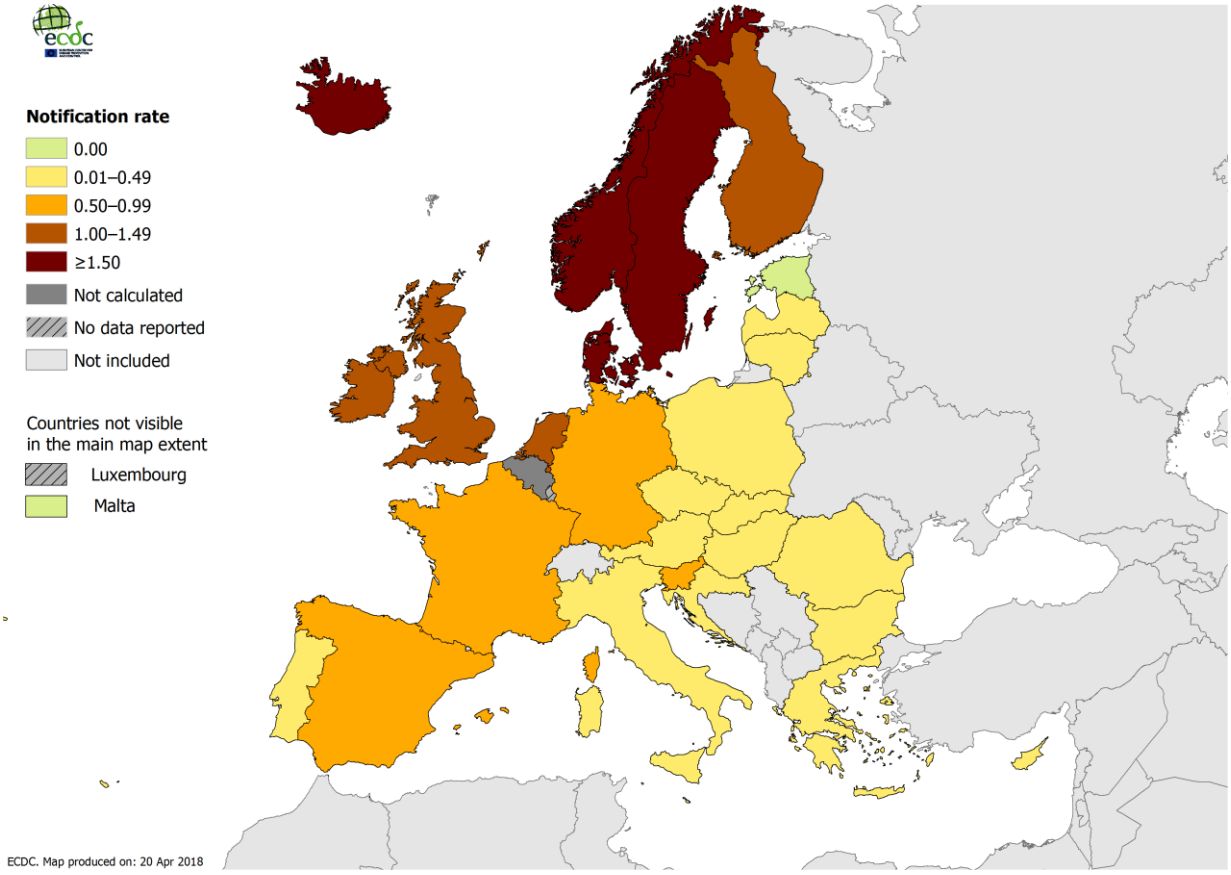
Table 1. Distribution of confirmed cases of invasive *Haemophilus influenzae*, EU/EEA, 2012 to 2016

