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Assessing Mumps Outbreak Risk in Highly Vaccinated Populations Using Spatial Seroprevalence Data

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Mumps is a potentially severe viral infection. The incidence of mumps has declined dramatically in high-income countries since the introduction of mumps antigen-containing vaccines. However, recent large outbreaks of mumps in highly vaccinated populations suggest waning of vaccine-induced immunity and primary vaccine failure. In this paper we present a simple method for identifying geographic regions with high outbreak potential, demonstrated using 2006 mumps seroprevalence data from Belgium and Belgian vaccination coverage data. Predictions of the outbreak potential in terms of the effective reproduction number in future years signal an increased risk of new mumps outbreaks. Literature reviews on serological information for both primary vaccine failure and waning immunity provide essential information for our predictions. Tailor-made additional vaccination campaigns would be valuable for decreasing local pockets of susceptibility, thereby reducing the risk of future large-scale mumps outbreaks.

disease outbreaks; effective reproduction number; mumps; next-generation operator; serology; social contact hypothesis; vaccination coverage; vaccines

Abbreviations: CI, confidence interval; MMR, measles-mumps-rubella.

Infection with mumps virus can cause parotitis, which is associated with painful swelling of the parotis gland and lifting of the ear lobe. Although the infection usually remains mild, severe complications such as orchitis, encephalitis, and meningitis may occur (1). The incidence of mumps has declined dramatically since the introduction of vaccines containing mumps antigen, such as combined measles-mumps-rubella (MMR) vaccines. In Belgium, partially reimbursed single-dose mumps vaccine was officially recommended for use in 1981, in a monovalent or bivalent (with measles) formulation, at ages 15 months and ages 10–12 years (for boys only). Vaccination coverage remained low until 1985, when the combined MMR vaccine was recommended and made available free of charge as part of the routine vaccination program at age 15 months only. In 1995, the second dose of the MMR vaccine at ages 11–12 years was added to the program (2). During the period 1982–1998, mumps incidence as recorded through general-practitioner sentinel surveillance decreased from 540 per 100,000 population to 40 per 100,000 in the region of Flanders and from 1,103 per 100,000 population to 47 per 100,000 in the region of Wallonia. In 2000, mumps surveillance through the sentinels was stopped (3). Currently, the recommended schedule for the MMR vaccine consists of a first dose at 12–13 months of age and a second dose at 10–13 years of age.

Outbreaks of mumps occur where vaccination coverage is low, and reemergence of mumps as an important childhood infection is possible when uptake of the MMR vaccine declines (4). During recent years, mumps outbreaks have been reported in highly vaccinated populations (5–7). In 2012, a large mumps outbreak occurred in Belgium, initially affecting mainly the region around Ghent before spreading throughout Flanders (8, 9). The highest attack rate was reported among university students who had been vaccinated with 2 doses of MMR vaccine. This was also observed during other recent mumps outbreaks in high-income countries (e.g., see Date et al. (10)), raising concerns about mumps vaccine failure. Some studies have suggested that outbreaks within highly vaccinated populations can be partly explained by waning of vaccine-induced immunity (11–13). Nevertheless, there are

still questions regarding the optimal level of protective mumps antibodies and the decay rate of antibody levels with time since vaccination or natural infection (14).

Our objective in the current study was to identify regions of high outbreak potential in Belgium based on regional estimates of the effective reproduction number, R. Estimates of the effective reproduction number in Belgium's 589 different municipalities in 2012 were obtained using Belgian serological and vaccination coverage data.

METHODS

Seroepidemiology of mumps

In order to estimate the seroprevalence from the pre-mumps-outbreak era, we use data from a previously described study (15). This study contains binary current status data with respect to past mumps immunization. That is, 3,568 serum samples were tested for the presence of immunoglobulin G antibodies against mumps. The serological test results are linked with the residences of the test subjects, if available; otherwise, the spatial locations of test laboratories are used as a proxy. Cases with equivocal and missing responses were excluded from our statistical analysis. A generalized additive model (16) with a complementary log-log link is considered to model the observed seroprevalence as a function of the individual's age a, gender g, and spatial location (x, y):

$$\text{cloglog}(\pi(a,x,y,g)) = f(a,x,y,g), \qquad (1)$$

where f is a smooth function and $\pi(a, x, y, g)$ is the proportion of seropositive individuals of age a with spatial coordinates (x, y) and gender g. Several submodels of equation 1 were considered, and model comparison was based on the Akaike Information Criterion (17).

The generalized additive model shown in equation 1 enables estimation of the proportion of susceptible individuals in the Belgian population in the year 2006. Consequently, susceptibility predictions for 2012 are obtained after multiplying the age-dependent fraction of seropositive persons with a factor $\exp(-\gamma(t-2006)_+)$, which represents an exponential decay function with decay rate γ and calendar time t.

The analyses based on serological test results from 2006 are restricted to subjects aged at least 13 years in 2006, since predictions for younger children are probably influenced by samples for which the second vaccine dose was not yet administered at the time of data collection. Therefore, predictions of the proportion of susceptible individuals in 2012 based on the generalized additive model are solely available for persons aged 19 years and above. Susceptibility in younger age groups is inferred from available vaccination coverage information.

Susceptibility in young age groups

Newborns are initially protected through maternal antibodies. However, maternal antibodies against mumps decline with time since birth (18–20). Leuridan et al. (20) showed that children of vaccinated women lose protective maternal antibodies for mumps after 2.4 months, on average, whereas children of naturally immune women do so after 3.8 months. In the analysis, the mean duration of maternal protection is assumed to be equal to 3.1 months to account for the mix of previously vaccinated and naturally immunized women of childbearing age (see Web Appendix 1, available at http://aje.oxfordjournals.org/).

