Journal of Epidemiology and Global Health
Vol. 9(4); December (2019), pp. 294–299
DOI: https://doi.org/10.2991/jegh.k.191007.001; ISSN 2210-6006; eISSN 2210-6014
https://www.atlantis-press.com/journals/jegh

Research Article

Measles Resurgence in Europe: Migrants and Travellers are not the Main Drivers

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ARTICLE INFO

Article History
Received 18 July 2019
Accepted 24 September 2019

Keywords
Measles
migration
travel
resurgence
vaccine hesitancy
global vaccine action plan
vaccine coverage

ABSTRACT

Measles is a highly transmissible viral infection that may lead to serious illness, lifelong complications, and death. As there is no animal reservoir for measles, measles resurgence is due to human movement of viremic persons. Therefore, some have blamed the enormous migration into Europe in the past 5 years for the measles resurgence in this region. We set out to determine the main driver for measles resurgence in Europe by assessing vaccine coverage rates and economic status in European countries, number of migrants, and travel volumes. Data on measles vaccine coverage rates with two vaccine doses of measles, mumps and rubella (MMR) [Measles Containing Vaccine (MCV)2] and total number of measles cases in 2017 for Europe, including Eastern European countries, were obtained, in addition to Gross Domestic Product (GDP), and number of migrants and tourist arrivals. The outcome measured, incidence of measles per 100,000, was log transformed and subsequently analyzed using multiple linear regression, along with predictor variables: number of international migrants, GDP per capita, tourist arrivals, and vaccine coverage. The final model was interpreted by exponentiating the regression coefficients. Incidence of measles was highest in Romania (46.1/100,000), followed by Ukraine (10.8/100,000) and Greece (8.7/100,000). MCV2 coverage in these countries is less than 84%, with lowest coverage rate (75%) reported in Romania. Only vaccine coverage appears to be the significant predictor in the model ($p < 0.001$) for incidence of measles even after adjusting for international migrants, international tourist arrivals, and GDP per capita. With one unit increase in vaccination coverage, the incidence of measles decreased by 18% [95% confidence interval (CI): 10–25]. Our results showed that number of migrants and international tourist arrivals into any of the European countries were not the drivers for increased measles cases. Countries with high vaccine coverage rates regardless of economic status did not experience a resurgence of measles, even if the number of migrants or incoming travellers was high. The statistically significant sole driver was vaccine coverage rates. These analyses reemphasize the importance of strategies to improve national measles vaccination to achieve coverage greater than 95%.

1. INTRODUCTION

Measles is one of the most transmissible viral infections that, although mild in most cases, can cause serious illness, lifelong complications, and death [1]. Before vaccine introduction, measles affected more than 90% of children globally by the age of 15 [2]. Effectiveness of the measles vaccine after one dose administered at the age of 12 months or later is 93% and after two doses is 97% [3]. Therefore, with such a highly efficacious vaccine, measles eradication is theoretically feasible. Hence, in 2010, the World Health Assembly (WHA) set three milestones for measles prevention to be achieved by 2015: first, aiming for a routine coverage of Measles Containing Vaccine (MCV)1 (first dose of MCV) to ≥90% at the national level and ≥80% at the district level; second, to reduce annual measles incidence globally to less than five cases per million population; and third, to reduce global mortality due to measles by 95% [2]. In 2012, the WHA endorsed the GVAP with the objective of eliminating measles in four of the six WHO regions by 2015 and in five regions by 2020 [4]. Indeed, between 2000 and 2017, the estimated MCV1 coverage has increased globally from 72% to 85%, while annual reported measles incidence decreased by 83% and the annual estimated mortality declined by 80% (from 545,174 to 109,638) [2].

The United States was the first WHO region to be declared having achieved measles elimination in 1999; a historic milestone that proved that measles elimination could be achieved through high routine coverage, engagement of regular immunization activities, and a robust and accurate case-based surveillance [5]. However, in 2018, the United States saw a major resurgence, mainly because of the migration crisis in Venezuela, combined with decreasing vaccine coverage in neighboring countries that increased the vulnerability to importation of measles [6,7]. The extent of the current outbreak has significantly hampered WHO's global measles and rubella elimination goals and efforts. If this persists for longer than 12 months, it will result in affected countries losing their elimination status.

