Impact of measles national vaccination coverage on burden of measles across 29 Member States of the European Union and European Economic Area, 2006–2011

E. Colzani a,⁎, S.A. McDonald b, P. Carrillo-Santistev e, M.C. Busana c, P. Lopalco a, A. Cassini a

a European Centre for Disease Prevention and Control (ECDC), Stockholm, Sweden
b National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
c London School of Hygiene and Preventive Medicine, London, United Kingdom

A R T I C L E   I N F O

Article history:
Received 28 November 2013
Received in revised form 24 January 2014
Accepted 30 January 2014
Available online 13 February 2014

Keywords:
Measles
Burden of disease
Vaccination coverage
Europe

A B S T R A C T

Background: Challenges in reaching good vaccination coverage against measles emerged in several European Union/European Economic Area Member States (EU/EEA MS) leading to progressive accumulation of susceptible individuals and outbreaks. The Burden of Communicable Diseases in Europe (BCoDE) project developed a methodology for measuring the burden of communicable diseases expressed in Disability-Adjusted Life Years (DALYs) in the EU/EEA MS. The aim of this study was to compare national vaccination coverage and burden of measles across EU/EEA MS.

Methods: Country-specific data on measles national vaccination coverage 2006–2011 from 29 EU/EEA MS (MCV1) were retrieved from Centralized Information System for Infectious Diseases (CISID). DALYs were calculated for each country separately using a disease progression model with a single input parameter (annual measles incidence, adjusted for under-estimation). A software application was used to compute estimated DALYs according to country-specific and year-specific population age-distributions (data retrieved from Eurostat). Log-linear mixed-effect regression modeling approach was used to investigate a linear relation between natural logarithm-transformed DALYs and coverage.

Results: The reported annual vaccination coverage ranged from 72.6% to 100%. The estimated national annual burden ranged from 0 to 30.6 DALYs/100,000. Adjusting for year, there was a significant negative relationship between coverage and burden. For a given country there was a decrease in log-transformed DALYs/100,000 of 0.025 (95% confidence interval: −0.047 to −0.003) for every percentage increase in vaccination coverage. The largest effect of calendar time on estimated burden of measles was observed for the year 2011, the smallest was for the year 2007.

Conclusions: This study shows that the degree of success of national measles vaccination programs, when measured by the coverage obtained, is significantly associated with overall impact of measles across EU/EEA MS. In EU/EEA MS each percentage point increase in national vaccination coverage seems to lead to early significant reduction of overall burden of measles.

© 2014 Published by Elsevier Ltd.

1. Introduction

A comprehensive assessment of the overall impact of a disease requires information not only on its occurrence, but also on severity, disease-related mortality, and morbidity due to the sequelae of the disease. Several composite health measures, or summary measures of population health, have been developed for this purpose, and many projects and studies have been carried out globally in the last few decades to reach the goal of assessing the burden of disease by taking into account all of these aspects of disease impact [1–7].

In order to gain insight into the overall impact of communicable diseases on population health in Europe and to support health policy-making, in 2009 the European Centre for Disease Prevention and Control (ECDC) initiated the Burden of Communicable Diseases in Europe (BCoDE) project. The BCoDE project developed a methodology and a software application (BCoDE toolkit) for measuring the current and future burden of communicable diseases in the European Union and European Economic Area Member States (EU/EEA MS). The burden of communicable diseases was obtained through a pathogen-based and incidence-based approach, which allows for the calculation of Disability-Adjusted Life Years (DALYs)
for 32 infectious diseases under ECDC’s remit, including measles [8,9].

Measles is a highly infectious disease and about 90% of individuals would be infected by the age of 10 in the absence of vaccination [10,11]. With the resolution of 16th September 2010, all countries in the European Region of the World Health Organization (WHO), which includes EU/EEA MS, have renewed their commitment to eliminate measles and rubella by 2015, and have identified essential criteria for elimination of measles and rubella in the WHO European region, including the demonstrated protection of at least 95% of the population against measles and rubella [12–14]. Challenges in reaching good vaccination coverage have emerged in several EU/EEA MS leading to progressive accumulation of susceptible individuals, loss of heard immunity and several outbreaks of measles across Europe in recent years [11,15–19]. These challenges are due, among other reasons, to the reluctance of specific subgroups of the population to undergo vaccination, and to the difficulty in reaching specific communities [20–24].