After the first year of life, Belgians gain vaccine-induced immunity from vaccination at the ages of about 12 months (first dose) and about 12 years (second dose; ages 10–13 years). In order to quantify vaccine-induced immunity, we rely on Belgian vaccination coverage estimates (21–28). Table 1 shows the estimated vaccination coverages for the period between 1995 and 2009, which are usually available at a

Table 1. Estimated Vaccination Coverage for the First and Second Doses of Measles-Mumps-Rubella Vaccine in Belgium, by Region, 1995–2009[a]

First Author, Year (Reference No.)	Study Year	Region	First Dose of MMR Vaccine		Second Dose of MMR Vaccine	
			EC, %	95% CI	EC, %	95% CI
Sabbe, 2011 (21)	1995	Brussels	68.1			
Vellinga, 2002 (22)	1999	Flanders	83.4	80.3, 86.5		
Sabbe, 2011 (21)	1999	Wallonia	82.4			
Robert, 2006 (23)	2000	Brussels	74.5	70.1, 78.9		
Robert, 2009 (24)	2003	Wallonia	82.5			
Theeten, 2007 (25); Vandermeulen, 2008 (26)	2005	Flanders	94.0	92.6, 95.3	83.6	81.4, 85.8
Robert, 2006 (23)	2006	Brussels	91.1	88.7, 93.6	70.5	
Robert, 2009 (24)	2006	Wallonia	89.0	86.3, 91.8	70.5	
Vandermeulen, 2008 (27); Theeten, 2009 (28)	2008	Flanders	96.6	95.2, 97.6	90.6	89.0, 92.2
Robert, 2009 (24)	2009	Wallonia	92.4	90.2, 94.6	75.5	

Abbreviations: CI, confidence interval; EC, estimated coverage; MMR, measles-mumps-rubella.
[a] 95% confidence intervals are shown when available.

regional level, together with 95% confidence intervals (when available).

The data in Table 1 are used to estimate age-dependent mumps susceptibility for persons aged ≤19 years. This can be illustrated using a Lexis diagram, which has its origin in demography, to display events that occur in persons belonging to different cohorts (29). In Figure 1, a Lexis diagram shows calendar time on the *x*-axis and the ages of persons from different cohorts on the *y*-axis.

Individuals are born into a specific cohort, and the cohort ages with calendar time. Vaccination of such cohorts decreases susceptibility and reduces the pathogen's transmission potential. After loss of maternal antibodies, children become susceptible to infection. A proportion of children younger than 12 years from birth year b have been vaccinated with a first dose of MMR (MMR1) in year $(b+1)$ according to the coverage percentage for year $(b+1)$. After that, these vaccinated children experience waning of immunity for $(2012-(b+1))$ years. At 12 years of age, children are immunized again through a second MMR vaccination (MMR2) with a coverage equal to the one reported for year $(b+12)$. Therefore, for all persons between ages 12 and 19 years, we rely on the corresponding vaccination coverages, with waning of immunity between the age at vaccination (12 years) and the current age in 2012. However, we assume that these persons are not exposed to the mumps virus, such that susceptibility to mumps infection is determined solely by the potential vaccination of subjects and potential vaccine failure.

Primary vaccine failure

Primary vaccine failure of the mumps component of the combined MMR vaccine has been shown to be important in explaining the observed high levels of mumps susceptibility (30). Seroconversion rates are included in the analysis to adjust coverage information with respect to vaccine uptake. An extensive literature search in PubMed and ISI Web of Knowledge yielded 21 eligible publications (see Web Appendix 2, Web Table 1, and Web Figure 1 for details). Since the current MMR vaccine in use in Belgium contains either the Jeryl Lynn mumps strain (MMRVaxPRO; Sanofi Pasteur MSD Ltd., Lyon, France) or the RIT4385 strain (Priorix; GlaxoSmithKline, Brentford, United Kingdom) derived therefrom, only articles studying these strains were included. Table 2 shows the estimated seroconversion rates, along with 95% Clopper-Pearson exact confidence intervals, for the eligible publications. These rates are combined using a meta-analysis random-effects model with the DerSimonian-Laird estimator for the between-study variability τ^2 (31),

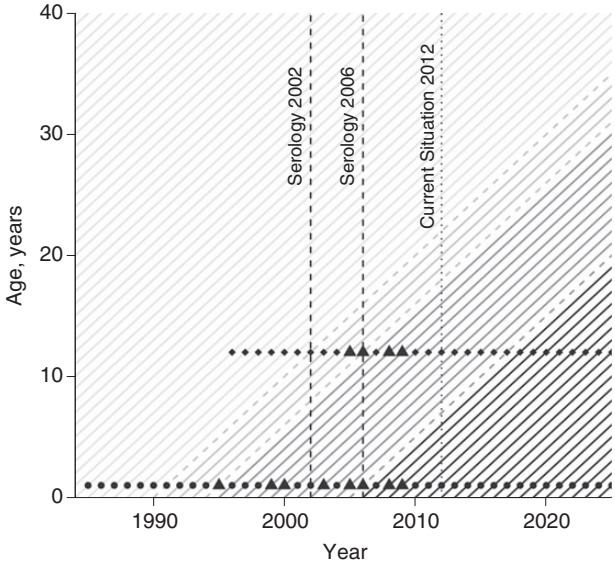

Figure 1. Lexis diagram (1985–2024) showing the aging of Belgian cohorts born at different calendar times, together with collection times of mumps serological data (2002 and 2006; black dashed lines) and the mumps immunity situation at the cross-sectional time point 2012 (black dotted line). The solid lines from light to dark represent age cohorts with waning immunity (light gray), age cohorts with the second vaccination dose between the serological sampling times (medium gray), age cohorts with only 1 vaccine injection at data collection in 2006 (dark gray), and age cohorts born after 2006 (black), respectively. The gray dashed lines correspond to age cohorts being vaccinated at sampling times. The availability of estimated vaccination coverage data is indicated by large black triangles; black circles represent the first dose of measles-mumps-rubella (MMR) vaccine (MMR1), and black diamonds represent the second dose (MMR2).

