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ORIGINAL ARTICLE

Low percentages of measles vaccination coverage with two doses of vaccine and low herd immunity levels explain measles incidence and persistence of measles in the European Union in 2017–2018

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Abstract
Several factors may explain why measles persisted in the European Union in 2017–2018. The study assessed mean measles vaccination coverage and anti-measles herd immunity levels in the target measles vaccination population in countries of the European Union during the 2015–2017 period. The study found that the measles vaccination coverage with two doses of vaccine was < 95% in 28 (96.5%) countries, and that the prevalence of individuals with vaccine-induced measles protection in the target vaccination population was lower than the herd immunity threshold of 94.4% in 22 (75.9%) countries during 2015–2017. The study found a significant negative correlation between the incidence of measles in 2017–2018 in different countries of the European Union and measles vaccination coverage with two doses of measles vaccine, prevalence of individuals with vaccine-induced measles protection and herd immunity levels in the target measles vaccination population during 2015–2017. Measles vaccination coverage and herd immunity levels did not improve from 2010–2015 to 2015–2017 in the European Union. Low percentages of measles vaccination coverage with two doses of vaccine and low herd immunity levels could explain measles incidence in countries of the European Union in 2017–2018. New measles prevention strategies should be developed to increase measles vaccination coverage and herd immunity levels in the European Union.

Keywords Incidence of measles · European Union · Measles vaccination coverage · Herd immunity

Introduction

In 2015, the European Region of the World Health Organization renewed their commitment to the elimination of measles by the year 2020 [1]. The elimination of measles from Europe is feasible because humans are the only reservoir for measles, effective vaccines are available, highly sensitive and specific diagnostic tests are available, and endemic measles transmission has been interrupted in America [2, 3]. Nevertheless, measles cases and outbreaks increased from 2015 to 2017–2018 [4–8]. In 2015, a total of 4396 measles cases, 442 hospitalizations, and one death due to measles were reported by countries of the European Union to the WHO's centralized information system for infectious diseases (CISID) [4–7]. In 2017, 14,451 measles cases, 7890 hospitalizations, and 32 deaths due to measles were reported by countries of the European Union to the CISID [4–7]. In 2018, 12,352 measles cases, 3017 hospitalizations, and 12 deaths due to measles were reported by countries of the European Union to the CISID [4–6, 8]. In 2018, 28% of cases occurred among children under 5 years, 18% occurred among 6–14-year-old children, and 53% occurred among individuals aged 15 or more years; and 79% of cases were unvaccinated and 21% had received one or more doses of measles vaccine [8]. The overall incidence of measles was above the elimination target (one case per million population) in 29 (97%) countries of the European Union in 2018 [8].

The strategy plan proposed by the World Health Organization to achieve measles elimination in Europe by the year 2020 is based on four main measures [9]:

1. Achieve and maintain measles vaccination coverage with two doses of MMR vaccines ≥ 95%

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2. Supplementary immunization activities to population groups at risk for measles and to individuals susceptible to measles
3. Intensive epidemiological surveillance
4. Rigorous outbreak control

Sustained high vaccination coverage with two doses of vaccine is the key preventive measure to successfully eliminating measles from Europe for two reasons. First, measles vaccination programs have reduced morbidity and mortality from measles in Europe. Second, measles vaccination programs have eliminated endemic measles from America and several countries of Europe [2, 9, 10]. In the European Union, children receive their initial measles vaccine when they are 12–15 months old and the second dose when they are 3–15 years old [11]. However, supplementary vaccination activities to immunize susceptible individuals have not been developed at either the national or regional level within the European Union [12].

The World Health Organization (WHO) Regional Office for Europe is aiming to achieve and maintain percentages of measles vaccination coverage of at least 95% with both the first and second doses of measles vaccine [3, 9]. The WHO assumes that the recommended percentages of measles vaccination coverage will generate and maintain the herd immunity required to block measles transmission in the community [3, 9, 13]. The persistence of measles in the European Union indicates therefore that measles vaccination coverage and herd immunity levels are possibly insufficient to prevent measles transmission [14].

A study carried out in 2016 found that two of the factors explaining persistence of measles in Europe in 2015 were the two-dose measles vaccination coverage < 95% and the low prevalence of individuals with vaccine-induce measles protection [15]. The objectives of this study were:

1. To assess the vaccination coverage with one and two doses of measles vaccine in the European Union from 1980 to 2017
2. To assess the mean vaccination coverage with one and two doses of measles vaccine in countries of the European Union during the 2015–2017 period
3. To assess the prevalence of individuals with anti-measles vaccine-induced measles protection, and to assess the establishment of herd immunity in the target measles vaccination population in countries of the European Union during the 2015–2017 period
4. To determine the herd immunity gaps and the additional measles vaccination coverage required to establish herd immunity in countries without herd immunity
5. To assess the association between measles incidence in 2017–2018 and measles vaccination coverage and herd immunity levels in countries of the European Union during 2015–2017
6. To compare measles vaccination coverage and herd immunity levels the European Union during the 2010–2015 and 2015–2017 periods