Unlike the United States, Europe has reasonably high measles vaccination coverage. In 1998, the WHO European Region set a

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Data availability statement: All data are publicly available.

target to eliminate measles by 2010 [8], which was not achieved. In 2018, Europe saw a major resurgence of measles; the total number of measles cases in 2018 was the highest in this decade, reaching three times the total cases in 2017 [9]. In 2018, Europe reported more than 21,000 cases of measles, including 35 deaths [10]. Early reports in 2019 show a further 300% increase [11]. As there is no animal reservoir for measles, measles resurgence is due to human movement of viremic persons [10]. With the increasing number of migrants to Europe from countries where measles virus is potentially circulating [12], there is concern that such migration could contribute to the measles resurgence in this region. Indeed, measles seroprotection in migrants is often suboptimal [13–15]. Measles outbreaks in migrant populations have been reported [16]. In addition to migrants, international travellers can also be a major source of measles importation [5,17,18]. Travel-associated measles transmission to household members and other contacts has been described [19,20]. Multiple measles cases can also occur as a result of exposure during air travel [21,22]. The second largest measles outbreak in the United States occurred in 2011 due to measles importation via a traveler [23]. Given the increasing travel volumes globally, including to countries with measles [24], the likelihood of importing measles into Europe is increasing.

We set out to determine the main driver for measles resurgence in Europe by assessing vaccine coverage rates and economic status in European countries, number of migrants, and tourist arrivals.

2. MATERIALS AND METHODS

For this analysis, European countries as listed by WHO Europe were selected (http://www.euro.who.int/en/countries). For these countries, we obtained the most recent data from WHO sources on measles vaccine coverage rates with two vaccine doses of Measles, Mumps, and Rubella (MMR) (MCV2) [25]; the most recent published data are from 2017. We then obtained the number of all measles cases for the year 2017 for each of these European countries [26]. To calculate the population incidence rate, we obtained population size from Eurostat database [27], and missing population size data for Monaco were substituted by the data from the World Bank. Number of international migrants (2017) for each country was obtained from Eurostat database: migrant and migration population statistics database [27]. A migrant is defined as any person who is moving or has moved across an international border or within a state away from his/her habitual place of residence, regardless of the person's legal status, whether the movement is voluntary or involuntary, what the causes for the movement are, or what the length of the stay is, according to the world migration report [28,29]. Missing data were substituted with the latest available data from the same Eurostat database or the Migration Data Portal [30], whichever provided the most current data.

Gross Domestic Product (GDP) per capita for the year 2017 by European country was obtained from the World Bank Database [31], and data for international tourist arrival (by country) was retrieved from the United Nations World Trade Organization Tourism Highlights 2018 Report [32]. The term "international tourist arrivals" encompasses tourists and those crossing international borders for purposes other than tourism, such as business and studies.

Since the outcome variable (incidence of measles per 100,000) is highly skewed, it was log transformed using log [(total measles cases + 1)/total population) × 100,000] and then subsequently analyzed using the multiple linear regression model with the exposure variables being measles vaccine coverage, international migrants, international arrivals, and GDP per capita. The interpretation of the final model was by exponentiating the regression coefficients. Statistical analysis was performed using STATA version 14 (STATA Corp., TX, USA).

3. RESULTS

Table 1 summarizes the vaccine coverage rate, GDP per capita, international migrant numbers, international tourist arrivals, and calculated incidence of measles in European countries in 2017. Romania (n = 9076), Ukraine (n = 4782), and Italy (n = 4042) had the highest reported number of measles cases, while incidence of measles was highest in Romania (46.1/100,000), followed by Ukraine (10.8/100,000) and Greece (8.7/100,000). Vaccine coverage (MCV2) in these countries is <84%, with lowest coverage rate (75%) reported in Romania. In the same year, we observed an average of 13,475,163 tourist arrivals compared to 118,974 migrants coming into the selected European countries.

