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1 **Inferring Rubella Outbreak Risk From Seroprevalence Data in Belgium**

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1 **Abstract.** Rubella is usually a mild disease for which infections often pass by unnoticed. In approximately
2 50% of the cases, there are no or only few clinical symptoms. However, rubella contracted during early
3 pregnancy could lead to spontaneous abortion, to central nervous system defects, or to one of a range
4 of other serious and debilitating conditions in a newborn such as the congenital rubella syndrome.
5 Before the introduction of mass vaccination, rubella was a common childhood infection occurring all
6 over the world. However, since the introduction of rubella antigen-containing vaccines, the incidence of
7 rubella has declined dramatically in high-income countries. Recent large-scale mumps outbreaks, one of
8 the components in the combined measles-mumps-rubella vaccine, occurring in countries throughout
9 Europe with high vaccination coverage, provide evidence of pathogen-specific waning of vaccine-
10 induced immunity and primary vaccine failure. In addition, recent measles outbreaks affecting
11 populations with suboptimal vaccination coverages stress the importance of maintaining high
12 vaccination coverages. In this paper, we focus on the assessment of rubella outbreak risk using a
13 previously developed method to identify geographic regions of high outbreak potential. The
14 methodology relies on 2006 rubella seroprevalence data and vaccination coverage data from Belgium
15 and information on primary and secondary vaccine failure obtained from extensive literature reviews.
16 We estimated the rubella outbreak risk in Belgium to be low, however maintaining high levels of
17 immunisation and surveillance are of utmost importance to avoid future outbreaks.

18
19 *Keywords:* disease outbreaks; effective reproduction number; next-generation operator; serology; social
20 contact hypothesis; vaccines

21 22 **1. Introduction**

23 Rubella infection causes usually mild or asymptomatic disease. However, rubella vaccination is of major public
24 health interest because rubella contracted during early to mid-pregnancy could lead to spontaneous abortion,
25 central nervous system defects, or one of a range of other serious and debilitating conditions in a newborn
26 (e.g., congenital rubella syndrome (CRS) leading to heart, brain, ear and eye problems). The rubella vaccine has
27 been used successfully in vaccination programs around the world targeted at girls only or girls and boys
28 combined, and usually successfully accompanied by catch-up vaccination up to pre-adolescence [1]. Rubella
29 vaccination has been available in Belgium since 1974 for teenage girls only until 1985 when universal

1 vaccination with the combined measles-mumps-rubella (MMR) vaccine was recommended and made available
2 free of charge on the routine program at age 15 months only. In 1995, the second dose of MMR was added to
3 the program at age 11-12 years [2]. Since 2003 the age at first dose administration was lowered to 12-13
4 months, in an attempt to offer protection as early as possible after waning of residual maternal antibodies.

5
6 Trivalent measles, mumps and rubella immunisation has been widely implemented throughout Europe and the
7 incidence of these diseases has declined dramatically. However, local and large-scale outbreaks of measles
8 have been reported in recent years and have been attributed to suboptimal vaccination coverage [see, e.g., 3-
9 5]. In addition to measles outbreaks, mumps outbreaks have been reported in highly vaccinated populations
10 during recent years [see, e.g., 6,7], raising concerns about mumps vaccine failure. Whereas there are no recent
11 reports on rubella outbreaks in Belgium, in Japan, an outbreak of 15,000 cases of rubella and 43 cases of CRS
12 was observed. This rubella resurgence mainly affected unvaccinated adult men and women belonging to
13 cohorts in which vaccination coverages were relatively low [8]. In 2012, rubella outbreaks were also reported in
14 Poland and Romania [9,10]. On the other hand, Finland was documented to be the first country in which
15 rubella is eliminated as a result of a 12 year, 2-dose MMR vaccination program [11].