Material and methods

The mean percentages of vaccination coverage in the European Union with one and two doses of measles vaccine from 1980 to 2017 were calculated using the information from the WHO-UNICEF global and regional immunization system [16, 17]. The mean vaccination coverage with one and two doses of measles vaccine during 2015–2017 in different countries of the European was calculated using the information of the WHO-UNICEF global and regional immunization system [16, 17]. In each country, the mean vaccination coverage with the first dose (MCV1) and the mean vaccination coverage with second dose (MCV2) of measles vaccine during 2015–2017 were determined from the percentages of vaccination coverage reported for 2015, 2016, and 2017. The mean vaccination coverage with two doses of measles vaccine during the 2015–2017 period (V_2) was determined from the mean vaccination coverage with the first dose (MCV1) and second dose (MCV2) of measles vaccine using the formula: $V_2 = \text{MCV1} \times \text{MCV2}$. The vaccination coverage with one dose of measles vaccine (V_1) was determined using the formula: $V_1 = (\text{MCV1} - V_2) + (\text{MCV2} - V_2)$.

The establishment of herd immunity against measles in different countries of the European Union in the 2015–2017 period was determined by assessing whether the prevalence of individuals with vaccine-induced measles protection was higher or lower than the critical prevalence of 94.4% associated with herd immunity for measles viruses with R_o equal to 18. Herd immunity is defined as the indirect protection of susceptible individuals brought about by the presence of immune individuals in the population. The generation of measles epidemics depends on the average number of individuals directly infected (secondary cases) by one infectious case during the entire infectious period, when the infectious agent has entered a totally susceptible population [18, 19]. This number is called the basic reproductive number R_o. The critical prevalence of protected individuals required to establish herd immunity against measles viruses (I_c), determined using the formula $I_c = [1 - (1/R_o)]$ [11], is equal to 94.4% for measles viruses with R_o equal to 18. Anderson and May found values of R_o ranging from 12 to 18 in the review carried out in 1991 [18], and a recent review of R_o values obtained in different studies found values of R_o ranging from 6 to 27 in the pre-vaccine era and ranging from 6.1 to 45.4 in European countries [20].

The prevalence of vaccine-induced protected individuals in the target measles vaccination population was determined in each country using the formula: $I_v = (V_1 \times E_1) + (V_2 \times E_2)$. In this formula, V_1 and V_2 are the percentages of vaccination coverage with one and two doses of measles vaccine, respectively; and E_1 and E_2 are the effectiveness in preventing secondary measles cases with one and two doses of measles vaccine, respectively. Effectiveness of 92% and 95% for one and two doses of measles vaccine, respectively, were assumed in this study [21, 22].

Measles vaccination programs can reduce measles transmission by means of generating a prevalence of vaccine-induced protected individuals (I_v) and reducing the prevalence of susceptible individuals, which results in an effective basic reproductive number R that is lower than R_o depending on the prevalence of vaccine-induced protected individuals: $R = R_o (1 - I_v)$. Measles vaccination programs can block measles transmission when the prevalence of vaccine-induced protected individuals (I_v) is higher than the critical prevalence ($I_v > I_c$) [23]. In this study, herd immunity was considered established in the target measles vaccination population in countries of the European Union when the prevalence of protected individuals in the target vaccination (I_v) was equal to or higher than 94.5%.

Anti-measles herd immunity gaps (I_G) were measured in terms of the additional prevalence of protected individuals required to establish herd immunity in countries without herd immunity. The herd immunity gap was determined from the difference between the prevalence of 94.5% necessary to establish herd immunity and the country-specific prevalence of individuals with vaccine-induced measles protection (I_v): $I_G = 94.5 - I_v$. The additional measles vaccination coverage required to establish herd immunity (V_a) was determined from the herd immunity gap and measles vaccine effectiveness (E): $V_a = I_G/E$. A 95% effectiveness was assumed for the additional measles vaccine [21, 22].

The SPSS program (v. 18) was used to calculate the measles vaccination coverage with one and two doses of measles vaccine, the prevalence of individuals with vaccine-induced measles protection, and to assess the establishment of herd immunity in different countries of the European Union during the 2015–2017 period. The chi-square test was used to compare percentages, considering a $p < 0.05$ as statistically significant.

The chi-square test and the ratio of proportions (Epidat program) were used to compare the measles vaccination coverage and herd immunity levels in countries with and without herd immunity during the 2015–2017 period. The chi-square test and the ratio of proportions (Epidat program) were used to compare measles vaccination coverage and herd immunity levels in countries of the European Union during the 2015–2017 and 2010–2015 periods. A $p < 0.05$ was considered statistically significant.

The study assessed the association between the mean incidence of measles in countries of the European Union in 2017–2018 and the following percentages of measles vaccination coverage and herd immunity levels during 2015–2017:

1. Measles vaccination coverage with two doses of measles vaccine
2. Measles vaccination coverage with one dose of measles vaccine
3. Measles vaccination coverage with the first dose of measles vaccine
4. Measles vaccination coverage with the second dose of measles vaccine
5. Prevalence of individuals with vaccine-induced measles protection
6. Herd immunity gap

The mean incidence of measles in 2017–2018 was determined in different countries of the European from the incidence of measles in 2017 and 2018 reported by the European Center for Disease Control (ECDC) [7, 8]. The Pearson's correlation coefficient (SPSS program) was used to assess the association between the mean incidence of measles in 2017–2018 and the following variables: two-dose measles vaccination coverage; one-dose measles vaccination coverage; measles vaccination coverage with the first dose of vaccine; measles vaccination coverage with the second dose of vaccine; prevalence of individuals with vaccine-induced measles protection; and herd immunity gap. A $p < 0.05$ was considered statistically significant.