Table 2 shows the exponentiated coefficients of the multiple linear regression model. Only vaccine coverage is the significant predictor in the model ($p < 0.001$) for measles incidence after adjusting for international migrants, international tourist arrivals, and GDP per capita. With one unit increase in vaccination coverage, the incidence of measles decreases by 18% [95% confidence interval (CI): 10–25].

4. DISCUSSION

Our findings show a statistically significant inverse relationship between MCV2 coverage rates and notified measles cases in European countries. With one unit increase in vaccination coverage, the incidence of measles is estimated to decrease by 18%. The linear regression model showed that number of migrants and international tourist arrivals into any of the European countries were not the main drivers for increased measles cases, instead suboptimal vaccine coverage was. Countries with high vaccine coverage rates regardless of economic status as measured by GDP did not experience a resurgence of measles, even if the number of migrants or travel arrivals was high.

Although Europe has seen a huge influx of migrants from low- to middle-income countries [12] and such migrants usually have a lower seroprotection for all vaccine preventable diseases including measles [13,14], our findings underpin that migrants are not the main drivers for measles resurgence in Europe. The number of migrants is possibly too low to account for such resurgence and is far surpassed by the number of international tourist arrivals. There were around 120,000 migrants versus 13 million tourist arrivals; in other words, migrants only present <1% of all persons crossing international borders to enter Europe. Tourist travellers would hence be much more likely to contribute to measles spread via population movements, even if their vaccine coverage rates are higher. This was shown in the United States where the majority of imported measles was due to travellers with inadequate

Table 1 | Number of international migrants, international tourist arrival, vaccination coverage, measles cases, calculated incidence of measles, population size, GDP per capita for the year 2017, by country in Europe

Country	International migrants (2017)[a,b]	GDP per capita (2017)[c]	International arrivals (×1000) (2017)[d]	MCV1 (%)[e]	MCV2 (%)[f]	Population[g]	Measles cases (2017)[h]	2017 Incidence of measles (per 100,000)
Albania	–	12,943.4	4,643,000	96	98	2,930,000	12	0.44
Andorra	–	49,900.0	3,003,000	99	94	77,000	0	1.30
Armenia	861*	9668.0	1,495,000	96	97	2,930,000	1	0.07
Austria	111,800	53,879.3	29,460,000	96	84	8,735,000	95	1.10
Azerbaijan	2300*	17,449.9	2,454,000	98	97	9,828,000	0	0.01
Belgium	126,700	49,366.7	8,358,000	96	85	11,429,000	367	3.22
Bulgaria	25,600	20,948.1	8,883,000	94	92	7,085,000	165	2.34
Bosnia and Herzegovina	5620*	13,107.7	922,000	69	80	3,507,000	18	0.54
Belarus	19,900*	18,895.6	2,000,000	97	98	9,468,000	1	0.02
Croatia	15,600	26,295.5	15,593,000	89	95	4,189,000	7	0.19
Cyprus	21,300	36,012.4	3,652,000	90	88	1,180,000	3	0.34
Czech Republic (Czechia)	51,800	38,019.6	12,808,000^	97	90	10,618,000	142	1.35
Denmark	68,600	54,356.4	10,781,000^	97	88	5,734,000	4	0.09
Estonia	17,600	33,447.8	3,245,000	93	91	1,310,000	1	0.15
Finland	31,800	46,343.6	3,181,000	94	92	5,523,000	11	0.22
France	370,000	44,032.9	86,918,000	90	80	64,980,000	519	0.80
Georgia	–	10,674.5	3,479,000	95	90	3,912,000	94	2.43
Germany	917,100	52,555.9	37,452,000	97	93	82,114,000	929	1.13
Greece	112,200	28,582.8	27,194,000	97	83	11,160,000	968	8.68
Hungary	68,100	28,798.6	15,785,000	99	99	9,722,000	36	0.38
Iceland	12,100	55,322.1	2,224,000	92	95	335,000	3	1.19
Ireland	78,500	76,744.7	10,388,000	92	–	4,762,000	25	0.55
Israel	–	38,867.8	3,613,000	98	96	8,322,000	42	0.52
Italy	343,400	40,923.7	58,253,000	92	86	59,360,000	4042	6.81
Kyrgyzstan	3960	3735.4	2,930,000^	95	96	6,045,000	5	0.10
Lithuania	20,400	33,252.7	2,523,000	94	92	2,890,000	2	0.10
Luxembourg	24,400	107,640.6	1,046,000	99	86	583,000	4	0.86
Latvia	9900	28,362.0	1,950,000	96	89	1,950,000	0	0.05
Monaco	–	115,700.0	355,000	87	79	39,000	1	5.13
Republic of Moldova	2070*	5710.8	145,000	93	92	4,051,000	0	0.02
The former Yugoslav Republic of Macedonia	1700*	15,290.3	631,000	83	–	2,083,000	19	0.96
Malta	21,700	40,796.8	2,274,000	91	83	431,000	0	0.23
Montenegro	–	19,354.9	1,877,000	58	83	629,000	0	0.16
The Netherlands	189,600	54,422.0	17,924,000	93	90	17,036,000	16	0.10
Norway	53,400	62,182.8	6,252,000	96	91	5,305,000	1	0.04
Poland	209,400	29,923.7	18,400,000	96	93	38,171,000	63	0.17
Portugal	36,600	32,554.3	21,200,000	98	95	10,330,000	34	0.34
Romania	177,400	26,660.2	2,760,000	86	75	19,679,000	9076	46.13
Russian Federation	191,700*	25,763.3	24,390,000	98	97	143,990,000	721	0.50
San Marino	429*	63,548.6	78,000	82	78	33,000	0	3.03
Serbia	–	15,431.9	1,497,000	86	91	8,791,000	721	8.21
Slovakia (Slovak Republic)	7200	32,371.2	5,415,000#	96	97	5,448,000	7	0.15
Slovenia	18,800	36,387.5	3,586,000	93	94	151,989,000	8	0.01
Spain	532,100	39,037.4	81,786,000	96	93	46,354,000	161	0.35
Sweden	144,500	51,404.8	6,865,000	97	95	9,911,000	41	0.42
Switzerland	143,400	66,307.4	11,133,000	95	89	8,476,000	105	1.25
Turkmenistan	–	18,030.9	–	99	99	5,758,000	0	0.02
Turkey	–	28,001.8	37,601,000	96	86	80,745,000	84	0.11
Ukraine	44,200*	8698.7	14,230,000	86	84	44,223,000	4782	10.82
United Kingdom	644,200	44,920.5	37,651,000	92	88	66,182,000	364	0.55