16
17 Despite MMR vaccination efforts throughout the world, it remains of interest to determine whether measles,
18 mumps and rubella resurgence is possible in countries with high vaccination coverage. Recently, Abrams et al.
19 [12] and Hens et al. [13] have conducted such studies for mumps and measles in Belgium. In the absence of
20 recent serological data, they showed that a multi-cohort model can be used, combining previously collected
21 serological survey data and vaccination coverage information, as well as data on social contact behavior. These
22 data are then combined with biomedical information on the duration of maternal immunity and of primary and
23 secondary vaccine failure, both based on extensive literature reviews. The objective of the current paper is to
24 complement the aforementioned analyses with an outbreak risk assessment for rubella in Belgium. More
25 specifically, our aim is to identify Belgian regions of high outbreak potential based on regional estimates of the
26 effective reproduction number R thereby closely following the approach by Abrams et al. [12].

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1 **2. Material and methods**

2 2.1. Data sources

3 *2.1.1. Serological survey data*

4 A previously published Belgian serological dataset on rubella from 2006 serves as the main data source for our
5 analyses. This database was compiled using a multi-tiered approach to collect a sufficient number of
6 geographically and age and gender representative serum samples ($n = 3823$) [14]. Samples were tested for
7 the presence of immunoglobulin G antibodies against rubella using a commercial ELISA (Enzygnost, Siemens,
8 Germany). Hence, these serological data contain information about past rubella immunisation, either by
9 vaccination (passive immunisation) or natural infection (active immunisation). Equivocal and missing test
10 results were excluded from our statistical analyses.

11

12 *2.1.2. Vaccination coverage information*

13 After the first year of life, Belgian infants gain vaccine-induced immunity through vaccination at the age of
14 about 12 months (first dose) and about 12 years (second dose; 10 years-13 years). In order to quantify vaccine-
15 induced immunity we rely on vaccination coverage estimates for both recommended MMR doses in this 2-dose
16 MMR program (see Table A1 in Appendix A).

17

18 *2.1.3. Social contact data*

19 We integrated social contact data from Belgium collected in the European POLYMOD study [15,16] in the
20 estimation of the age-specific relative incidence of rubella resurgence. Age-dependent contact rates are
21 estimated from Belgian empirical data according to a bivariate smoothing approach [17]. These social contact
22 rates provide information on the mixing behaviour of individuals between different age-groups important to
23 explain the spread of airborne infections such as rubella in the target population.

24

25 *2.1.4. Primary and secondary vaccine failure*

26 Extensive literature searches in PubMed and ISI Web of Knowledge and meta-analyses were conducted to
27 obtain estimates for seroconversion (as a proxy for primary vaccine failure) and waning rubella immunity
28 following MMR vaccination (see Appendix A for details on inclusion criteria and estimates and meta-analysis in

1 Appendix B). The seroconversion rate is assumed identical after first and second MMR dose, and estimated to
 2 be 0.984 (95% CI: [0.974, 0.999]) in line with estimates obtained by Wood et al. [18] relying on serial serological
 3 data. Note that seropositivity for anti-rubella IgG was used as a proxy for natural infection or vaccine-induced
 4 protection, and seronegativity as a proxy for susceptibility. A common annual waning rate $\hat{\gamma} =$
 5 0.016 [0.014, 0.018] is obtained from the literature review. Alternatively, we estimated an overall waning rate
 6 for rubella based on Belgian serological data anno 2006 in the age interval 13 to 20 years in order to select
 7 individuals vaccinated twice with the combined MMR vaccine (i.e., under the assumption that rubella
 8 circulation was interrupted after the introduction of mass vaccination). More specifically, the log-transformed
 9 antibody levels for seropositive individuals were linearly modelled as a function of age, yielding an exponential
 10 annual waning rate of $\hat{\gamma} = 0.003$ [0.000, 0.026]. The estimated waning rate derived from the second approach
 11 is very close to the estimate obtained by Wood et al. [18] (i.e., 0.002 [0.000, 0.004]), albeit less precise, and
 12 will be used in our analyses as a conservative approach.

