RISK ASSESSMENT

Who is at risk for measles in the EU/EEA?

Identifying susceptible groups to close immunity gaps towards measles elimination

28 May 2019

Summary

A large epidemic of measles has affected the EU/EEA Member States in the past three years, with 44 074 cases reported to ECDC by 30 Member States between 1 January 2016 and 31 March 2019. This is an exceptionally high number of cases compared to the previous three years (2012–2015). In this period, all EU/EEA countries reported measles cases, with an average annual notification rate in 2016–2019 of 26.1 per million people. Member States presented heterogeneous epidemiological profiles, proportion of susceptible individuals and vaccination coverage data over time.

Based on ECDC's epidemiological assessment, there is a high risk of continued widespread circulation of measles in EU/EEA in the near future, as long as significant immunity gaps and suboptimal vaccination coverage remain. We have focused on three of the main factors driving this risk:

- A large pool of individuals susceptible to measles in the EU/EEA, due to low historical and current vaccination coverage. Due to failures to vaccinate, over four-and-a-half million children and teenagers born in the EU/EEA in the last 20 years are unnecessarily susceptible to measles. This number equals almost one full birth EU/EEA cohort. The total number of people susceptible to measles in the EU/EEA will greatly exceed this figure after accounting for infants too old to be protected by maternal antibodies but too young to be vaccinated, and the substantial immunity gaps that exist among adults born pre-1999. Only four EU/EEA Member States achieved the WHO target of 95% vaccination coverage for two doses of measles-containing vaccine (MCV) in 2017 compared to 14 in 2007.
- A high burden of measles among infants and adults, the groups at the highest risk of complications. EU/EEA cases have become older over the past ten years, with the median (interquartile range) age of cases increasing from 10 (2–18) years in 2009–10 to 17 (3–31) years in 2018–19. Adults aged 20 years and above represented 35% of reported cases in 2016–19, and nineteen countries have adults as the most affected age group. In 2016–19, the average annual notification rates were highest in infants, up to 44 times higher than the other age groups. Almost half (45%) of all measles deaths were reported in infants.
- The continued potential of importations, which can worsen existing outbreaks or start new ones in communities where measles is not currently circulating and where immunity gaps persist. In 2016–2019 almost half (43%) of the cases imported into EU/EEA countries acquired their infection in another EU/EEA country, mainly those which were endemic for measles and/or experiencing large outbreaks. As measles continues to circulate widely within the region, it remains an EU-wide threat capable of affecting any country with immunity gaps.

Measles is a serious cross-border threat to health in the EU, even though most Member States are deemed to have interrupted endemic transmission. Re-establishment of transmission in these Member States is possible when vaccination coverage is suboptimal and immunity gaps remain.

Options for response

For public health measures, please refer to the 'Options for response' section.

Suggested citation: European Centre for Disease Prevention and Control. Who is at risk for measles in the EU/EEA? Identifying susceptible groups to close immunity gaps towards measles elimination. Stockholm: ECDC; 2019.

Public health issue

What is the risk of continued widespread circulation of measles in the EU/EEA and what factors are driving this risk?

Consulted experts

ECDC experts: Cornelia Adlhoch, Sabrina Bacci, Chiara Bellegarde de Saint Lary, Sergio Brusin, Nick Bundle, Edoardo Colzani, Grazina Mirinaviciute, Teymur Noori, Lucia Pastore Celentano, Benedetto Simone.

External experts (in alphabetical order of countries):

Belgium: Chloé Wyndham-Thomas (Sciensano)
Bulgaria: Nadezhda Vladimirova (National Centre of Infectious and Parasitic Diseases)
Canada: Natasha Sarah Crowcroft (University of Toronto)
Croatia: Bernard Kaić and Vesna Višekruna Vučina (Croatian Institute of Public Health)
Denmark: Palle Valentiner-Branth (Statens Serum Institut)
Estonia: Natalia Kerbo (Health Board)
Finland: Mia Kontio (National Institute for Health and Welfare)
France: Daniel LEVY-BRUHL and Denise ANTONA (French Public Health Agency)
Germany: Dorothea Matysiak-Klose (Robert Koch Institute)
Greece: Theano Georgakopoulou (Hellenic Centre for Disease Control and Prevention)
Italy: Antonietta Filia (National Institute of Health)
Latvia: Darja Vasilevska (Centre for Disease Prevention and Control)
Lithuania: Algirdas Griškevičius (National Public and Health Surveillance laboratory) and Loreta Ašoklienė (on behalf of the Department of Public Health, Ministry of Health of the Republic of Lithuania)
Netherlands: Irene Veldhuijzen (National Institute for Public Health and the Environment (RIVM))
Romania: Adriana Pistol and Aurora Stanescu (National Institute of Public Health)
Slovenia: Katarina Prosenc Trilar (National Laboratory for Health, Environment and Food) and Marta Grgič Vitek (National Institute of Public Health)
Spain: Josefa Masa Calles and Noemí López-Perea (Instituto de Salud Carlos III)
Sweden: Hélène Englund (The Public Health Agency of Sweden)
United Kingdom: Jamie Lopez Bernal (Public Health England)

The EU/EEA Operational Contact Points for measles and the National Focal Points for Vaccine-Preventable Diseases were approached for a preliminary review of the data presented in Annex 1.

All consulted experts submitted declarations of interest; a review of these declarations did not reveal any conflict of interest.

Disease background

Measles is an acute, highly infectious illness caused by viruses of the species Measles *morbillivirus*. The disease is transmitted via airborne respiratory droplets, or by direct contact with nasal and throat secretions of infected individuals. The main symptoms are fever, rash, cough, coryza and conjunctivitis. The measles rash, an erythematous maculopapular exanthema, develops 2–4 days after the onset of fever and spreads from the head to the body over the following 3–4 days. The first symptoms appear on average 10 days after exposure, but with a range of 7–21 days from exposure to onset of fever. Complications can include pneumonia, encephalitis, otitis media, diarrhoea, laryngotracheo-bronchitis and subacute sclerosing panencephalitis. The period of communicability is usually 4 days before rash onset to 4 days after rash appearance. Mortality from measles is predominantly caused by complicating bacterial infections. Case fatality is estimated at 1–3 per 1 000 cases. Children under 5 years, immunocompromised individuals and adults above 20 years of age are at higher risk of severe disease, complications and death following infection [1].

Measles is preventable by vaccination, which provides lifelong immunity in most recipients. Due to the very high basic reproduction number (R_0, estimated between 12 and 18 new infections deriving from an index case), a vaccine uptake of at least 95% with two doses of measles-containing vaccine (MCV) in the target population is recommended to interrupt disease circulation and achieve elimination. More details on measles can be found on the ECDC factsheet [2] and the ECDC health topic page on measles [3].

Event background

A resurgence of measles has been observed since October 2016 in the EU/EEA, with outbreaks in several Member States reported to ECDC and described in the literature [4-10].

Several countries outside the EU/EEA, with important connections to Europe, are also currently experiencing significant or unexpected outbreaks of measles, including Ukraine, Madagascar, Brazil, Venezuela, the United States, Philippines and Japan. Further information on measles outbreaks worldwide can be found in ECDC's Communicable Disease Threats Reports [11].

Measles elimination status in the WHO European Region

An expert advisory committee, convened by the World Health Organization (WHO) in 2010, stated that 'global measles eradication is biologically, technically and operationally feasible' [12, 13]. Eradication is defined as the worldwide interruption of measles transmission in the presence of a verified, well-performing surveillance system [14]. Under the WHO Global Vaccine Action Plan, measles is targeted for elimination in the five WHO Regions by 2020 [15]; all countries of the WHO European Region, and therefore all EU/EEA countries, agreed, by adopting the European Vaccine Action Plan 2015–20 (EVAP), that the elimination of measles is feasible. The World Health Organisation defines elimination as

> 'the absence of endemic measles […] cases in a defined geographical area for a period of at least 12 months, in the presence of a well-performing surveillance system'.

Regional elimination can be declared after 36 or more months of the absence of endemic measles or rubella in all Member States [14].

The Regional Verification Commission for Measles and Rubella Elimination (RVC) was established in 2011 [16] and monitors progress towards elimination of measles in the WHO European Region. The RVC annually reviews data from the preceding calendar year on the epidemiological situation, molecular epidemiology, surveillance performance and population immunity; as submitted by National Verification Committees in the Member States [17].

In 2014, in the WHO European Region, the verification procedures were modified by the RVC to allow verification of elimination at the national level as opposed to only at the regional level [18]. In two other WHO Regions (Western Pacific and South East Asia) the process has been similar [19, 20], while in the WHO Region of the Americas verification was postponed until all countries had eliminated the disease [21]. So far, the Region of the Americas is the only one where in 2016 measles was declared as eliminated [22]. At the seventh meeting of the RVC in June 2018, 37 (23 of which are in EU/EEA) countries in the WHO European Region were declared to have reached the elimination goal for measles, based on the 2017 data review. Additionally, two Member States (Austria and Poland) were assessed to have interrupted endemic transmission for 24 months. Five Member States (Belgium, France, Germany, Italy and Romania) were assessed to still have endemic transmission of measles (Table 1) [17]. Five non-EU/EEA countries were assessed to still have endemic transmission in the WHO Europe Region. Of these, four share land borders with the EU/EEA: Bosnia and Herzegovina, Russia, Serbia and Ukraine. Four additional countries, including two that share land borders with the EU/EEA (Switzerland and Turkey), were assessed to have interrupted endemic transmission (Table 1).

Although most individual Member States have achieved elimination status, the elimination of measles is yet to be achieved in the WHO European Region as a whole. As expected, several countries that were assessed to have eliminated measles reported sporadic cases or outbreaks due to importation in 2017 and 2018 [23, 24]. In countries that have eliminated measles [25], intense movement of people to and from countries endemic for measles, poses a threat not only of importation but also of sustained transmission in areas and communities with suboptimal vaccination coverage.

Table 1. Measles elimination status of the WHO European Region, 2017 data review of the Regional Verification Commission for Measles and Rubella elimination (EU/EEA countries in green)

Elimination status	Country
Countries that have eliminated the disease (N=37, **23** of which are EU/EEA countries)	Bulgaria, Croatia, Cyprus, the Czech Republic, Denmark, Estonia, Finland, Greece, Hungary, Iceland, Ireland, Latvia, Lithuania, Luxembourg, Malta, the Netherlands, Norway, Portugal, Slovakia, Slovenia, Spain, Sweden, the United Kingdom Albania, Andorra, Armenia, Azerbaijan, Belarus, Israel, Monaco, Montenegro, Moldova, North Macedonia, San Marino, Tajikistan, Turkmenistan, Uzbekistan
Countries with interrupted endemic transmission for 24 months (N=5, **2** of which are EU/EEA countries)	Austria, Poland Kyrgyzstan, Switzerland, Turkey

Elimination status	Country
Countries with interrupted endemic transmission for 12 months (N=1, no EU/EEA countries)	Kazakhstan
Countries with endemic transmission (N=10, **5** of which are EU/EEA countries)	Belgium, France, Germany, Italy, Romania Bosnia and Herzegovina, Georgia, Russia, Serbia, Ukraine

Movement of people towards and within the EU/EEA

A total of 4.4 million people immigrated to one of the EU countries during 2017, while at least 3.1 million emigrants were reported to have left EU countries. There are an estimated 2 million citizens of non-EU countries, 1.3 million people with citizenship of a different EU country from the one to which they immigrated, and around 1 million people who migrated to an EU country of which they had citizenship (for example, returning nationals or nationals born abroad). The number of people residing in an EU country with citizenship of a non-member country on 1 January 2018 was 22.3 million, representing 4.4% of the EU population. In addition, there were 17.6 million persons living in one of the EU countries on 1 January 2018 with the citizenship of another EU country [26].

According to the International Air Transport Association (IATA), there were around 422 600 000 international travellers within the EU/EEA in 2017. IATA data refer to the number of flight passengers and therefore and do not take into account movement of people using other means of transport [27].

Methods

This risk assessment is based on analyses at the level of individual EU/EEA country, and where appropriate, for the entire EU/EEA. We used data on measles cases, vaccination coverage, vaccination schedules and measles elimination status, with the objectives of:

- describing the epidemiology of measles cases reported by 30 EU/EEA countries;
- describing country-level trends in vaccination coverage since 1980; and
- estimating the number of individuals born in the EU/EEA since 1999 and of an age eligible for vaccination that are non-immune due to missed vaccination or not being infected

One-page country profiles that were prepared using data from a range of sources formed the basis of our assessment. We shared draft profiles for comment with ECDC Coordinating Competent Bodies in Member States, with the resulting comments incorporated to the extent possible.

The first section of the results chapter describes measles epidemiology in the EU/EEA in two periods: the ten-year period 1 January 2009 to 31 March 2019, chosen to provide a historical perspective; and the 39-month period 1 January 2016 to 31 March 2019, chosen as it covers the duration of the current EU/EEA-wide epidemic. Figures in this section were generated by analyses of EU/EEA-level data and by aggregating data from the country profiles.

The second part of the results section includes tables with selected data from and a qualitative interpretation of the country profiles. Each profile comprises six figures and one table. The table and three of the figures focus on the epidemiology of the current epidemic, the other three figures incorporate data from longer periods. Individual country profiles are accessible via the ECDC website (see Annex 1).

A detailed description of each data source and methods used for all analysis in this risk assessment is presented in Annex 2.

Limitations

The limitations in the available data and the methods used to analyse them should be considered as part of the interpretation of the results of this risk assessment. A full description is available in Annex 3.

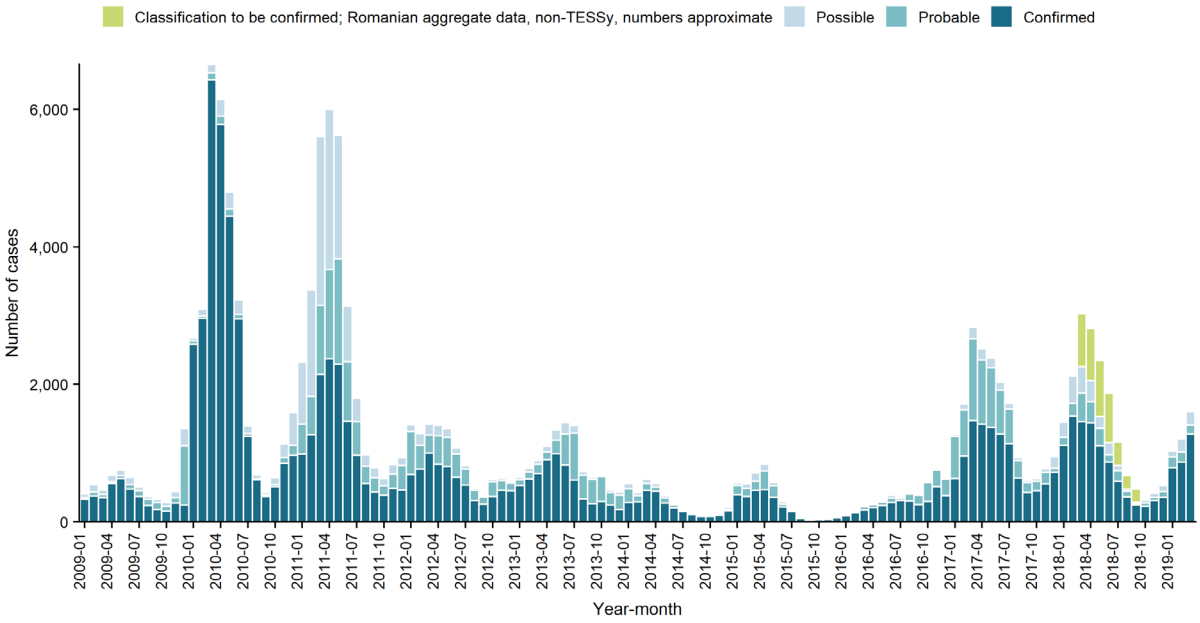
Results

Measles epidemiology in the EU/EEA

Temporal trends of reported cases from January 2009 to March 2019

Between 1 January 2009 and 31 March 2019, 144 954 cases of measles were reported by EU/EEA Member States. Multiple countries were affected by large outbreaks in 2010 and 2011, most notably Bulgaria (22 162 cases), France (19 985), Italy (8 161), Romania (4 352) and Spain (3 816). Between 2012 and 2016, the number of reported cases declined substantially before increasing again, with a four-fold increase in cases in 2017 (18 363) and 2018 (17 228), compared to 2016 (4 642). In 2019, a total of 3 841 cases have been reported to date (Figure 1).

