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The epidemiology of invasive meningococcal disease in EU/EEA countries, 2004–2014

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ABSTRACT

Background: Invasive meningococcal disease (IMD) is a major cause of bacterial meningitis and septicaemia although infection by some serogroups may be prevented through vaccination. We aimed to describe the epidemiology of IMD in EU/EEA countries during 2004–2014 to monitor serogroup- and age-specific trends, and compare country trends by the period of meningococcal C conjugate (MCC) vaccine introduction.

Methods: We analysed IMD surveillance data by age, gender, serogroup, country and outcome. We estimated the percentage change in annual notification rate (NR), using linear regression analysis of the log of the annual NR. We grouped countries by the year they introduced MCC vaccination into their routine immunisation programmes.

Results: The overall NR was 0.9/100 000 population, and decreased 6.6% (95%CI: −8.0%;−5.1%) annually. Infants had the highest NR (16.0/100 000), and there were decreasing trends in all age groups <50 years. Serogroup B (SgB) caused 74% of all cases, and the majority of cases in all age groups. There were decreasing trends in SgB and serogroup C (SgC) and an increasing trend in serogroup Y. Countries that introduced MCC vaccination before, and between 2004 and 2014, had decreasing trends in NR of SgC, but not countries without routine MCC vaccination.

Conclusions: Our findings support evidence that routine MCC vaccination was the driving force behind the decreasing SgC trend. Vaccinating against SgB in the first year of life could help reduce the burden of IMD due to this serogroup. Changing serogroup-specific NR trends highlight the need for high-quality surveillance data to accurately assess the changing epidemiology of IMD, the effectiveness and impact of implemented vaccines, and the need for future vaccines.

1. Introduction

Invasive meningococcal disease (IMD), caused by *Neisseria meningitidis*, is a major cause of bacterial meningitis and septicaemia, with high case fatality and up to one-fifth of survivors suffering from long-term sequelae [1,2]. Twelve serogroups of *N. meningitidis* have been identified, of which six (A, B, C, W, Y, and X) are responsible for the majority of IMD cases worldwide. Serogroup distribution varies by region, and serogroups B (SgB) and C (SgC) have been the most common in Europe [2–4]. While epidemics of IMD may occur – and certain groups are more at risk of IMD, such as infants, immunocompromised persons and men who have sex with men – in Europe cases are normally sporadic and IMD is considered rare [2–6].

The serogroup distribution and incidence of IMD within a geographical area may change due to an epidemic or shift slowly over

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time. It is not always clear why these changes occur, but they may be explained by secular trends, the emergence of hypervirulent clones, or changes in vaccination strategies, population immunity, or environmental and behavioural risk factors [2–4,7,8]. Many European countries experienced an increase in the incidence of SgC IMD in the late 1990s, mostly due to the circulation of a hypervirulent ST-11 clone [2,9–11]. Following this increase, 14 countries of the European Union and European Economic Area (EU/EEA) successively introduced the meningococcal C conjugate (MCC) vaccine into their routine national childhood immunisation programmes, starting with the United Kingdom (UK) in 1999 [12]. Moreover, some countries implemented routine vaccination or catch-up campaigns in adolescents and young adults [9,12,13]. Following these interventions, a decline in SgC IMD was observed in several countries [11,14–17]. Over the last 10–15 years, some European countries have reported a decline in SgB [11,18], and some have reported increases in serogroup Y (SgY) [18,19] and W (SgW) [7,8]. Recently, the United Kingdom and Ireland introduced a SgB vaccine (4CMenB) into their routine national childhood immunisation programme, while a quadrivalent meningococcal conjugate vaccine (MCV4) has been introduced in adolescents in the United Kingdom, Greece, Austria and Czech Republic since 2011 [12,20].

High-quality surveillance is necessary to monitor changes in the epidemiology of IMD and inform vaccination policies. The surveillance of IMD in the EU/EEA is coordinated by the European Centre for Disease Prevention and Control (ECDC), having been transferred from the European Union Invasive Bacterial Infections Surveillance Network (EU-IBIS) in 2007 [13]. We aimed to describe the epidemiology of IMD in EU/EEA countries during 2004–2014 to monitor serogroup and age-specific trends, and compare country trends by the period of MCC vaccine introduction.

2. Methods

2.1. The European surveillance of IMD

All 28 EU member states and two EEA countries report routine national surveillance data on cases of IMD to a central database at ECDC on an annual basis. The majority of the 30 reporting countries report from passive surveillance systems with mandatory reporting, and all report from systems that cover their entire national population [21]. Under the EU case definition, a confirmed case of IMD is defined as any person with the isolation or detection of *N. meningitidis* from a normally sterile site, or the detection of *N. meningitidis* antigen or Gramme-negative diplococci in cerebrospinal fluid [22]. All countries reported using the EU case definition or a case definition with compatible criteria for laboratory confirmation during the study period.