Note: *There are no available data from 2017. Data are substituted with the latest available data from either Eurostat database or Migration Data Portal (whichever is more current). ^Data from 2016. #Data from 2010. [a]https://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00176&plugin=1. [b]https://migrationdataportal.org/?i=stock_abs_&t=2017&cm49=795. [c]https://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD. [d]https://www.e-unwto.org/doi/pdf/10.18111/9789284419876. [e]http://apps.who.int/gho/data/node.main.A826?lang=en. [f]http://apps.who.int/gho/data/node.main.MCV2n?lang=en. [g]https://population.un.org/wpp/DataQuery/. [h]http://apps.who.int/gho/data/view.main.1540_62?lang=en.

Table 2 | Exponentiated coefficient of multiple linear regression model for incidence of measles

Incidence of measles (2017)	Coefficient	95% CI (coefficient)	Exponentiated (coefficient)	Exponentiatied (95% CI coefficient)
Vaccine coverage	−0.19	−0.28, −0.10	0.82 (p < 0.0001)	0.75, 0.90
International migrants	$1.72e^{-7}$	$-2.04e^{-7}$, $5.48e^{-7}$	1.00 (p = 0.359)	1.00, 1.00
GDP per capita	$-3.68e^{-7}$	$-2.73e^{-5}$, $2.66e^{-5}$	1.00 (p = 0.978)	1.00, 1.00
International tourist arrival	$5.69e^{-9}$	$-2.979e^{-8}$, $4.11e^{-8}$	1.00 (p = 0.749)	1.00, 1.00