Figure 1. Number of measles cases by month and case classification, 1 January 2009 to 31 March 2019, EU/EEA countries (n = 144 954)



Case numbers shown are approximate, as based on more than one data source for 2018. 8 cases with missing month used for statistics in TESSY have been excluded. Sources: TESSy case-based data, aggregate data and Romanian aggregate data (non-TESSy). Romanian aggregate data describe all cases as confirmed, but their final classification will be assigned upon upload to TESSy. Thirty EU/EEA countries reported data for the whole period with the exception of March 2019.

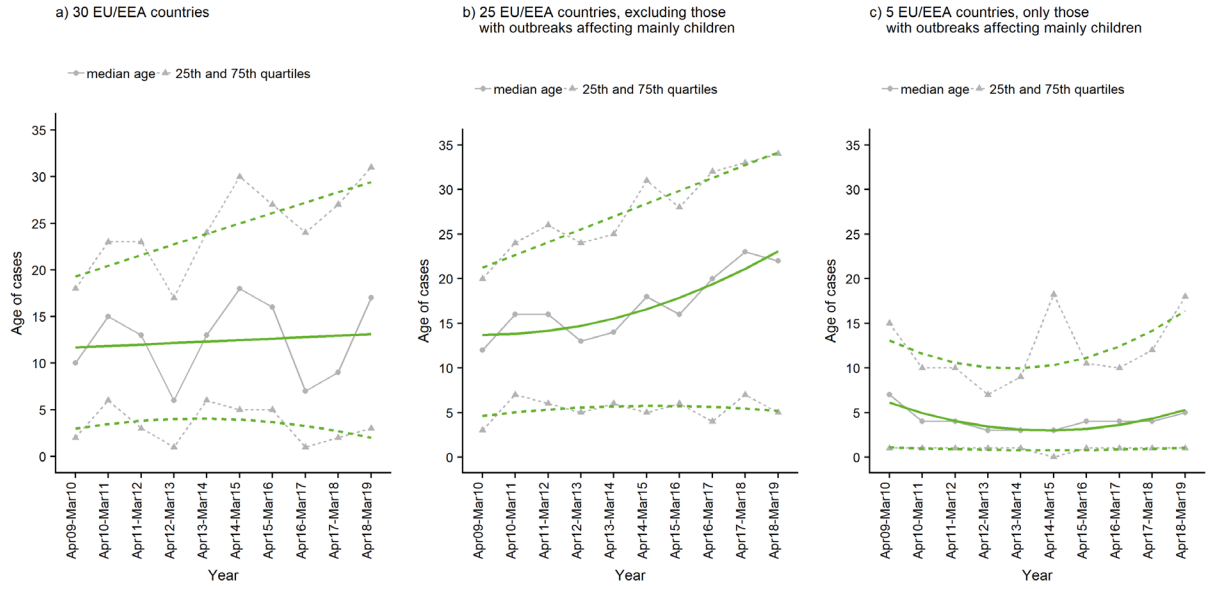
Age distribution in the last ten years

There was a general trend of increased age of cases over the last ten years, with considerable between-year fluctuation. Across the EU/EEA, the median age of cases reported annually increased from 10 years in the period April 2009 to March 2010 to 17 years in the period April 2018 to March 2019. The annual age distribution also became more skewed, with the 75th centile increasing from 18 years to 31 years (Figure 2a). These figures do not take into account cases reported as aggregate data (AGD) to The European Surveillance System (TESSy)[1], including the many children affected by the Bulgarian outbreak in 2010 (22 005 cases, 59% aged under 10 years).

The age distribution is affected by countries reporting case-based data (CBD) during outbreaks affecting mainly children, namely Romania (25 789 cases in the period), Greece (3 472), Bulgaria (2 836), Slovakia (724) and Cyprus (47). If these countries are excluded from the analysis, the increasing trend in the age distribution for the remaining 25 EU/EEA Member States becomes even more pronounced (median: 12 years in 2009–10 to 22 years in 2018–19; 75th centile 20 to 34 years), and the between-year variation present in the underlying annual estimates is greatly reduced (Figure 2b). Restricting the data to only those five countries with outbreaks affecting children reveals a U-shaped pattern; the median age was slightly higher in periods during which there was high circulation in EU/EEA (Figure 2c).

[1] https://ecdc.europa.eu/en/publications-data/european-surveillance-system-tessy

Figure 2. Median age and interquartile range (IQR) of measles cases per year, 1 April 2009 to 31 March 2019, a) 30 EU/EEA countries; b) 25 EU/EEA countries (excluding Romania, Greece, Slovakia, Bulgaria and Cyprus), c) Romania, Greece, Slovakia, Bulgaria and Cyprus only

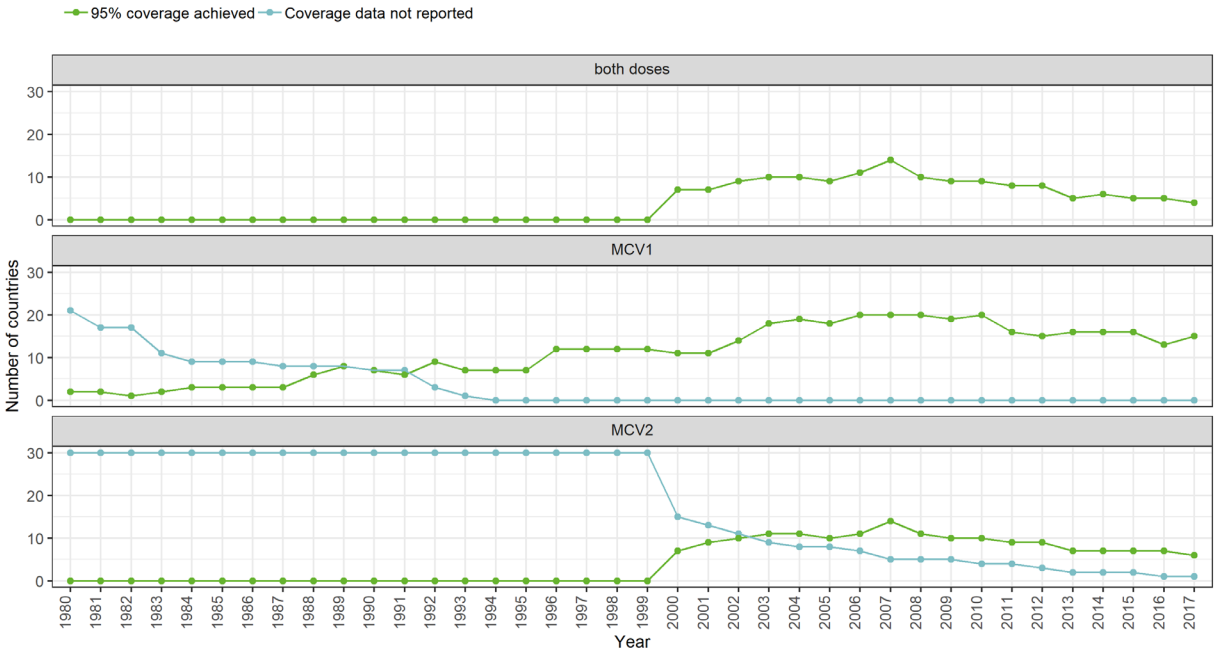


LOESS-smoothed trend shown in green. Source: TESSy CBD

Trends in vaccination coverage in EU/EEA countries

In recent years, there has been a decreasing trend in the number of EU/EEA countries achieving the WHO target of 95% vaccination coverage for two doses of MCV, falling from 14 countries in 2007 to four in 2017. This cannot be explained by non-reporting of coverage data since there has been a steady reduction in the number of countries not reporting data for the second dose (MCV2) since 2000 and complete reporting for the first dose (MCV1) since 1994. The reduction is due to a fall in the number of countries achieving 95% coverage for both MCV1 and MVC2, which have been going down, respectively, since 2010 and 2007 (Figure 3).

Figure 3. Number of countries per year with missing vaccine coverage data (blue) or reporting 95% coverage for dose 1, dose 2 and both doses of MCV (green), EU/EEA countries, 1980 to 2017



MCV: measles-containing vaccine. Source: WHO/UNICEF estimates of national immunisation coverage.

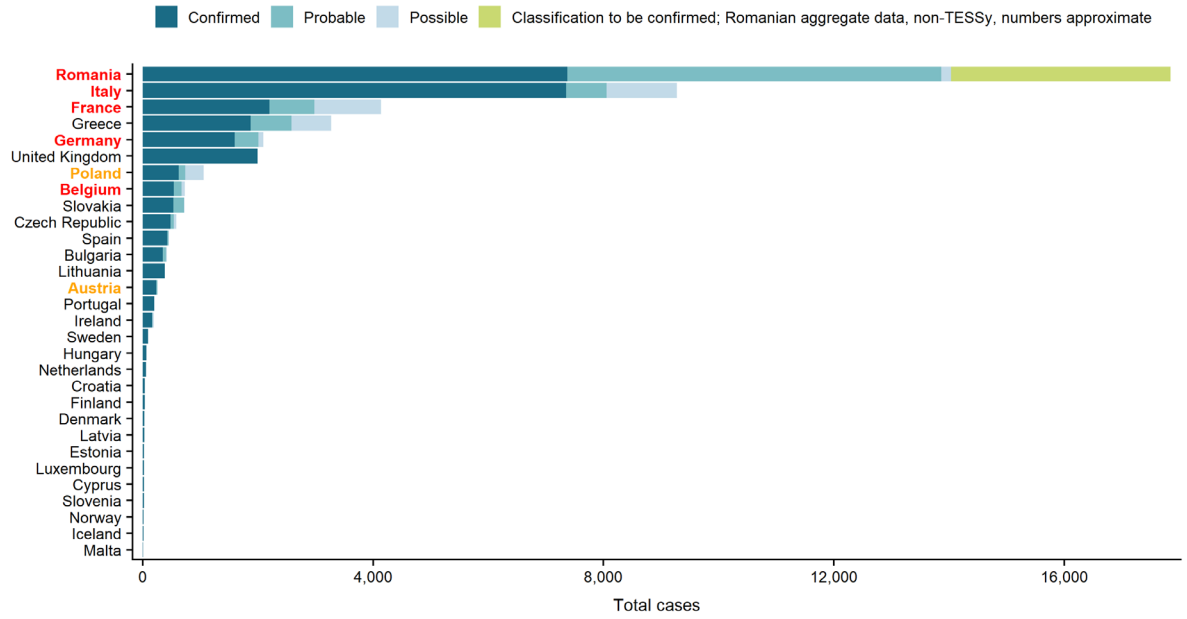
Estimate of the EU/EEA population non-immune to measles born since 1999

Based on the calculations described in the methods section, an estimated 4 640 132 (4.4%) of the 105 745 457 children born in 30 EU/EEA countries since 1999 are not immune to measles, either due to missed vaccination or not being infected. This is roughly equivalent to almost one full EU/EEA birth cohort being completely unvaccinated.

Current epidemic, 2016–2019

All data presented in this section refer to the 39-month period 1 January 2016 to 31 March 2019. In this period, a total of 44 074 cases were reported (40 262 to TESSy and an estimated 3 812 additional cases for Romania in 2018). Among those cases reported to TESSy, 26 763 (66.5%) were confirmed. All of the additional Romanian cases are reported online as being confirmed, but their final classification will be assigned upon upload to TESSy. Six countries, including four of the five countries most recently assessed by the RVC as having endemic transmission, accounted for 88% of all cases (Figure 4).

Figure 4. Measles case numbers by classification and country, EU/EEA countries, 1 January 2016 to 31 March 2019 (n = 44 074)

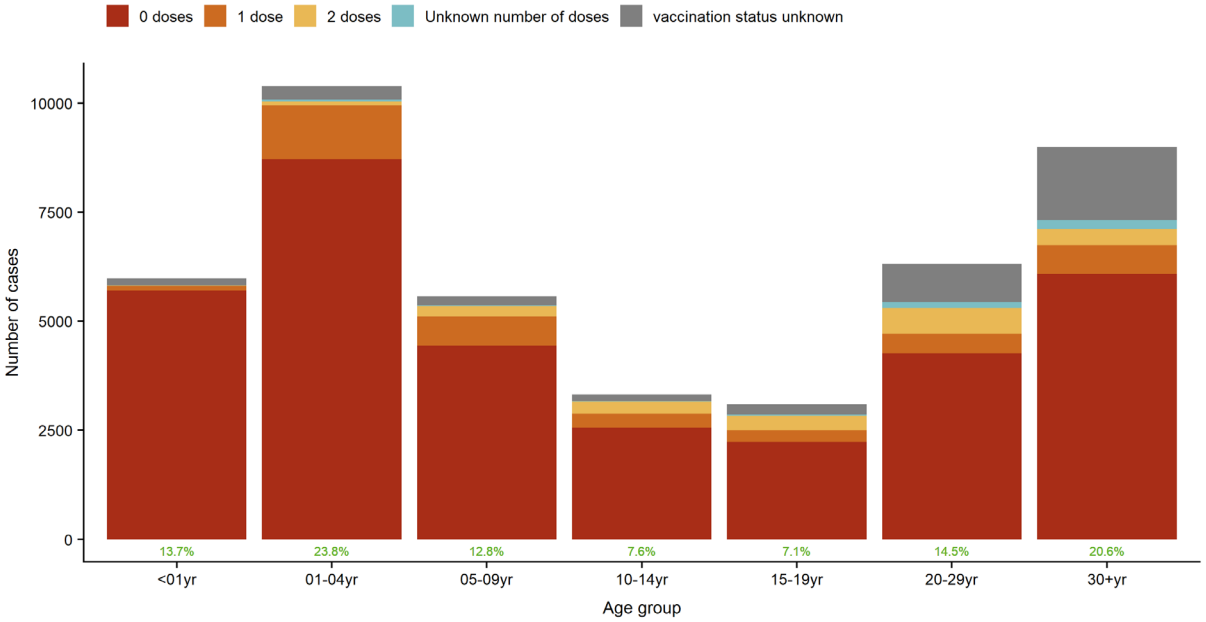


Colour of countries on y-axis indicates 2017 elimination status: eliminated (black), interrupted (orange), endemic (red). Sources: TESSy CBD, AGD and Romanian aggregate data (non-TESSy), RVC 2018 report. Romanian aggregate data describe all cases as confirmed, but their final classification will be assigned upon upload to TESSy.