2.2. Data selection and preparation

We analysed data on IMD reported to EU-IBIS from 2004 to 2006 and to ECDC from 2007 to 2014. We excluded cases not reported as laboratory-confirmed or cases with unknown age or gender. We also excluded data from countries that had not reported case-based data for all study years, or had reported serogroup data for <70% of cases. We categorised data by age into the following groups;<1 (infants), 1–4, 5–14, 15–24, 25–49 and ≥50 years old. We grouped countries based on the year in which they introduced MCC vaccination into their routine national childhood immunisation programmes: countries that introduced MCC vaccination before 2004 (MCCpre2004); countries that introduced MCC vaccination during 2004–2014 (MCC2004-14); countries that had not introduced routine MCC vaccination (noMCC) (Fig. 1). In

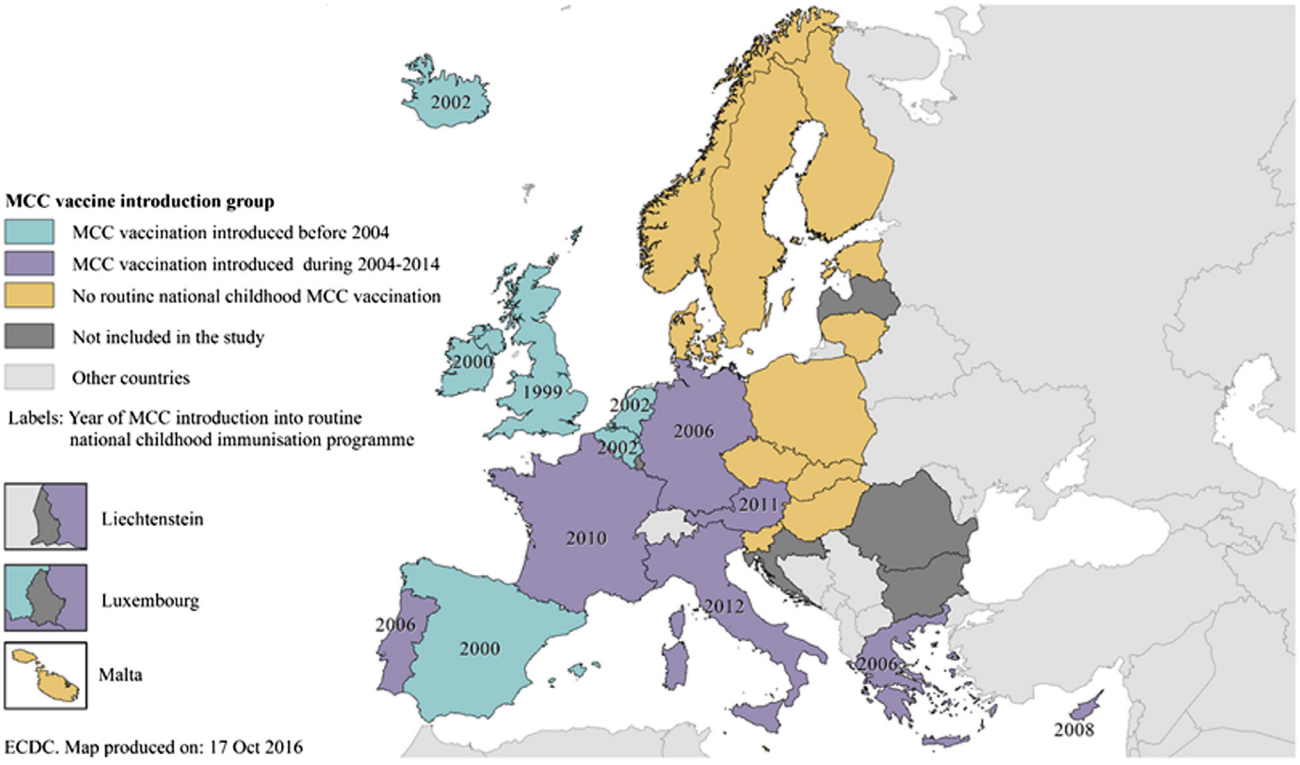

Fig. 1. Year of introduction of routine childhood MCC vaccination among the 25 European countries included in the study, and the respective MCC vaccine introduction group into which they were classified.

Table 1
Annual notification rate per 100,000 population and percent of change in annual notification rate of invasive meningococcal disease by age, gender and MCC vaccine introduction group*, 25 European countries, 2004–2014.