Previous studies have investigated the relationship between the incidence of measles, or the likelihood of new outbreaks, and the vaccination coverage of a population [25–28]; however, no studies to our knowledge have studied the relationship between vaccination coverage across EU/EEA MS and the burden of measles using DALYs. In this study we wanted to investigate the effect of vaccination programs on the burden of measles in Europe. In order to reach this goal we compared measles national vaccination coverage and burden of measles expressed in DALYs across EU/EEA MS and studied their correlation in the period 2006–2011.

2. Methods

We obtained measles incidence and vaccination coverage data for 29 EU/EEA MS, from 1998 through 2011 inclusive. Age-group specific incidence data were available from The European Surveillance System (TESSy), an European database held by ECDC [29]. The incidence data reported to TESSy were corrected for underestimation by applying a multiplication factor of 2.5 as suggested by Stein et al., under the assumption that EU/EEA MS have good measles control [6]. Vaccination coverage (MCV1: measles containing vaccine, first dose) was obtained from WHO’s Centralized Information System for Infectious Diseases (CISID) [30]. Country names were anonymised before analysis.

Because of extensive missing coverage data and the sparse availability of incidence data before 2006, the dataset was reduced by restricting to the period 2006–2011. For 14 countries, vaccination coverage for one or more years in the period 2006–2011 was missing; these missing values were imputed using the previous year’s value (or the value from two or more years previous, if the previous year’s value was also missing); 13.8% (24/174) of vaccination coverage values were consequently imputed.

2.1. DALY calculation

The DALY is a standard summary measure of population health obtained by adding two independent quantities: years of life lost due to premature mortality (YLL), which reflect the mortality contribution of a certain disease or condition, and years of life lived with a disability (YLD), which account for the morbidity of the disease or condition under study. DALYs were calculated for each country separately using a disease natural history model with a single input parameter (annual measles incidence, adjusted for under-estimation) and the "BCoDE toolkit" software application was used to compute estimated DALYs according to country-specific and year-specific population age-distributions (data retrieved from Eurostat) [31].

The measles disease model was created from the information collected through an extensive literature review and via consultation with measles experts, by linking the incidence of measles to all possible sequelae (health outcomes) through a disease progression model, or outcome tree. Health outcomes were considered part of the outcome tree if there was evidence of a causal relationship between measles and the health outcome (Fig. 1). In the disease burden calculations, years of life lost (YLL) were estimated using the Standard Expected Years of Life Lost (SEYLL) based on the highest observed life expectancy, which is that of the Japanese population. The Japanese population has been commonly used as a standard population in DALYs calculations since it has the longest life expectancy, so that in principle every human being can be expected to live at least as long [32–36]. Data on mortality were embedded into the model and were taken from both national sources and Eurostat [31]. Severity weights (i.e., disability weights) for non-fatal health outcomes were obtained from the Global Burden of Disease (GBD) study [2,5]. In conditions for which no weights existed, weights were adapted from existing GBD severity weights for similar conditions. Transition probabilities and mean duration of each health outcome were derived from the literature review. Time discounting and age-weighting were not applied in the base case analysis. The modeling approach applied assumed a steady-state and is therefore not suitable for forecasting of burden.

Information on gender was not provided, so cases were distributed evenly between males and females in each age group. Cases (<1%) for which information on age was missing were not included in the analysis.

2.2. Statistical modeling

Our dataset consists of time-series cross-sectional data [28], and therefore appropriate methods are required given the non-independence of observations. We used log-linear mixed-effect regression modeling approach to investigate a linear relation between natural logarithm-transformed outcome and predictor variables. The outcome variable was burden (in DALYs per 100,000 persons, transformed using log(DALYs + 1)), and the primary predictor variable was vaccination coverage (coded as a percentage). We assumed all cases in a given year, t, relate to the ability of the vaccination program to immunize the target population, estimated by using vaccination coverage to MCV1 in the same year. A Hausman test was conducted to assess the appropriateness of specifying country as a random instead of a fixed effect, and the need to include year as an additional fixed effect was assessed using a Lagrange multiplier test. Based on the tests, year was fitted as dummy-coded fixed effect, and country was fitted as a random effect. By specifying a random intercept for country, unexplained heterogeneity between countries is taken into consideration (i.e., burden values for a given country across years are more similar to other than compared with other countries). As the single coefficient for coverage aggregates both between-country and within-country effects (i.e., time-invariant and time-varying components), a test for equality of these parameters was conducted before final model specification [37,38].