Despite partial reporting from the Czech Republic and non-reporting of data by Norway and Italy in March 2019, case numbers between January and March (527 cases in 2016, 5 814 in 2017, 5 824 in 2018 and 3 841 in 2019) suggest that the seasonally expected increase currently occurring in the first three months of 2019 is of a smaller magnitude than observed in 2017 and 2018. However, comparison of data for January to March 2019 in TESSy (The European Surveillance System, run by ECDC) with the latest figures obtained by ECDC's epidemic intelligence (based on screening a range of sources, including media and the websites of national public health institutes [11]) suggests that measles activity in the EU/EEA is continuing to increase. These figures suggest a large number of cases may be reported to TESSy in April, making it possible that the pattern observed in 2017 and 2018 of March being the peak month for measles (Figure 1) may not be repeated in 2019.

A vast majority of cases (78%) occurred among unvaccinated people across all age groups. This is an indication of low levels of vaccination coverage since highly vaccinated populations tend to have a higher proportion of vaccinated cases. Children under five years and adults aged 20 years and above accounted for 38% and 35% of all cases for whom vaccination status and age was reported (Figure 5).

Figure 5. Number of measles cases by age and vaccination status, EU/EEA countries, 1 January 2016 to 31 March 2019 (n = 43 673)

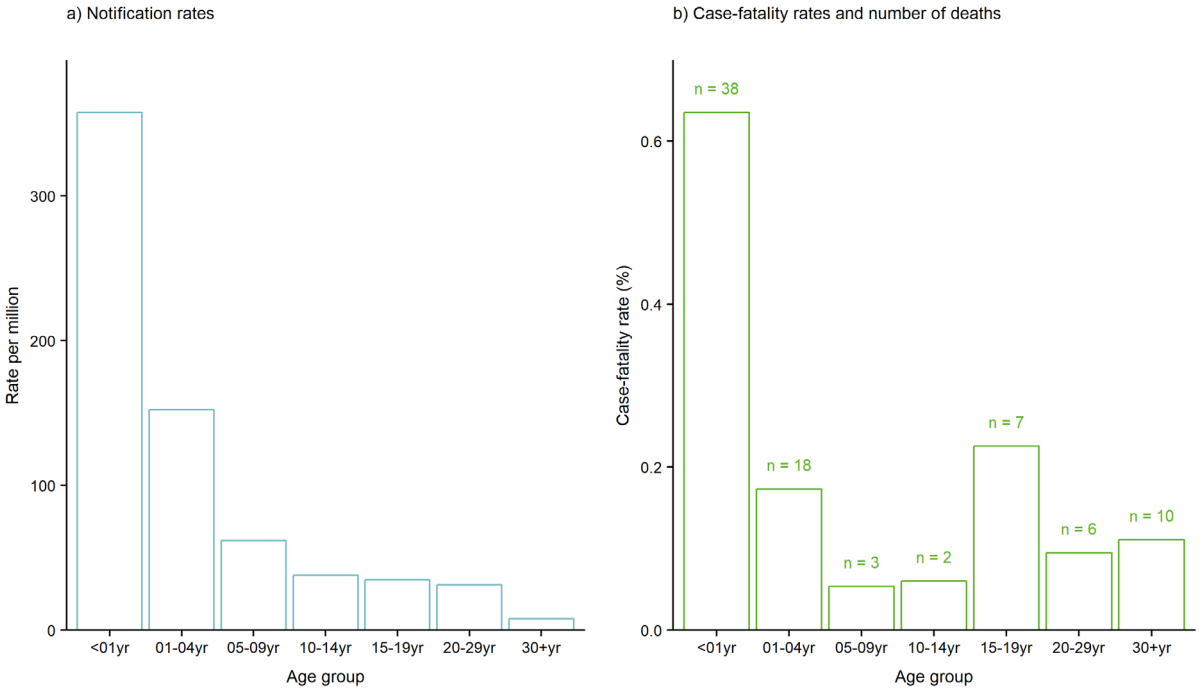


Percentage age distribution shown in green text below bars; 401 cases with missing age excluded; 0 doses (n = 4), vaccination status unknown (n = 397). Sources: TESSy CBD, AGD and Romanian aggregate data (non-TESSy).

Despite the high proportion of cases among adults, the overall burden of measles occurred disproportionally in infants under one year of age, with average annual notification rates in the period that were between two and 44 times higher than children aged 1–4 years and adults aged 30 years and above, respectively (Figure 6a). The reported number of deaths in the period (35 out of 84 deaths; 45%) and case–fatality rates (CFR, 0.64%) were also highest among infants (Figure 6b).

It is possible that there is increased under-reporting of measles cases among the older age groups [28], and the proportion of cases with an 'unknown' outcome (which can be dead, alive or unknown) was higher among cases aged 20 years and above (19.9%) than among those aged under 20 years (7.5%). Taken together, these factors suggest that the burden of measles among adults observed here (Figures 5 and 6) may be underestimated.

Figure 6. Age-specific a) average annual notification rates per million population and b) case-fatality rates and counts of deaths, EU/EEA countries, 1 January 2016 to 31 March 2019

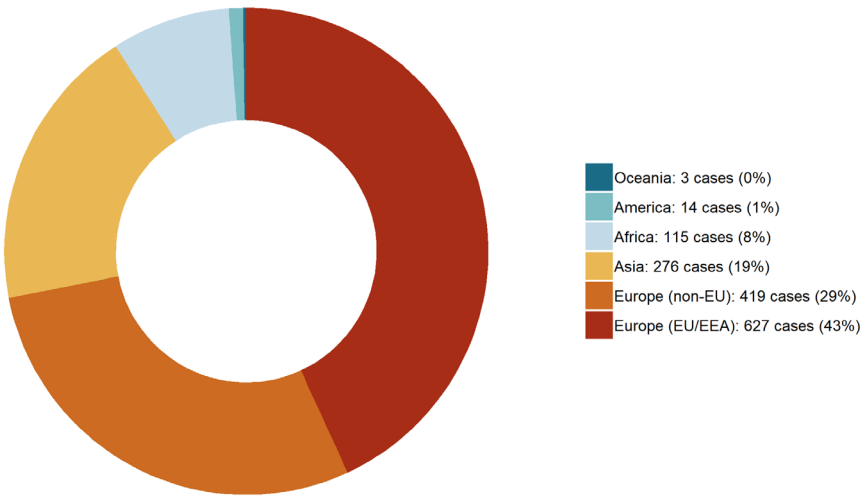


401 cases with missing age excluded from a). Number of deaths shown in green text in b) and based on CBD. Denominator for case-fatality is all cases from CBD and AGD. Sources: TESSy CBD, AGD and Romanian aggregate data (non-TESSy).

Of 39 173 cases submitted in a case-based format to ECDC, 1 599 (4.1%) were recorded as imported. 4 275 (10.9%) cases were recorded as import related. Accurately defining a case as import related requires a good understanding of chains of transmission following importation; in most countries, this is undertaken on an annual basis in preparation for the RVC meeting; for 2018–19, the information in TESSy may not have been updated.

Almost three-quarters of the 1 454 imported cases with a 'probable country of infection' that was known (1 046; 72%) acquired their infection in Europe, with EU/EEA countries contributing a greater number (627 cases, 43% of the total) than non-EU/EEA European countries (419 cases; 29%). A slightly smaller proportion (408 cases, 28%) of importations were from countries outside of Europe, mostly Asia (276 cases, 19%) and Africa (115 cases, 8%, Figure 7).

Figure 7. Distribution of origin of infection of cases defined as imported by probable continent of importation, 1 January 2016 to 31 March 2019, EU/EEA countries (n=1 454)



1 599 (4.1%) of 39 173 cases submitted as case-based data were recorded as imported. 1 454 imported cases (3.7%) had a known probable country of infection and 145 cases had unknown probable country of infection. Source: TESSy CBD.

Summary of measles country profiles

Country profiles describing the epidemiology of measles by each individual country within the EU/EEA are available online (see Annex 1). This section briefly summarises the key features from these profiles.

Notification rates and deaths, 1 January 2016 to 31 March 2019

There was considerable variation between countries in the average annual notification rate during the above period. The age-standardised rate for the EU/EEA was 26.1 cases per million population, with the highest rates reported by Romania and Greece (283.4 and 101.8, respectively) and the lowest rates reported by Denmark, the Netherlands and Norway (1.3, 1.0 and 0.8, respectively). The 84 deaths (CFR 0.19%) were reported by eight countries during the period. Romania accounted for the highest number of deaths (59; CFR 0.33%), followed by Italy (13; CFR 0.14%, Table 3).

Age groups affected

Three categories of country can be distinguished with regard to affected age groups.

- In five countries (Romania, Bulgaria, Greece, Slovakia and Cyprus) children were the most affected.
- Six countries (France, Germany, Belgium, Norway, United Kingdom and Ireland) reported cases in all age groups.
- In the remaining 19 countries, adults above 20 years of age were most affected.

The above categories are based on an inspection of the figures in the country profiles (age distribution of cases between January 2016 and March 2019, case distribution from all available years by birth cohort, and median age).

Despite the majority of Member States having an older age distribution, the median age for the EU/EEA during the period 1 January 2016 to 31 March 2019 was 10 years. This figure is skewed downwards by the large outbreaks affecting mainly children in Romania (17 850 cases) and Greece (3 270 cases). Figure 2 provides a 10-year trend of annual median age at the EU/EEA level.

Importation and exportation

Most of the Member States that eliminated measles reported a much higher proportion of imported cases compared with endemic countries (Table 3). Conversely, endemic countries exported the most cases to other EU/EEA countries (Romania: 253 cases; Italy: 81 cases; Germany: 36 cases; France: 33 cases). Several Member States, despite having eliminated measles, exported a consistent number of cases to other EU/EEA countries (UK: 52 cases; Spain: 39 cases; Poland: 22 cases).

The origin of imported cases varied significantly by country, possibly in line with specific patterns in the movement of people in and out of the country. For example, between 71% and 100% of the imported cases in Bulgaria, Cyprus, Romania, Ireland and UK had a 'probable country of infection' in the EU/EEA; Poland, Lithuania and Czech Republic reported most imported cases from European non-EU/EEA countries; Iceland and Sweden reported that the highest proportion of imported cases originated in Asia; France and Netherlands had the highest proportion of imported cases associated with Africa (Annex 1).

Vaccination schedules

Recommended vaccination schedules vary significantly in the EU/EEA. Broadly speaking, four groups can be identified (Table 2) [29]:

- Countries recommending MCV1 at 12 months of age and MCV2 in the second year of life (five Member States)
- Countries recommending MCV1 between 12–18 months of age and MCV2 at 3-4 years of age (four Member States)
- Countries recommending MCV1 between 12–18 months and MCV2 at 5–9 years of age (15 Member States)
- Countries recommending MCV1 between 12–18 months of age and MCV2 between 10–13 years of age (seven Member States)

Table 2. MCV vaccination schedule in the EU/EEA by country, grouped by broad recommendation

Country	MCV1	MCV2
Group 1 – MCV1: ≤12 months; MCV2: 12–23 months		
Austria	9–11 months	12–14 months
France	12 months	16–18 months
Germany	11–14 months	15–23 months
Liechtenstein	12 months	15 months–2 years
Luxembourg	12 months	15–23 months
Group 2 – MCV1: 12–18 months; MCV2: 3–4 years		
Denmark	15 months	4 years
Malta	13 months	3–4 years
Spain	12 months	3–4 years
United Kingdom	12 months	3 years
Group 3 – MCV1: 12–18 months; MCV2: 5–9 years		
Croatia	12 months	5–7 years
Cyprus	13–15 months	4–6 years
Czech Republic	13–18 months	5–6 years
Finland	12–18 months	6 years
Greece	12–15 months	4–5 years
Ireland	12 months	4–5 years
Italy	12–15 months	5 years
Latvia	12–15 months	7 years
Lithuania	15–16 months	6–7 years
Netherlands	14 months	9 years
Poland	13 months	6 years
Portugal	12 months	5 years
Romania	12 months	5 years
Slovenia	12–18 months	5–6 years
Sweden	18 months	6–8 years
Group 4 – MCV1: 12–18 months; MCV2: 10–13 years		
Belgium	12 months	10–13 years
Bulgaria	13 months	12 years
Estonia	12 months	13 years
Hungary	15 months	11–12 years
Iceland	18 months	12 years
Norway	15 months	11 years
Slovakia	14–17 months	10 years

MCV: Measles-containing vaccine, dose 1 (MCV1) and dose 2 (MCV2)

Vaccination coverage and non-immune population

A qualitative assessment of historical vaccination coverage time series (1980–2017), primarily focused on MCV1, and of the age groups most affected by measles in 2016–19 (with an overview of an analysis by birth cohort) points to three different epidemiological profiles in the EU/EEA countries (Table 4).

- Several countries have a sustained coverage above the 95% threshold of at least one dose of MCV; these countries were considered as having eliminated measles or interrupted the disease circulation for at least 24 months at the last RVC. As expected, the few measles cases that occur are observed in the adult population. In this group of countries, exceptions to this pattern – with overrepresentation of children – could be due to the low number of cases reported, or a high proportion of cases in children too young to be vaccinated. Included in this group are countries in which the majority of cases was vaccinated with two doses, an indication that the reported vaccination coverage is consistent with the epidemiological pattern [30, 31].
- Vaccination coverage in other countries has been below the 95% threshold for one or more (sometimes extended) periods. Three of the five endemic countries are part of this group; in these three countries, the age pattern is heterogeneous (e.g. mostly children affected, mostly adults affected, or all age groups affected); such findings could be due to differences related to subnational data, historical levels, and how long vaccination coverage has remained below 95%. In this group of countries with coverage below 95% for one or more periods, 13 were considered as having eliminated measles by the RVC, with 11/13 countries having the majority of cases reported among adults, or all age groups. Exceptions to this age pattern could be explained by differences in levels of vaccination coverage (both nationally and subnationally), data sources, data quality, and small countries reporting a low number of cases with small, local outbreaks.

- The remaining countries can be described as having historically low coverage but high current coverage. Two of the five endemic countries are in this group. The historical level of vaccination coverage (low or extremely low, <80%) may be the cause of the epidemiological picture we see today. As expected, in most of the countries in this group, the highest number of cases was reported among adults. In the remaining countries (where children or all age categories are most affected), factors such as the point in time when coverage reached a high level or the levels of coverage achieved previously may play a role.