13

14 Although evidence for waning of vaccine-induced immunity exists, rubella infections are generally accepted to
 15 induce lifelong immunity [19], which we assume here, yielding a conservative approach when estimating
 16 rubella outbreak risk.

17

18 2.2. Multi-cohort model formulation

19 We use a multi-cohort model for the assessment of rubella outbreak risk in Belgium. We closely follow the
 20 work by Abrams et al. [13] and Hens et al. [13]. Briefly, with $\pi(a, t)$ representing the proportion seropositive
 21 individuals of age a at calendar time t in the population, suppressing dependence on other individual covariate
 22 information for the time being, the multi-cohort model is partly based on the following set of equations for
 23 $\pi(a, t) = 1 - S(a, t)$, with $S(a, t)$ the age- and time-dependent susceptible fraction:

$$24 \quad \pi(a, t) = \begin{cases} \exp(-\eta a) \times [1 - S(0, t - a)] & \text{if } 0 \leq a < 1, \\ \exp[-\gamma_1(a - 1)] \times \rho v_1(t - a + 1) & \text{if } 1 \leq a < 12, \\ \exp[-\gamma_2(a - 12)] \times \rho v_2(t - a + 12) & \text{if } 12 \leq a, \end{cases} \quad (1)$$

25 where η represents the rate at which maternal antibodies decay, ρ the seroconversion rate, γ_1 and γ_2 waning
 26 rates of vaccine-induced immunity after the first (MMR1) and second dose of the MMR vaccine (MMR2), $v_1(\cdot)$,
 27 $v_2(\cdot)$ the time-dependent proportion vaccinated with MMR1 and MMR2, and $S(0, t - a)$ is the proportion of
 28 susceptible newborns at calendar time $(t - a)$. In order to calculate the age-dependent proportion of

1 susceptible individuals at calendar time $t = yr^R$, we need to apply and adapt the aforementioned cohort
2 model as follows. First, for individuals aged $[13 + (yr^R - 2006)]$ or older in reference year yr^R (i.e., those
3 aged 13 years or older in 2006) we account for vaccine-induced and naturally acquired immunity by combining
4 time-specific vaccination coverage information with $S(a, t)$ derived from the 2006 serological data. In order to
5 propagate $S(a, t)$ to future years, waning of vaccine-induced immunity is accommodated through
6 multiplication with a factor $\exp[-\gamma_2(a - a_0)]$, i.e., a_0 the individual's age in 2006, and natural immunity is
7 assumed to persist for life. Second, for individuals younger than $[13 + (yr^R - 2006)]$ years of age, we cannot
8 use the 2006 serology to estimate the proportion susceptible, because a second MMR dose has been offered to
9 these children later on. Therefore, we need to rely entirely on the more recent vaccination coverage data. In
10 order to do so, we use the equations in (1) to determine the age-dependent proportion susceptible (see also
11 Appendix C). Note that we also adapted the third equation to account for those who received the first dose
12 only. The equations in (1) are based on the assumption that circulation is interrupted since 1993 (i.e.,
13 serological data for individuals aged 13 or more in 2006 are included in the estimation of the susceptibility
14 profile, and hence transmission resulting in humoral immunity in these age groups is accounted for).
15 Transmission is not accounted for in the estimation of susceptibility in those aged 12 or less in 2006.
16 Considering the absence of reported rubella outbreaks in Belgium since 1994, this seems unlikely to have a
17 large impact.

