2012•2013
FACULTY OF SCIENCES
Master of Statistics: Biostatistics

Masterproef

Estimation of vaccination coverage and waning immunity for measles, mumps, and rubella from serological surveys in Belgium, 2002 and 2006

Promotor :
Prof. dr. Niel HENS
dr. Nele GOEYVAERTS

Renata Tiene De Carvalho Yokota

Master Thesis nominated to obtain the degree of Master of Statistics , specialization Biostatistics

Transnational University Limburg is a unique collaboration of two universities in two countries: the University of Hasselt and Maastricht University.

universiteit hasselt
KNOWLEDGE IN ACTION

Universiteit Hasselt | Campus Hasselt | Martelarenlaan 42 | BE-3500 Hasselt
Universiteit Hasselt | Campus Diepenbeek | Agoralaan Gebouw D | BE-3590 Diepenbeek

universiteit hasselt | Maastricht University

2012•2013
FACULTY OF SCIENCES
Master of Statistics: Biostatistics

Masterproef

Estimation of vaccination coverage and waning immunity for measles, mumps, and rubella from serological surveys in Belgium, 2002 and 2006

Promotor :
Prof. dr. Niel HENS
dr. Nele GOEYVAERTS

Renata Tiene De Carvalho Yokota
Master Thesis nominated to obtain the degree of Master of Statistics , specialization Biostatistics

universiteit hasselt | Maastricht University

Abstract

The degree of protection and susceptibility related to a certain vaccine can be assessed by the estimation of vaccination coverage. However, the comparison across countries is difficult due to the existence of several methods to estimate the immunization coverage. In this report, two existing methods ignoring waning were fitted to the 2002 and 2006 serological surveys conducted in Belgium to estimate the vaccination coverage: the saturated model proposed by Gay (2000), based on parametric assumptions related to the disease-specific seroconversion rates and natural exposure to infection (exposure probability) for the measles, mumps, and rubella (MMR) vaccine, and the restricted cubic splines (RCS) model for the exposure probabilities proposed by Goeyvaerts et al. (2012). In addition, an extension of these models to include waning of immunity to estimate the vaccination coverage, by using serological data from at least two time points, as recently developed by Wood, Goeyvaerts, and Hens (unpublished manuscript), was fitted. In total, 1363 and 1979 serum samples were included in this analysis, representing children born from 1984 to 2005, from the 2002 and 2006 serological surveys, respectively. Among the methods ignoring waning, the best models were the RCS model with five and three knots for the 2002 and 2006 data, respectively, according to both AIC and BIC. By including waning parameters in the model, the vaccination coverage for older birth cohorts was larger, suggesting an underestimation of the vaccination coverage by the models without waning. The lowest seroconversion rate was observed for mumps (0.85; 95%CI=0.82; 0.88) and measles (0.90; 95%CI=0.88; 0.92) for the 2002 and 2006 RCS models, respectively. When relying on the waning model, mumps presented the lowest seroconversion rate (0.92; 95%CI=0.90; 0.94). An increasing trend of the exposure probabilities over age was observed for the three diseases for both models ignoring waning. The estimated waning parameters were ω_1=0.0050 (95%CI=0.0036; 0.0071), ω_2=0.0045 (95%CI=0.0032; 0.0064), and ω_3=0 for measles, mumps, and rubella, respectively. The vaccination coverage estimates for all models was below the target proposed by World Health Organization for children with one year of age (90%) to eliminate measles by 2015. The lower estimates for the waning parameters as compared to the literature may be related to the non-inclusion of potential confounders, such as region of residence, and the effect of the second MMR dose.