Table 3. Epidemiological overview of measles by EU/EEA country, 1 January 2016 to 31 March 2019

Country	Cases	Population (million)	Average annual notification rate per million population		Median (IQR) age, years	Deaths (CFR)	Total imported cases (%)	Cases exported to EU/EEA
			Crude	Age standardised (95% CI)				
Romania	17 850	19.53	281.2	283.4 (279.2-287.6)	4 (1-10)	59 (0.33%)	53 (0.4%)	253
Greece	3 270	10.74	93.7	101.8 (98.3-105.4)	8 (2-26)	4 (0.12%)	12 (0.4%)	9
Italy	9 277	60.48	47.2	51.5 (50.4-52.6)	26 (11-35)	13 (0.14%)	164 (1.8%)	81
Lithuania	386	2.81	42.3	41.8 (37.7-46.2)	35 (21-41)	0 (0%)	39 (10.1%)	3
Slovakia	721	5.44	40.8	40.5 (37.6-43.6)	7 (1-17)	0 (0%)	23 (3.2%)	13
Bulgaria	415	7.05	18.1	19.7 (17.9-21.7)	4 (1-14)	1 (0.24%)	9 (2.2%)	5
Belgium	734	11.40	19.8	19.2 (17.8-20.6)	12 (1-23)	0 (0%)	NA	13
France	4 138	66.93	19	18 (17.4-18.5)	13 (2-26)	4 (0.1%)	215 (5.2%)	33
Czech Republic	583	10.61	16.9	17 (15.6-18.4)	31 (14-41)	0 (0%)	71 (12.2%)	8
Luxembourg	23	0.60	11.8	12.1 (7.7-18.2)	17 (14-27)	0 (0%)	8 (34.8%)	1
Iceland	11	0.35	9.7	11.2 (5.5-20.4)	27 (0-40)	0 (0%)	4 (36.4%)	2
Ireland	188	4.83	12	10.6 (9.1-12.2)	14 (3-26)	0 (0%)	12 (6.4%)	4
Austria	258	8.82	9	9.1 (8-10.3)	22 (6-32)	0 (0%)	53 (20.5%)	15
United Kingdom	1 997	66.27	9.3	8.7 (8.3-9.1)	16 (5-27)	1 (0.05%)	295 (14.8%)	52
Germany	2 093	82.79	7.8	8.3 (8-8.7)	16 (3-27)	1 (0.05%)	216 (10.3%)	36
Cyprus	19	0.86	6.8	6.4 (3.8-10)	6 (2-21)	0 (0%)	9 (47.4%)	2
Portugal	202	10.29	6	6.4 (5.5-7.3)	28 (23-34)	1 (0.5%)	18 (8.9%)	4
Estonia	24	1.32	5.6	6.1 (3.9-9.1)	37 (22-43)	0 (0%)	13 (54.2%)	3
Malta	8	0.48	5.2	5.9 (2.5-12.1)	33 (24-39)	0 (0%)	4 (50%)	0
Poland	1 056	37.98	8.6	5.4 (5-5.8)	22 (4-36)	0 (0%)	160 (24.3%)	22
Latvia	25	1.93	4	4.4 (2.8-6.5)	26 (6-34)	0 (0%)	9 (36%)	1
Spain	457	46.66	3	3.1 (2.9-3.5)	29 (14-38)	0 (0%)	76 (16.6%)	39
Slovenia	18	2.07	2.7	2.9 (1.7-4.6)	36 (22-46)	0 (0%)	6 (33.3%)	0
Croatia	35	4.11	2.6	2.8 (1.9-3.9)	35 (20-42)	0 (0%)	13 (37.1%)	14
Sweden	92	10.12	2.8	2.7 (2.2-3.3)	26 (3-37)	0 (0%)	35 (38%)	1
Finland	35	5.51	2	2 (1.4-2.8)	26 (18-38)	0 (0%)	18 (51.4%)	2
Hungary	61	9.78	1.9	2 (1.6-2.6)	29 (3-40)	0 (0%)	19 (31.1%)	5
Denmark	26	5.78	1.4	1.3 (0.9-1.9)	17 (5-27)	0 (0%)	12 (46.2%)	1
Netherlands	58	17.18	1	1 (0.8-1.3)	26 (18-39)	0 (0%)	25 (43.1%)	6
Norway	14	5.30	0.8	0.8 (0.4-1.4)	16 (3-34)	0 (0%)	8 (57.1%)	0
EU/EEA	44 074	518.02	26.2	26.1 (25.9-26.4)	10 (2-27)	84 (0.19%)	1 599 (4.1%)	0

CI: confidence interval; IQR: interquartile range; CFR: case–fatality rate. Total imported cases include importations for which probable country of infection is unknown. Belgium not included in importations since data have been provided in aggregated format since May 2016. Countries ordered by descending notification rate. Endemic countries shaded blue.

Table 4. Measles elimination status, vaccination coverage profile, age groups most affected and estimated non-immune population aged 0–20 years by EU/EEA country

Country	Elimination status from 2017 data	Vaccination coverage profile			Age groups most affected by measles	Estimated non-immune population 0–20 years*	
		Historical trend	Years of data	2 doses ≥95% in 2017		Number	% of all births
Romania	Endemic	Extended period(s) <95%	1983 to 2017	No	Children	94 705	2.3
Greece	Eliminated	Historically low, now high	1984 to 2017	No	Children	37 854	1.8
Italy	Endemic	Extended period(s) <95%	1990 to 2017	No	Adults	1 135 694	10.6
Lithuania	Eliminated	Extended period(s) <95%	1992 to 2017	No	Adults	27 353	4.4
Slovakia	Eliminated	Sustained above 95%	1994 to 2017	Yes	Children	19 836	1.8
Bulgaria	Eliminated	Extended period(s) <95%	1980 to 2017	No	Children	58 515	4.3
Belgium	Endemic	Historically low, now high	1981 to 2017	No	All	177 630	7.3
France	Endemic	Extended period(s) <95%	1983 to 2017	No	All	564 937	3.5
Czech Republic	Eliminated	Sustained above 95%	1993 to 2017	No	Adults	43 052	2
Luxembourg	Eliminated	Historically low, now high	1983 to 2017	No	Adults	3 190	2.8
Iceland	Eliminated	Extended period(s) <95%	1983 to 2017	No	Adults	6 892	7.8
Ireland	Eliminated	Extended period(s) <95%	1983 to 2017	No	All	138 388	10.7
Austria	Interrupted 24 months	Extended period(s) <95%	1981 to 2017	No	Adults	217 427	13.6
United Kingdom	Eliminated	Extended period(s) <95%	1980 to 2017	No	All	600 000	4
Germany	Endemic	Historically low, now high	1980 to 2017	No	All	417 915	2.9
Cyprus	Eliminated	Extended period(s) <95%	1980 to 2017	No	Children	22 651	12.4
Portugal	Eliminated	Historically low, now high	1980 to 2017	Yes	Adults	78 727	3.9
Estonia	Eliminated	Extended period(s) <95%	1993 to 2017	No	Adults	15 730	5.5
Malta	Eliminated	Extended period(s) <95%	1984 to 2017	No	Adults	10 654	12.8
Poland	Interrupted 24 months	Sustained above 95%	1980 to 2017	No	Adults	195 175	2.6
Latvia	Eliminated	Extended period(s) <95%	1992 to 2018	No	Adults	19 240	4.6
Spain	Eliminated	Historically low, now high	1981 to 2017	No	Adults	267 728	3
Slovenia	Eliminated	Extended period(s) <95%	1992 to 2017	No	Adults	22 495	5.6
Croatia	Eliminated	Extended period(s) <95%	1980 to 2017	No	Adults	32 640	4.4
Sweden	Eliminated	Sustained above 95%	1980 to 2017	Yes	Adults	61 849	2.9
Finland	Eliminated	Sustained above 95%	1982 to 2017	No	Adults	7 657	0.7
Hungary	Eliminated	Sustained above 95%	1980 to 2017	Yes	Adults	18 492	1
Denmark	Eliminated	Extended period(s) <95%	1987 to 2017	No	Adults	106 284	8.3
Netherlands	Eliminated	Historically low, now high	1980 to 2017	No	Adults	151 021	4
Norway	Eliminated	Extended period(s) <95%	1983 to 2017	No	All	86 402	7.3
EU/EEA	NA	NA	NA	No	NA	4 640 132	4.4

ANR: Annual notification rate per million people; CI: confidence interval; MCV2: second dose of measles-containing vaccine.

**For Croatia, the analysis of non-immune population was for birth cohorts 2001–2019. Vaccination coverage profile is a qualitative assessment primarily focused on with on the first dose. Countries ordered by descending notification rate. Endemic countries shaded blue.*

ECDC risk assessment for the EU/EEA

Overview

A large epidemic of measles has affected the EU/EEA as a whole in the past three years with an exceptionally high number of cases compared to 2013–2015 (Figure 1).

The historical and current epidemiological data show the continued and widespread circulation of measles in the EU/EEA, despite the fact that the RVC verified that the majority of countries successfully eliminated measles in the last three years [17]. Importations and small outbreaks are expected in the post elimination era, but widespread and continued circulation, as currently experienced, should not, suggesting that the necessary levels of immunity to sustain elimination may not be present in the affected countries.

It is essential for every Member State to investigate all clusters and outbreaks in order to identify which cases are due to endemic circulation and which to importation [32]. The characterisation of transmission patterns is also very important in this phase in the EU/EEA, including which age groups are the main transmitters of infection to infants, in order to plan effective public health interventions and guide vaccination strategies.

Measles is still a cross-border health threat in the EU/EEA. The fact that countries characterised by low virus circulation (and effective reproduction number, R<1) share borders with countries with high and sustained virus circulation (and R>=1) threatens to substantially delay the elimination of the disease in the EU/EEA. It also poses a number of challenges to individual Member States to maintain their elimination status.

We have focused our assessment on three of the main factors driving the risk of continued widespread circulation of measles in EU/EEA:

- Accumulation of susceptible people due to low historical and current vaccination coverage.
- High burden of cases in infants and in adults.
- The continued potential of importation.

Accumulation of susceptible people due to low vaccination coverage

Immunity gaps

Historical data on vaccination coverage, as well as current notification rates, indicate that the EU/EEA has a large pool of unvaccinated people in several age groups (Tables 5 and 6). The susceptibility age profile differs across Member States.

We estimate that four-and-a-half million people born since 1999 of an age eligible for vaccination are potentially non-immune to measles due to missing one dose of vaccine and never experiencing a primary infection. This number represents over 4% of the people born in the EU/EEA since 1999 and is roughly equivalent an entire EU/EEA birth cohort being completely unvaccinated. This number has considerable uncertainty associated with it that might vary substantially between countries (see Methods and Limitations, Annexes 2 and 3). However, as an estimate of the size of the total non-immune population across all age groups, it is likely to be highly conservative. It doesn't account for infants aged between 6 and 12–18 months whose maternal antibodies have waned [33] but are too young to be vaccinated according to the national vaccination schedule, or people born pre-1999, among whom substantial immunity gaps exist. Of particular interest is those people born between after the start of measles vaccination programmes (around 1970) as they are less likely to have been immunised through previous measles infection.

This figure greatly exceeds the critical community size to sustain measles transmission, which is in the order of several hundred thousand susceptible individuals [34, 35]. In 1960, Bartlett [36] defined the critical community size for measles as

> 'the size for which measles is as likely as not to fade out after a major epidemic until reintroduced from outside, corresponding to a mean time to fade-out of about two years or about 30 in terms of average weekly notifications'.

Geographical clusters with high proportions of unvaccinated people can support large outbreaks, even though the rest of the population is well protected with adequate vaccination coverage [37, 38]. Such outbreaks were reported in countries such as United States [39] that otherwise have excellent measles control, and at this point in time there are several such outbreaks in EU/EEA Member States [37, 38]. These outbreaks do not necessarily pose a serious threat to the elimination status as long as they are limited in time and space and herd immunity is high.

However, when the immunity gaps are too large in a community and vaccination coverage over time has been suboptimal, then if outbreak response is not timely and comprehensive, the virus will circulate first in pockets of vulnerable individuals, then in large proportions of communities, and eventually spread to other countries [40].

This is the current scenario in the EU/EEA – the result of inadequate vaccination coverage over the past years in most of the Member States.

In some countries in the WHO European Region, the high number of individuals susceptible to measles was responsible for sustained chains of transmission even though the country was already in its post-elimination era. This opens the possibility of reestablishment of endemic transmission in countries that have already eliminated measles [41].

If transmission of measles from cases related to importation persists for ≥12 months within a country, cases are no longer considered import related but endemic [32]. In this context, the distinction between endemic and import-related cases and outbreaks is crucial, and monitoring chains of transmission through epidemiological and molecular typing analysis is essential [42].

According to the last RVC report [17], published in June 2018,

> 'a small number of Member States that achieved interruption or elimination of endemic measles transmission have experienced widespread outbreaks following importation of the virus in 2017. In some cases, these import-related outbreaks have lasted for many months'.
>
> 'Some Member States have reported repeated importations and import-related outbreaks. Complete epidemiological and laboratory investigation to distinguish separate chains of transmission may give inconclusive results in the context of repeated importations of viruses with the same genomic sequence'.

Recent trends in vaccination coverage

In recent years, we observed a decreasing trend in vaccination coverage in many EU/EEA countries (Figure 3). The number of Member States achieving the WHO target of 95% vaccination coverage for two doses of MCV fell from 14 in 2007 to only four in 2017.

These figures highlight that progress towards measles elimination in EU/EEA proceeds very slowly. The elimination goal might not be sustainable on the long term as coverage levels are below those recommended by WHO. High coverage relies on a strong integrated health system. Therefore, equitable and convenient access to vaccination services to all populations must be ensured. Outreach services for hard-to-reach populations are particularly important in this context.

Roadmap to immunity

In October 2017, the Strategic Advisory Group of Experts (SAGE) on Immunization reviewed data on the level of immunity necessary for achieving and sustaining measles elimination [43]. SAGE reiterated that achieving

> 'at least 95% immunity across all age groups, geographical regions, and population subgroups…. should remain the primary strategy of measles elimination' and that 'countries should attempt to identify specific age groups and subpopulations with immunity gaps, i.e. those with below 95% immunity, and offer vaccination accordingly.'

A *Roadmap to Immunity* was developed and published in April 2018 [44], with the idea that identifying and estimating the scale of immunity gaps within a country, and understanding the general epidemiological profile of a country are an integral part of progressing from control to elimination.

Furthermore, the document outlined that

> 'countries need to understand the strengths and weaknesses of possible data sources and methodologies used to understand their epidemiologic profiles. As there is no perfect measure of immunity, a combination of coverage data, outbreak demographics and serosurveillance data can assist. With an understanding of a country's epidemiology and immunity gaps, countries can best target their interventions to raise population immunity and close gaps.'

How to best estimate immunity gaps in the population?

The SAGE *Roadmap to Immunity* provides a comprehensive list of methods for estimating immunity gaps for countries at different levels of measles elimination, based on evidence in the literature.

> 'SAGE reviewed peer-reviewed and grey literature for reports that discussed and utilized the following data sources and analytic methods/tools for estimating immunity gaps: 1) case-based surveillance data, 2) outbreak investigations, 3) historical coverage data (administrative and WUENIC), 4) population coverage surveys (including post-campaign, Multiple Indicator Cluster Surveys [MICS], Demographic and Health Surveys [DHS], etc.), 5) serosurveys, 6) WHO Measles Strategic Planning (MSP) tool and other excel-based tools, 7) data triangulation, and 8) mathematical modelling.'