18
19 In order to estimate the seroprevalence, data from a previously described seroprevalence study conducted in
20 2006 is used containing binary current status data with respect to past rubella immunisation (see Section
21 2.1.1). A generalised additive model (GAM) [20,21] with complementary log-log link function, denoted by
22 $cloglog(\cdot)$, is considered to model the observed seroprevalence as a function of the individual's age a , gender
23 g and spatial location (x, y) :

$$24 \quad cloglog[\pi(a, x, y, g)] = f(a, x, y, g), \quad (2)$$

25 where $f(\cdot)$ is a smooth function and $\pi(a, x, y, g)$ is the proportion of seropositives of age a with spatial
26 coordinates (x, y) and gender g . The coordinates (x, y) refer to the centroids of the municipalities in which
27 test subjects reside, if available; otherwise spatial locations of the test laboratories are used as a proxy. Several
28 submodels of equation (2) were considered and a model comparison was performed based on Akaike's
29 Information Criterion [AIC, 22]. The smooth function $f(\cdot)$ was decomposed in smooth components $s_i(\cdot)$, $i = 1,$

1 2, which were fitted using one-dimensional cubic splines and two-dimensional thin-plate regression splines,
2 respectively, and/or components $te(.,.)$ referring to tensor product thin-plate regression splines allowing for
3 differential smoothing along the two dimensions. As a result, the GAM in (2) enables estimating the age-,
4 gender- and location-specific proportion of susceptible individuals in Belgium anno 2006, denoted by
5 $S(a, 2006, x, y, g) = 1 - \pi(a, x, y, g)$, by averaging data points with their neighbours. Consequently,
6 susceptibility predictions for reference year yr^R are obtained after multiplying the age-dependent fraction of
7 seropositive individuals with a factor $\exp[-\gamma(yr^R - 2006)_+]$ which represents an exponential decay function
8 with decay rate γ and $(u)_+ = u$ if and only if $u > 0$. The analyses based on serology from 2006 are restricted
9 to subjects aged at least 13 years in 2006, since predictions for younger ages are likely influenced by samples
10 for which the second vaccine dose was not yet administered at the time of data collection. Therefore,
11 predictions of the proportion of susceptible individuals in reference year yr^R based on the GAM are solely
12 available for individuals aged $[13 + (yr^R - 2006)]$ years and above. Susceptibility in younger age groups is
13 inferred from available Belgian vaccination coverage information (see Appendix C). Finally, the estimated
14 spatial age- and time-dependent susceptibility profile in yr^R is used to infer the effective reproduction number
15 R (see Appendix D).

16

17 **3. Results**

18 **3.1. Local effective reproduction numbers in Belgium**

19 Several GAMs are fitted to the Belgian rubella serology using the R package "mgcv" package in order to
20 determine the age- and location-specific susceptibility profiles (Table 1).

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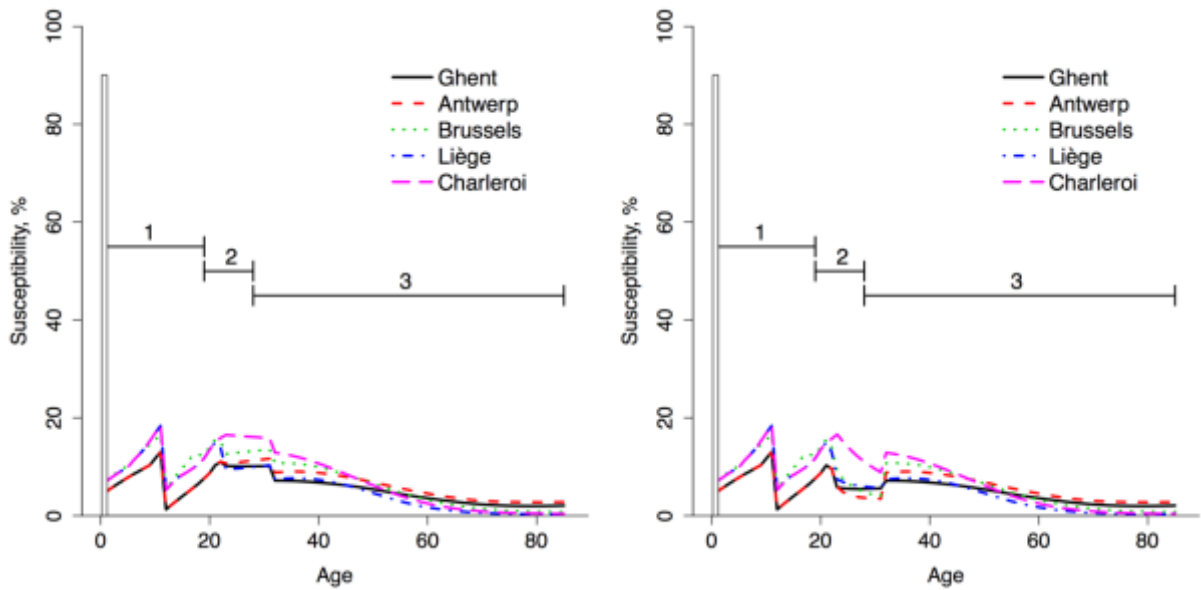
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28