Keywords: *vaccination coverage; waning; seroconversion rate; exposure probability; serological survey; immunization*

Contents

1. Introduction

Vaccination is the most effective strategy to reduce morbidity and mortality from vaccine-preventable diseases (Dannetun et al., 2004). For vaccination programs to be effective, it is essential to reach and maintain high vaccine coverage and rates of acceptance (Vyse et al., 2002; Omer et al., 2009). Vaccination coverage assessment aims at the estimation of the achieved degree of protection and remaining susceptibility in a population, the evaluation of immunization programs performance, and identification of partially or non-vaccinated subpopulations (Theeten, 2011). This assessment can guide public health interventions, including vaccination policy, to prevent the disease spread and outbreak occurrence (Vellinga, Depoorter, and Van Damme, 2002). However, comparison across countries is difficult due to the existence of several methods to estimate the vaccination coverage.

Gay (2000) (unpublished manuscript), as cited by Altmann and Altmann (2000) proposed the use of antibody prevalence data from serological studies to estimate the vaccination coverage. By using trivalent serological data for which a trivalent vaccine is used, such as measles, mumps, and rubella (MMR), Gay's modeling equations also allow the estimation of the disease-specific seroconversion rates and disease and age-specific exposure probabilities. As an extension of Gay's saturated model, Goeyvaerts et al. (2012), proposed the use of restricted cubic splines models, as more parsimonious semiparametric models for the exposure probabilities.

Although both approaches allow the estimation of vaccination coverage from trivariate data, they assume that the MMR vaccine confers long-lasting immunity. However, there is strong evidence that antibody levels for some diseases, including measles (Rouderfer, Becker, and Hethcote et al., 1994; Wood et al., 2009) mumps (Brockhoff et al., 2010), and rubella (Johnson et al., 1996) tend to decline over time after natural exposure or vaccination. Wood, Goeyvaerts, and Hens (unpublished manuscript) extended the previous models to estimate the vaccination coverage by taking into account disease-specific waning, using trivalent MMR data from three serological surveys from Australia.

In this report, the saturated model (Altman and Altman, 2000) and the semiparametric model for the exposure probabilities (Goeyvaerts et al., 2012) were fitted to the 2002 and 2006 serological surveys data from Belgium. Furthermore, the method proposed by Wood, Goeyvaerts, and Hens (unpublished manuscript) was applied to the two serological surveys conducted in Belgium. The report is organized as follows: a brief introduction about measles, mumps, and rubella transmission and complications, and the MMR vaccine in Belgium is presented in Section 2; the data description is presented in Section 3; the methods and the results are presented in Sections 4 and 5, respectively; in Section 6, a sensitivity analysis is presented; finally, the discussion and conclusions and recommendations are presented in Sections 7 and 8.

2. Measles, mumps, and rubella vaccination in Belgium

Measles, mumps and rubella are vaccine-preventable viral infectious diseases that share similar transmission – routes (airborne) – and can cause significant morbidity (Demicheli et al., 2005). Measles can cause complications such as otitis media, pneumonia, and encephalitis; mumps is a common cause of aseptic meningitis and can cause orchitis (testicle inflammation) in adult males; although rubella infection is usually mild, when acquired during pregnancy can cause miscarriage or congenital rubella syndrome, which is characterized by congenital abnormalities including nerve deafness, cardiac abnormalities, and mental retardation (Vyse et al., 2002).

In Belgium, the combined measles, mumps, and rubella (MMR) vaccine was introduced in 1985 for children 12 to 15 months of age and the second dose of the MMR vaccine was implemented in 1995 for children 10 to 13 years of age. In 2003, the administration of the first dose of the MMR vaccine was modified to 12 months (Theeten, 2011).

Currently, the vaccination coverage in Belgium is monitored using different methods: (i) household cluster surveys for infants, based on the Expanded Programme on Immunization (EPI), as proposed by the World Health Organization (WHO, 2005); (ii) school surveys for older children; and (iii) cross-sectional antibody prevalence studies (serological surveys). Despite the higher cost as compared to Epi-surveys, serological surveys do not rely on the existence of vaccination documentation and are not prone to participation bias (Theeten, 2011). Furthermore, the use of data from serological surveys conducted in Belgium adds useful information to vaccination coverage data, as in Belgium immunization coverage surveys were performed at regional level and not simultaneous in all regions – Brussels, Flanders, and Wallonia (Theeten et al., 2011).