Country	2012		2013		2014		2015		2016			
	Number	Rate	Number	Rate	Number	Rate	Number	Rate	Confirmed cases	Rate	ASR	Reported cases
Austria	6	0.1	25	0.3	28	0.3	45	0.5	41	0.5	0.5	41
Belgium	78	-	67	-	56	-	64	-	85	-	-	85
Bulgaria	3	0.0	1	0.0	2	0.0	4	0.1	3	0.0	0.0	3
Croatia	2	0.0	4	0.1	1	0.0	0	0.0	1	0.0	0.0	1
Cyprus	8	0.9	2	0.2	1	0.1	0	0.0	2	0.2	0.2	2
Czech Republic	11	0.1	22	0.2	19	0.2	32	0.3	22	0.2	0.2	22
Denmark	65	1.2	69	1.2	82	1.5	90	1.6	106	1.9	1.8	106
Estonia	3	0.2	2	0.2	4	0.3	1	0.1	0	0.0	0.0	0
Finland	81	1.5	48	0.9	59	1.1	52	1.0	69	1.3	1.2	69
France	491	1.0	489	1.0	453	0.9	508	1.1	588	0.9	0.9	588
Germany	321	0.4	415	0.5	458	0.6	542	0.7	608	0.7	0.7	622
Greece	6	0.1	9	0.1	6	0.1	10	0.1	4	0.0	0.0	4
Hungary	4	0.0	2	0.0	7	0.1	8	0.1	16	0.2	0.2	16
Iceland	0	0.0	0	0.0	4	1.2	1	0.3	12	3.6	4.4	12
Ireland	41	0.9	41	0.9	61	1.3	51	1.1	58	1.2	1.3	58
Italy	60	0.1	78	0.1	101	0.2	123	0.2	141	0.2	0.2	141
Latvia	1	0.0	0	0.0	1	0.0	2	0.1	2	0.1	0.1	2
Liechtenstein	.	.	.	.	.	.	.	.	.	.	.	.
Lithuania	3	0.1	2	0.1	2	0.1	14	0.5	7	0.2	0.2	7
Luxembourg	.	.	.	.	.	.	0	0.0	.	.	.	.
Malta	5	1.2	0	0.0	0	0.0	0	0.0	0	0.0	0.0	0
Netherlands	135	0.8	159	0.9	160	1.0	195	1.2	190	1.1	1.1	190
Norway	78	1.6	86	1.7	71	1.4	98	1.9	85	1.6	1.7	85
Poland	35	0.1	25	0.1	41	0.1	62	0.2	69	0.2	0.2	69
Portugal	45	0.4	28	0.3	40	0.4	18	0.2	17	0.2	0.2	19
Romania	9	0.0	5	0.0	2	0.0	4	0.0	5	0.0	0.0	5
Slovakia	3	0.1	5	0.1	4	0.1	7	0.1	1	0.0	0.0	1
Slovenia	18	0.9	16	0.8	15	0.7	31	1.5	20	1.0	0.9	20
Spain	87	0.4	90	0.4	130	0.6	147	0.6	242	0.6	0.6	242
Sweden	214	2.3	196	2.1	204	2.1	221	2.3	178	1.8	1.7	178
United Kingdom	726	1.1	715	1.1	787	1.2	850	1.3	807	1.2	1.2	807
EU/EEA	**2539**	**0.5**	**2601**	**0.6**	**2799**	**0.6**	**3180**	**0.7**	**3379**	**0.7**	**0.6**	**3395**

Source: Country reports
-: No notification rate calculated
.: No data reported
ASR: Age-standardised rate.

National coverage in Spain was estimated to be 85% in 2016 and 50% in previous years.

Figure 1. Distribution of confirmed invasive *Haemophilus influenzae* cases per 100 000 population by country, EU/EEA, 2016