or absent immunization coverage against measles, rather than migrants [33]. Another study compared the potential risk of measles importation from migrants versus travellers into the United States using a cross-sectional, ecological design [34]. The study showed that there are 10 times more annual U.S. visitors to high measles incidence countries than there are U.S. immigrants from high measles incidence countries. In The Netherlands, travellers introduced measles resulting in a cluster of measles in unvaccinated persons, but due to the high vaccine coverage rate in this country it did not spread further [35]. GeoSentinel is a global sentinel surveillance of infectious diseases in returning travelers [36]. Measles remains a risk for travellers, with 94 measles diagnoses reported to the GeoSentinel network from 2000 to 2014, two-thirds since 2010 [37], with Asia being the most common exposure region, followed by Africa and Europe. The years 2018 and 2019, however, saw a further increase of measles in travellers seen at GeoSentinel sites [38]. Efforts to reduce travel-associated measles should target all travellers, with a particular focus on catch-up vaccination initiatives of susceptible adults [5]. To minimize the risk of introducing measles, clinicians should advise persons who are planning international travel to have received at least two doses of measles vaccination before travel [1]. Persons born before 1957 are considered to be immune to measles [2].

However, the key message is that introduction of measles into areas or countries in Europe should not result in autochthonous transmission if vaccine coverage rates were to be high. Our analyses reemphasize the importance of strategies to improve national measles vaccination to achieve coverage far greater than 95%. Measles vaccination is integrated in all European national immunization programs; therefore, the reasons for the continuing suboptimal MCV2 vaccine coverage in some countries need to be determined in order to implement policies to improve coverage and thereby eliminate measles in the European region.

While reported childhood immunization coverage rates demonstrate high two-dose MMR coverage of >95% in many European countries, such coverage rates only provide data on the current program; hence, such data are limited to younger age groups and are often not available for adolescents or adults. For example, in Australia, young adults have been shown to be an important group at risk of under-immunization, as a result of lower vaccine coverage during childhood in an era of decline disease rates and single-vaccine dose recommendations [39]. Another concern is that measles-specific IgG antibodies may decline with time since vaccination; however, the implications of declining measles-specific IgG antibody levels for maintaining measles elimination are unclear. The plaque reduction neutralization measurement of functional measles-specific antibodies does not assess cellular immunity that may be associated with durable protective immunity after vaccination [40]. Despite of declining antibody levels, there is currently no evidence that booster doses would be considered in any country at higher age. There is a need to determine correlates of protection against measles transmission and disease in the post-elimination era [39].

Although the vast majority of measles cases in Europe occur in countries with weak health systems, vaccine refusal is emerging as a risk factor in countries with strong health systems: vaccine hesitancy was nominated as one of the top 10 global health threats in 2019 [41]. Vaccine hesitancy encompasses the broad spectrum from total refusal to delayed acceptance, despite the availability of vaccination services [42]. With the increasing role of social media in spreading inaccurate information regarding vaccine-associated risks, clinicians need to scale up their efforts in managing parental concerns about vaccination and responding to questions from the public regarding the rationale for, and safety of, measles vaccines [1,43].

In summary, our study confirmed that vaccine coverage rates are the main drivers of measles resurgence in Europe. Countries with MCV2 >95% in Europe do not see a high measles incidence, even if the number of migrants and travellers are high. This notion is also consistent with observations for polio: polio importation will not result in secondary transmission if the vaccine coverage is high [44]. Nevertheless, pockets of unvaccinated persons even in high coverage countries can trigger small outbreaks [35]. In addition to maintaining and increasing high vaccine coverage rates of new birth cohorts in Europe, prevention of measles outbreaks requires the identification and vaccination of high-risk persons such as school-attending children, college students, international travellers, migrants, and health care workers, or those persons from communities with certain religious or other worldviews that are associated with vaccine hesitancy. Clinicians should consider measles among patients presenting with febrile rash illness and history of recent travel, and clinicians should promptly report suspected illnesses. Early identification of infectious patients, rapid public health investigation, and maintenance of high vaccine coverage are critical for the prevention and control of measles outbreaks. Because adults and adolescents are usually missed in national vaccination programs, travel medicine consultations should fill the gap [45]. Homogeneous consistent coverage >95% needs to be achieved.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

W.Y.L. did the statistical analyses, W.Y.L. and A.B.W-S. obtained the data from various public sources and both wrote the final manuscript.

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