3. Data description

In this study, two serological datasets from Belgium were analyzed. The 2002 data were collected as part of the European sero-epidemiology network 2 (ESEN2) from November 2001 and March 2003 and the 2006 data were prospectively collected by diagnostic laboratories and blood transfusion centers in Belgium, from January 2006 to October 2007.

Serum antibodies concentration against measles, mumps, and rubella were measured by enzyme-linked immunosorbent assay (ELISA). The cut-off points were determined by the ELISA manufacturer for each disease. Overall, immunoglobulin G (IgG) levels above the threshold are classified as seropositive, below as seronegative, and in between as inconclusive (equivocal). In this report, the cut-off points of 0.35 IU/mL, 12 arbitrary units (AU)/mL, and 10 IU/mL were used for measles, mumps, and rubella, respectively (Theeten, 2011). A standardization of the serological results was performed, as proposed by Kafatos et al. (2005) to adjust for laboratory and assay differences.

The analysis of the serological surveys data from Belgium included 1363 samples from 2002 and 1979 samples from 2006 (Figure 1). By assuming that the serological data provide a

perfect marker of immunity, the individuals were classified into one of the eight immunity states, based on the unequivocally dichotomized serological results for measles, mumps, and rubella. The equivocal results represented 22% and 24% of the serum samples collected in 2002 and 2006, respectively. The analyses for the models ignoring waning were restricted to individuals between 1 to 18 years of age, which corresponds to the birth cohorts of 1984 to 2001 and 1988 to 2005 for the 2002 and 2006 serological surveys, respectively. However, since the waning model uses two time points, the analysis of the same birth cohorts in the two serological surveys is required. Thus, the analysis of the 2006 serological survey also included the 1984 to 2001 birth cohorts (children with 5 to 22 years of age).

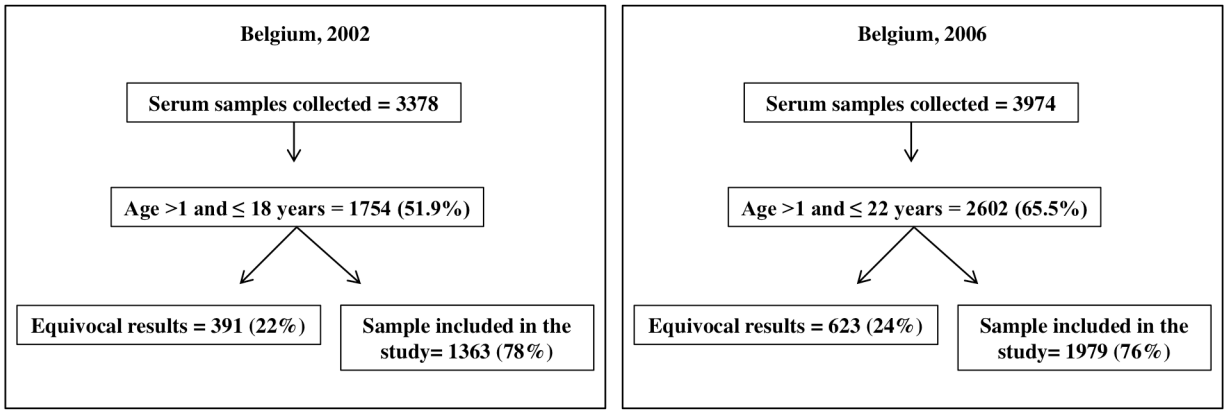


Figure 1. Serum samples for Belgium included in the analysis in 2002 and 2006.

The 2002 and 2006 datasets analyzed are presented in Tables 1 and 2, respectively. In 2002, 11% of the individuals did not seroconvert to mumps, although they were seropositive for measles and rubella (Table 1), while in 2006, 8% of the individuals were seronegative for measles, but seropositive for mumps and rubella (Table 2). The proportion of individuals who were seropositive (2002 = 72%; 2006 = 77%) and seronegative (2002 = 8%; 2006 = 7%) for all three diseases were similar in both serological surveys.