1 **Table 1.** Generalized additive models fitted to the Belgian seroprevalence data anno 2006 on rubella infections
 2 with corresponding AIC-values; individual's age a , gender g and spatial location (x, y) ; $s_i(\cdot)$, $i = 1, 2$, one-
 3 dimensional cubic splines and two-dimensional thin-plate regression splines, respectively, $te(\cdot, \cdot)$ tensor
 4 product thin-plate regression splines.

Model	Linear predictor	AIC
(1)	$te(x, y, a, by = g) + te(x, y, a, by = 1 - g)$	899.98
(2)	$te(x, y, a)$	932.89
(3)	$s_1(a) + te(x, y)$	935.04
(4)	$s_1(a) + s_2(x, y)$	933.15
(5)	$s_1(a)$	969.86

6
 7 Model (1) outperforms all other fitted models based on AIC. Hence, gender is an important variable in
 8 explaining the observed seroprevalence data. Henceforth, gender-specific susceptibility profiles for reference
 9 year $yr^R = 2016$ are derived based on model (1) and relying on vaccination coverages, seroconversion and
 10 waning rates, and subsequently used in the assessment of rubella outbreak risk in Belgium. A parametric
 11 bootstrap approach is used to construct 1,000 bootstrap samples, and model (1) is fitted to each of the
 12 generated samples. Furthermore, for each bootstrap sample and municipality, vaccination coverages are
 13 randomly sampled from a normal distribution with 95% confidence intervals approximately equal to those
 14 reported in Table A1. In order to end up with a smooth susceptibility curve for each municipality, a gradual
 15 evolution of the vaccination coverages is assumed and an interpolating-spline model is fitted to each of the
 16 generated data sets. In Figure 1, the estimated susceptibility profiles in 2016 for males (left panel) and females
 17 (right panel) are shown for the five largest Belgian cities (i.e., Ghent, Antwerp, Brussels, Liège and Charleroi) for
 18 the purpose of illustration. The profiles are similar in shape; the susceptibility is higher in Charleroi and Brussels
 19 than in other cities. In the estimation of the spatial effective reproduction numbers R , a weighted average of
 20 gender and age-specific susceptibility is calculated per municipality with weights equal to the age-dependent
 21 proportion of males/females.