SAGE recommends that prior to using any of these methods, countries need to critically evaluate the quality of their collected data, as this will greatly impact the accuracy of their analysis.

As an example of experience at the country level, we would like to mention a study conducted in the US in 2004 to assess elimination status, using the effective reproduction number R [45]. The authors demonstrated three methods for estimating R from surveillance data once the disease is eliminated in a country or region. Using these methods, they analysed US measles data for 1995–1997 and concluded that endemic transmission had indeed been eliminated. More recently, Public Health England (UK) published the 'UK measles and rubella elimination strategy 2019' [46]. In this document, they appropriately remark that

> 'the herd immunity threshold for measles is often quoted at 90–95% for the whole population. However, in the 1990s the WHO European Region derived age-specific target immunity profiles, or the levels of immunity necessary in different age groups to achieve elimination [47]. Gaps in immunity can exist despite high routine MMR coverage if coverage targets were not met in the past, or because of population mixing patterns and migration.

They also highlight that

> 'Funk and colleagues have recently updated these age-specific immunity targets taking into account the latest evidence around mixing patterns in different age groups and settings [48]. The key message from this research is that 95% immunity needs to be achieved for each cohort at the time of school entry to guarantee elimination'.

The analysis presented in this document can be considered as a first preliminary step to provide support to Member States in line with the *Roadmap to Immunity* recommendations. However, a more in-depth analysis with a view on the immunologic profile, including subnational levels of countries' administrative coverage and data from outbreak investigations, may certainly further assist the identification of gaps.

Three patterns of vaccination coverage in EU/EEA countries

As described in the *Results* section, we identified three main patterns of vaccine coverage in Member States, although there is a large variation of vaccine coverage levels in time and geographical areas across Member States.

Countries with sustained coverage above 95% have all eliminated measles; the few cases they still experience are reported among adults.

Countries that experienced low or suboptimal vaccine coverage for one or more extended periods, or historically had low coverage and only recently moved above 95%, are both endemic or without endemic transmission. It seems that the coverage profile at national level does not fully predict the occurrence of an outbreak.

This could be due to the methods used to estimate vaccination coverage in a country, to the fact that subnational vaccination coverage data were not available for this analysis, or to pockets of under immunised individuals in specific geographical areas, that are not fully represented by the national vaccination coverage estimate.

On the contrary, current outbreaks represent a way to identify low vaccination coverage levels over time and space in Member States.

This further stresses the key importance of collecting and providing high quality vaccine coverage data in a timely manner and at subnational level, something lacking in a number of Member States. In particular, electronic registers to document vaccination status of individuals can be of support [4].

High burden of measles in infants and adults

Infants are historically the age group with the highest burden in terms of notification rate and number of deaths, as also shown by EU/EEA data. Due to low herd immunity, the probability of infections in infants who are too young to be vaccinated remains high.

However, our results also showed that the median age of measles cases in 2019 was 17 years, with an upper quartile of 31 years (Figure 2a).

The median age of measles cases was even higher, and on the increase, when excluding Romania, Bulgaria, Greece, Slovakia and Cyprus from the analysis (Figure 2b): the latter are the only countries in the EU/EEA where children are the most affected by measles (Table 5). In the other EU/EEA countries, measles occurs predominantly in adults. In six Member States, the median age of measles is now between 30 and 40 years of age (Table 3).

This descriptive epidemiology of cases is relevant for three main reasons:

- Adults, as well as infants, are known to suffer from more severe forms of measles [49] [50, 51].
- Cases of measles among adults may be detected late, due to the common misperception of measles as a childhood disease. Management of cases and contact tracing can therefore be delayed, contributing to further spread of the virus.
- Infectious adults may be more likely than children to transmit the disease in specific setting, such as hospitals (where they may expose vulnerable patients) or in the workplace, as well as during travel.

In our analysis, the highest numbers of deaths (and case-fatality rate) are reported among infants too young to be vaccinated and who can only be protected by a high herd immunity in the population.

The fact that in recent years thousands of adults were reported with measles in the EU/EEA represents an additional challenge. This is especially relevant for defining the best vaccination strategy to be applied at the national level, with the goal to achieve 95% immunity among older birth cohorts and close immunity gaps. It is less straightforward, from a strategic and operational point of view, to target older birth cohorts with vaccination campaigns [52].

In the majority of the Member States, the national schedule for MCV currently targets mainly children and teens. However, in an attempt to increase immunity levels in adolescents and adults (who historically missed MCV vaccination), several countries have conducted catch-up campaigns, as part of outbreak response and/or to strengthen national immunisation programmes for measles.

According to the ECDC vaccination scheduler [29], ten countries (Austria, Belgium, the Czech Republic, France, Germany, Greece, Latvia, Luxembourg, Poland and the United Kingdom) carried out measles catch-up vaccinations. In addition, Bulgaria and Croatia informed ECDC about catch-up vaccinations carried out during measles outbreaks and at school entry, respectively. More data are needed on the impact of such campaigns on population immunity.

Importation of measles in EU/EEA countries

The EU/EEA countries reported 1 599 imported cases of measles in 2016–2019, or 4.1% of all cases. This proportion tended to be significantly higher in countries that already achieved elimination status, exceeding 40% in Denmark, Estonia, Finland, the Netherlands and Norway.

Movement of people, both short-term (tourism, work, visiting friends and relatives) and long-term (education, work, family), carries the risk of measles importation.

Five EU countries are endemic for measles, which makes it likely that a substantial number of infectious people are also travelling within the EU/EEA (Table 3).

There is also intense movement of people to/from countries bordering the EU/EEA. Five non-EU/EEA countries in the WHO European Region are endemic, four of which share a border with the EU/EEA (e.g. Ukraine and Romania).

There is also considerable movement of people from outside Europe (including endemic areas) into the EU/EEA.

In 2016–2019, EU/EEA countries imported 627 cases (43%) from other EU/EEA countries; 29% of all cases (419 cases) originated from the rest of the WHO European Region – a total of 72% of cases imported from countries of the WHO European Region. Only 408 cases (28%) were imported from outside Europe.

While some importation of measles from Asia (276 cases) and Africa (115 cases) occurs, the data show clearly that the main source of introduction of measles to EU/EEA countries are the endemic countries in the EU/EEA and the rest of Europe.

In the last ten years, the most predominant measles virus genotypes detected in the WHO European Region were D4 (21% overall, 66% during 2009–2012), D8 (45% overall, 76% during 2013–2016), and B3 (33% overall, 58% during 2017–2018) [53].

Measles is an EU/EEA-wide threat

Five EU/EEA countries, Belgium, France, Germany, Italy and Romania, are endemic for measles. Transmission is established and ongoing. All other countries in the EU/EEA have interrupted endemic transmission.

Our review of data from EU/EEA countries showed heterogeneity in their epidemiological profiles, the estimated number of susceptible individuals and vaccination coverage over time. In many countries there was no immediate correlation between these parameters and the measles elimination status or the annual measles notification rates (Table 4 and Annex 1). Low data quality could partially explain this finding in some countries.

This led to two main considerations:

- Our data support the RVC concern from 2018 regarding the occurrence of import-related outbreaks.

  'Repeated outbreaks are suggestive of sizable populations with low population immunity and suboptimal vaccination coverage. While the current definition of elimination refers to cessation of transmission of endemic measles, continued susceptibility to wide-scale import-related outbreaks raises questions over the relevance of such a definition' [17].

  Individual countries that have interrupted measles transmission but still have suboptimal vaccination coverage and pools of susceptible individuals, remain prone to the re-establishment of the disease due to the high likelihood of importation. Germany, which had interrupted endemic transmission for 12 months in 2017, was reclassified as 'endemic' in 2018 by the RCV [17]. On the basis of their current epidemiological

profile, other countries may also lose their elimination status. Criteria for sustainability in the post-elimination era need to be defined and implemented. Some other countries that have achieved elimination status and met the target vaccination coverage have been experiencing repeated importations and sizeable import-related outbreaks, although not to the extent of threatening the elimination status [54].

- The EU/EEA today is a common space where internal movement of people is unrestricted and very intense.

  The continued potential of importations, which can worsen existing outbreaks or start new ones in communities where measles is not currently circulating and where immunity gaps persist. In 2016–2019 almost half (43%) of the cases imported into EU/EEA countries acquired their infection in another EU/EEA country, mainly those which were endemic for measles and/or experiencing large outbreaks.

  Although individual countries have made significant progress (25 of them achieved elimination status in 2018), the EU/EEA as a whole has been experiencing a large and uninterrupted epidemic since the end of 2016, mainly due to EU/EEA 'endemic' transmission. Measles continues to circulate widely within in the region and it thus remains an EU-wide threat capable of affecting any country with immunity gaps.

  The shift towards moving the verification process from the regional perspective towards the country perspective [18] has been considered to be a valuable approach in the WHO European Region as it opened opportunities for country-targeted interventions. On the other hand, since the EU/EEA is characterised by intense internal movement of people, this may lead to the apparent paradox of most Member States having eliminated the disease while the EU/EEA as a whole still needs to work towards elimination.

On 9 May 2019, the WHO Regional Office for Europe published a press release informing that WHO has recognised the ongoing measles outbreaks in the European Region as a health emergency. According to WHO, 'this alarming resurgence is a warning that the Region's immunization coverage is not yet sufficient to achieve community-wide protection'. This health emergency concerns the entire WHO European Region, and action will be tailored to specific country needs, taking into account the national epidemiological situation and the health system response [55].

Knowledge gaps

Important knowledge gaps remain.

Recent priority areas for operational research needs were outlined by SAGE [43]. These include:

- identification of the populations that should be targeted for additional efforts;
- optimal strategies to enhance surveillance;
- approaches on how to measure coverage; and
- optimal strategies to reach hard-to-reach population groups, adolescents and adults.

In addition, the Measles and Rubella Initiative [56] identified 19 high-priority research areas to be further developed in order to achieve measles and rubella elimination. These include: 1) how to improve vaccine delivery, 2) developing innovative planning tools and implementation methods to identify target populations and characterise chains of transmission, 3) strengthening surveillance to better monitor progress towards elimination, 4) generating evidence for country decision-making, 5) developing tools to better use data for advocacy and decision-making 6) development of a micro-array patch for vaccine administration, 7) use of point-of-care testing for improved surveillance and outbreak response.

In contrast to two previous prioritisation exercises, better data for decision-making and improved identification of susceptible populations at the national level are now considered of higher priority.

While a well-managed routine immunisation programme (resulting in high coverage in children and supported by high-quality data) is essential, it is not clear which segment of the population should be targeted for additional vaccination efforts. Modelling suggests a series of interventions based on the context, but in reality implementation can be challenging and public health efforts in this area may be questioned [57]. Catch-up vaccination activities for susceptible populations have been described as paramount in order to reach the elimination goal, but are only feasible if a multi-component approach is in place [18, 58]. A number of initiatives, from catch-up campaigns to free vaccinations for those not routinely targeted by the programme, have been conducted across EU/EEA countries. In some settings, vaccine uptake was substantially improved in the context of a targeted immunisation campaigns [59], while similar campaigns were less successful in other areas [60]. One evaluation concluded that similar campaigns should not be repeated, but priority should be given to identifying factors associated with non-vaccination and then possibly compare the success rate of strategies during the campaign [52].

The path towards elimination would benefit from systematically documenting the impact of interventions and sharing the results with policymakers and the scientific community.

Conclusions

There has been a resurgence of measles in the EU/EEA and a high risk of continued widespread circulation will remain as long as significant immunity gaps exist. Measles outbreaks will reduce the immunity gap but at a high cost, both in terms of health impact and burden on healthcare systems.

The measles risk is driven mainly by suboptimal vaccination rates in most EU/EEA countries, by a very large pool of susceptible individuals, by the high burden of disease in infants and adults, and by the intense movement of people within the EU/EEA.

- **Over four-and-a-half million people born in the EU/EEA since 1999 and of an age eligible for vaccination are estimated to be non-immune to measles** due to missing vaccination or never experiencing infection; roughly equivalent an entire EU/EEA birth cohort being completely unvaccinated. The total non-immune EU/EEA population will greatly exceed this figure after accounting for infants too old to be protected by maternal antibodies but too young to be vaccinated, and the substantial immunity gaps that exist among adults born pre-1999. Vaccination coverage has been declining in recent years: only four EU/EEA Member States met the target of 95% coverage with two doses of MCV in 2017 compared to 14 in 2007. Measles is likely to keep having a high impact in the EU/EEA, due to low historical and current coverage; this also includes those countries that achieved measles elimination.
- Along with infants too young to be vaccinated, **measles is now a disease of adults in most of the EU/EEA**, mainly due to an accumulation of susceptible people. Measles is associated with a high proportion of complications in adults, as well as challenges in the early detection and management of cases. Closing the gaps in immunity in the adult population presents significant strategic and operational challenges. In order to accelerate measles elimination efforts in the WHO European Region, the WHO Regional Office for Europe has targeted five areas of action, among them the need for closing immunity gaps in the population through innovative and locally tailored approaches [41].
- **Measles is a serious cross-border health threat in the EU/EEA**, even though most EU/EEA countries are deemed to have interrupted endemic transmission. Almost half of all imported cases come from within the EU/EEA: due to intense movement of people within the EU/EEA, there is a high probability of continued mutual importation and exportation of measles. Introduction of measles through importation is likely to keep occurring throughout the EU/EEA. Re-establishment of transmission in countries that have eliminated measles is possible when vaccination coverage is suboptimal and immunity gaps remain.
- **Knowledge gaps remain: what are the best strategies to reach elimination?** Operational research aimed at providing elements for programmatic consideration, including strategies for identifying at-risk individuals, is believed to be pivotal in this respect.

Options for response

Immunisation is the only effective preventive measure for measles, and two doses are needed to ensure best protection. All countries in the EU/EEA have measles vaccination policies in place, and all recommend two doses of MCV. A high-quality routine vaccination programme ensuring coverage of at least 95% among those targeted is the immediate priority. Vaccination programmes should address national and subnational levels and ensure the timeliness of vaccination [61]. Actions to achieve this should be tailored to the specific settings [41].

Every Member State should have a structured elimination or post-elimination strategy [46], in line with the RVC, to guide public health actions.

Strengthening and ensuring high-quality surveillance, including monitoring the changing epidemiology of measles, helps guide public health actions. All suspected cases need to be investigated in order to break chains of transmission as soon as possible. Epidemiological investigations, including assessing the susceptibility of contacts, are needed to guide control measures and offer vaccination as appropriate. Adequate laboratory investigation is essential because data on viral genotype are needed to track transmission chains.

Measles vaccine may be administered within 72 hours of exposure to measles virus in order to protect against disease. If disease develops, its clinical course is shorter. Immunoglobulins may be given after exposure to the virus when vaccination is contraindicated, ideally within six days, such as in pregnant women and infants under six months of age, in order to prevent disease and reduce severity [43].