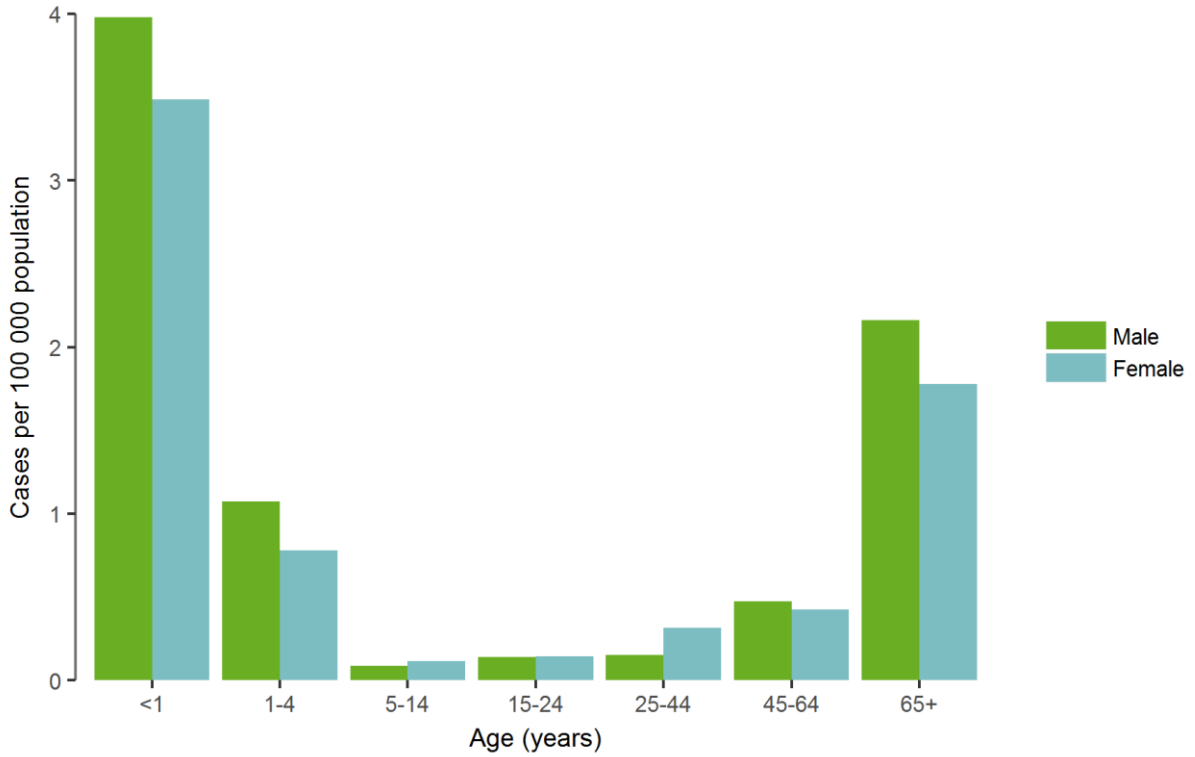
Source: Country reports from Austria, Belgium, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United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

Age and gender distribution

In 2016, invasive *H. influenzae* disease was predominantly reported in infants and the elderly, with a notification rate of 3.8 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 and over (Figure 2). The highest rates among infants were reported in the Netherlands (11.2 cases per 100 000 population), Ireland (10.6), Denmark (8.5) and the United Kingdom (7.9). In adults aged 65 years and over, the highest rates were reported in Iceland (19.5 per 100 000 population), Denmark (6.1), Norway (6.0) and Sweden (5.4).

When stratified by gender, rates were higher among males in the age groups under 5 years and over 45 years of age. The overall male-to-female ratio was 0.9:1.

Figure 2. Distribution of confirmed invasive *Haemophilus influenzae* cases per 100 000 population by age and gender, EU/EEA, 2016