The t test (SPSS program) was used to compare the mean measles incidence in 2017–2018 in the following groups: countries with and without two-dose measles vaccination coverage $\geq 95\%$; countries with and without first-dose measles vaccination coverage $\geq 95\%$; countries with and without second-dose measles vaccination coverage $\geq 95\%$; and countries with and without herd immunity. A $p < 0.05$ was considered statistically significant.

A sensitivity analysis of the results obtained in the study was developed by determining the establishment of herd immunity for values of R_o ranging from 6 to 45, and values of measles vaccination effectiveness lower and higher than those assumed in the study (95% for two doses and 92% for one dose of measles vaccine). The range of R_o values considered in the sensitivity analysis was obtained in a systematic review from the studies carried out in the WHO European region [20]. The values for measles vaccination effectiveness with one and two doses of measles vaccine considered in the sensitivity analysis were 2.5% higher, 2.5% lower, and 5% lower than the reference effectiveness (95% and 92%).

Results

In the European Union, the mean vaccination coverage for the first dose of measles vaccine increased from 69.9% in 1980 to 93.9–94.7% during 2006–2017; and the mean vaccination coverage for the second dose of measles vaccine increased from 85.9% in 2000 to 89–90% during 2005–2017 (Fig. 1). The mean vaccination coverage with two doses of measles vaccine increased from 77.7% in 2000 to 84.4–86.3% during 2006–2017, but it was < 90% from 2000 to 2017 (Fig. 1).

All countries of the European Union reported percentages of vaccination coverage for the first dose of measles vaccine in 2015, 2016, and 2017, and 27 countries reported percentages of vaccination coverage for the second dose of measles vaccine in 2015, 2016, and 2017. One country (Finland) reported the vaccination coverage for the second dose of measles vaccine in 2016 and 2017, and the herd immunity assessment was carried out for this country using the mean vaccination coverage with the second dose in 2016–2017. One country (Ireland) was excluded from the analysis because it did not report the vaccination coverage for the second dose of measles vaccine during 2015–2017 to the WHO-UNICEF global and regional immunization system.

Table 1 presents the mean vaccination coverage with one and two doses of measles vaccine, the mean vaccination coverage with the first and second dose of the measles vaccine, and the prevalence of individuals with vaccine-induced measles protection in the target vaccination population in countries of the European Union during 2015–2017. The study found that the measles vaccination coverage with two doses of vaccine was < 95% in 28 countries (96.5%), and the prevalence of vaccine-induced protected individuals in the target vaccination population was lower than the herd immunity threshold of 94.4% in 22 countries (75.9%) during 2015–2017. The vaccination coverage with the first dose of measles vaccine was < 95% in 16 countries (79.3%), and the vaccination coverage with the second dose of measles vaccine was < 95% in 28 countries (96.5%).

Herd immunity was considered established in only 7 countries (24.1%) of the European Union. Herd immunity was established in the target measles vaccination population in 1 country (14.3%) with two-dose vaccination coverage ≥ 95% and 6 countries (85.7%) with two-dose vaccination coverage < 95% and 7–10% one-dose measles vaccination coverage. The herd immunity gap in terms of additional measles immunity required to establish herd immunity ranged from 0.1% in Luxemburg and Poland to 3.5% in Romania (Table 1). The additional vaccination coverage required to establish herd immunity, calculated assuming 95% effectiveness, ranged from 0.1% in Luxemburg and Poland to 3.7% in Romania.

The percentage of countries with two-dose measles vaccination coverage > 90% and first-dose measles vaccination coverage ≥ 95% was significantly higher in countries with herd immunity than in countries without herd immunity (Table 2). The percentage of countries with two-dose measles vaccination coverage ≥ 95% and second-dose measles vaccination coverage ≥ 95% was significantly higher in countries with herd immunity than in countries without herd immunity, but differences were not statistically significant.

Measles vaccination coverage indicators and herd immunity levels were higher during 2015–2017 than during 2010–2015. The percentage of countries with two-dose measles vaccination coverage ≥ 95%, two-dose measles vaccination coverage > 90%, first-dose measles vaccination coverage ≥ 95%, and second-dose measles vaccination coverage ≥ 95% were higher during 2015–2017 than during 2010–2015 (Table 3).