Table 2. Estimated Seroconversion Rates $\hat{\rho}$ Based on Different Persistence Studies With Respect to the Mumps Component of the Combined Measles-Mumps-Rubella Vaccine, 1960–2013

First Author, Year (Reference No.)	$\hat{\rho}$	95% Confidence Interval[a]
Böttiger, 1987 (66)	0.867	0.821, 0.905
Crovari, 2000 (67)	0.970	0.951, 0.983
dos Santos, 2006 (68)	0.793	0.666, 0.888
Ehrenkranz, 1975 (69)	0.944	0.863, 0.985
Feiterna-Sperling, 2005 (70)	0.912	0.883, 0.936
Gatchalian, 1999 (71)	0.927	0.870, 0.964
Gothefors, 2001 (72)	0.971	0.899, 0.996
Khalil, 1999 (73)	0.929	0.805, 0.985
Klinge, 2000 (74)	0.949	0.893, 0.981
Lee, 2002 (75)	0.945	0.904, 0.972
Lee, 2001 (76)	0.876	0.794, 0.934
Lim, 2007 (77)	0.981	0.945, 0.998
Mitchell, 1998 (78)	0.766	0.683, 0.836
Nolan, 2002 (79)	0.966	0.916, 0.991
Rager-Zisman, 2004 (80)	0.947	0.871, 0.985
Redd, 2004 (81)	0.916	0.897, 0.933
Schwarzer, 1998 (82)	0.965	0.920, 0.989
Stück, 2002 (83)	0.949	0.885, 0.983
Tischer, 2000 (84)	0.974	0.940, 0.991
Usonis, 1998 (85)	0.936	0.898, 0.962
Vesikari, 1984 (86)	0.961	0.865, 0.995

[a] Clopper-Pearson 95% confidence interval.

the Freeman-Tukey double arcsine variance-stabilizing transformation (32), and inverse-variance weighting. In addition, we constructed confidence intervals for the combined effect using the method proposed by Freeman and Tukey (33) in order to account for uncertainty in τ^2. The estimated combined seroconversion rate equals 0.934 (approximate 95% confidence interval (CI): 0.910, 0.954). The seroconversion rates after the first and second doses of MMR vaccine are assumed to be identical, and the seroconversion rate is considered independent of age at vaccination.

Waning of mumps antibodies

Waning of mumps-specific immunoglobulin G antibodies after vaccination with combined MMR vaccines has been reported in numerous publications. We performed a literature search, again including only papers studying the Jeryl Lynn and RIT4385 mumps strains (see Web Appendix 3 and Web Figure 2). Table 3 lists the 7 studies retrieved by our search, showing the estimated exponential waning rates $\hat{\gamma}$, the 95% confidence intervals, and corresponding vaccination information. Based on a meta-analysis random-effects model in which the rates are log-transformed, the overall exponential waning rates after back-transformation are equal to 0.043 (approximate 95% CI: 0.029, 0.065) and 0.021 (approximate 95% CI: 0.014, 0.030) after the first and second MMR doses, respectively.

Although evidence for waning of vaccine-induced immunity exists, mumps infection is generally accepted to induce lifelong immunity (34). Therefore, we will assume that naturally acquired immunity is preserved for life, which is a conservative approach.

Estimating the effective reproduction number

The effective reproduction number R represents the expected number of secondary cases produced by 1 infectious individual during his/her entire infectious period when introduced into a population that is not necessarily completely susceptible to infection (35). The effective reproduction number is closely related to the basic reproduction number R_0, which expresses the same quantity in a completely susceptible population. If R is considerably greater than 1, large efforts are required to contain epidemics. However, maintaining R well below 1 forces outbreaks to be self-limiting. The basic reproduction number R_0 is defined as the leading eigenvalue of the next-generation operator defined by the next-generation matrix (35):

$$DN(a,t)\beta(a,a',t), \tag{2}$$

where D is the mean duration of infectiousness, $N(a, t)$ denotes the number of individuals of age a in the population at calendar time t, and $\beta(a, a', t)$ represents the time-heterogeneous transmission rates—that is, the per capita rate at which an infectious individual of age a' makes an effective contact with a susceptible individual of age a. Multiplying equation 2 with the proportion of susceptible individuals of age a at calendar time t, that is, $S(a, t)$, and taking the maximum eigenvalue of the resulting matrix yields the estimated effective reproduction number. The population age distribution $N(a, t)$ can be estimated from demographic data (36) (see Web Appendix 4 and Web Figure 3).

Several authors (37–39) have advocated improved estimation of $\beta(a, a', t)$ by using empirical social contact data. Here, the effective contact function $\beta(a, a', t)$ is decomposed according to the so-called social contact hypothesis (37):

$$\beta(a,a',t) = q(a,a',t|c)c(a,a'), \tag{3}$$

where $q(a, a', t|c)$ is an age- and time-dependent proportionality factor related to the susceptibility and infectivity of individuals and $c(a, a')$ are annual per capita contact rates between individuals of age a and a'. For the purposes of this paper, the proportionality factor $q(a, a', t|c) \equiv q(t)$ is restricted to be age-invariant. The contact rates $c(a, a')$ are estimated from empirical data (39, 40).