Thus, we fitted a linear mixed-effects regression model with two fixed effects (coverage and year) and one random effect (country). Model fitting and inference were carried out using the plm package [39] for the R statistical computing environment [40].

3. Results

MCV1 was recommended by all national vaccination calendars to occur during the second year of life [41]. The reported annual MCV1 vaccination coverage ranged from 72.6% to 100%. The country

with the highest national coverage, averaged over the study period, reached a proportion of 99.7%. The calculated national annual burden of measles ranged from 0 to 30.6 DALYs/100,000, with the greatest burden in a country across the study period being 7.90 DALYs/100,000/year.

Table 1 shows the median vaccination coverage, the median DALYs per 100,000 and the median age group of the cases over all countries by calendar year. The year with the highest reported vaccination coverage was 2008 with 96.0% of children being administered a first dose of measles vaccine. The year with the greatest median burden was the year 2011 with 0.52 DALYs/100,000/year as compared to 2007 and 2009 being the years with the lowest median burden (0.01 DALYs/100,000/year). The median age of the cases was 7.5 years (interquartile range: 3–17.5) years for 2006 and 2007 while it slightly increased in the following years. The mean age of measles cases over the whole time period was 12.5 years (interquartile range: 3–22.5).

Table 2 shows the fitted model coefficients. Adjusting for year, there was a significant negative relationship between coverage and burden; for a given country there was a decrease in log-transformed DALYs/100,000 of 0.025 (95% CI: 0.018–0.032) for every percentage point increase in vaccination coverage. Compared with 2006, the burden in 2011 was significantly larger by 0.46 log DALYs/100,000 (95% CI: 0.20–0.73).

When using incidence of measles in a given year, and not DALYs, as a health outcome, there was also a significant decrease of −0.02 (95% CI: −0.046; −0.002) in log-transformed incidence/100,000 for each percentage point increase in vaccination coverage (data not shown).

Fig. 1 shows the measles disease progression model that was used to calculate the DALYs. Each box represents a different health outcome defined by a specific duration (in years) and disability weight (0 = best possible health state, 1 = worst possible health state) (data not shown). The acute symptomatic illness is

<table>
<thead>
<tr>
<th>Year</th>
<th>Median coverage (IQR)</th>
<th>Median DALYs per 100,000 (IQR)</th>
<th>Median age (years) of cases (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>95.4 (91.0–96.7)</td>
<td>0.03 (0.00–0.57)</td>
<td>7.5 (3–17.5)</td>
</tr>
<tr>
<td>2007</td>
<td>95.5 (91.9–97.0)</td>
<td>0.01 (0.00–0.47)</td>
<td>7.5 (3–17.5)</td>
</tr>
<tr>
<td>2008</td>
<td>96.0 (89.0–97.0)</td>
<td>0.05 (0.00–0.61)</td>
<td>17.5 (7.5–22.5)</td>
</tr>
<tr>
<td>2009</td>
<td>95.4 (90.4–96.7)</td>
<td>0.01 (0.00–0.29)</td>
<td>12.5 (7–22.5)</td>
</tr>
<tr>
<td>2010</td>
<td>95.1 (91.6–96.2)</td>
<td>0.03 (0.00–0.71)</td>
<td>17.5 (7.5–22.5)</td>
</tr>
<tr>
<td>2011</td>
<td>95.0 (92.0–97.0)</td>
<td>0.05 (0.00–1.76)</td>
<td>12.5 (3–22.5)</td>
</tr>
<tr>
<td>Overall</td>
<td>95.0 (88.0–97.0)</td>
<td>0.07 (0.00–0.59)</td>
<td>12.5 (3–22.5)</td>
</tr>
</tbody>
</table>