		Annual notification rate (number of cases)											Mean annual notification rate (number of cases)	Percent change in annual NR (95% CI)	p-value
		2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014			
Overall		1.13 (5201)	1.19 (5485)	0.97 (4499)	1.03 (4810)	0.98 (4597)	0.92 (4315)	0.76 (3601)	0.79 (3734)	0.71 (3363)	0.70 (3345)	0.55 (2629)	0.88 (45,579)	**−6.55 (−7.97;−5.10)**	**<0.0001**
Age group	<1 year	21.39 (1019)	21.51 (1038)	16.12 (781)	16.62 (818)	21.79 (1086)	18.55 (947)	13.34 (675)	12.81 (648)	11.61 (574)	12.04 (590)	10.42 (500)	16.00 (8676)	**−6.94 (−9.58;−4.23)**	**0.0003**
	1–4 years	6.76 (1299)	7.14 (1372)	6.06 (1165)	6.70 (1295)	4.82 (942)	4.49 (888)	4.32 (867)	4.21 (854)	3.77 (768)	3.24 (660)	2.50 (505)	4.88 (10,615)	**−9.18 (−11.04;−7.27)**	**<0.0001**
	5–14 years	1.37 (714)	1.53 (789)	1.23 (625)	1.29 (652)	1.13 (565)	1.19 (593)	0.81 (402)	0.85 (422)	0.66 (326)	0.75 (373)	0.51 (255)	1.03 (5716)	**−9.40 (−11.83;−6.91)**	**<0.0001**
	15–24 years	1.70 (997)	1.75 (1025)	1.61 (937)	1.63 (947)	1.56 (904)	1.51 (867)	1.29 (730)	1.36 (764)	1.18 (656)	1.11 (610)	0.80 (432)	1.42 (8869)	**−6.27 (−8.33;−4.17)**	**0.0001**
	25–49 years	0.31 (526)	0.34 (576)	0.26 (447)	0.31 (525)	0.29 (494)	0.26 (434)	0.23 (388)	0.25 (419)	0.25 (418)	0.26 (426)	0.22 (362)	0.27 (5015)	**−3.37 (−5.06;−1.66)**	**0.0017**
	≥50 years	0.41 (646)	0.43 (685)	0.34 (544)	0.35 (573)	0.36 (606)	0.35 (586)	0.31 (539)	0.36 (627)	0.35 (621)	0.38 (686)	0.31 (575)	0.36 (6688)	−1.65 (−3.50;0.24)	0.0791
Gender	Male	1.18 (2652)	1.27 (2858)	1.07 (2431)	1.10 (2497)	1.07 (2442)	0.99 (2274)	0.81 (1864)	0.83 (1925)	0.75 (1743)	0.72 (1669)	0.58 (1344)	0.94 (23,699)	**−6.83 (−8.28;−5.37)**	**<0.0001**
	Female	1.08 (2549)	1.11 (2627)	0.87 (2068)	0.97 (2313)	0.90 (2155)	0.85 (2041)	0.72 (1737)	0.75 (1809)	0.67 (1620)	0.69 (1676)	0.53 (1285)	0.83 (21,880)	**−6.24 (−7.76;−4.68)**	**<0.0001**
MCC vaccine introduction group[a]	MCCpre2004	2.09 (2784)	2.15 (2886)	1.65 (2232)	1.80 (2470)	1.69 (2347)	1.49 (2091)	1.22 (1720)	1.24 (1764)	1.03 (1467)	1.00 (1430)	0.79 (1135)	1.46 (22,326)	**−9.04 (−10.62;−7.44)**	**<0.0001**
	MCC2004-14	0.78 (1824)	0.84 (1940)	0.70 (1647)	0.67 (1561)	0.63 (1493)	0.63 (1490)	0.53 (1252)	0.53 (1258)	0.52 (1228)	0.53 (1260)	0.42 (1000)	0.62 (15,953)	**−5.74 (−6.97;−4.49)**	**<0.0001**
	noMCC	0.62 (593)	0.69 (659)	0.65 (620)	0.82 (779)	0.79 (757)	0.77 (734)	0.66 (629)	0.74 (712)	0.70 (668)	0.68 (655)	0.51 (494)	0.69 (7300)	−1.12 (−3.89;1.73)	0.3950

[a] MCCpre2004: countries that introduced MCC vaccination before 2004 (Belgium, Iceland, Ireland, the Netherlands, Spain, the United Kingdom); MCC2004-14: countries that introduced MCC vaccination during 2004–2014 (Austria, Cyprus, France, Germany, Greece, Italy, Portugal); noMCC: countries that did not have routine MCC vaccination (Denmark, the Czech Republic, Estonia, Finland, Hungary, Lithuania, Malta, Norway, Poland, Slovakia, Slovenia, Sweden). **Bold text**: Statistically significant trends.