Strengthening routine immunisation by facilitating access to vaccination is essential. Mechanisms to identify people not (or incompletely) vaccinated should be improved. Electronic immunisation registries should be promoted [62].

From a programmatic point of view, public health authorities and research institutes should address knowledge gaps and develop sustainable action plans. This could include data quality initiatives; electronic medical records (plus integration with public health systems to enable better quality coverage monitoring); sero-epidemiology studies in countries where immunity gaps are poorly described; and mathematical models of immunity gaps based on coverage, disease incidence, migration and other parameters.

A range of options for response is listed below for each of the three factors identified in the analysis.

Reducing immunity gaps and raising vaccination coverage

Infants and children

- Routine immunisation programmes should be strengthened, whenever appropriate, also ensuring the timeliness of vaccination through vaccination delivery services.
- As an immediate response to outbreak situations, or prior to travelling to endemic countries, a supplementary dose of MCV (MCV0) may be given to infants above the age of six months at high risk of measles as part of an intensified service delivery. MCV0 should be considered supplementary. MCV1 and MCV2 should still be administered at the ages recommended in the national schedule [43].
- Evidence from modelling studies indicates that a 95% immunity (hence, vaccination coverage with MCV2) by the age of 5–9 years is needed to reach and maintain measles elimination [48]. Member States where MCV2 is administered at ≥10 years of age may consider lowering the recommended age to reach higher immunity levels in younger children [46]. However, the choice of the optimal age for delivery of the routine MCV2 in each Member State should be based primarily on programmatic considerations to achieve the highest possible MCV2 vaccination coverage [43]. In order to be effective, MCV2 should be administered at least four weeks apart from MCV1 [43].
- Opportunities for vaccination checks at medical appointments, including at healthcare centres, should be implemented if not already existing [43].
- The beginning and the end of school cycle (day care entry, school entry, university entry) should be seen as an opportunity for vaccination checks or vaccination delivery.
- Checking and updating vaccination against measles should be a routine practice during travel medicine consultations and general health checks prior to travelling to all endemic countries, including EU/EEA Member States.

Adults

- Any encounter with the healthcare system, including post-partum visits, should be used as an opportunity to check vaccination status and provide vaccination against measles as appropriate.
- Available literature suggests that supplementary immunisation programmes [57] may be useful to meet elimination targets and provide a significant societal return on investments also in highly immunised countries [57, 61, 63-71]. Therefore supplementary immunisation activities have to be considered to close large immunity gaps in older populations [43] with an age-targeted approach, after careful assessment of feasibility and expected impact [60, 72].
- Checking and updating vaccination against measles should be a routine practice during travel medicine consultations and general health checks prior to travelling to all endemic countries, including EU/EEA Member States.
- Employees of health services, including occupational health, especially for those professions that involve frequent direct contact with other individuals, are at particular risk of exposure and potential sources of transmission of measles and as such are a priority target group for measles immunisation. Opportunities for assessing vaccination status should be taken, e.g. at pre-employment health checks [73, 74]. Patient reminders and recall interventions in primary care settings are likely to be effective at improving vaccination coverage and may be considered in areas of suboptimal vaccination coverage [75].
- Literature shows gaps in knowledge, attitudes and practices of healthcare workers towards MCV [76, 77]. Training opportunities should be offered to healthcare workers to ensure they have adequate knowledge about measles and MCV so that they can address vaccination hesitancy and make recommendations to patients.
- High-quality, evidence-based and appropriate information on the effectiveness and safety of MCV should be easily accessible to the general public and all healthcare workers [43].
- Public trust and acceptance of vaccines may be improved through targeted social mobilisation, advocacy and communication activities [78, 79], also using examples of good practices from other countries and for other vaccine-preventable diseases. Regular surveys on attitudes towards vaccination may be considered in this respect.
- Equitable and convenient access to vaccination services to all population groups should be ensured, including outreach services to hard-to-reach populations [44].

Detecting and managing adult cases in a timely fashion

- Awareness of the age shift of measles towards older age groups should be raised, both among healthcare workers and the general public.
- Training opportunities for the early detection and management of adult cases should be offered to healthcare workers, especially general practitioners [72].
- Investigation and testing of all adults with rash and fever is strongly encouraged; this could decrease under-ascertainment among adults, prevent severe cases, and reduce the number of hospitalisations [80]. Policies and procedures need to be in place to ensure infection prevention and control when patients with rash fever illnesses come to healthcare facilities.

Reducing transmission of measles after importation of cases

- Checking and updating vaccination against measles should be a routine practice during travel medicine consultations and general health checks prior to travelling to all endemic countries, including EU/EEA Member States.
- Training opportunities should be offered to healthcare workers to ensure they have adequate knowledge about measles and MCV so that they can recommend vaccination to travellers seeking health advice, including those travelling within the EU/EEA.
- Training opportunities should be offered to healthcare workers for early detection and management of cases in returning travellers: measles should be considered in the differential diagnosis of patients, regardless of their age and the country visited, especially in the presence of fever, flu-like symptoms, and rash. Information should be routinely collected on their immunisation status and contact with sick people [81].

Source and date of request

ECDC internal decision, 1 April 2019.

Disclaimer

ECDC issues this risk assessment document based on an internal decision and in accordance with Article 10 of Decision No 1082/13/EC and Article 7(1) of Regulation (EC) No 851/2004 establishing a European centre for disease prevention and control (ECDC). In the framework of ECDC's mandate, the specific purpose of an ECDC risk assessment is to present different options on a certain matter. The responsibility on the choice of which option to pursue and which actions to take, including the adoption of mandatory rules or guidelines, lies exclusively with the EU/EEA Member States. In its activities, ECDC strives to ensure its independence, high scientific quality, transparency and efficiency.

This report was written with the coordination and assistance of an Internal Response Team at the European Centre for Disease Prevention and Control. All data published in this risk assessment are correct to the best of our knowledge at the time of publication. Maps and figures published do not represent a statement on the part of ECDC or its partners on the legal or border status of the countries and territories shown.

References

1. Centers for Disease Control and Prevention. Measles (Rubeola) - Complications [internet]. Altanta: US Centers for Disease Control and Prevention; 2018 [cited 18 May 2019]. Available from: https://www.cdc.gov/measles/about/complications.html
2. European Centre for Disease Prevention and Control. Factsheet about measles [internet]. Stockholm: European Centre for Disease Prevention and Control; [cited 9 April 2019]. Available from: https://ecdc.europa.eu/en/measles/facts/factsheet
3. European Centre for Disease Prevention and Control. Measles [internet]. Stockholm: European Centre for Disease Prevention and Control; 2019 [cited 9 April 2019]. Available from: https://ecdc.europa.eu/en/measles
4. European Centre for Disease Prevention and Control. Risk of measles transmission in the EU/EEA. Stockholm: European Centre for Disease Prevention and Control; 2018.
5. Godefroy R, Chaud P, Ninove L, Dina J, Decoppet A, Casha P, et al. Measles outbreak in a French Roma community in the Provence-Alpes-Cote d'Azur region, France, May to July 2017. Int J Infect Dis. 2018;76:97-101.
6. Komitova R, Kevorkyan A, Boykinova O, Krumova S, Atanasova M, Raycheva R, et al. Difficulties in achieving and maintaining the goal of measles elimination in Bulgaria. Rev Epidemiol Sante Publique. 2019.
7. Augusto GF, Silva A, Pereira N, Fernandes T, Leca A, Valente P, et al. Report of simultaneous measles outbreaks in two different health regions in Portugal, February to May 2017: lessons learnt and upcoming challenges. Euro surveillance: bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin. 2019;24(3).
8. Rovida F, Brianese N, Piralla A, Sarasini A, Girello A, Giardina F, et al. Outbreak of measles genotype H1 in Northern Italy originated from a case imported from Southeast Asia, 2017. Clin Microbiol Infect. 2019;25(4):526-8.
9. Magurano F, Baggieri M, Mazzilli F, Bucci P, Marchi A, Nicoletti L, et al. Measles in Italy: Viral strains and crossing borders. Int J Infect Dis. 2019;79:199-201.
10. European Centre for Disease Prevention and Control. Weekly threats reports (CDTR): Communicable disease threats reports [internet]. Stockholm: European Centre for Disease Prevention and Control; 2019 [cited 10 April 2019]. Available from: https://ecdc.europa.eu/en/threats-and-outbreaks/reports-and-data/weekly-threats
11. European Centre for Disease Prevention and Control. Communicable disease threats report (CDTR) for week 15, 7-13 April 2019. Stockholm: European Centre for Disease Prevention and Control; 2019.
12. Keegan R, Dabbagh A, Strebel PM, Cochi SL. Comparing measles with previous eradication programs: enabling and constraining factors. J Infect Dis. 2011;204 Suppl 1:S54-61.
13. Durrheim DN. Measles Elimination - Using Outbreaks to Identify and Close Immunity Gaps. N Engl J Med. 2016;375(14):1392-3.
14. World Health Organization Regional Office for Europe. Eliminating Measles and Rubella. Framework for the Verification Process in the WHO European Region. Copenhagen: WHO Regional Office for Europe; 2014.
15. World Health Organization. Global vaccine action plan 2011–2020. Geneva: World Health Organization; 2013.
16. World Health Organization Regional Office for Europe. Regional Committee for Europe, Sixtieth session; Moscow, 13–16 September 2010. Copenhagen: WHO Regional Office for Europe 2010.
17. World Health Organization Regional Office for Europe. Seventh meeting of the European Regional Verification Commission for measles and rubella elimination (RVC); 13–15 June 2018, Paris France. Copenhagen: WHO Regional Office for Europe 2018.
18. Datta S, O'Connor PM, Jankovic D, Muscat M, Mamou MCB, Singh S, et al. Progress and challenges in measles and rubella elimination in the WHO European Region. Vaccine. 2017;36(36):5408-15.
19. World Health Organization Regional Office for the Western Pacific. Regional strategy and plan of action for measles and rubella elimination in the Western Pacific. Manila, Philippines: WHO Regional Office for the Western Pacific; 2017.
20. World Health Organization Regional Office for South-East Asia. Strategic plan for measles elimination and rubella and congenital rubella syndrome control in the South-East Asia Region, 2014-2020. New Dehli: WHO Regional Office for South-East Asia; 2015.
21. Castillo-Solorzano C, Marsigli C, Danovaro-Holliday MC, Ruiz-Matus C, Tambini G, Andrus JK. Measles and Rubella Elimination Initiatives in the Americas: Lessons Learned and Best Practices. The Journal of Infectious Diseases. 2011;204(suppl_1):S279-S83.
22. World Health Organisation Regional Office for the Americas. Bye bye, measles and rubella! Measles and rubella elimination in the Americas 1960 to 2016. Washington DC: WHO Regional Office for the Americas; 2016.
23. European Centre for Disease Prevention and Control. Monthly measles and rubella monitoring report February 2018. Stockholm: European Centre for Disease Prevention and Control; 2018.
24. European Centre for Disease Prevention and Control. Monthly measles and rubella monitoring report February 2019. Stockholm: European Centre for Disease Prevention and Control; 2019.
25. Durrheim DN, Crowcroft NS. The price of delaying measles eradication. The Lancet Public Health. 2017;2(3):e130-e1.
26. Eurostat. Migration and migrant population statistics [internet]. Eurostat; 2019 [cited 12 April 2019]. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php/Migration_and_migrant_population_statistics#Migration_flows:_Immigration_to_the_EU_from_non-member_countries_was_2.4_million_in_2017
27. International Air Transport Association (IATA). Volume of air passengers. 2019.

28. Takla A, Wichmann O, Rieck T, Matysiak-Klose D. Measles incidence and reporting trends in Germany, 2007-2011. Bulletin of the World Health Organization. 2014;92(10):742-9.
29. European Centre for Disease Prevention and Control. Vaccine Scheduler [internet]. Stockholm: European Centre for Disease Prevention and Control; 2019 [cited 12 April 2019]. Available from: http://vaccine-schedule.ecdc.europa.eu/pages/scheduler.aspx.
30. Arima Y, Oishi K. Letter to the editor: Measles cases among fully vaccinated persons. Eurosurveillance. 2018;23(34):1800449.
31. Sundell N, Dotevall L, Sansone M, Andersson M, Lindh M, Wahlberg T, et al. Measles outbreak in Gothenburg urban area, Sweden, 2017 to 2018: low viral load in breakthrough infections. Eurosurveillance. 2019;24(17):1900114.
32. World Health Organization. Surveillance standards for vaccine-preventable diseases, second edition. Geneva: World Health Organization; 2018.
33. Gagneur A, Pinquier D, Aubert M, Balu L, Brissaud O, De Pontual L, et al. Kinetics of decline of maternal measles virus-neutralizing antibodies in sera of infants in France in 2006. Clinical and vaccine immunology : CVI. 2008;15(12):1845-50.
34. Nigel GJ, De Serres G, Farrington PC, Redd SB. Assessment of the Status of Measles Elimination from Reported Outbreaks: United States, 1997–1999. The Journal of Infectious Diseases. 2004;189(Supplement_1):S36-S42.
35. Conlan AJK, Grenfell BT. Seasonality and the persistence and invasion of measles. Proc Biol Sci. 2007;274(1614):1133-41.
36. Bartlett MS. The Critical Community Size for Measles in the United States. Journal of the Royal Statistical Society Series A (General). 1960;123(1):37-44.
37. King A, Varughese P, De Serres G, Tipples GA, Waters J, Working Group on Measles E. Measles elimination in Canada. J Infect Dis. 2004;189 Suppl 1:S236-42.
38. Lam P, Williams L, Gadient S, Squires S, St-Laurent M. Maintaining measles elimination in Canada: Moving forward. Can Commun Dis Rep. 2015;41(7):175-8.
39. Centers for Disease Control and Prevention. Measles Cases and Outbreaks [internet]. Atlanta: Centers for Disease Control and Prevention; 2019 [cited 12 April 2019]. Available from: https://www.cdc.gov/measles/cases-outbreaks.html
40. World Health Organization. Measles – European Region; Disease outbreak news - update 6 May 2019 [internet]. Geneva: World Health Organization; 2019 [cited 9 May 2019]. Available from: https://www.who.int/csr/don/06-may-2019-measles-euro/en/
41. Zimmerman LA, Muscat M, Singh S, Singh S, Ben Mamou M, Jankovic D, et al. Progress Toward Measles Elimination — European Region, 2009–2018. MMWR Morb Mortal Wkly Rep 2019.68(17):396–401.
42. World Health Organization. Manual for the Laboratory-based Surveillance of Measles, Rubella, and Congenital Rubella Syndrome [internet]. Geneva: World Health Organization; 2018 [cited 1 May 2019]. Available from: https://www.who.int/immunization/monitoring_surveillance/burden/laboratory/manual_chapter10/en/
43. World Health Organization. Measles vaccines: WHO position paper - April 2017. Geneva: World Health Organization; 2017.
44. Reef SE, Harris JB, Kriss JL, Durrheim DN, Crowcroft NS, Dabbagh AJ. Report for the SAGE Working Group on Measles and Rubella: The Roadmap to Immunity. Geneva: Strategic Advisory Group of Experts (SAGE) on Immunization; 2018.
45. Gay NJ, De Serres G, Farrington CP, Redd SB, Papania MJ. Assessment of the status of measles elimination from reported outbreaks: United States, 1997-1999. J Infect Dis. 2004;189 Suppl 1:S36-42.
46. Public Health England. UK Measles and Rubella elimination strategy 2019. London: Public Health England; 2019.
47. Ramsay M. A strategic framework for the elimination of measles in the European Region. Copenhagen: WHO Regional Office for Europe; 1999.
48. Funk S, Knapp JK, Lebo E, Reef SE, Dabbagh AJ, Kretsinger K, et al. Target immunity levels for achieving and maintaining measles elimination. bioRxiv. 2018:201574.
49. Fefferman NH, Naumova EN. Dangers of vaccine refusal near the herd immunity threshold: a modelling study. The Lancet Infectious Diseases. 2015;15(8):922-6.
50. Perry RT, Halsey NA. The Clinical Significance of Measles: A Review. The Journal of Infectious Diseases. 2004;189(Supplement_1):S4-S16.
51. Muscat M, Bang H, Wohlfahrt J, Glismann S, Molbak K. Measles in Europe: an epidemiological assessment. Lancet. 2009;373(9661):383-9.
52. Simone B, Balasegaram S, Gobin M, Anderson C, Charlett A, Coole L, et al. Evaluation of the measles, mumps and rubella vaccination catch-up campaign in England in 2013. Vaccine. 2014;32(36):4681-8.
53. World Health Organization. Genetic diversity of wildtype measles viruses and the global measles nucleotide surveillance database (MeaNS) = La diversité génétique des virus rougeoleux de type sauvage et la base de données MeaNS (Measles Nucleotide Surveillance). Weekly Epidemiological Record = Relevé épidémiologique hebdomadaire. 2015;90(30):373 - 80.
54. World Health Organization Regional Office for Europe. Sixth meeting of the European Regional Verification Commission for measles and rubella elimination (RVC); 15–17 June 2017, Bucharest, Romania. 2017.
55. World Health Organization Regional Office for Europe. Over 100 000 people sick with measles in 14 months: with measles cases at an alarming level in the European Region, WHO scales up response [internet]. Copenhagen: WHO Regional Office for Europe [cited 13 May 2019]. Available from: http://www.euro.who.int/en/media-centre/sections/press-releases/2019/over-100-000-people-sick-with-measles-in-14-months-with-measles-cases-at-an-alarming-level-in-the-european-region,-who-scales-up-response