Given the basic reproduction number R_0, the corresponding constant proportionality factor $q(2012) \equiv q$ in 2012 is estimated. Published estimates of the basic reproduction number in different European countries vary from 10 to 14 (41, 42). As a conservative approach, R_0 is assumed to be 10. A sensitivity analysis on R_0 is included in Web Appendix 5 and graphically displayed in Web Figures 4 and 5. On this basis, we can estimate the effective reproduction number R in each of the Belgian municipalities, thereby expressing local information on the potential for epidemics to occur.

Table 3. Estimated Exponential Waning Rates $\hat{\gamma}$ Based on Different Persistence Studies With Respect to the Mumps Component of the Combined Measles-Mumps-Rubella Vaccine, 1960–2013

First Author, Year (Reference No.)	$\hat{\gamma}$	95% Confidence Interval	No. of Doses
Boulianne, 1995 (87)	0.029	0.020, 0.039	1
Broliden, 1998 (88)	0.031	0.023, 0.039	1
Davidkin, 1995 (89)	0.054	0.034, 0.075	1
	0.027	0.009, 0.044	2
Davidkin, 2008 (12)	0.020	0.012, 0.028	2
LeBaron, 2009 (13)	0.013	0.010, 0.016	2
	0.027	0.021, 0.033	2
Miller, 1995 (90)	0.053	0.036, 0.070	1
Poethko-Müller, 2012 (91)	0.057	0.049, 0.063	1
	0.022	0.019, 0.025	2

RESULTS

Local effective reproduction numbers in Belgium

In order to estimate R in each of the Belgian municipalities in 2012, one requires the age- and location-dependent susceptibility profiles for each of the municipalities. As mentioned above, the profiles are partly informed by serological results from 2006 and partly by information on regional vaccination coverages. Using version 1.7-18 of the R package "mgcv" by Wood (16), in R 2.15.1 (43), several generalized additive models derived from equation 1 are fitted to the seroprevalence data from 2006. All of the R code we used is

Table 4. Generalized Additive Models Fitted to 2006 Belgian Seroprevalence Data on Mumps Infection, With Corresponding AIC Values

Model	Linear Predictor	AIC
1	$te(x, y, a, by = g) + te(x, y, a, by = 1 - g)$	922.97
2	$te(x, y, a)$	921.30
3	$s_1(a) + te(x, y)$	917.13
4	$s_1(a) + s_2(x, y)$	916.65
5	$s_1(a)$	935.45

Abbreviation: AIC, Akaike Information Criterion.

available upon request. The model fit results are shown in Table 4. Based on the Akaike Information Criterion, the following final generalized additive model is retained:

$$\begin{aligned} \text{cloglog}(\pi(a,x,y)) &= \log(-\log(1-\pi(a,x,y))) \\ &= s_1(a) + s_2(x,y), \end{aligned} \quad (4)$$

where $\pi(a, x, y)$ is the proportion of seropositive individuals of age a with spatial coordinates (x, y), $s_1(.)$ is a smooth function of age, and $s_2(., .)$ is a bivariate smooth function of the spatial location. The smooth components s_i, $i = 1, 2$, were fitted using 1- and 2-dimensional thin-plate regression splines, respectively. Furthermore, *te* represents tensor product thin-plate regression splines for which the basis is built up from tensor products of 1-dimensional thin-plate regression splines.

The semiparametric model shown in equation 4 is used to predict the proportion of susceptible individuals older than 19 years. A parametric bootstrap approach is used to construct $M = 1{,}000$ bootstrap samples, and model 4 is fitted to each of the generated samples. Furthermore, for each bootstrap sample and municipality, vaccination coverages are randomly sampled from a normal distribution with 95% confidence intervals approximately equal to those reported in Table 1. In order to end up with a smooth susceptibility curve for each municipality, an interpolating-spline model is fitted to each of the generated data sets.

For the purpose of illustration, Figure 2 shows the estimated susceptibility curves for 3 urban localities in Belgium: Hasselt (panel A), Liège (panel B), and Brussels (panel C).