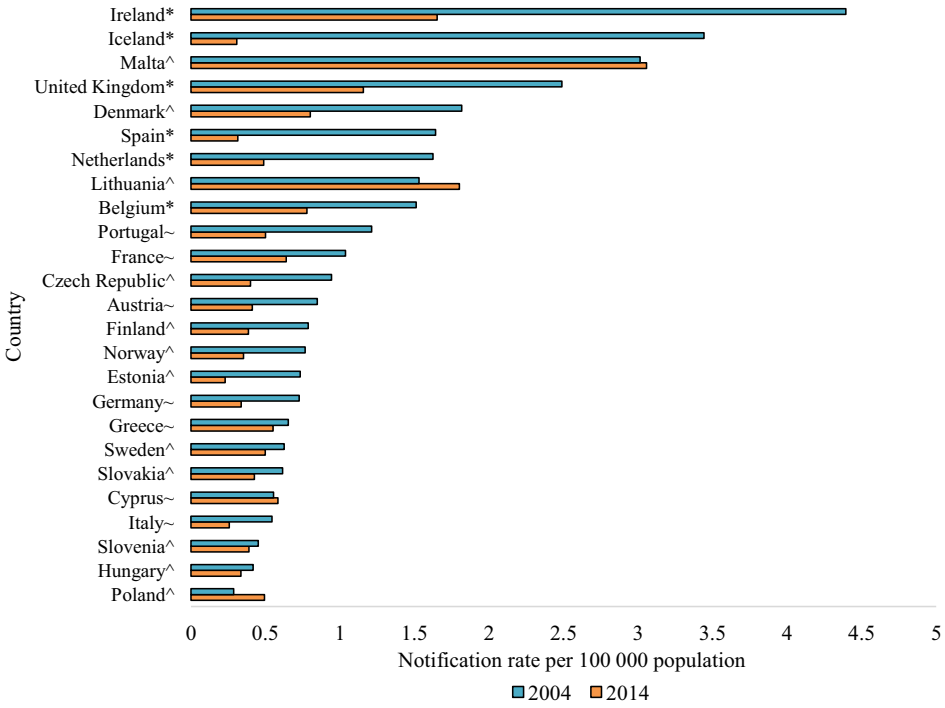

Fig. 2. Annual notification rate per 100,000 population of invasive meningococcal disease in 2004 and 2014, by country, 25 European countries. *MCCpre2004: countries that introduced MCC vaccination before 2004; ~MCC2004-14: countries that introduced MCC vaccination during 2004–2014; ^noMCC: countries that did not have routine MCC vaccination.

MCCpre2004 and MCC2004-14 countries, the initial target age group for the routine schedule were those no older than 18 months (excluding catch-up campaigns).

2.3. Data analysis

We calculated notification rates (NR) as cases per 100,000 population using population data obtained from Eurostat (www.ec.europa.eu/eurostat). We assessed temporal trends by estimating the percentage change in annual NR, using linear regression analysis of the log of the annual NR.

We compared categorical variables (gender, age group, serogroup and MCC vaccine introduction group) by chi-square test. We used adjusted residuals to assess the significance in each cell of the contingency tables. We compared age as a numerical variable across different serogroups by calculating median and interquartile ranges (IQR), and comparing them using the Kruskal-Wallis test. We used Dunn's test to perform multiple pairwise comparisons. To calculate the 95% confidence interval for the gender NR ratio, we used Poisson regression for rates using the population as exposure.

A p-value <0.05 was considered to indicate statistical significance. Statistical analyses were performed with Stata software, version 14.0.

3. Results

Data from 25 countries were included in the analysis, covering 93% of the EU/EEA population. Six countries belonged to the MCCpre2004 vaccine introduction group, seven to MCC2004-14 and 12 to noMCC (Fig. 1). Bulgaria, Croatia and Romania did not report case-based data for all years, and Luxembourg and Latvia reported serogroup data for <70% of cases.

A total of 49,269 cases of IMD were reported by the 25 countries during 2004–2014, of which 3 008 were not laboratory-confirmed and an additional 682 had unknown age and/or gender. The remaining 45,579 cases were included in the analysis. Serogroup-specific analysis was performed for 42,392 cases with known serogroup.

The overall mean annual NR was 0.9/100,000, ranging from 0.3/100,000 in Italy (n = 2051) to 2.9/100,000 in Ireland (n = 1387). There was an overall decrease of 6.6% (95%CI: −8.0%;−5.1%) annually (Table 1), with significantly decreasing trends in 19 countries. In six countries (Hungary, Lithuania, Malta, Poland, Slovenia, and Sweden), no significant trend was observed. Country-specific NRs for 2004 and 2014 are shown in Fig. 2. Infants had the highest mean NR (16.0/100,000), followed by 1–4 years olds (4.9/100,000), and 15–24 year-olds (1.4/100,000). There were significant decreasing trends in all age groups <50 years. The mean NR among males was 1.13 (95%CI: 1.11;1.16) times higher than among females (Table 1).

3.1. Serogroup analysis

During 2004–2014, SgB accounted for 74% (n = 31,529) and SgC for 16% (n = 6 573) of cases with known serogroup. There were significant decreasing annual trends for both serogroups: 8.2% (95%CI: −10.2;−6.1) for SgB and 7.0% (95%CI: −8.4;−5.5) for SgC (Table 2, Fig. 3). Significant decreasing trends in SgB were found in 18 countries, and significant decreasing trends in SgC were found in eight countries. No country presented a significant increasing trend for either serogroup.