56. Grant GB, Masresha BG, Moss WJ, Mulders MN, Rota PA, Omer SB, et al. Accelerating measles and rubella elimination through research and innovation – Findings from the Measles & Rubella Initiative research prioritization process, 2016. Vaccine. 2019.
57. Hayman DTS. Measles vaccination in an increasingly immunized and developed world. Human Vaccines & Immunotherapeutics. 2019;15(1):28-33.
58. Carrillo-Santisteve P, Lopalco PL. Measles still spreads in Europe: who is responsible for the failure to vaccinate? Clin Microbiol Infect. 2012;18 Suppl 5:50-6.
59. Le Menach A, Boxall N, Amirthalingam G, Maddock L, Balasegaram S, Mindlin M. Increased measles–mumps–rubella (MMR) vaccine uptake in the context of a targeted immunisation campaign during a measles outbreak in a vaccine-reluctant community in England. Vaccine. 2014;32(10):1147-52.
60. Braeckman T, Theeten H, Roelants M, Blaizot S, Hoppenbrouwers K, Maertens K, et al. Can Flanders resist the measles outbreak? Assessing vaccination coverage in different age groups among Flemish residents. Epidemiology and Infection. 2018;146(8):1043-7.
61. Trentini F, Poletti P, Merler S, Melegaro A. Measles immunity gaps and the progress towards elimination: a multi-country modelling analysis. The Lancet Infectious Diseases. 2017;17(10):1089-97.
62. European Centre for Disease Prevention and Control. Designing and implementing an immunisation information system. Stockholm: European Centre for Disease Prevention and Control; 2018.
63. Li S, Ma C, Hao L, Su Q, An Z, Ma F, et al. Demographic transition and the dynamics of measles in six provinces in China: A modeling study2017. e1002255 p.
64. de Vries RD, Mesman AW, Geijtenbeek TB, Duprex WP, de Swart RL. The pathogenesis of measles. Current Opinion in Virology.2(3):248-55.
65. Hayman DTS, Marshall JC, French NP, Carpenter TE, Roberts MG, Kiedrzynski T. Global importation and population risk factors for measles in New Zealand: a case study for highly immunized populations. Epidemiology and Infection. 2017;145(9):1875-85.
66. Hayman DTS, Marshall JC, French NP, Carpenter TE, Roberts MG, Kiedrzynski T. Cost-benefit analyses of supplementary measles immunisation in the highly immunized population of New Zealand. Vaccine.35(37):4913-22.
67. Nishiura H, Mizumoto K, Asai Y. Assessing the transmission dynamics of measles in Japan, 20162017.
68. Inaida S, Matsuno S, Kobune F. Measles elimination and immunisation: national surveillance trends in Japan, 2008–2015. Epidemiology and Infection. 2017;145(11):2374-81.
69. Jansen VAA, Stollenwerk N, Jensen HJ, Ramsay ME, Edmunds WJ, Rhodes CJ. Measles Outbreaks in a Population with Declining Vaccine Uptake. Science. 2003;301(5634):804-.
70. Bae G-R, Choe YJ, Yeong Go U, Kim Y-I, Lee W-J. Economic analysis of measles elimination program in the Republic of Korea, 2001: A cost benefit analysis study 2013. Vaccine. 2013;31:2661–2666
71. Sundhedsstyrelsen. Børnevaccinationsprogrammet Årsrapport 2018. Copenhagen: Sundhedsstyrelsen; 2019.
72. Antona D, Morel P, Jacquot C, Fonteneau L, Dina J, Vauloup-Fellous C, et al. Measles and rubella seroprevalence in a population of young adult blood donors, France 2013. Epidemilogy and Infection 2019;147.
73. Syndor E, Perl TM. Healthcare providers as sources of vaccine-preventable diseases. Vaccine. 2014;32(38):4814-22.
74. Fiebelkorn AP, Seward JF, Orenstein W. A global perspective of vaccination of healthcare personnel against measles: systematic review. Vaccine.32(38).
75. Jacobson Vann, Jacobson R, Coyne-Beasley T, Asafu-Adjei J, Szilagyi P. Patient reminder and recall interventions to improve immunization rates. Cochrane Database of Systematic Reviews. 2018.
76. Dubé E. Addressing vaccine hesitancy: the crucial role of healthcare providers. Clinical Microbioloy and Infection.23(5):279-80.
77. Simone B, Carrillo-Santisteve P, Lopalco PL. Healthcare workers' role in keeping MMR vaccination uptake high in Europe: a review of evidence. Eurosurveillance. 2012;17(26):20206.
78. Odone A, Ferrari A, Spagnoli F, Visciarelli S, Shefer A, Pasquarella C, et al. Effectiveness of interventions that apply new media to improve vaccine uptake and vaccine coverage. Human Vaccines & Immunotherapeutics. 2015;11(1):72-82.
79. Nowak GJ, Shen AK, Schwartz JL. Using campaigns to improve perceptions of the value of adult vaccination in the United States: Health communication considerations and insights. Vaccine. 2017;35(42):5543-50.
80. Kobaidze K, Wallace G. Forgotten but Not Gone: Update on Measles Infection for Hospitalists. Journal of Hospital Medicine. 2017;12(6):472-6.
81. Cockbain BC, Bharucha T, Irish D, Jacobs M. Measles in older children and adults. BMJ. 2017;356:j426.
82. National Institute of Public Health Romania. Situatia rujeolei in Romania (Measles situation reports, Romania) [internet]. Bucharest: Centrul Național de Supraveghere și Control al Bolilor Transmisibile; 2019 [cited 7 May 2019]. Available from: http://www.cnscbt.ro/index.php/informari-saptamanale/rujeola-1
83. World Health Organization. WHO/UNICEF estimates of MCV1 coverage [internet]. Geneva: World Health Organization; 2018 [cited 1 April 2019]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragemcv1.html
84. World Health Organization. WHO/UNICEF estimates of MCV2 coverage [internet]. Geneva: World Health Organization; 2018 [cited 1 April 2019]. Available from: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragemcv2.html
85. Gibbons CL, Mangen M-JJ, Plass D, Havelaar AH, Brooke RJ, Kramarz P, et al. Measuring underreporting and under-ascertainment in infectious disease datasets: a comparison of methods. BMC public health. 2014;14:147-.

86. Ciofi Degli Atti ML, Salmaso S, Bella A, Arigliani R, Gangemi M, Chiamenti G, et al. Pediatric sentinel surveillance of vaccine-preventable diseases in Italy. The Pediatric Infectious Disease Journal. 2002;21(8):763-8.
87. Bier M, Brak B. A simple model to quantitatively account for periodic outbreaks of the measles in the Dutch Bible Belt. The European Physical Journal B. 2015;88(4):107.
88. van Isterdael CED, van Essen GA, Kuyvenhoven MM, Hoes AW, Stalman WAB, de Wit NJ. Measles incidence estimations based on the notification by general practioners were suboptimal. Journal of Clinical Epidemiology. 2004;57(6):633-7.
89. Six C, Blanes de Canecaude J, Duponchel JL, Lafont E, Decoppet A, Travanut M, et al. Spotlight on measles 2010: Measles outbreak in the Provence-Alpes-Côte d'Azur region, France, January to November 2010 - substantial underreporting of cases. Eurosurveillance. 2010;15(50):19754.

Annex 1. EU/EEA country profiles

Individual country profiles can be downloaded from the ECDC website.

Annex 2. Detailed methods

Data sources

Measles notifications submitted to The European Surveillance System (TESSy) as case-based data (CBD) and aggregate data (AGD), with date used for statistics between 1 January 1999 and 31 March 2019, were extracted on 26 April 2019. All dates used to describe measles case data in this risk assessment refer to the date used for statistics.

The data in TESSy in the early part of this period were transferred from EUVAC.NET and validated by the Member States at the time of network transition to ECDC. The dates on which measles data were first reported vary by country and are reported in the 'cases by birth cohort and vaccination status' figure of each country profile.

Cases with an 'unknown' or 'discarded' case classification were excluded from all analyses.

AGD in TESSy aggregate cases by country, age group, vaccination status and gender. Information on outcome (dead/alive), importation status[1] or single year of age are not available, thereby limiting the analysis that is possible with these data. Countries reporting AGD include Belgium (692 cases, May 2016 to March 2019), Bulgaria (22 005 cases, 2010), Luxembourg (1 case, January 2014), Poland (397 cases, February and March 2019) and Romania (9 195 cases, 2005–2007).

Additional AGD were downloaded from the National Institute of Public Health Romania for 2018 [82] to make up for delays in reporting case-based data to TESSy. Weekly data on cases aggregated by age group and vaccination status were assigned to months in 2018 and summed to create monthly totals by age group and vaccination status. The amount that was in excess of the corresponding monthly total for Romania in TESSy was retained. These cases were described as confirmed in the online reports but were coded with a different case classification in the combined dataset to distinguish them from TESSy data.

Unless otherwise stated, we used WHO/UNICEF estimates of national immunisation coverage (WUENIC) for the first [83] and second [84] dose of measles-containing vaccine (MCV1, MCV2) and Eurostat 2018 estimates of country and age-specific population sizes.

[1] Imported case defined as a returning traveller or visitor exposed to measles outside the country during the 7–23 days prior to rash onset and supported by epidemiological or virological evidence. For cases that were outside the country for only a part of the 7–23 day period prior to rash onset, investigate whether the exposure to another measles case likely occurred outside or within the country to determine the source of infection and whether the case can be considered imported. Imported cases are defined by the place where the case was infected, not the country of residence or origin of the case [31].

Analysis

EU/EEA

Table 5 provides an overview of the methods used to generate each of the EU/EEA-level figures presented in the first section of the results.

Table 5. Overview of data sources and analyses for the EU/EEA-level figures

Section	Figure	Data source	Analysis
Temporal trends of reported cases	Fig 1. Number of measles cases by month and case classification	TESSy CBD, AGD and Romanian AGD, 1 Jan 2009 to 31 Mar 2019	Monthly total case counts aggregated by case classification. 8 cases missing month used for statistics in TESSY were excluded.
Age distribution in the last ten years	Fig 2. Median annual age and IQR of measles cases	TESSy CBD for ten 12-month periods, 1 April 2009 to 31 March 2019	Cases assigned to ten 12-month periods (1 April to 31 March) according to date used for statistics. Median age and interquartile range (IQR) of cases per period calculated and plotted with LOESS smoothed line to facilitate visual inspection of trends. Three plots produced: a) using data from all 30 Member States before stratifying to include only b) Member States that haven't, and c) Member States that have, had outbreaks affecting mainly children (Romania, Greece, Slovakia, Bulgaria and Cyprus).
Trends in vaccination coverage	Fig 3. Number of countries per year with missing vaccine coverage data or reporting 95% coverage for dose 1, dose 2 and both doses of MCV	WUENIC, 1980 to 2017	For each year in the time series, the number of Member States achieving at least 95% vaccination coverage was calculated separately for MCV1 and MCV2. Similarly, the number of Member States per year with missing data for each dose. Finally, number of countries per year achieving 95% for both MCV1 and MCV2 (WHO target) per year was calculated. Results for MCV1, MCV2 and both doses were plotted in three separate panels.
Estimate of the EU/EEA population born 1999 to 2019 non-immune against measles	No figure	Aggregated from country profiles, see details in Table 6	Numerator: Sum of the estimates of cumulative non-immune population in 2019 for each Member State. Denominator: Sum of the population in each Member State birth cohort per Member State between 1999 and 2019. For Croatia, population data were only available in Eurostat from 2001.
Current epidemic	Fig 4. Measles case numbers by classification and country	TESSy CBD, AGD and Romanian AGD, 1 Jan 2016 to 31 Mar 2019. RVC report 2018	Case numbers in the period aggregated by country and case classification. Member State names on y-axis coloured according to 2017 elimination status from the 2018 RVC report.
	Fig 5. Number of measles cases by age and vaccination status	Aggregated from country profiles, see details in Table 6	See details in Table 6; aggregated from country profiles following inclusion of additional data from countries that differed from TESSy; 401 cases with missing age excluded, four of which had received 0 doses and 397 had vaccination status unknown. The overall distribution of cases by age group are shown as proportions in text on the figure.