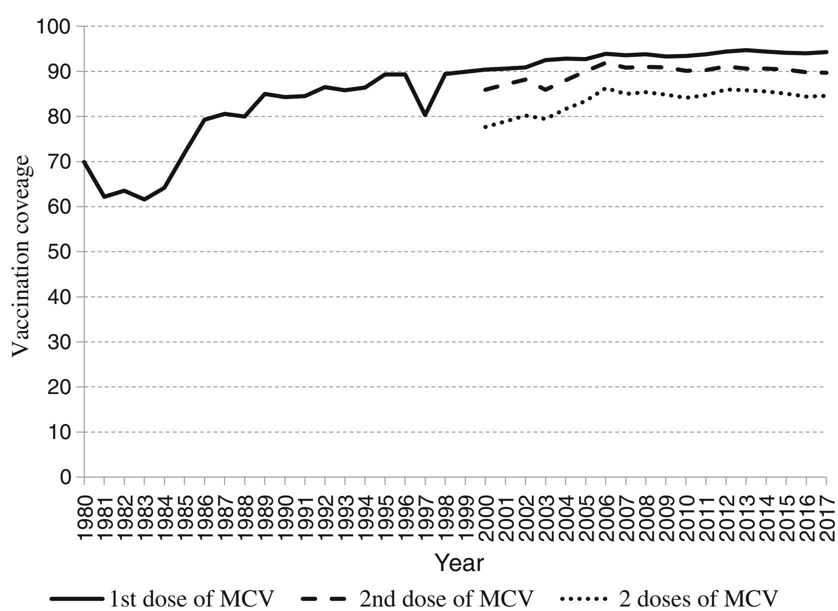

Fig. 1 Reported vaccination coverage in children for the first, second, and two doses of measles containing vaccine (MCV) in the European Union, 1980–2017. Source: WHO. Global and regional immunization profile. European Region 1980–2017

Table 1 Measles cases per million population in 2017, 2018, and 2017–18, mean vaccination coverage with one (M1) and two (M2) doses of measles vaccine, prevalence of vaccine-induced protected individuals (I_v) in the target measles vaccination population, and establishment of herd immunity during 2015–2017 in countries of the European Union

Country	Measles cases per million[8,24]			Mean measles vaccination coverage during 2015–17				Prevalence of vaccine-induced protected individuals (I_v)[a] %	Herd immunity (HI) assessment in the target vaccination population:[b] + HI established: $I_v \geq 94.5\%$ − HI not established: $I_v < 94.5\%$. Negative value = herd immunity gap[c]
	2017	2018	Mean of 2017–2018	First dose of measles vaccine %	Second dose of measles vaccine %	Two doses of measles vaccine (M2) %	One dose of measles vaccine (M1) %		
Austria	10.9	8.8	9.9	95.7	87.0	83.2	16.2	94.0	− 0.5
Belgium	32.5	10.6	21.6	96.0	85.0	81.6	17.8	93.9	− 0.6
Bulgaria	23.2	1.8	12.5	92.7	89.0	82.5	16.7	93.7	− 0.8
Croatia	1.7	5.5	3.6	90.7	95.7	86.7	12.9	94.2	− 0.3
Cyprus	3.5	17.6	10.6	90.0	88.0	79.2	19.6	93.3	− 1.2
Czech Republic	13.8	19.1	16.5	97.5	94.0	91.6	8.2	94.6	+
Denmark	0.7	1.4	1.0	94.0	84.3	79.3	19.8	93.5	− 1.0
Estonia	0.8	7.6	4.2	93.0	91.7	85.3	14.2	94.0	− 0.5
Finland	1.8	2.7	2.3	94.7	88.5	83.8	15.6	93.9	− 0.6
France	7.8	43.5	25.6	90.3	79.7	72.0	26.1	92.4	− 2.1
Germany	11.3	6.6	9.0	97.0	93.0	90.2	9.6	94.5	+
Greece	89.7	212.9	151.3	97.0	83.0	80.5	19.0	93.9	− 0.6
Hungary	3.7	1.4	2.5	99.0	99.0	98.0	2.0	94.9	+
Iceland	9.0	0	4.5	92.0	94.7	87.1	12.5	94.2	− 0.3
Italy	84.0	41.5	62.8	88.7	84.7	75.1	23.2	92.7	− 1.8
Latvia	0	12.8	6.4	95.0	90.0	85.5	14.0	94.1	− 0.4
Lithuania	0.7	10.5	5.6	94.0	92.0	86.5	13.0	94.2	− 0.3
Luxembourg	6.9	6.8	6.9	99.0	86.0	85.1	14.7	94.4	− 0.1
Malta	0	10.9	5.5	91.0	86.7	78.9	19.9	93.3	− 1.2
Netherlands	0.9	1.4	1.2	94.0	91.0	85.5	13.9	94.1	− 0.4
Norway	0.2	2.3	1.2	95.7	91.0	87.1	12.6	94.3	− 0.2
Poland	1.6	8.9	5.3	95.3	93.3	89.0	10.7	94.4	− 0.1
Portugal	3.3	16.6	9.9	98.0	95.0	93.1	6.8	94.7	+
Romania	283.8	55.3	169.6	86.0	77.0	66.2	30.6	91.0	− 3.5
Slovakia	1.1	105.2	53.2	95.3	97.3	92.8	7.1	94.7	+
Slovenia	3.4	4.4	3.9	93.0	94.3	87.7	11.9	94.3	− 0.2
Spain	3.5	4.8	4.2	96.3	94.0	90.6	9.2	94.5	+
Sweden	4.2	4.3	4.2	97.3	95.0	92.5	7.4	94.7	+
United Kingdom	4.3	14.5	9.4	92.3	88.7	81.9	17.3	93.7	− 0.8
European Union[d]	20.8	22.1	21.4	94.2	89.9	84.8	14.6	93.9	− 0.6

[a] Prevalence of vaccine-induced protected individuals: $I_v = (M2 \times 0.95) + (M1 \times 0.92)$