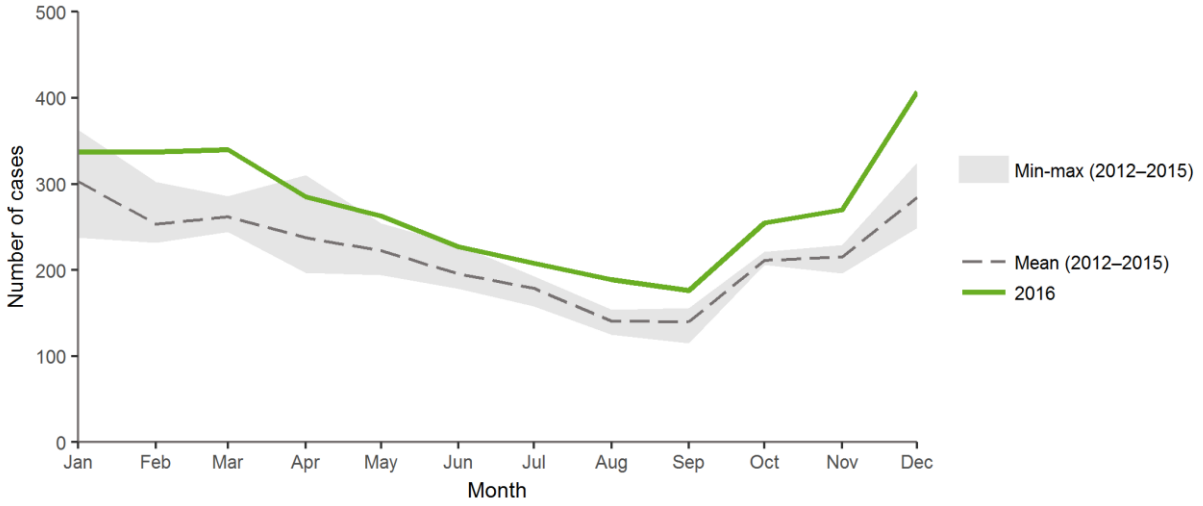


Source: Country reports from Austria, Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

Seasonality and trend

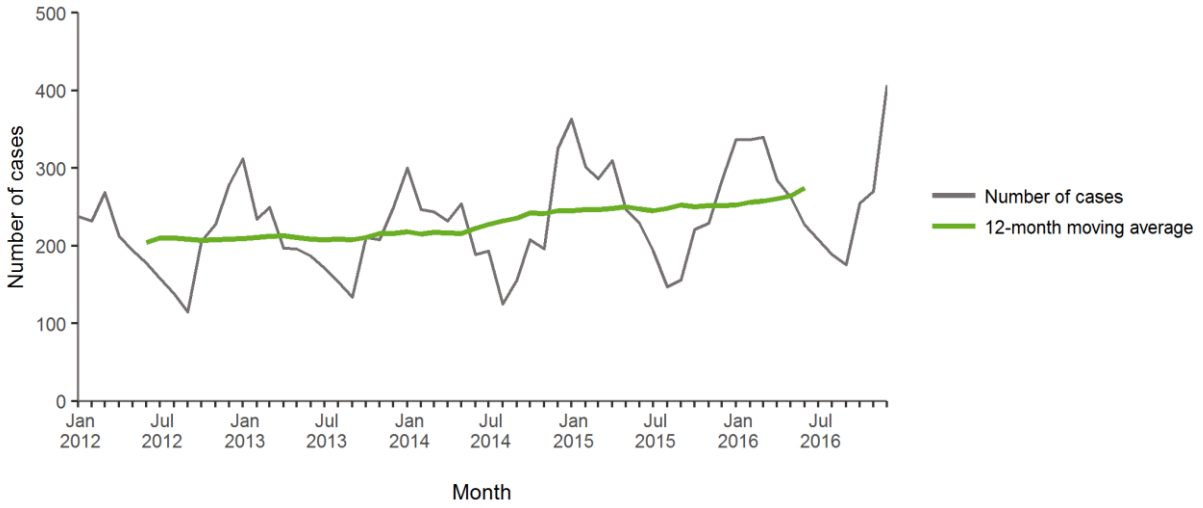
The distribution of invasive *H. influenzae* cases by month follows a seasonal pattern, with the highest number of cases reported in the winter months, followed by a steady decrease until September and an increasing trend toward the end of the year, reaching a peak in December. Compared with the mean number of cases reported from 2012 to 2015, a higher number of cases was observed in 2016 (Figure 3). Figure 4 shows an increasing trend in the number of cases reported from 2012 to 2016.

Figure 3. Distribution of confirmed invasive *Haemophilus influenzae* cases by month, EU/EEA, 2016 and 2012 to 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, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

Figure 4. Distribution of confirmed invasive *Haemophilus influenzae* cases by month, EU/EEA, 2012 to 2016