SgY accounted for 5% of cases (n = 2087) and increased 10.6% (95% CI: 7.4;14.0) annually (Table 2, Fig. 3), driven by significant increasing trends in eight countries. No country presented a significant decreasing trend in SgY. SgW accounted for 3% of cases (n = 1246), with no significant trend (Table 2, Fig. 3). There was a

Table 2
Mean annual notification rate per 100,000 population and number of cases of invasive meningococcal disease by serogroup and age group, 25 European countries, 2004–2014.

Serogroup		B		C		W		Y		Other[a]	
		Mean annual notification rate (number of cases)	Percentage change in annual notification rate (95%CI)	Mean annual notification rate (number of cases)	Percentage change in annual notification rate (95%CI)	Mean annual notification rate (number of cases)	Percentage change in annual notification rate (95%CI)	Mean annual notification rate (number of cases)	Percentage change in annual notification rate (95%CI)	Mean annual notification rate (number of cases)	Percentage change in annual notification rate (95%CI)
Age group	<1 year	13.34 (7233)	**−7.73 (−10.71;−4.67)**	1.07 (581)	**−5.01 (−8.26;−1.64)**	0.28 (151)	−5.14 (−16.36;7.59)	0.19 (105)	**10.11 (4.98;15.48)**	0.27 (145)	−2.05 (−11.55;8.47)
	1–4 years	3.88 (8447)	**−9.38 (−11.62;−7.07)**	0.40 (1062)	**−12.14 (−14.19;−10.04)**	0.08 (167)	−3.59 (−12.50;6.22)	0.04 (85)	0.83 (−7.31;9.69)	0.10 (208)	−4.89 (−14.50;5.81)
	5–14 years	0.71 (3928)	**−9.70 (−12.50;−6.81)**	0.16 (906)	**−13.44 (−16.51;−10.26)**	0.01 (77)	−2.53 (−10.89;6.61)	0.03 (170)	**14.09 (8.87;19.57)**	0.03 (157)	−6.90 (13.51;0.23)
	15–24 years	0.91 (5723)	**−7.84 (−10.54;−5.06)**	0.27 (1703)	**−8.23 (−10.97;−5.40)**	0.04 (238)	**9.34 (3.23;15.80)**	0.07 (448)	**11.28 (3.91;19.18)**	0.02 (133)	−0.24 (−9.62;10.12)
	25–49 years	0.15 (2855)	**−5.32 (−7.58;−3.01)**	0.06 (1182)	−1.56 (−4.17;1.13)	0.01 (144)	0.56 (−13.10;16.36)	0.01 (249)	**13.77 (2.67;26.07)**	0.01 (133)	−6.02 (−13.08;1.60)
	≥50 years	0.18 (3343)	**−5.62 (−7.71;−3.47)**	0.06 (1139)	−2.16 (−6.08;1.92)	0.03 (469)	4.48 (−0.99;10.25)	0.06 (1030)	**10.24 (7.24;13.33)**	0.01 (181)	−5.36 (−10.84;0.46)
Overall		0.61 (32,529)	**−8.16 (−10.22;−6.05)**	0.13 (6573)	**−6.96 (−8.35;−5.54)**	0.02 (1246)	2.29 (−3.88;8.87)	0.04 (2087)	**10.63 (7.37;13.99)**	0.02 (957)	−4.49 (−10.83;2.30)

[a] Includes all cases reported as serogroup A, 29E, X, Z, other or non-groupable. **Bold text**: Statistically significant trends.

visible increase in SgW from 2011 to 2014 (Fig. 3), driven by a 49.4% (95% CI: 41.4;57.9) annual increase in this serogroup in the UK from 2010 to 2014. No other countries reported significant increasing trends in SgW. Other serogroups collectively accounted for 2% of cases (n = 957) and did not show a significant trend in any age group (Table 2, Fig. 3).

The NR for all serogroups was highest among infants, however, the age distribution varied between serogroups (Table 2). The median age was lowest for SgB (5 years, IQR 1–20), higher in SgC (18 years, IQR 5–37) and SgW (24 years, IQR 4–66) and highest for SgY (49 years, IQR 18–74) (p = 0.0001). Of all serogroups, SgB had the highest NR in all age groups, notably among infants where the NR of 13.3/100,000 was more than 12-fold higher than the infant NR for any other serogroup (Table 2). There was a significant decreasing trend in the NR of SgB in all age groups. SgC showed a significant decreasing trend in all age groups <25 years. An increasing trend in SgY was observed in all age groups except 1–4 year-olds. An increasing trend in SgW was observed among 15–24 year-olds (Table 2).