[b] Herd immunity assessment: Herd immunity was considered established in the target measles vaccination population when the prevalence vaccine-induced of protected individuals (I_v) was equal to or higher than 94.5% because the critical prevalence associated with herd immunity (I_c) is 94.4% for measles viruses with $R_o = 18$

[c] Herd immunity gap calculated from the critical prevalence associated with herd immunity (94.5%) less the prevalence of vaccine-induced protected individuals (I_v): $94.5 - I_v$

[d] Mean values for the 29 countries of the European Union that reported percentages of measles vaccination coverage for the first and second dose of measles vaccine during 2015–2017

Table 2 Percentage of countries with different vaccination coverage indicators in countries of the European Union with and without herd immunity in then target measles vaccination population during 2015–2017

	Countries with herd immunity[a] ($n = 7$) % (95% CI)	Countries without herd immunity[a] ($n = 22$) % (95% CI)	Coverage ratio (95% CI)
Coverage with two doses of measles vaccine ≥ 95%	14.3 (0.4–57.9)	0.0 (0–15.4)	
Coverage with two doses of measles vaccine > 90%	100 (59.0–100)	0.0 (0–15.4)	*
Coverage with first dose of measles vaccine ≥ 95%	100 (59.0–100)	31.8 (13.9–54.9)	3.14 (1.70–5.79)**
Coverage with second dose of measles vaccine ≥95%	57.1 (18.4–90.1)	4.5 (0.1–22.8)	12.6 (1.67–94.7)**

*$p < 0.001$; **$p < 0.01$

[a] Herd immunity was considered established the prevalence of individuals with vaccine-induced protection in the target vaccination population was ≥ 94.5%

The percentage of countries with two-dose measles vaccination coverage < 95% was 7.6% higher (96.5% vs. 89.3%) during 2015–2017 than during 2010–2015, and the percentage of countries without herd immunity was 1.2% higher (75.9% vs. 75%) during 2015–2017 than during 2010–2015. However, the differences observed between 2015–2017 and 2010–2015 were not statistically significant.

The mean incidence of measles in the European Union during 2017–2018 was 21.82 per million inhabitants, and measles incidence ranged from 0 per million in Malta to 902 per million in Iceland (Table 1). The study found a significant negative correlation between the mean incidence of measles in 2017–2018 and the prevalence of individuals with vaccine-induced measles protection, the two-dose measles vaccination coverage, the second-dose vaccination coverage, and the herd immunity gap in the target measles vaccination population during 2015–2017 (Table 4). By contrast, the correlation was positive with the one-dose measles vaccination coverage.

The two-dose measles vaccination coverage correlated with the one-dose measles vaccination coverage ($r = -0.99$, $p < 0.001$), first-dose measles vaccination coverage ($r = 0.77$, $p < 0.001$), second-dose measles vaccination coverage ($r = 0.93$, $p < 0.001$), prevalence of individuals with vaccine-induced measles protection ($r = 0.95$, $p < 0.001$), and herd immunity gap ($r = 0.95$, $p < 0.001$). The one-dose measles vaccination coverage correlated with the first-dose coverage ($r = -0.76$, $p < 0.001$), second-dose measles vaccination coverage ($r = -0.94$, $p < 0.001$), prevalence of individuals with vaccine-induced measles protection ($r = -0.94$, $p < 0.001$), and herd immunity gap ($r = -0.94$, $p < 0.001$). The first-dose measles vaccination coverage correlated with the second-dose measles vaccination coverage ($r = 0.50$, $p < 0.001$), prevalence of individuals with vaccine-induced measles protection ($r = 0.83$, $p < 0.001$), and herd immunity gap ($r = 0.83$, $p < 0.001$). The second-dose measles vaccination coverage correlated with the prevalence of individuals

Table 3 Percentage of countries with different vaccination coverage indicators and herd immunity in the European Union during 2010–2015 and 2015–2017

	2010–2015 period ($n = 28$)[a] % (95% CI)	2015–2017 period ($n = 29$)[b] % (95% CI)	Coverage ratio (95% CI)
Coverage with two doses of measles vaccine ≥ 95%	10.7 (2.3–28.2)	3.4 (0.1–17.8)	3.11 (0.34–28.1)
Coverage with two doses of measles vaccine < 95%	89.3 (71.8–97.7)	96.6 (82.2–99.9)	0.92 (0.80–1.07)
Coverage with two doses of measles vaccine > 90%	32.1 (13.1–51.2)	24.1 (6.8–41.4)	1.20 (0.52–2.79)
Coverage with the first dose of measles vaccine ≥ 95%	46.4 (26.2–66.7)	24.1 (6.8–41.4)	1.86 (0.87–3.95)
Coverage with the second dose of measles vaccine ≥ 95%	21.4 (8.3–40.9)	13.8 (3.9–31.7)	1.55 (0.49–4.92)
Herd immunity established ($I_v \geq 94.5\%$)[c]	25.0 (7.2–42,8)	21.4 (6.8–41.4)	1.03 (0.42–2.57)

[a] The number of countries was 28 because Finland and Ireland did not report second-dose measles vaccination coverage during the 2010–2015 period

[b] The number of countries was 29 because Ireland did not report second-dose measles vaccination coverage during the 2015–2017 period

[c] Herd immunity was considered established when the prevalence of individuals with vaccine-induced protection in the target vaccination population was ≥ 94.5%