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

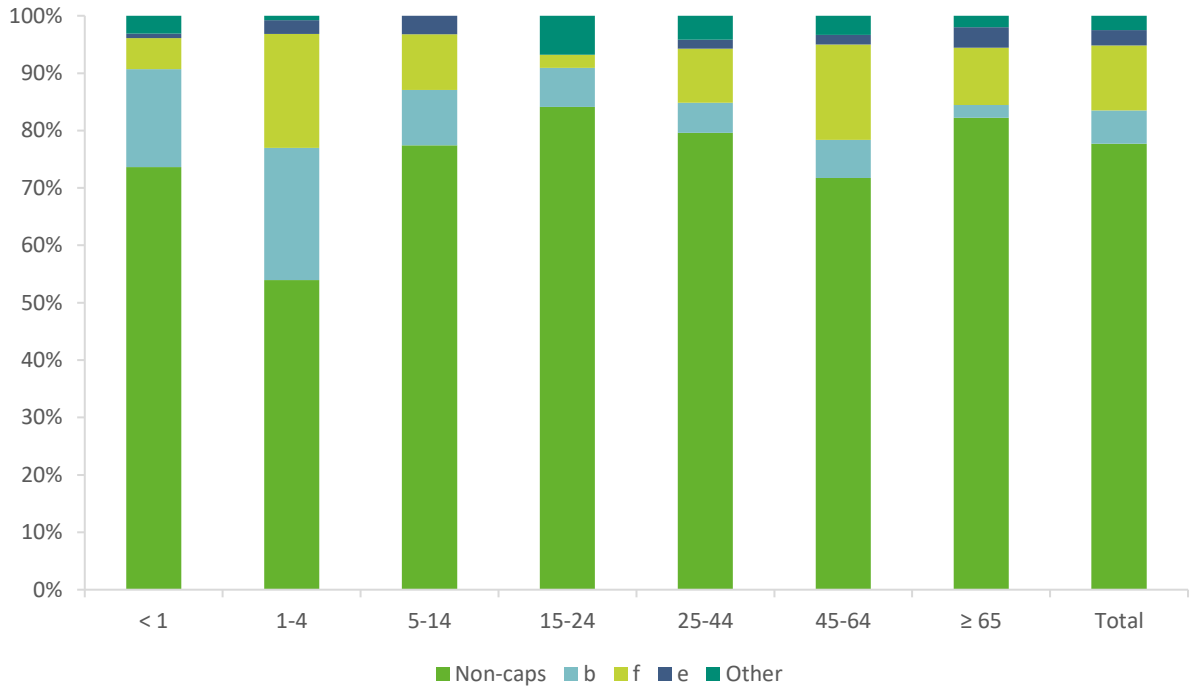
Serotype

Of the 3 379 confirmed cases of invasive *H. influenzae* disease, 1 985 (59%) reported by 22 Member States, had a known serotyping result. Of these cases, 78% (n=1 542) were non-capsulated (non-typeable). Non-capsulated strains were the most common cause in all age groups (Figure 5). The majority of invasive non-capsulated strains were observed among cases 65 years of age and over (Figure 6). Serotype b (Hib) caused 6% (n=115) of cases in 2016. Among cases of Hib invasive disease, 50% were aged 25 years and over (Figure 6).

Among non-b capsulated serotypes (serotypes a, c, d, e, f and those reported as 'non-b', n=328), serotype f was the most commonly reported serotype (68%, n=224) and the second most common cause of invasive *H. influenzae* disease overall (11%). Serotype e contributed to 16% (n=53) of non-b capsulated serotype cases and 3% of all cases. The majority of cases caused by serotypes e and f were in persons aged 45 years and over (Figure 6). Thirteen cases of serotype a and three cases of d were reported. For 35 cases, the serotype reported was 'non-b'. There were no reported cases of serotype c in 2016.

Notification rates of confirmed invasive *H. influenzae* cases among 18 Member States that consistently reported serotype data from 2012 to 2016 by serotype and year are shown in Figure 7. A consistent upward trend in non-capsulated strains from 2012 to 2015 was followed by a 9% decrease in 2016.