Table 1. Number of individuals in each immunity state ("+" for seropositive and "–" for seronegative) for measles, mumps, and rubella, respectively, by birth cohort (1985-2002), Belgium, 2002 (N=1363).

Birth cohort	Immunity states								Total
	+ + +	+ + –	+ – +	+ – –	– + +	– + –	– – +	– – –	
1984	103	1	15	2	4	0	6	5	136
1985	57	3	5	1	1	1	2	2	72
1986	61	0	4	0	6	1	1	1	74
1987	54	1	5	1	4	0	3	1	69
1988	54	1	1	0	4	1	3	2	66
1989	49	1	4	2	3	1	3	3	66
1990	55	1	3	4	6	1	2	2	74
1991	56	1	5	2	2	1	1	3	71
1992	56	0	13	4	0	0	1	3	77
1993	37	0	12	6	0	1	3	6	65
1994	49	0	15	1	1	0	1	7	74
1995	51	2	10	2	0	0	4	4	73
1996	46	1	11	2	0	0	2	9	71
1997	55	0	8	0	0	2	2	8	75
1998	57	1	9	0	2	0	1	10	80
1999	60	1	10	0	0	0	1	5	77
2000	58	0	11	2	1	0	1	7	80
2001	25	0	3	4	1	1	3	26	63
Total	983 (72%)	14 (1%)	145 (11%)	32 (2%)	35 (3%)	10 (1%)	40 (3%)	104 (8%)	1363

Table 2. Number of individuals in each immunity state ("+" for seropositive and "–" for seronegative) for measles, mumps, and rubella, respectively, by birth cohort (1985-2006), Belgium, 2006 (N=1979).

Birth cohort	Immunity states								Total
	+ + +	+ + –	+ – +	+ – –	– + +	– + –	– – +	– – –	
1984	36	1	1	1	1	0	0	0	40
1985	39	4	1	0	3	0	0	1	48
1986	32	1	0	0	2	0	1	1	37
1987	56	1	3	1	11	2	0	1	75
1988	71	1	5	2	14	2	1	3	99
1989	68	0	4	0	7	2	1	2	84
1990	80	0	1	2	12	0	0	1	96
1991	78	1	5	0	8	0	0	3	95
1992	97	2	5	2	11	0	1	4	122
1993	71	2	2	1	8	1	5	5	95
1994	66	2	5	1	5	0	0	4	83
1995	60	3	1	1	2	1	0	4	72
1996	58	1	4	4	9	0	2	11	89
1997	58	1	8	0	5	3	0	11	86
1998	67	2	3	0	7	2	0	3	84
1999	76	3	3	3	9	1	1	12	108
2000	71	2	6	0	6	0	3	7	95
2001	86	0	3	1	5	0	0	8	103
2002	85	2	5	1	6	1	1	3	104
2003	84	0	5	0	8	1	2	3	103
2004	109	1	5	0	8	0	2	10	135
2005	66	1	5	0	4	4	3	43	126
Total	1514 (77%)	31 (2%)	80 (4%)	20 (1%)	151 (8%)	20 (1%)	23 (1%)	140 (7%)	1979

The timing of the serological surveys should be related to the age at which the birth cohorts were target by universal immunization programs (Theeten, 2011). The Lexis diagram (Figure

2) shows the vaccination schedule for the birth cohorts analyzed for the 2002 and 2006 serological surveys.