Table 4 Linear bivariate correlation between the mean incidence of measles in 2017–2018 and measles vaccination coverage and herd immunity levels during 2015–2017 in countries of the European Union

	Linear correlation coefficient	p
Coverage with two doses of measles vaccine	− 0.533	0.003
Coverage with one dose of measles vaccine	0.523	0.004
Coverage with first dose of measles vaccine	− 0.332	0.079
Coverage with second dose of measles vaccine	− 0.559	0.002
Prevalence of individuals with vaccine-induced measles protection (I_v)	− 0.580	0.001
Herd immunity gap ($94.5 - I_v$)[a]	− 0.580	0.001

[a] The herd immunity gap indicates the additional prevalence of individuals with measles immunity requited to established herd immunity. It is calculated from 94.5 less the immunity gap because herd immunity can be considered established with the prevalence of individuals with measles protection is > 94.4%

with vaccine-induced measles protection ($r = 0.84$, $p < 0.001$), and herd immunity gap ($r = 0.84$, $p < 0.001$).

The incidence of measles per million population in 2017–2018 was lower in countries with herd immunity than in countries without herd immunity (14.20 vs. 23.84); in countries with two-dose measles vaccination coverage ≥ 95% than in countries with vaccination coverage < 95% (2.53 vs. 22.2); and in countries with second-dose coverage ≥ 95% than in countries with vaccination coverage < 95% (14.7 vs. 22.9). The differences were however not statistically significant.

The sensitivity analysis showed that the percentage of countries with herd immunity obtained in the study (24.1%) increased when the R_o of measles viruses were lower than 18 and when measles vaccination effectiveness increased (Table 5). By contrast, the percentage decreased when measles vaccination effectiveness decreased. The sensitivity analysis showed that the herd immunity assessment based on $R_o = 18$, 95% effectiveness for two doses of measles vaccine and 92% effectiveness for one dose of vaccine was very consistent because the mean incidence of measles was lower in countries with herd immunity than in those without herd immunity for values of R_o from 12 to 19. Lower values of measles vaccination effectiveness were associated with very low percentages of countries with herd immunity, while higher values of effectiveness were associated with very high percentages of countries with herd immunity.

Discussion

The study found that the persistence of measles in the European Union in 2017–2018 could be explained by the low percentages of vaccination coverage with two doses of measles vaccine and the low herd immunity levels in the target measles vaccination population in most countries of the European Union during the 2015–2018 period. First, measles incidence in 2017–2018 had a significant negative correlation with the percentage of vaccination coverage with two doses of measles vaccine, the prevalence of individuals with vaccine-induced measles protection, the percentage of vaccination coverage with the second dose of measles vaccine, and herd immunity levels in countries of the European Union during 2015–2017. Second, the vaccination coverage with two doses of measles vaccine was < 95% in 96.5% of the countries during 2015–2017. Third, herd immunity was established in only 24.1% of the countries during 2015–2017. Fourth, the percentage of countries with two-dose measles vaccination coverage < 95% increased by 7.6% and the percentage of countries without herd immunity increased by 1.2% from the 2010–2015 period to the 2015–2017 period.

The high percentage of countries (96.6%) with measles vaccination coverage with two doses of vaccine < 95% during 2015–2017 could be explained by the following factors: insufficient resources for vaccination programs; lack of adequate immunization information systems, and anti-vaccination activities. Anti-vaccination activities have reduced measles vaccination coverage in countries, areas, and communities by questioning the effectiveness, safety, and necessity for measles vaccinations [24]. The spectrum of anti-vaccinationists ranges from people who are ignorant of the effectiveness and safety of recommended vaccines to radical individuals and groups who use deliberate mistruths and falsified data in efforts to prevent the use of vaccines [25]. Nevertheless, many studies have demonstrated that measles is an effective, safe, and cost-effective preventive intervention [26]. In addition, high percentages of measles vaccination coverage are necessary to generate sufficient herd immunity to block measles transmission and protect susceptible individuals in the community [12, 13, 18].

The study found a negative correlation between the incidence of measles in 2017–2018 and two-dose measles vaccination and herd immunity levels in the target measles vaccination population during 2015–2017. These correlations indicate that vaccination of children aged 1–15 years old with two doses of measles vaccine could reduce the incidence of measles in children as well as in other population groups. Measles vaccination with the two-dose measles vaccine could reduce measles by direct and indirect protection in the target

Table 5. Sensitivity analysis of the results obtained in the study in terms of percentage of countries of the European Union with and without herd immunity, and mean incidence of measles (per million population) in 2017−18 in countries of the European Union with and without herd immunity. The Ro values considered in the sensitivity analysis ranged from 6 to >20. The values for measles vaccination effectiveness with two doses (E_1) and one dose (E_2) of measles vaccine considered in the sensitivity analyses were the values assumed in the study (95% and 92%), and values 2.5% higher, 2.5% lower and 5% lower.