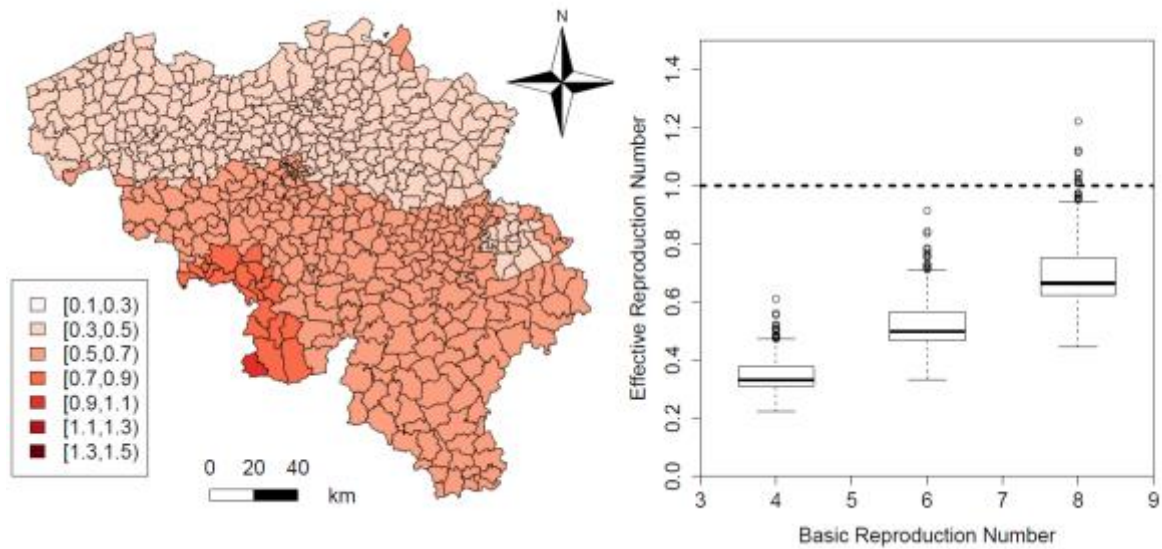


1

2 **Figure 1.** Estimated susceptibility to rubella infection in the five largest Belgian cities: Ghent, Antwerp, Brussels,
 3 Liège and Charleroi in 2016 for males (left panel) and females (right panel). The susceptibility curve is based on
 4 (1) coverage information + waning of vaccine-induced immunity; (2) serology with waning of vaccine-induced
 5 immunity; and (3) serology with lifelong natural immunity.

6

7 Estimates for the basic reproduction R_0 in the literature range from 4 to 8 [23,24]. Based on the left panel of
 8 Figure 2, displaying the estimated effective reproduction numbers for the intermediate setting with $R_0 = 6$,
 9 one can conclude that rubella outbreak risk is relatively low in all Belgian municipalities with slightly higher R
 10 values in Sivry-Rance (0.835), Chimay (0.843) and Momignies (0.916) (red regions). Results of a sensitivity
 11 analysis with values of R_0 ranging from 4 to 8 are presented in the right panel of Figure 2. Obviously, a higher
 12 value for R_0 implies higher values of R . Again, the rubella outbreak risk is estimated to be quite low, albeit that
 13 in the extreme case of $R_0 = 8$, the effective reproduction numbers tend to exceed the threshold value one in
 14 10 municipalities, mainly in Brussels and the Walloon region where vaccination coverage is lower relative to
 15 Flanders.