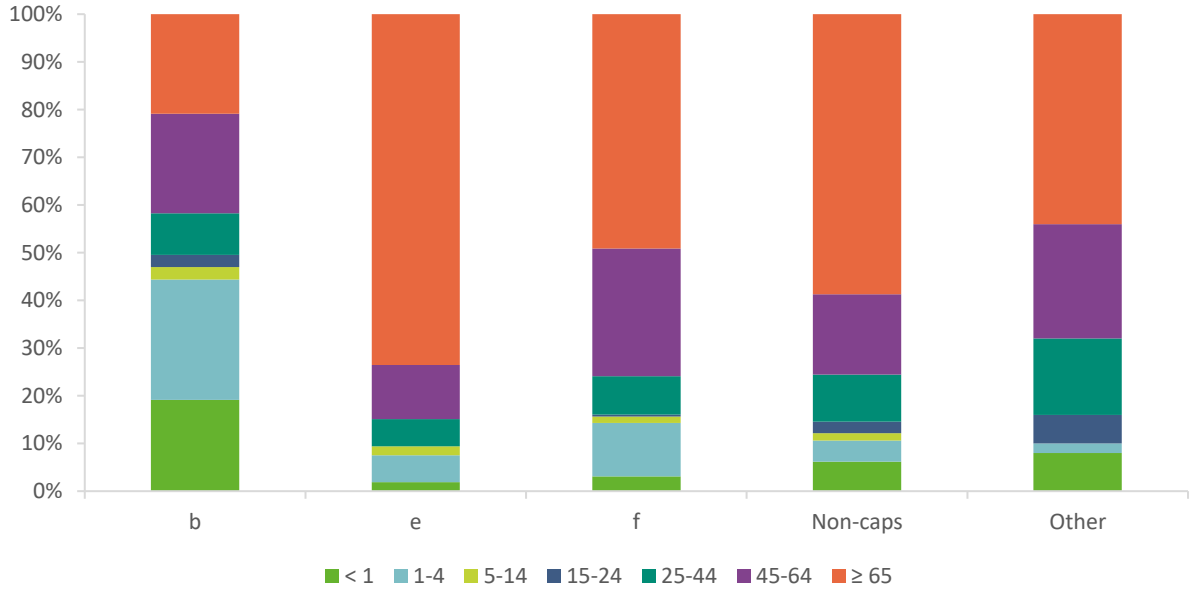
Figure 5. Serotype distribution of confirmed invasive *Haemophilus influenzae* cases by age group in years, EU/EEA, 2016



'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, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

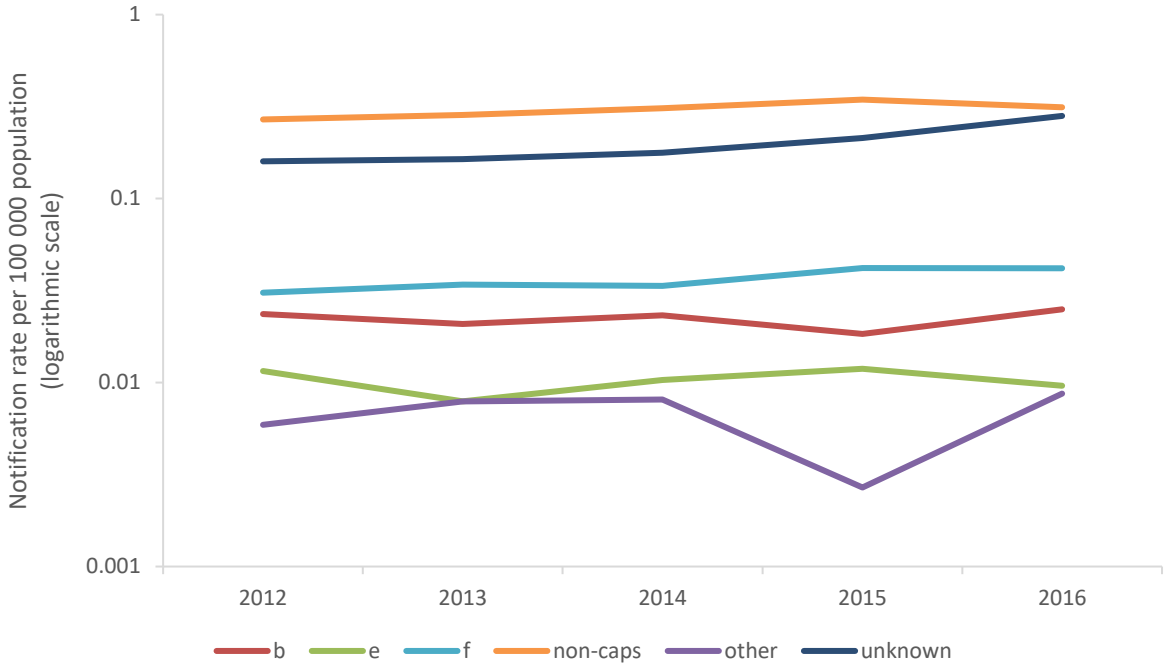
Figure 6. Age group distribution of confirmed invasive *Haemophilus influenzae* cases by serotype, EU/EEA, 2016



'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, Cyprus, the Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Lithuania, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom.