R_o for measles viruses	Herd immunity assessment[b]		Effectiveness for measles vaccination with two doses (E_1) and one dose (E_1) of measles vaccine												
			E_1= 95% E_2= 92%			E_1= 97.4% E_2= 94.3%			E_1= 92.6% E_2= 89.7%			E_1= 90.25% E_2= 87.4%		
	Ic[a] %	Herd immunity established (I > Ic)	Countries with herd immunity No.	%	Mean incidence of measles Cases per million	Countries with herd immunity No.	%	Mean incidence of measles Cases per million	Countries with herd immunity No.	%	Mean incidence of measles Cases per million	Countries with herd immunity No.	%	Mean incidence of measles Cases per million
6	83.3	yes	28	96.5	21.9	29	100	21.5	28	96.5	21.9	28	96.5	21.9
		no	1	3.5	10.6	0	0	–	1	3.5	10.6	1	3.5	10.6
7	85.7	yes	28	96.5	21.9	29	100	21.5	28	96.5	21.9	27	93.1	11.2
		no	1	3.5	10.6	0	0	–	1	3.5	10.6	2	6.9	58.0
8	87.5	yes	28	96.5	21.9	29	100	21.5	27	93.1	11.2	26	89.7	11.2
		no	1	3.5	10.6	0	0	–	2	6.9	58.0	3	10.3	110.5
9	88.9	yes	28	96.5	21.9	29	100	21.5	26	89.7	11.2	21	72.4	9.0
		no	1	3.5	10.6	0	0	–	3	10.3	110.5	8	27.6	54.5
10	90	yes	27	93.1	11.2	29	100	21.5	25	86.2	10.7	1	3.4	2.5
		no	2	6.9	58.0	0	0	–	4	13.8	89.3	28	96.6	22.2
11	90.9	yes	26	89.7	11.2	29	100	21.5	23	79.3	8.6	0	0.0	–
		no	3	10.3	110.5	0	0	–	6	20.7	70.9	29	100.0	21.5
12	91.7	yes	26	89.7	11.2	29	100	21.5	13	44.8	9.6			
		no	3	10.3	110.5	0	0	–	16	55.2	31.2			
13	92.3	yes	25	86.2	10.7	29	100	21.5	1	3.4	2.5			
		no	4	13.8	89.3	0	0	–	28	96.6	22.2			
14	92.9	yes	24	82.8	8.5	29	100	21.5	0	0.0	–			
		no	5	17.2	84.0	0	0	–	29	100.0	21.5			
15	93.3	yes	23	79.3	8.6	28	96.5	21.9						
		no	6	20.7	70.9	1	3.5	10.6						
16	93.8	yes	20	69.0	8.8	28	96.5	21.9						
		no	9	31.0	49.8	1	3.5	10.6						
17	94.1	yes	13	44.8	9.6	28	96.5	21.9						
		no	16	55.2	31.2	1	3.5	10.6						
18	94.4	yes	7	24.1	14.2	28	96.5	21.9						
		no	22	75.9	23.8	1	3.5	10.6						
19	94.7	yes	1	3.4	2.5	27	93.1	11.2						
		no	28	96.6	22.2	2	6.9	58.0						
25	96.1	yes	0	0.0	–	22	75.9	15.4						
		no	29	100.0	21.5	7	24.1	40.6						
30	96.7	yes				9	31.0	12.4						
		no				20	69.0	25.6						

Table 5. (continued)

R_o for measles viruses	Herd immunity assessment[b]		Effectiveness for measles vaccination with two doses (E_1) and one dose (E_1) of measles vaccine							
			E_1= 95% E_2= 92%		E_1= 97.4% E_2= 94.3%		E_1= 92.6% E_2= 89.7%		E_1= 90.25% E_2= 87.4%	
	Ic[a] %	Herd immunity established (I > Ic)	Countries with herd immunity No. %	Mean incidence of measles Cases per million	Countries with herd immunity No. %	Mean incidence of measles Cases per million	Countries with herd immunity No. %	Mean incidence of measles Cases per million	Countries with herd immunity No. %	Mean incidence of measles Cases per million
35	97.2	yes			1 3.5	2.5				
		no			28 96.5	22.2				

a. The critical prevalence of protected individuals was calculated from: Ic = 1 − (1/Ro).

b. Herd immunity assessment: Herd immunity was considered established in the target vaccination population of each country when the prevalence of protected individuals (I) was higher than the critical prevalence associated with herd immunity (I > Ic). For example, for measles viruses with Ro=18, herd immunity was considered established when prevalence of protected individuals was ≥94.5% and it was considered not established when the prevalence was <94.5%.

vaccination population and by indirect herd immunity protection in other population groups. In fact, 45% and 53% of cases occurred among individuals aged 15 or more years in 2017 and 2018 [7, 8]. Indirect herd immunity effects have been assessed using modelling studies where dynamics of measles is modelled under varying vaccination strategies [27]. A randomized controlled trial of Hutterite colonies carried out in Canada assessing the indirect protective effectiveness of vaccinating more than 80% of children and adolescents with influenza vaccine obtained a 60% indirect effectiveness in terms of reduction of laboratory-confirmed influenza among unvaccinated community members [28]. Similar studies could be developed to assess the indirect measles protection of the population achieved with measles vaccination during childhood.