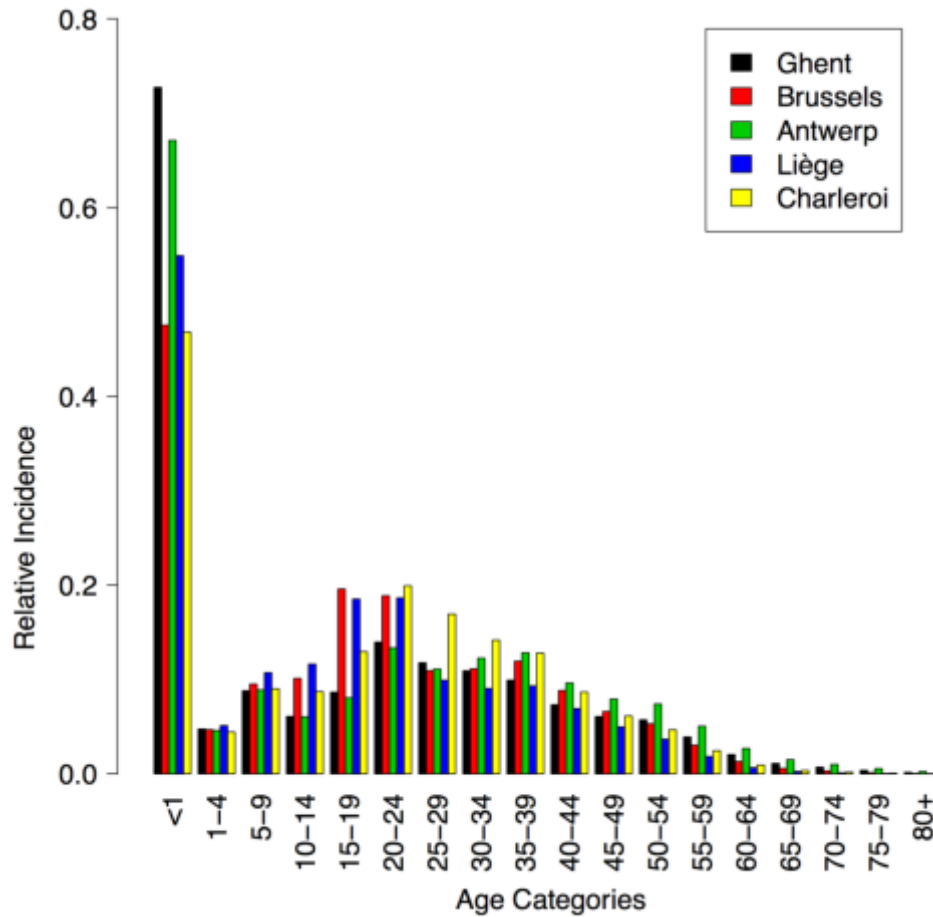
1

2 **Figure 2.** Estimated effective reproduction numbers for rubella in the Belgian municipalities on a spatial map
 3 for $R_0 = 6$ (left panel) and spatial boxplots of the estimated effective reproduction numbers with basic
 4 reproduction number R_0 equal to 4, 6 or 8.

5

6 3.2. Relative incidence in a future rubella outbreak

7 The expected age-dependent relative incidence of a rubella outbreak upon importation of a rubella case is
 8 calculated based on the susceptibility in the aforementioned five Belgian cities (Figure 3). Infants younger than
 9 one year of age are the most vulnerable to rubella infection due to a rapid decay of maternal protection as
 10 demonstrated by Leuridan et al. [25] and Goeyvaerts et al. [26]. The incidence in the age groups 15-19 and 20-
 11 24 years is expected to be highest and results from an increased susceptibility together with higher social
 12 contact frequencies in these age groups.



1

2 **Figure 3.** Expected age-specific relative incidence of a re-emergence of rubella in Belgium for five cities: Ghent,
 3 Antwerp, Brussels, Liège and Charleroi.

4

5

6 **5. Discussion**

7 In this paper, we investigated the possibility of rubella resurgence in the Belgian population. Differences in

8 estimated susceptibility between males and females reflect the sequence of female only (prior to 1985) and

9 gender neutral (from 1985 onwards) rubella immunisation activities in Belgium. Based on the projected

10 susceptibility in 2016, the effective reproduction numbers in Belgian municipalities are estimated relying on a

11 range of previously published basic reproduction numbers. Although the risk of large-scale rubella outbreaks is

12 found to be low at the moment, monitoring rubella seropositivity in the population remains of crucial

13 importance in order to evaluate the risk of outbreaks in the future. The low outbreak risk is mainly driven by

14 pre-existing vaccine-induced immunity in females from cohorts vaccinated with a monovalent rubella vaccine

15 prior to the administration of the combined MMR vaccine. However, seropositivity of vaccinated females in

16 these cohorts is not subjected to waning of vaccine-induced immunity between 2006 and 2016 as reliable

17 coverage estimates for the period 1973-1985 are unavailable. Therefore, seropositivity in females born before