Table 2
Coefficients from the fitted mixed-effects regression model (year and coverage specified as fixed effects; country specified as a random effect), with 95% confidence intervals (CI).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coeff.</th>
<th>95% CI interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccination coverage</td>
<td>−0.025</td>
<td>−0.047 to −0.003</td>
</tr>
<tr>
<td>Year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006</td>
<td>Reference</td>
<td>−</td>
</tr>
<tr>
<td>2007</td>
<td>−0.118</td>
<td>−0.383 to −0.147</td>
</tr>
<tr>
<td>2008</td>
<td>0.047</td>
<td>−0.215 to −0.311</td>
</tr>
<tr>
<td>2009</td>
<td>0.049</td>
<td>−0.214 to −0.311</td>
</tr>
<tr>
<td>2010</td>
<td>0.099</td>
<td>−0.167 to −0.364</td>
</tr>
<tr>
<td>2011</td>
<td>0.464</td>
<td>0.201 to 0.726</td>
</tr>
<tr>
<td>Intercept</td>
<td>2.66</td>
<td>0.602 to 4.72</td>
</tr>
</tbody>
</table>

Fig. 1. Disease progression model for measles. Complicated health states include pneumonia, otitis media, diarrhea, convulsions, encephalitis, post-infectious encephalomyelitis SSPE=Subacute Sclerosing Panencephalitis.
highlighted in yellow since it is where the incident measles cases were entered into the model for the DALYs calculation. The possible endpoints considered were recovery (R), death (fatal cases) and long term disabilities. The Greek letters describe the transition probabilities for moving from one health outcome to the next. The DALYs attributable to each health outcome, including those attributable to fatal cases, were derived through this disease model and eventually added in order to obtain the overall burden of measles.

Fig. 2 plots vaccination coverage against estimated burden, separately for each year of the study period, and shows the negative linear relationship between measles vaccination coverage and the log burden of DALYs/100,000 by calendar year. Data points were more often located above 90% vaccination coverage during the entire study period than below. For more recent years (2009–2011) some observations showed high DALYS/100,000 estimates, despite reported national vaccination coverage above 90%.

4. Discussion

Using data from a 6-year period from 29 EU/EEA MS, we observed a significant negative association between measles vaccination coverage and the estimated burden of measles in a given year. This result is in the expected direction, and importantly takes between-country heterogeneity in burden and time-varying effects (i.e., outbreak years) into account. Our finding is also consistent with the negative association recently reported between vaccination coverage and measles incidence at the global level in the period 1980–2008 [28].

By investigating the relationship between vaccination coverage and DALYS – as opposed to incidence – we are in fact estimating the relationship between the success of national vaccination programmes and the estimated health burden (i.e., from both mortality and morbidity) attributable to infection, hence also accounting for possible variations in the age-distribution of cases between countries (to which the DALY measure obtained from our disease model is sensitive). For instance, two countries with similar incidence rates might have a very different age distribution of cases, and therefore will differ in estimated DALYs. In 2011, an incidence rate of 0.06 cases/100,000 was observed for a certain country (of which 25.7% cases were below the age of 10 years); for the same year, another country (74.1% cases below the age of 10 years) had a very similar incidence rate, of 0.05 cases/100,000. The estimated burden was 0.19 DALYS/100,000 for the first country, but three-fold greater, 0.65, for the second country. The current disease progression model is however unable to attribute different sets of disability weights according to different ages at infection (i.e., measles is assumed to have the same severity irrespective of age at infection). Therefore the presence of a positive shift in the median age at measles infection in a population (e.g., more measles cases among adults causing a subsequent increase in the average severity of the disease) will not be reflected in the current DALYs calculation and will possibly lead to an underestimation of the actual burden of measles that will be larger for those countries with more susceptible adults.

We used reported national vaccination coverage for any given year t to estimate the quality of measles control in a given country at a given time [6]. The use of national vaccination coverage from the same year of measles infection in the analysis is not meant to provide direct information on the susceptible population in a given country at a given year. In fact, in order to perform a direct assessment of the impact of vaccination coverage on burden of measles, one would instead need specific information on the vaccination coverage for each birth cohort rather than for each year. As we found consistent results when running the analysis by using as exposure variable the vaccination coverage in years prior to measles infection, in the main analysis we decided to use coverage and infection data from the same year.