This study has several limitations. First, herd immunity was assessed by comparing the prevalence of individuals with vaccine-induced measles protection and the critical prevalence associated with herd immunity. This method is based on the following assumptions: (1) homogeneous mixing of individuals within the population, and (2) homogeneous distribution of protected individuals within the population [18, 19]. Nevertheless, it is possible to assume a homogeneous mixing of persons and homogeneous distribution of protected individuals within the measles target population [12, 13]. Second, herd was assessed immunity in different countries of the European Union using the critical prevalence of protected individuals of 94.4% for measles viruses with a R_o equal to 18. Lower R_o values would increase the percentage of countries with herd immunity and higher R_o values would decrease the percentage of countries with herd immunity. Nevertheless, it was necessary to assume a R_o of 18 for assessing the establishment of herd immunity against most measles viruses; and the sensitivity analysis showed that the R_o value, which was assumed in the study, was optimal. Third, the prevalence of individuals in different countries with vaccine-induced measles protection was calculated by assuming a measles vaccination effectiveness of 95% in preventing secondary cases of measles when two doses of vaccine were administered and 92% effectiveness when one dose of vaccine was administered. Higher and lower values of effectiveness would increase and decrease the percentage of countries with herd immunity, respectively. Nevertheless, these values of effectiveness were obtained from the Cochrane Collaboration review [21]; and the sensitivity analysis showed that the values of effectiveness assumed in the study were optimal for determining herd immunity levels in the European Union. Fourth, the analysis carried out in this study used the information on measles incidence and measles vaccination coverage reported by countries of the European Union to the ECDC information system and the WHO-UNICEF global and regional immunization systems, respectively. This information was validated by the ECDC and the World Health Organization, although it is subject to potential bias due to underreporting of measles cases and to misreporting of measles vaccination coverage. The annual percentages of measles vaccination coverage reported by different countries of the European Union to the WHO-UNICEF global and regional immunization system is obtained using two basic methods: administrative data and survey data [29]. The annual vaccination coverage determined using administrative data is obtained from the number of vaccines administered in different vaccination centers (numerator) and the target population (denominator). The main advantage of this information system is that it is possible to collect and review the number of vaccines administered per month in different vaccination centers and obtain the aggregated national vaccination coverage per year. The main disadvantage is that it is subject to numerator and denominator bias. The vaccination coverage obtained from national representative surveys is subject to less potential bias than the administrative method. The main disadvantages of the survey method are that it is necessary to obtain a representative sample of the population (numerator and denominator) and it is subject to potential respondent recall bias.

Great elimination efforts have been made in Europe in the last 20 years, but measles cases and outbreaks are still occurring in countries of the European Union [8]. The results obtained in this study indicates that it is necessary to increase two-dose measles vaccination coverage in children and to conduct supplementary vaccination programs to increase measles immunity in population groups with low measles immunity levels. Advanced immunization information systems could be developed for detecting unvaccinated individuals and areas and population groups with low measles vaccination rates, but they can not be used to detect areas and population groups with low anti-measles immunity levels due to primary vaccination failures and waning vaccine-induced immunity [30]. The difficulties for increasing the two-dose measles vaccination coverage and for detecting population pockets with low measles immunity levels supports the development of the following measles prevention strategies: (1) supplementary measles vaccination activities based on mass “catch-up” vaccination campaign in low coverage/low immunity population groups and periodic “follow up” vaccination campaigns, (2) screening for measles antibody levels and vaccination of susceptible individuals, and (3) vaccination of adults. Supplementary catch-up vaccinations are recommended for children, adolescents, and adults who have not received the first or second dose of measles vaccine or have lost their vaccination records [3]. The catch-up and follow-up measles vaccination strategy was used by American countries in 1980–1990 and has succeeded in interrupting the transmission of measles [31]. During the campaign, all children aged 1–14 years were offered vaccination, regardless of previous vaccination status [31]. Romania conducted a nationwide measles vaccination campaign in response to an outbreak of more than 30,000 measles cases in 1996–1998 [32]. In this campaign, 2.1 million children aged 7–18 years were vaccinated against measles from October 1998 through January 1999, and measles susceptibility was reduced from 10 to 4% among children aged 7–14 years, and from 15 to 5% among children aged 15–18 years [32]. Romania serves as model for countries with similar infrastructure in that it demonstrates the feasibility of conducting a safe and successful nationwide measles immunization campaign.

The strategy of measles prevention based on screening and vaccination of susceptible individuals could increase measles vaccination coverage and establish herd immunity in areas and population groups with low levels of measles immunity, but this strategy has not been developed in the European Union. Measles prevention programs based on screening and vaccination of susceptible individuals should be developed with the following objectives: (1) to detect and immunize susceptible individuals in areas and population groups without herd immunity; (2) to detect and immunize susceptible individuals with a high-risk for measles infections; (3) to detect and immunize health professionals and adults who work in healthcare centers; (4) to detect and immunize susceptible close-contacts of high-risk individuals; and (5) to detect and immunize susceptible individuals of the target measles vaccination population.

In conclusion, the study determined that the incidence of measles in the European Union in 2017–2018 was associated with the low vaccination coverage with two doses of measles vaccine, the low prevalence of individuals with vaccine-induced measles protection, and the low herd immunity level in the target measles vaccination population during 2015–2017. To meet the goal of measles elimination in the European Union, it is necessary to improve routine measles immunization coverage, and to conduct supplementary measles vaccination campaigns among population groups with low measles immunity levels.

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1. http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragemcv1.html
2. http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragemcv2.html

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

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