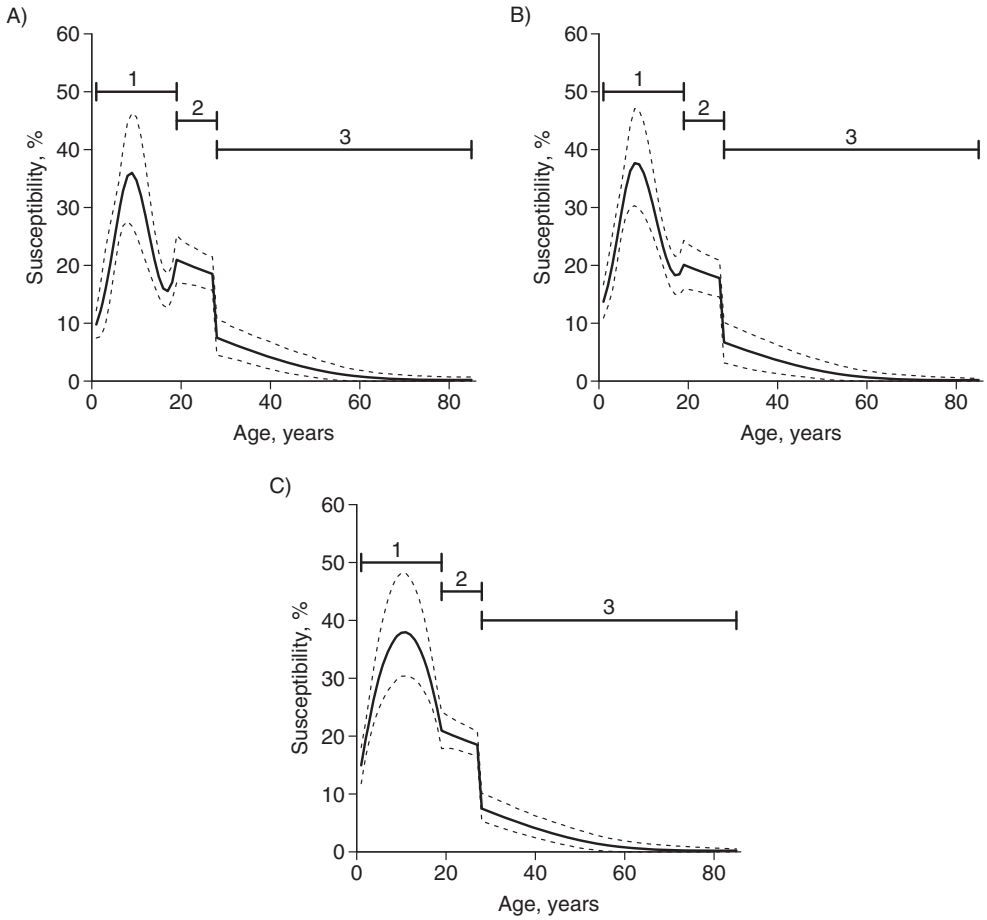

Figure 2. Estimated susceptibility to mumps in the urban areas of A) Hasselt, B) Liège, and C) Brussels, Belgium, in 2012. The susceptibility curve is based on 1) coverage information + waning of vaccine-induced immunity; 2) serological testing with waning of vaccine-induced immunity; and 3) serological testing with lifelong natural immunity. Dashed lines, 95% bootstrap-based confidence intervals.

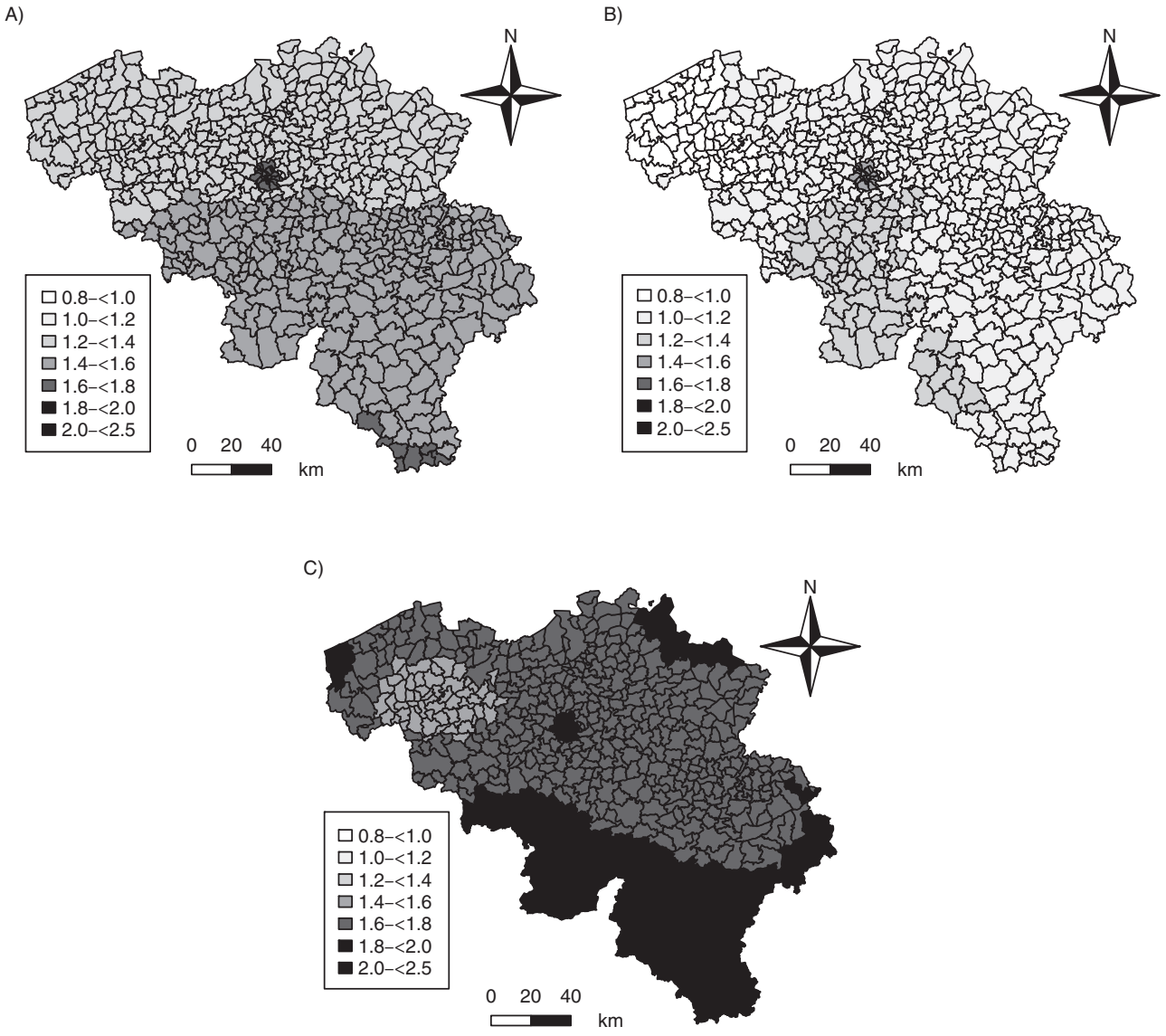

Figure 3. Estimated effective reproduction numbers (R) for mumps in Belgian municipalities on a spatial map (panel A), with lower (panel B) and upper (panel C) 95% confidence limits.