Section	Figure	Data source	Analysis
	Fig 6. Age-specific average a) annual notification rates and b) case-fatality rates and counts of deaths	TESSy CBD, AGD and Romanian AGD, 1 Jan 2016 to 31 Mar 2019. Eurostat 2018 population	Notification rates: 401 cases with missing age excluded. 1 000 000 x age-specific counts/(age-specific population in 2018 x 39/12). 39/12 used to derive an average annual rate for the 39-month period. We assumed the 2018 population was valid for the entire period. Case-fatality rates (CFR): 100 x total age-specific deaths reported in CBD/Total age-specific cases (from CBD and AGD). Use of CBD and AGD in the denominator but CBD in the numerator may underestimate CFR but considered prudent as most deaths in this period occurred in Romania and were included in the subset of cases reported to TESSy as CBD; using only CBD as the denominator would therefore have overestimated CFR for Romania.
	Fig 7. Distribution of origin of infection of cases defined as imported by probable continent of importation	Aggregated from country profiles, see details in Table 5	See details in Table 6; aggregated following inclusion of additional data from countries that differed from TESSy. Total of 145 imported cases had unknown probable continent of infection; 143 cases for which this was reported as unknown and 2 cases with multiple values for 'probable country of infection' that were located in >1 continent. Proportion calculated as total importations (including unknown origin)/total cases submitted as CBD. There was no material difference in the proportions if total cases from both CBD and AGD were included in the denominator.

Country profiles

Table 6 provides an overview of the methods used to generate the country profiles and the summary tables presented in the second section of the results. In general, we used identical methods to facilitate comparison of figures/tables between countries, but sometimes Member State feedback prompted the use of alternative data that they provided, or changes to the presentation of certain figures. All exceptions are summarised in Table 6 and explicitly stated in the titles of the relevant figure of the country profile. Further explanation for some of the analyses in Table 6 is found in the corresponding entry, where it exists, in Table 5.

Table 6. Overview of data sources, analyses and specific exceptions made that were requested by Member States for the measles country profiles

Figure/table	Item	Data source	Analysis	Exceptions or additional data
Summary table	Population	Eurostat 2018 estimate	n/a	None
	Elimination status	2018 RVC report (2017 data)	n/a	None
	MCV schedule	ECDC vaccine scheduler [29]	Ages in months or years for the start and end of the recommended window for MCV1 and MCV2	Italy proposed one correction
	Cases (confirmed; %)	TESSy CBD, AGD and Romanian AGD, 1 Jan 2016 to 31 Mar 2019.	Total cases: CBD and AGD aggregated on case classification variable. Proportion: 100 x confirmed cases/total cases	
	Average annual notification rates	Eurostat 2018 age-specific population estimates. 2013 European standard population (ESP) TESSy CBD, AGD and Romanian AGD, 1 Jan 2016 to 31 Mar 2019	Crude: 1 000 000 x total cases/(population x 39/12) Age-standardised: 'epitools' R package to standardise to ESP, using age-specific case counts (age groups <1, 1-4, 5-9, 10-14, 15-19, 20-29, 30+ years) and age-specific populations x 39/12. Cases with unknown age excluded. Note: as information on the number of imported cases is provided, a crude average annual notification rate among only endemic and import-related cases can be calculated.	

Figure/table	Item	Data source	Analysis	Exceptions or additional data
	Number of deaths (CFR)	TESSy CBD, AGD and Romanian AGD, 1 Jan 2016 to 31 Mar 2019.	CFR: 100 x total deaths reported in CBD/Total cases (from CBD and AGD). See explanation in Table 2.	
	Median (IQR) age:	TESSy CBD, 1 Jan 2016 to 31 Mar 2019	Distribution of single year of age reported in CBD. Cases with missing age excluded.	
	Exportations	TESSy CBD, 1 Jan 2016 to 31 Mar 2019	Count of cases in CBD in which country was named as probable country of infection for a case where 'Imported' = YES	
Probable continent of infection	Figure	TESSy CBD, 1 Jan 2016 to 31 Mar 2019	Data restricted to cases with 'Imported' = YES. Probable continent of infection derived from probable country of infection variable, with Europe divided into EU/EEA and non-EU/EEA countries. Cases with multiple 'probable country of infection' located in >1 continent were recoded as unknown for probable continent of infection. Distribution by probable continent of infection calculated for all cases for which this was known. Overall proportion of importations presented in Table 5 of the results calculated as total importations (including unknown origin)/total cases submitted as CBD. There was no material difference in the proportions if total cases from both CBD and AGD were used as the denominator.	Number of importations in TESSy revised for Finland and Croatia. Removed 2 importations reported by Belgium prior to a shift to reporting only AGD in May 2016.
National-level vaccination coverage	Figure	WUENIC 1980–2017	Time series for MCV1 and MCV2 plotted using all years of available data	Additional years' data provided by Latvia, Croatia and Finland. A third time series provided by UK. Explanatory comments added to plots for Belgium, Germany, Sweden and Netherlands.
Cases by birth cohort and vaccination status	Figure	TESSy CBD, all available years of data.	Cases with missing age were excluded. Birth cohort estimated by subtracting age in years from date used for statistics year for cases aged >2 years or aged <2 but with missing age in months. For cases with age in months, birth cohort was estimated by subtracting this from date used for statics year and month. Number of cases by vaccination status were plotted per birth cohort. All cases in birth cohorts prior to 1960 were grouped together	Explanatory comments added for Spain. France requested that the plot be restricted to cases aged 1 year and above and born since 1980 to reflect the population targeted by the national vaccination programme.

Figure/table	Item	Data source	Analysis	Exceptions or additional data
Estimated cumulative population non-immune	Figure	TESSy CBD, all available years of data. WUENIC 2001–2017 plus any additional data provided by Member State (see 'national-level vaccination coverage' above) Eurostat population estimates aged <1 year for 1999 to 2018.	Assumptions: 100% vaccine effectiveness (VE) of 1 dose Under-ascertainment factor of 10 (i.e. for every case reported to TESSy an additional 9 cases occurred that were not reported; see detailed limitations for a justification) Vaccination coverage years beyond 2017 estimated as the mean of the estimates for the last 5 years of data (2013-17 for all Member States except Latvia) and applied to birth cohorts 2016-18 (2017-18 for Latvia). 2019 birth cohort = 2018 population x 3/12 (3 months Jan–Mar 2019. This cohort is protected by maternal antibodies so does not contribute to non-immune population 2018 birth cohort is assumed to be vaccinated according to the projected vaccination coverage and the fraction of this cohort that would too old to be protected by maternal antibodies and too young to be vaccinated has not been included among the total non-immune population. Estimation: Non-immune population for year Y = birth cohort in year Y x (1-MCV1 vaccine coverage at Y+2) – (number of cases in TESSy from that birth cohort x 10). A negative result here was corrected to zero as it was indicative of the under-ascertainment factor being too high. Accumulation of non-immune children from current and previous birth cohorts plotted in figure. Estimated proportion in 2019 of people born 1999–2019 that are non-immune = cumulative non-immune population by 2019/cumulative population born in that period.	Croatia: Eurostat population data only available from 2001 so calculation is for birth cohort 2001–19. Used MCV2 coverage at year Y + 6 (school entry) for birth cohorts 2001-13, MCV1 coverage at year Y + 2 for birth cohorts 2014–19 MCV2 coverage. Adjustments to vaccination coverage used in calculations for Member States with evidence of higher vaccination coverage at later ages due to postponed vaccination: Sweden and Finland. Adjustments made where data provided on the impact of supplementary immunisation activities: UK (plot by year not shown. Estimate of the total susceptible population from birth cohorts 1999–2019 provided and used to calculated the proportion non-immune); France (alternative data provided to reconstruct the figure, including population estimates that differed slightly from Eurostat 2018) and evidence of 45% case ascertainment in France. Comments from Bulgaria and Belgium were added to their figures but no data were available to modify estimates
Measles by case classification (epidemic curve)	Figure	TESSy CBD, AGD and Romanian AGD, 1 Jan 2016 to 31 Mar 2019.	See Table 2 'Number of measles cases by month and case classification'	None
Measles cases by age and vaccination status	Figure	TESSy CBD for ten 12-month periods, 1 April 2009 to 31 March 2019	All cases had vaccination status recorded as either 0, 1, 2 doses, vaccinated with an unknown number of doses, or vaccination status unknown. Cases with missing age were excluded; the number can be calculated as the difference between the number of cases listed in the titles of this plot and of the epidemic curve. The remaining cases were aggregated by age group and vaccination status.	Finland provided breakdown by age group and vaccination status which was not available in TESSy

MCV: Measles-containing vaccine; MCV1: dose 1; MCV2: dose 2

Annex 3. Detailed limitations

Analysis at low spatial resolution

EU/EEA-level analyses

EU/EEA-level figures and trends provide a useful overview and should be included within an EU/EEA risk assessment. However, when interpreting them it is essential to recognise the considerable heterogeneity between Member States in terms of measles epidemiology and the level of measles control achieved. EU/EEA-level statistics are heavily affected by a small number of countries that are either endemic for measles, or non-endemic but still reporting large numbers of cases.

National-level analysis

Analysis below a national level of spatial resolution was beyond the scope of this risk assessment. Accordingly, the descriptive epidemiology presents only an average picture of each country, which may mask considerable variation between subnational areas and hard to reach communities. Vaccination coverage data were also only available at the national level, and the same considerations apply. TESSy CBD can be analysed subnationally for some Member States, although the resolution varies by country, and this is an area to develop further in future.

Aggregate measles case data

As mentioned in the *Methods* chapter, there are a restricted number of variables included in TESSy AGD. Accordingly, AGD was excluded from all analyses requiring single year of age of cases (birth cohort plots, estimates of non-immune population, median age), importation status or outcome.

That AGD had to be used for the analysis of the current epidemic in two of the five endemic countries limits our understanding of measles epidemiology in these important settings. Belgium has been providing AGD since May 2016; resulting in its exclusion from analysis on importation, and of the cases used in this period from Romania, 3 812 (21%) were estimates added to TESSy as AGD.

The analysis of EU/EEA-level age distributions in the last ten years was biased by AGD. All cases reported by Bulgaria in 2010 (22 005, 59% aged under 10 years) were AGD. Had these cases been included in the calculations for Figure 2a, the EU/EEA-wide median age in 2009–10 and 2010–11 would have been lower than presented. The inclusion AGD from Romania in 2018 (67% aged under 10 years) would have had a similar effect on median ages for 2017–18 and 2018–19, although less dramatic since the majority of cases (79%) from Romania, since the 2016 outbreak, have been reported as CBD.

Age standardisation

Age-standardised notification rates may be unstable for countries with small number of cases and/or age groups with no cases. This limits the comparability of the rates for such countries, although the reporting of confidence intervals helps to quantify some of the associated uncertainty.

Vaccination coverage data

The lack of agreed definitions for and methods of measuring vaccination coverage between countries limits comparability between them. Our analysis has focused largely on within-country trends over time, which will be most affected in changes to the way vaccination coverage has been defined or reported by any particular country, but the absolute values form the basis of the estimates of the non-immune population, as described below.

Estimate of the non-immune population due to missed vaccination

The estimates come from a relatively crude method recommended by SAGE [44], and their accuracy depends greatly on the accuracy of national-level vaccination coverage estimates. The method used does not account adequately for a number of important factors:

Immunisation through infection. Numerous methods exist for estimating under-ascertainment of infectious diseases in surveillance systems [85]. Studies using a range of methods conducted in Italy [86], Germany [28], Netherlands [87, 88] and France [72, 89] estimate the actual number of infections to be between two and ten times higher than the number notified. The actual size of this under-ascertainment factor will vary between countries and depend on context; for example, considerable variation by age and incidence was observed in Germany (higher under-reporting in older age groups and in low-incidence years), and by region in Italy (much

higher under-reporting in the south than the north). To be conservative we used ten as the under-ascertainment factor for our analysis, which is at the upper end of the reported range from these studies. It is possible that during large outbreaks, case under-ascertainment exceeds this and that a much larger part of the population becomes immunised through infection. Conversely, this factor may be too high. A sensitivity analysis should be included when developing this work further to cover a range of scenarios for under-ascertainment of case numbers. Sensitivity analyses should also account for different levels of uncertainty about vaccine coverage, as included in similar analysis in the UK [46], since for most countries vaccination coverage which was a much bigger driver of the size of the non-immune population than immunisation through infection. A limitation remains that the subtraction of cases from the non-immune population can only account for those reported to TESSy as CBD and not those reported as AGD (36 102 cases in total), since the latter cannot be assigned to a birth cohort. For Romania and Bulgaria, with large numbers of such cases, the number of non-immune individuals will be overestimated accordingly. This represents a substantial overestimation (relative to the total non-immune) in Bulgaria but not in Romania.

MCV2 coverage. For many countries, the conservative, simplifying assumption of 100% VE for MCV1 makes it acceptable to disregard MCV2. Where MCV1 coverage is higher than MCV2 coverage, MCV1 represents a more conservative choice. However, the way in which MCV2 is delivered and measured needs to be considered and ignoring MCV2 coverage may pose a particular problem where it is higher than MCV1 coverage. This is true only in a small number of countries and may be explained by the methods or the timing of vaccination coverage estimation used. For example, in Croatia, MCV2 at school entry can be a delayed first dose for those that missed MCV1 at one year of age; for this reason, MCV2 coverage was used for Croatia at the request of the Member State. A greater understanding of the immunisation programmes and definitions of vaccination coverage used in each Member State would enable more refined estimates to be made that are tailored to the specific situation in each country.

Supplementary immunisation activities such as catch-up campaigns, and cohorts in which vaccination was postponed for any reason. Supplementary immunisation activities were excluded since data are often not readily available and postponed vaccinations tend not to be captured in routine vaccination coverage estimates, so remain an inherent challenge. We adjusted down our original estimates using data provided by four countries (including UK and France, both of which have large populations and sizeable pool of unvaccinated individuals) which were able to demonstrate much higher proportions immunised than the vaccination coverage data alone would suggest. These revisions were incorporated, in turn, into the EU/EEA aggregate estimate. Data from Sweden and Finland were incorporated which show evidence of postponed vaccination, with much higher coverage at later ages than the MCV1 coverage estimates for the relevant birth cohort would suggest. Other countries that raised similar concerns about the vaccination coverage not reflecting their understanding of true coverage but did not have data available with which to refine our estimates included Belgium (where school health services offer catch-up vaccinations and there have been previous and planned catch-up vaccinations targeting adults in Flanders) and Bulgaria (where vaccination campaigns have been carried out in response to outbreaks in 2009–2011 and since February 2019).

Despite the adjustments made to our initial estimates following incorporation of additional data by Member State, there is still considerable uncertainty in our estimates of non-immune individuals that were born in the last twenty years. Misreported or inaccurately measured vaccination coverage, the assumptions of 100% VE, 10% case ascertainment and the disregard of MCV2 in the calculation could have biased the estimates in either direction. Incompletely accounting for supplementary immunisation activities or cohorts in which vaccination was postponed for any reason would likely have biased them upwards. The relative importance of these factors will vary between countries. However, as estimates of the size of the total non-immune population across all age groups, they are likely to be highly conservative, since they do not include infants aged between 6 and 12–18 months whose maternal antibodies have waned [33] but are too young to be vaccinated according to the national vaccination schedule. Adults aged 20 years and above are also not considered. Inspection of the age distributions of measles outbreaks gives a good indication of where the immunity gaps lie. We have shown that in most Member States a considerable proportion of cases occur among adults and that vaccination coverage was low in the years prior to 1999, both of which suggest a sizeable non-immune population aged over 20 years. The decision to start the analysis from 1999 was a pragmatic one since 1 January 1999 it is the earliest date for which we have TESSy data; a more complete analysis would require cases by Member States reported prior to this date and consideration of a longer time series of vaccination coverage data.