Several measles outbreaks have been reported, in particular in the years 2010 and 2011, when in fact more variability in the data is apparent (Table 1), this could be consistent with the secular trend of the disease that shows cycles of outbreaks every 6–10 years in the vaccine era when a sufficient number of susceptible individuals have accumulated in the population or in subgroups of the population [11,19]. In the latter case, outbreaks may also in fact arise from a country with relatively high national vaccination coverage if undervaccinated pockets of the population exist. Consistent
with epidemiological reporting, our analysis indicated the largest ‘baseline burden’ occurred in 2011 (i.e., the fitted coefficient for the year 2011 was 3.13 on the log scale) when rather large outbreaks occurred in some European countries [15]. ECDC’s 2012 Annual Epidemiologic Report showed continuous national outbreaks across EU/EESA MS in 2010 and 2011 in particular, and concluded that the renewed commitment to eliminate indigenous measles by 2015 will probably not be achieved unless effective measures aimed at increasing measles vaccination coverage are carried out [15].

This study has some limitations. Healthcare and surveillance systems across EU/EESA MS are quite heterogeneous and, although the quality and comparability of data reported continue to improve, some heterogeneity in the ratio between cases of measles reported to TESSy and the actual occurrence of measles may be present. Cases reported to TESSy without age information were not included; however, their proportion was between 0.4% and 1.2% of the total reported cases of measles for the period 2007–2001 and of 5% in 2006, so we do not believe this might have biased our findings. Although the authors are well aware of the recommendation of two doses of measles vaccination, only data on MCV1 coverage was taken into account due to the vast heterogeneity in data availability for MCV2 doses across EU/EESA MS. Our dataset lacked information for certain countries and certain years on both vaccination coverage (n = 24 data points) and burden (n = 3). We imputed the former using the previous years’ value, and deleted those cases missing the latter from the statistical analysis; it is not known if results would vary given the availability of complete data on these two variables, although this is unlikely. When removing the countries with one or more missing coverage years, the regression coefficient for vaccination coverage was similar (−0.013) to the result we reported (coefficient = −0.025). It was however no longer statistically significant (95% CI: −0.045 to 0.019), perhaps due to the smaller sample size and the associated reduction in statistical power.

This study has also some relevant strengths. In order to calculate DALYs attributed to measles, a well-defined and detailed disease progression model (Fig. 1) that comprehensively takes into account the possible consequences of a measles infection was used. To our knowledge no other study to date has tried to assess the impact of national measles vaccination coverage on the burden of measles using DALYs across 29 EU/EESA MS over several years with this level of detail. Also, the statistical approach used allowed unexplained heterogeneity across countries to be taken into account, and so that the non-independence of burden estimates from the same country within the study period was not overlooked.

5. Conclusions

In conclusion, this study shows that the higher the vaccination coverage, the lower the burden of measles, suggesting that the degree of success of national measles vaccination programs, when measured by the coverage obtained, is significantly associated with the burden of measles across EU/EESA MS. Attaining a higher measles vaccination coverage would thus result in important benefits in terms of early significant reduction of the overall impact of measles in the population, and would put EU/EESA MS on the right track toward the goal of eventual elimination.

E.C. and S.A.M. drafted the manuscript and all other co-authors extensively contributed to its writing and finalization.

Conflicts of interest statement

The authors declare no conflict of interest.

Acknowledgments

The BcoDE project is funded through the Specific agreement No 1 to Framework Partnership Agreement GRANT/2008/003. This study builds on the methodology and disease models outlined by the BcoDE project. The authors acknowledge the Burden of Communicable Disease in Europe (BcoDE) Consortium for the disease progression model and the BcoDE toolkit software application. In particular we thank Dr Alies van Lier and Dr Silvia Longhi for the work on the measles disease progression model and Prof Mirjam Kretzschmar for the support provided in the review of the manuscript. We also would like to thank Daniel Dr Lewandowski for the BcoDE toolkit software application.

References


[38] Leyland AH. No quick fix: understanding the difference between fixed and random effect models. J Epidemiol Commun Health 2010;64(12):1027–8.