First, an increase in susceptibility is the result of waning of vaccine-induced immunity after the first dose of MMR vaccine. At age 12 years, the estimated susceptibility decreases sharply due to vaccination with a second dose of MMR vaccine, at least in Hasselt and Liège. Afterwards, an increase in susceptibility results from waning of vaccine-induced immunity. Since seropositive persons aged 28 years or more in 2012 could not have been vaccinated, they are protected for life against mumps infection. Consequently, the susceptibility profile remains low in groups aged ≥28 years. In Brussels, limited coverage information results in a somewhat distinct susceptibility curve. The estimated profiles rely, at least to some extent, on the Belgian MMR coverage levels, which are in line with vaccination coverages estimated from trivariate serological data (44). The latter method based on trivariate serological data can provide estimates of vaccination coverage if vaccine surveys are not available.

Based on the estimated age- and location-specific susceptibility in 2012, one is able to estimate the effective reproduction numbers R as described previously. Based on a mean duration of infectiousness equal to $D = 6/365$ years^{-1} (42) and an R_0 equal to 10, the estimated constant proportionality factor is $\hat{q} = 0.0909$. Using the estimates for the fraction of susceptible individuals in each age class and the estimated constant proportionality factor $\hat{q}$, the leading eigenvector of the next-generation operator is determined per municipality (see Web Figure 6). The estimates for R are graphically displayed on a spatial map of Belgium to show areas of potential outbreak risk (Figures 3 and 4). The reproduction numbers are highest in the Walloon region. This is as expected, since

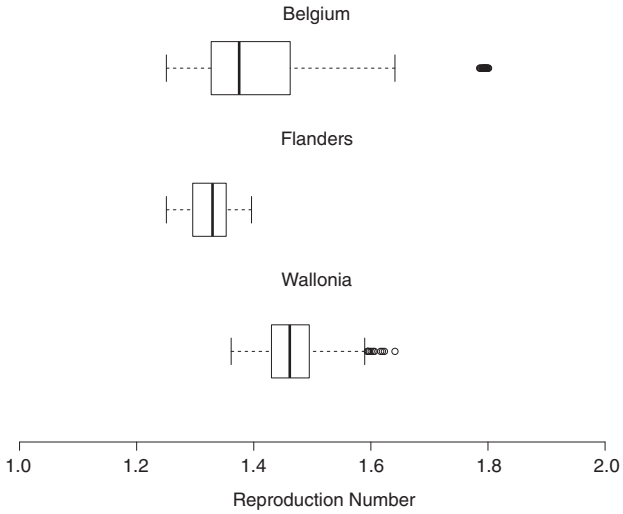

Figure 4. Estimated reproduction numbers (R) for mumps in Belgium and in the regions of Flanders and Wallonia.

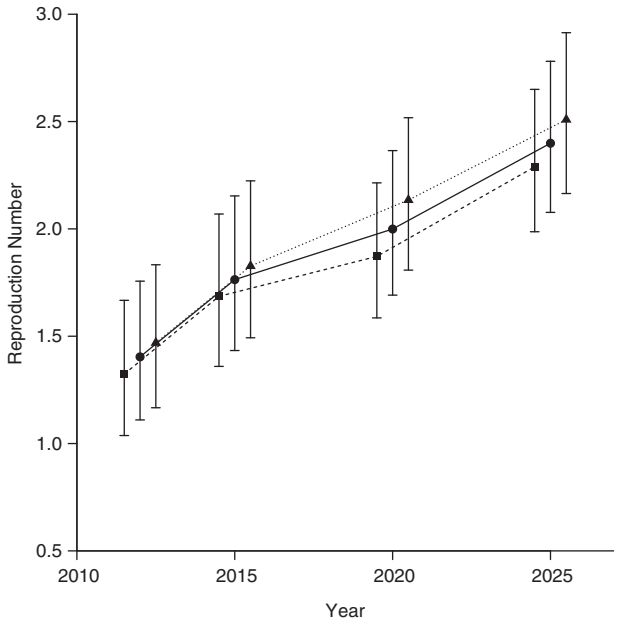

Figure 5. Average estimated effective reproduction numbers (R) for mumps in Belgium (circles with solid line) and in the regions of Flanders (squares with dashed line) and Wallonia (triangles with dotted line). T-shaped bars, 95% confidence intervals.

the vaccination coverages in Wallonia are substantially lower than those in Flanders. Moreover, the estimated effective reproduction numbers are well above the epidemic threshold value of 1. This implies that efforts are required in order to reduce susceptibility and outbreak risk.

Future outbreak potential

Although uptake of mumps vaccine in Belgium remained low until 1985, the introduction of the combined MMR vaccine offered the means to lower the incidence of mumps in Belgium substantially. However, in highly vaccinated populations, the spread of a vaccine-preventable disease can still be invoked by importations of the pathogen. In the presence of a mumps vaccination program, active acquired immunity tends to decrease and waning of vaccine-induced immunity leaves an increasing number of young adults at risk of acquiring infection after importation.

Without any adequate intervention measures, the Belgian population remains at risk of acquiring mumps infection, even in the presence of a 2-dose MMR vaccination program. The estimated effective reproduction numbers for mumps in 2012 already identify areas of high outbreak potential throughout the country. Our approach can be readily extended to make future predictions of mumps susceptibility, and hence of effective reproduction numbers. In Figure 5, the estimated effective reproduction numbers R in Belgium are shown for 2012, 2015, 2020, and 2025 under the assumption of time-invariant regional vaccination coverages equal to the latest available ones.