3.2. MCC vaccine introduction groups

Among SgC cases, there was an annual decrease of 10.2% (95% CI: −13.9%;−6.3%) in MCCpre2004 countries, and a decrease of 8.3% (95% CI: −11.3%;−5.2%) in MCC2004-14 countries. No significant trend was observed in noMCC countries. The noMCC countries had a higher SgC NR than MCCpre2004 countries from 2005 onwards and MCC2004-14 countries from 2007 onwards. In 2014, SgC accounted for 6.2% of cases in MCCpre2004 countries, 23.4% in MCC2004-14 countries, and 27.6% in noMCC countries (p < 0.0001).

In MCCpre2004 countries, the NR of SgC cases among 1–4 year-olds decreased 19.3% (95%CI: −23.1%;−15.2%) annually. Significant decreasing trends were also observed in all age groups ≥15 years old. Low numbers of SgC were reported in infants (n = 64), 1–4 year-olds (n = 129) and 5–14 year-olds (n = 136) in MCCpre2004 countries. In MCC2004-14 countries, there were significant decreasing trends in SgC in all age groups <25 years, notably 17.5% (95%CI: −20.7%;−14.1%) among 1–4 year-olds. In noMCC countries, only 5–14 year-olds showed a decreasing trend in SgC, while an increase was observed in ≥50 year-olds (Table 3). In 2014, the median age of SgC cases was 41 years in MCCpre2004 (IQR 18–53), 27 years in MCC2004-14 (IQR 10–56), and 22 years in noMCC countries (IQR 2–47.5).

There were no differences in the significance or direction of the trends for SgB, SgW or SgY between the MCC vaccine introduction groups. Trends were decreasing for SgB (MCCpre2004: −10.8% (95% CI: −12.9%;−8.6%); MCC2004-14: −5.5% (95% CI: −7.4%;−3.7%); noMCC −3.7% (95% CI: −7.1%;−0.3%)), statistically insignificant for SgW (MCCpre2004: 5.0% (95% CI: −2.9%;13.5%); MCC2004-14: −1.2% (95% CI: −6.9%;4.8%); noMCC −3.2% (95% CI: −9.6%;3.6%)) and increasing for SgY (MCCpre2004: 9.3% (95% CI: 5.3%;13.5%); MCC2004-14: 9.4% (95% CI: 6.4%;12.5%); noMCC 15.8% (95% CI: 7.4%;24.9%)).

3.3. Outcome

Data on outcome, i.e. if the patient had survived or died from IMD, were available for 90% of cases (n = 41,206), with 3 537 deaths, giving a case fatality of 8.6% for cases with known outcome. When assuming that cases with missing outcome data survived, the case fatality was 7.8%. Considering only cases with known outcome, case fatality was 14.3% among SgC, 10.3% among SgW, 10.2% among SgY and 7.4% among SgB cases. The highest case fatality observed in ≥50 year-olds (15.6%), and the lowest in 5–14 year-olds (4.8%).

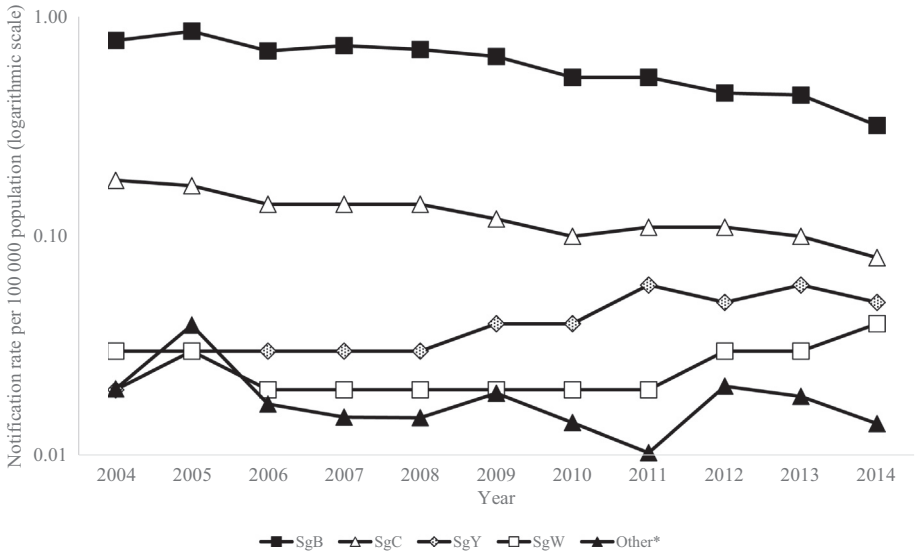

Fig. 3. Annual notification rate per 100,000 population of invasive meningococcal disease by serogroup, 25 European countries, 2004–2014. *Includes all cases reported as serogroup A, 29E, X, Z, other or non-groupable. Percentage change in annual notification rate: SgB: −8.2% (95%CI: −10.2; −6.1); SgC: −7.0% (95%CI: −8.4; −5.5); SgY: 10.6% (95% CI: 7.4; 14.0); SgW: 2.29 (95%CI: −3.88; 8.87); Other: −4.49 (95%CI: −10.83; 2.30).