1 1985 is assumed to be the result of natural infection without waning rather than immunisation through
2 vaccination. This could lead to an underestimation of susceptibility in the population. In addition, the
3 seroconversion rate after MMR vaccination for rubella is estimated to be almost one (see Table A2). This
4 implies that a large part of the vaccinated population is protected against rubella infection immediately after
5 vaccination. Exponential waning rates are estimated to be quite small compared to those reported by Abrams
6 et al. [12] for mumps (i.e., 0.043 and 0.021 after MMR1 and MMR2, respectively). As individuals with naturally
7 acquired immunity to rubella start to disappear as they increasingly die, and waning of vaccine-induced
8 immunity enlarges the susceptible proportion in the population, rubella outbreaks are not unlikely to occur in
9 the future. This is especially important for health services, as rubella outbreaks can lead to an increased
10 incidence of CRS in newborns [see, e.g., 27]. However, until now, rubella outbreaks in the vaccination era are
11 mainly affecting countries with suboptimal vaccination levels.

12

13 In general, the methodology presented in this manuscript enables the estimation of outbreak risk for vaccine-
14 preventable diseases in highly vaccinated populations. Our model is informed by data that is commonly
15 available at the country level, namely (spatial) serological data, vaccination coverage information and social
16 contact data, and accounts for loss of maternal immunity, primary vaccine failure and waning of vaccine-
17 induced immunity. Nevertheless, our study suffers from several limitations. A proportion of persons who do
18 not have detectable antibodies may have a level of protection via cellular immunity [28], but this proportion
19 remains unknown and could therefore not be taken into account. However, if outbreaks would emerge we
20 could at least partially estimate the role of cellular immunity as a potential dampening factor in the outbreak
21 size. Moreover, ELISA results do not perfectly correlate with the plaque reduction neutralisation values, used in
22 the few other existing studies relating circulating antibodies to clinical protection against rubella, which are
23 generally more sensitive [see, e.g., 29]. Naturally acquired immunity after rubella infection is believed to be
24 lifelong. However, any deviation from this assumption is easily incorporated, leaving a larger part of the
25 population unprotected against new rubella infections. The latter situation increases the estimated
26 reproduction numbers and consequently enlarges the efforts required to prevent future rubella outbreaks.

27

28 Although the location- and age-dependent susceptibility profiles are constructed based upon various data
29 sources and therefore apprehensive graphical indications of regions with high outbreak risk are provided, one

1 should remain cautious about over-interpreting these spatial results. The spatial resolution of the various data
2 sources we used was limited. The analysis of the serological data clearly indicated spatially heterogeneous
3 serological profiles for the different infections, with differences between Flanders, Wallonia and Brussels
4 mainly driven by differences in vaccination coverages, which are in line with those reported by others [see
5 references in Table A1 and 30]. Coverage data in the Belgian regions was fragmented, leading to a substantial
6 amount of uncertainty about the susceptibility in young age groups, and the spatial distribution of our social
7 contact data was not detailed enough due to sample size restrictions, limiting spatial estimates of
8 susceptibility. More detailed information at a smaller (spatial) resolution could improve prediction, and would
9 enable us to account for spatial correlation in vaccine activities and correlation of vaccine activities (first and
10 second dose) within individuals. Finally, susceptibility was only allowed to change over time as a result of
11 waning of vaccine-induced immunity, and therefore, very rarely, decreases in susceptibility caused by sporadic
12 infections over the years are ignored.

13

14 Currently rubella surveillance in Belgium is suboptimal and relies mainly on sentinel surveillance of congenital
15 rubella. Periodic monitoring of seropositivity and inferring outbreak risk as conducted in this study remains
16 desirable to complement clinical surveillance and detect effects such as waning of vaccine-induced immunity.

17

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21 and the Antwerp Study Centre for Infectious Diseases (ASCID), both at the University of Antwerp.

22 Conflicts of interest: none declared.

23 *Authors' contribution to the manuscript:*

24 SA, EK and NH performed the analyses and interpreted the results. SA and NH wrote the initial draft of the
25 manuscript after which all authors critically revised the article and contributed to drafting the final manuscript.

26 All authors read and approved the final manuscript.

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1 **Supplementary materials**

2 Supplementary materials associated with this article can be found in Appendix A-F.

3

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