Figure 7. Notification rate of confirmed invasive *Haemophilus influenzae* cases per 100 000 population by serotype and year, EU/EEA, 2012–2016



'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, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, the United Kingdom.

Clinical presentation

The clinical presentation was known for 1 276 cases (38%). Of these cases, pneumonia was reported in 467 (37%), septicaemia in 458 (36%) and meningitis in 171 (13%). Sixteen cases (1%) presented with both septicaemia and meningitis and 31 (2%) had other clinical presentations (epiglottitis, cellulitis and septic arthritis/osteomyelitis). For a further 133 cases (10%), the clinical presentation was reported as 'other'.

Septicaemia was the most common clinical presentation among infants below 1 year and those aged 15-64 years; meningitis among children aged 1-4 and 5-14 years, while for cases aged 65 years and older, pneumonia was the most common clinical presentation. Across serotypes, meningitis was the most common presentation for Hib, d and 'non-b' serotypes, septicaemia for non-capsulated and e serotypes and pneumonia for a and f serotypes.

Outcome

The outcome was known for 1 804 cases (53%). Ninety-four fatal cases were reported, a case fatality of 5% considering only cases with known outcome. Case fatality was highest among cases of non-capsulated strains (5%, n=45/970). One death due to Hib was reported in 2016. Ninety-four percent (n=88) of deaths occurred in persons aged ≥45 years and 83% of deaths (n=78) were in those ≥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 are caused by infection with a non-capsulated strain. As in previous years, the disease was most commonly reported in the north of Europe 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, outcome, as well as serotype was low. In addition, there is no common definition of fatal outcome due to invasive *H. influenzae* disease, particularly in the context of multiple co-morbidities.

WHO recommends the inclusion of conjugate Hib vaccines in all infant immunisation programmes, either in three primary doses without a booster or alternatively two or three primary doses with a booster depending on disease burden by age in different settings. The introduction of Hib vaccines has led to a substantial reduction in invasive Hib disease and pharyngeal Hib carriage, resulting in herd protection [4]. Since 2010, Hib vaccination has been part of national immunisation programmes in all EU/EEA Member States and high coverage has been

maintained [5]. The sustained low number of Hib cases reported in all age groups highlights the success of this intervention. Serotype f is now the most common capsulated serotype observed in Europe and accounted for 11% of all cases reported for 2016, although the overall incidence of invasive disease caused by other non-b capsulated 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 [6]. In 2016, half of Hib cases were observed in ≥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 [7–10]. The majority of Hib cases now occur in older adults with underlying co-morbidities [9].

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 those who are more susceptible to infection, including neonates, the elderly and persons with underlying co-morbidities [5, 11–13]. The rate of reported non-capsulated cases steadily increased between 2012 and 2015: an analysis of data in 12 European countries from 2007 to 2014 showed significant increasing trends in non-capsulated invasive *H. influenzae* disease among <1-month-olds and ≥20-year-olds [5]. This may reflect a true increase in the incidence of disease, but also increased life expectancy among persons more susceptible to infection and the increased use of immunosuppressive therapy [13]. 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 [14–16].

Several studies have reported increasing trends in non-capsulated *H. influenzae* as well as capsulated serotypes a, e and f following the introduction of routine Hib vaccination [5, 17–20]. However, most studies do not report evidence of strain replacement due to the introduction of routine Hib vaccination [7, 17, 19, 21].

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 warrants continuous monitoring of all strains and genetic typing for non-capsulated strains considering its genetic diversity. Further emphasis on the collection of serotype and clinical presentation data in routine surveillance systems for invasive *H. influenzae* disease would enhance the detection of changes in epidemiology and advance preventive interventions.

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