4. Discussion

Although IMD is rare in Europe, it is a severe and life-threatening disease which some countries consider justifies prevention through routine vaccination. We found decreasing trends in SgC in countries who had introduced MCC vaccination into their routine national childhood immunisation programmes, but no significant change overtime in SgC in countries who had not. These results support evidence from country-specific studies from the UK [10,15,23], Spain [14,15,17], the Netherlands [11,15], Germany [18] and Italy [24,25] that routine MCC vaccination was the driving force behind a decrease in SgC. However, the decrease in SgC found in this study may not be solely attributed to MCC vaccination. In Germany for example, SgC NRs were decreasing even prior to the introduction of the MCC vaccine [18]. An increase in SgC among MCC2004-14 countries in 2012–2013 was mainly related to the emergence of a new epidemic cycle in France, an increase in incidence having been observed among unvaccinated groups when vaccination coverage was insufficient for herd protection [26].

The median age of SgC cases was highest in MCCpre2004 countries, and lowest in noMCC countries, highlighting a shift in SgC cases towards older age groups following vaccine introduction in some countries [11,18,27]. Decreasing trends in SgC were observed in different age groups depending on the MCC vaccine group. Trends were likely affected by the type of vaccination policy and implementation strategy in each country as different childhood vaccination schedules have been shown to impact herd protection. Evidence suggests that long-term immunity is higher in those vaccinated at an older age [10,14–17,28,29]. In most countries that vaccinate infants, a booster dose in the second year of life has been included, while others first vaccinate in the second year of life, relying on herd protection for infants. In addition to childhood vaccination, some countries administer MCC vaccination to adolescents and young adults, which has had a high impact on nasopharyngeal carriage [9,30] and provides both direct and herd protection [10,16,29–31]. Vaccination of older age groups has been implemented either as a time-limited catch-up campaign, where herd protection may wane, or as a routine immunisation programme, which may give longer lasting herd protection [15,18,29]. In Germany, where no catch-up campaigns were conducted, a stronger decrease in SgC compared to SgB was only observed in 1–5 year olds by 2010 [18]. Conversely, in the Netherlands [11], Spain [17], and the UK [10,16,31] where catch-up campaigns were implemented soon after routine MCC introduction, sustained decreases were observed in all age groups.

The reasons for the decrease in SgB across all age groups are unknown, however, fluctuating and unpredictable secular trends over time in serogroup-specific IMD have been reported [2,11]. During the study period, the majority of IMD cases in Europe were caused by serogroup B, with the highest NR among infants. Therefore, vaccinating with a serogroup B vaccine in the first year of life could further reduce the burden of IMD [18,24]. A multicomponent recombinant meningococcal B vaccine (4CMenB) for infants was licensed in Europe in 2013 and has been fully funded as part of the routine vaccination schedule in the UK since September 2015 and Ireland since October 2016. The 4CMenB vaccine may provide some cross-protection against other serogroups [9,20,32], although the impact on cases and nasopharyngeal carriage is not yet fully understood.

While they cause a small proportion of all cases of IMD, SgY and SgW were increasing in some countries, as reported by others [7,11,18,19,33]. The increasing trend in SgW in recent years in the UK is due to a rapidly expanding single clone belonging to clonal complex 11 [7], an increase in which is now also being observed in other countries [8]. Both SgY and SgW were more common among older age groups and countries with higher burden of SgY and SgW may choose to introduce a meningococcal quadrivalent conjugate vaccine (MCV4) against serogroups A, C, Y, and W, or replace some or all MCC vaccine doses. In the UK in 2015, the MCC dose administered to adolescents was replaced with MCV4, aiming to generate both direct and herd protection against these four serogroups [20].

Many factors are key in determining the best vaccination policy against IMD including the severity of the disease, and the age-dependent effectiveness and safety of the vaccine [34]. The impact on pathogen carriage, herd protection, and the duration of protection are also important [9,31], but may not be fully understood at the time policy decisions are made. Thus post-marketing studies covering these and other aspects are essential. Meningococcal conjugate vaccines may possibly induce capsular replacement, but there has been no evidence of this following MCC vaccine introduction [9,30]. Some context-specific factors include the IMD and age

Table 3
Notification rate per 100,000 population in 2004 and 2014, and percentage change in annual notification rate in cases of serogroup C invasive meningococcal disease by MCC vaccine introduction group* and age group, 25 European countries, 2004–2014.