In general, the average estimated effective reproduction numbers increase steadily over time and tend to exceed the epidemic threshold from 2012 onwards. Although these predictions are based on a limited amount of information provided by either serological testing or epidemiologic surveys and rely on the assumption of constant vaccination coverages over time, these estimates are believed to show indications of increasing outbreak potential in subsequent years. Since the situation only becomes more worrisome as time progresses, adequate intervention measures to avoid large mumps epidemics are important.

Intervention strategies

Despite the fact that estimated reproduction numbers are well above 1, additional vaccination campaigns could offer opportunities to reduce susceptibility in the overall population and thus prevent outbreaks. The aim here is to investigate the impact of vaccination strategies on the effective reproduction number without relying on results derived from mathematical transmission models. Lowering susceptibility to infection facilitates a reduction in R and helps in containing mumps outbreaks.

A grid search is performed to obtain optimal levels of vaccination in 6 age intervals: 14–<18, 18–<24, 24–<30, 30–<40, 40–<60, and ≥60 years. The vaccination coverages are selected in order to force the estimated reproduction number R below the epidemic threshold value while minimizing the absolute number of vaccinations. In total, 8 different vaccination coverages are considered in the grid search (i.e., 0, 0.5, 0.6, 0.7, 0.8, 0.8, 0.95, and 0.98), yielding 262,144 different coverage combinations regarding the 6 age groups. As a conservative approach, the lower 95% confidence limit of the estimated seroconversion rate is used to account for primary vaccine failure. Results from a less conservative approach using the upper 95% confidence limit of the seroconversion rate are included in Web Table 2. Additionally, either the estimated susceptibility or the lower and upper 95% confidence

Table 5. Optimal Mumps Vaccination Coverage With Respect to a Catch-up Vaccination in Belgium, Based on the Average Estimated Effective Reproduction Number (R) in Each Province (Average) or the Corresponding 95% Confidence Limits (Lower Limit and Upper Limit)

Province	Age Category, years[a]						*R* After Vaccination	No. of Vaccinees[b]
	14–<18	18–<24	24–<30	30–<40	40–<60	≥60		
Limburg								
Average	0.90	0.00	0.00	0.00	0.00	0.00	0.999	89,118
Lower limit	0.80	0.00	0.00	0.00	0.00	0.00	1.157[c]	29,864
Upper limit	0.95	0.90	0.00	0.00	0.00	0.00	0.906	189,437
Antwerp								
Average	0.95	0.60	0.50	0.00	0.00	0.00	0.998	218,143
Lower limit	0.80	0.00	0.00	0.00	0.00	0.00	1.175[c]	62,785
Upper limit	0.95	0.70	0.50	0.98	0.00	0.00	0.893	453,526
Flemish Brabant								
Average	0.90	0.90	0.00	0.00	0.00	0.00	0.999	114,754
Lower limit	0.50	0.50	0.00	0.00	0.00	0.00	1.089[c]	63,752
Upper limit	0.98	0.90	0.00	0.70	0.00	0.00	0.923	215,374
West Flanders								
Average	0.80	0.50	0.00	0.00	0.00	0.00	0.996	84,007
Lower limit	0.50	0.00	0.00	0.00	0.00	0.00	1.142[c]	26,269
Upper limit	0.98	0.90	0.00	0.60	0.00	0.00	0.909	209,560
East Flanders								
Average	0.90	0.50	0.00	0.00	0.00	0.00	0.999	107,185
Lower limit	0.70	0.00	0.00	0.00	0.00	0.00	1.119[c]	44,367
Upper limit	0.98	0.95	0.00	0.60	0.00	0.00	0.912	273,893
Walloon Brabant								
Average	0.98	0.70	0.00	0.80	0.00	0.00	0.998	78,790
Lower limit	0.90	0.50	0.00	0.00	0.00	0.00	1.109[c]	33,199
Upper limit	0.98	0.98	0.80	0.98	0.00	0.00	0.939	116,317
Hainaut								
Average	0.98	0.80	0.00	0.70	0.00	0.00	0.999	262,090
Lower limit	0.90	0.50	0.00	0.00	0.00	0.00	1.103[c]	106,403
Upper limit	0.98	0.98	0.80	0.98	0.00	0.00	0.940	403,854
Liège								
Average	0.98	0.95	0.00	0.50	0.00	0.00	0.998	199,667
Lower limit	0.95	0.00	0.00	0.00	0.00	0.00	1.155[c]	48,050
Upper limit	0.98	0.90	0.98	0.98	0.00	0.00	0.935	341,428
Namur								
Average	0.98	0.70	0.00	0.90	0.00	0.00	0.999	104,313
Lower limit	0.90	0.50	0.00	0.00	0.00	0.00	1.137[c]	39,666
Upper limit	0.98	0.90	0.95	0.98	0.50	0.00	0.932	217,093
Luxembourg								
Average	0.95	0.80	0.00	0.90	0.00	0.00	0.999	63,048
Lower limit	0.80	0.50	0.00	0.00	0.00	0.00	1.162[c]	22,078
Upper limit	0.98	0.95	0.70	0.98	0.50	0.00	0.938	121,025
Brussels								
Average	0.98	0.95	0.70	0.98	0.00	0.00	0.999	392,395
Lower limit	0.98	0.70	0.50	0.00	0.00	0.00	1.105[c]	161,470
Upper limit[d]	0.98	0.98	0.98	0.98	0.98	0.98		

[a] The age categories used in the grid search were defined as nonoverlapping left-closed, right-open intervals [a, b), including persons with age ranging from a up to, but not including, b.

[b] The number of vaccinations required (assuming 1 injection per person) to force the effective reproduction number below the threshold value of 1.

[c] The estimated reproduction number is above the threshold value of 1.

[d] Scenarios in which the objective value cannot be forced below the threshold value.

limits (in the worst case) are used. Furthermore, weighted averages of the susceptibility profiles per municipality are used to obtain susceptibility estimates for each province.