MCC vaccine introduction group[a]		MCCpre2004			MCC2004-14			noMCC		
		2004 notification rate (number of cases)	2014 notification rate (number of cases)	Percentage change in annual notification rate (95%CI)	2004 notification rate (number of cases)	2014 notification rate (number of cases)	Percentage change in annual notification rate (95%CI)	2004 notification rate (number of cases)	2014 notification rate (number of cases)	Percentage change in annual notification rate (95%CI)
Age group	<1 year	0.59	0.25	−8.83	2.24	1.07	**−6.61**	1.83	1.34	−0.27
		(9)	(4)	(−19.60;3.37)	(52)	(24)	**(−11.68;−1.26)**	(17)	(13)	(−6.71;6.62)
	1–4 years	0.54	0.04	**−19.25**	1.07	0.23	**−17.47**	0.63	0.43	−0.89
		(32)	(3)	**(−23.14;−15.16)**	(102)	(21)	**(−20.67;−14.14)**	(24)	(18)	(−7.96;6.73)
	5–14 years	0.18	0.04	−6.95	0.36	0.06	**−16.82**	0.21	0.07	**−9.95**
		(27)	(7)	(−15.08;1.95)	(89)	(15)	**(−21.46;−11.90)**	(24)	(7)	**(−17.23;−2.02)**
	15–24 years	0.28	0.06	**−11.57**	0.45	0.15	**−9.02**	0.27	0.18	−4.00
		(48)	(10)	**(−17.03;−5.76)**	(126)	(38)	**(−11.83;−6.11)**	(38)	(21)	(−10.36;2.81)
	25–49 years	0.16	0.05	**−7.88**	0.05	0.06	1.38	0.02	0.07	6.06
		(79)	(24)	**(−13.15;−2.29)**	(44)	(47)	(−2.93;5.88)	(8)	(25)	(−1.85;14.60)
	≥50 years	0.14	0.04	**−10.52**	0.07	0.07	0.01	0.04	0.07	**8.08**
		(62)	(21)	**(−15.17;−5.62)**	(54)	(66)	(−6.96;7.51)	(11)	(24)	**(1.73;14.82)**
Overall		0.19	0.05	**−10.16**	0.20	0.09	**−8.25**	0.13	0.11	−1.12
		(257)	(69)	**(−13.86;−6.30)**	(467)	(211)	**(−11.25;−5.15)**	(122)	(108)	(−6.64;4.73)

[a] MCCpre2004: countries that introduced MCC vaccination before 2004 (Belgium, Iceland, Ireland, the Netherlands, Spain, the United Kingdom); MCC2004-14: countries that introduced MCC vaccination during 2004–2014 (Austria, Cyprus, France, Germany, Greece, Italy, Portugal); noMCC: countries that did not have routine MCC vaccination (Denmark, the Czech Republic, Estonia, Finland, Hungary, Lithuania, Malta, Norway, Poland, Slovakia, Slovenia, Sweden). **Bold text**: Statistically significant trends.

group-specific serogroup burden in a country, estimation of strain coverage of the vaccine (particularly concerning 4CMenB), and vaccination coverage [9,35]. Thus, high-quality surveillance, including molecular methods and fine typing, is crucial to accurately detect and assess changes in the epidemiology of IMD and ensure sufficient understanding of the need for, and impact and effectiveness of, vaccination. The priority of the vaccine and how it can be integrated into the national immunisation programme are also important to consider [9]. Considering these factors, the cost-effectiveness and feasibility of introducing a new vaccine needs to be based on country-specific assessments [34].

The surveillance of IMD on a European level allows the pooling of data from many countries and increases the precision of estimates for a rare disease. There are limitations in combining and comparing data from different countries, nevertheless, the European surveillance of IMD is long-standing [2,21], and all countries reported using comparable case definitions with consistently high-quality data. National reference laboratories in all countries participate in external quality assurance schemes and training, run by the ECDC funded European invasive bacterial disease laboratory surveillance network (IBD-Labnet). We stratified countries into three groups according to the period of MCC vaccine introduction into routine national childhood immunisation programmes. This was not intended as an impact analysis, and did not include the precise year of vaccine introduction, type of policy implemented (e.g. age of vaccination, number of doses, catch-up campaigns), nor vaccination coverage. Also, our analysis did not capture decreases in NR in the initial years after MCC introduction in MCCpre2004 countries [13], which could explain the low number of SgC cases <15 years old and insignificant trends in infants and 5–14 year-olds in these countries. Furthermore, we considered the year of introduction as the year in which the MCC vaccine was introduced in the childhood immunisation programme on a national level. However, in some countries, such as Italy, the introduction was done gradually in different regions [24], while in Greece paediatricians offered the vaccine on a large scale several years before national implementation [36]. Notwithstanding these limitations, the results of the chosen method support evidence from country-specific studies. A complete analysis of the impact of routine vaccination against IMD in Europe, incorporating the aspects mentioned above, could be of added value.

Contributions

RW, JGD, MR, NB and LPC designed the study. RW, MR, NB and the network co-authors contributed to the reporting of data to ECDC. JGD and NB managed the data analysis, with input from RW and LPC. NB drafted the manuscript. RW, JGD, MR, AE, CK, NB, LPC and network co-authors reviewed the manuscript. RW revised the manuscript based on comments from co-authors and prepared it for submission. All co-authors approved the final manuscript.

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Conflicts of interests

None.

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