The results of the grid search based on the conservative scenario are summarized in Table 5. The required vaccination coverages are presented in order to force the average, the lower 95% confidence limit, or the upper 95% confidence limit of the estimated reproduction number below the epidemic threshold value. In general, more effort is required to force the reproduction numbers below 1 in the Walloon region because of the higher estimated susceptibility there. Unfortunately, vaccinating 98% of the persons in each of the 6 age categories in Brussels cannot force the upper 95% confidence limit of the reproduction number below 1.

DISCUSSION

Despite long-standing 2-dose mumps vaccination with moderate-to-high vaccination coverages in the Belgian regions, this analysis reveals that large mumps outbreaks are likely to occur in the future if no appropriate intervention measures are undertaken. In this paper we present a simple method for identifying regions of high outbreak potential, informed by serological survey data predating the 2012 mumps outbreaks and vaccination coverage information. Outbreak potential is quantified in terms of local estimates for the effective reproduction number R. Although the age-dependent susceptibility profile is constructed on the basis of various data sources, care is needed to interpret the derived reproduction numbers.

First, susceptibility in 2012, which is partly informed by the susceptibility estimates obtained from serological data in 2006, was estimated using a generalized additive model including age and spatial location as covariates. By allowing the susceptibility to increase solely as a result of waning of vaccine-induced immunity, one ignores decreases in susceptibility caused by sporadic infections over the years. However, the effects with respect to the presented results should be limited, given that since 2006, mumps has hardly circulated outside of outbreak situations (45). Additionally, the use of cross-sectional serological testing as a marker for immunity relies on the assumption of a perfect test. If the sensitivity and specificity of the applied test are known, the seroprevalence can be corrected for misclassification (46) or can be estimated directly from antibody titers (47). Because the sensitivity and specificity estimates of the applied mumps test are close to unity, the impact thereof on our results is considered negligible.

Second, naturally acquired immunity to mumps infection is believed to be lifelong. However, any deviation from the lifelong immunity assumption is easily incorporated, leaving an even larger part of the population unprotected against new infections. The latter situation only increases the estimated effective reproduction numbers and consequently enlarges the efforts required to prevent future mumps outbreaks.

Third, information on vaccination coverage in different Belgian regions is fragmented, leading to a substantial amount of uncertainty about susceptibility in young age groups. Nevertheless, differences in susceptibility between Flanders, Wallonia, and Brussels are mainly driven by differences in vaccination coverage, which are in line with those reported by other investigators (21, 23, 24, 28, 44). The proposed method relies on several inputs, including a rough estimate of the true basic reproduction number R_0 in the study population. It provides easy-to-understand graphical indications of regions with high outbreak risk, but one should remain cautious about overinterpreting these results. The compilation of more detailed information at a smaller (spatial) resolution (e.g., provincial vaccination coverage estimates, proportions of individuals who are systematically missed, etc.) could improve prediction and would enable us to account for spatial correlation in vaccine activities and correlation of vaccine activities (first and second doses) within individuals.

Numerous examples in the literature show that mumps is resurgent in older, previously vaccinated adolescents, and outbreaks are predominantly seen on college and university campuses. Outbreaks in adolescent populations with high vaccine coverage have been reported in the United States (48, 49), the Netherlands (30, 50, 51), Israel (52), South Korea (53), and Australia (54). Large mumps outbreaks in highly vaccinated populations probably result from a decline in protection with time since mumps vaccination (7). This has been shown through age-specific decreases in vaccine effectiveness (6) and an increased risk of developing mumps with time after vaccination (30, 48). Furthermore, numerous studies have demonstrated decreased levels of antibodies against mumps with time since vaccination (55). In several outbreak reports, the effectiveness of the live attenuated vaccine against mumps appeared to range from 61% to 96% (6, 48, 56).

In addition to primary vaccine failure, waning of vaccine-induced immunity might be responsible for an increase in susceptibility. Although the role of waning immunity in vaccine failure could not be proven in 2 studies (5, 11), 2 more recent studies (49, 57) showed that secondary vaccine failure is one of the drivers of mumps outbreaks in highly vaccinated populations. Recently, Plotkin (58) commented that waning immunity could explain partial failure of the mumps vaccine. Although this hypothesis is supported by declining antibody levels (7, 13) and observations of decreased vaccine effectiveness with time postvaccination (6, 30, 59), correlates of mumps protection are not well understood. Whereas neutralizing antibodies are generally accepted as the best mechanistic correlate of virus protection, no specific protective level can be identified for mumps (60). Furthermore, the avidity of antibodies induced by the mumps virus was shown to be low (61), and relatively low numbers of memory B cells were found in MMR vaccinees compared with those for measles and rubella (62, 63). Cellular immune responses do not appear to play a role in vaccine failure, as they seem to persist (64, 65).

Waning of vaccine-induced immunity is included in our analysis through the specification of an exponential decay model. The exponential waning rates after the first and second doses of MMR vaccine are estimated from an elaborate literature review using a random-effects meta-analysis model. Other models, such as the logistic decay model, are also frequently used to describe decay processes but have been found to have no advantages over the exponential model when modeling mumps antibody decay.

Preventing mumps outbreaks most likely requires various ingredients, in addition to a routine high-coverage 2-dose vaccination program. Targeting specific age groups in specific localities could be an efficient way of reducing the

risk of new outbreaks. In Belgium, the risk of mumps outbreaks in the immediate future has been slightly lowered as a result of the 2012–2013 outbreak in Flanders. Therefore, a new analysis for Belgium would require a new serological study. This illustrates that the reliability of the methodology depends on the availability of serological and vaccine coverage information combined with low pathogen circulation since the time of serological data collection.

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