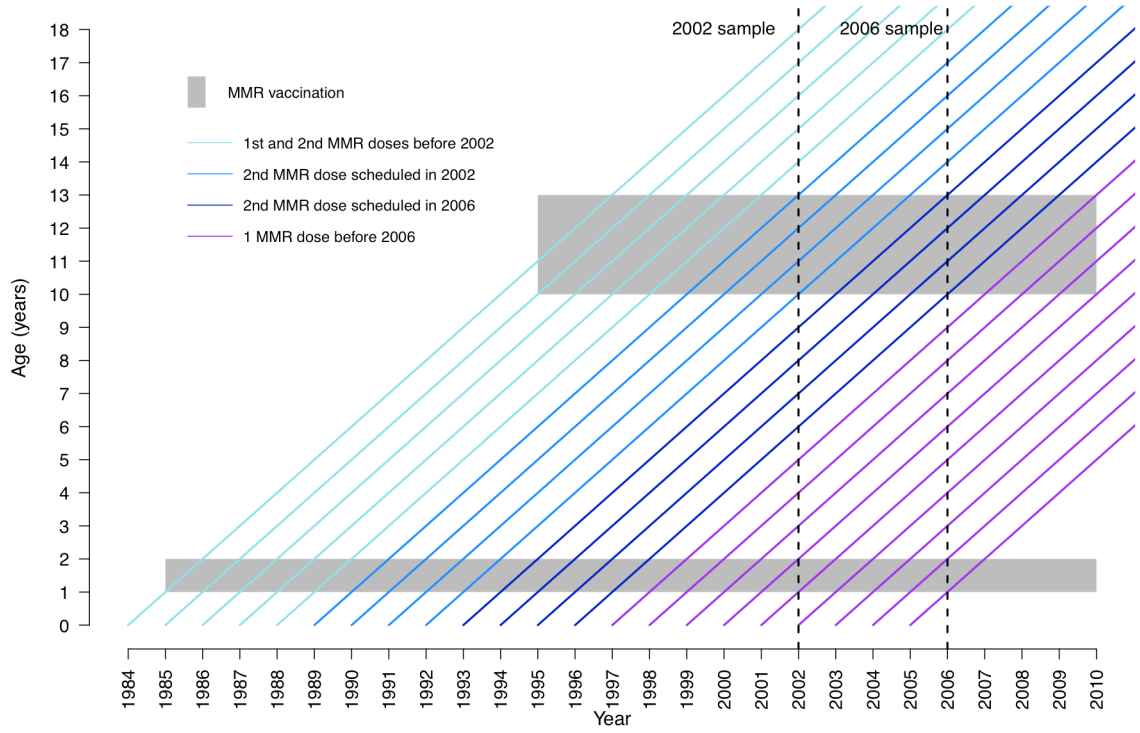


Figure 2. Lexis diagram of the MMR vaccination schedule in Belgium. The cohorts of 1984 to 1988 (lightest blue lines) should have received the two doses of MMR vaccine before the 2002 survey; the following blue lines (birth cohorts of 1989 to 1992) represent the children who are eligible to receive the second dose of the MMR vaccine at the year of the 2002 serological survey; the darkest blue lines indicate that children born between 1993 and 1996 were eligible to receive the second dose of the MMR vaccine in the year of the second serological survey (2006); and the purple lines represent the children born between 1997 and 2005, who should have received only the first MMR dose before the 2006 serological survey.

4. Methods

4.1. Notation

In this report, the index $d = 1, 2, 3$, refers to measles, mumps, and rubella, respectively and j, represents the birth cohorts of each individual i. The trivariate response was defined as shown in (1).

$$\boldsymbol{Y}_{ij} = \begin{cases} 1, \text{if seropositive} \\ 0, \text{if seronegative} \end{cases} \quad (1)$$

Where $\boldsymbol{Y}_{ij} = (Y_{ij1}, Y_{ij2}, Y_{ij3})$ represents the trivariate response for each individual i of birth cohort j.

The following parameters were used in the models fitted ignoring waning, which will be presented in Sections 4.2 and 4.3:

- v_j, the vaccination coverage, representing the proportion of children of birth cohort j who were vaccinated against MMR;
- ζ_{jd}, the seroconversion rate, i.e., the proportion of vaccinated children of birth cohort j who tested seropositive to disease d due to vaccination;
- η_{jd}, the exposure probability, i.e., the proportion of unvaccinated children of birth cohort j who tested seropositive for disease d due to exposure to natural infection;

4.2. Saturated model

The assumptions for the estimation of vaccination coverage according to Gay's saturated model (2000) were:

1. Vaccinated individuals who did not seroconvert due to vaccination have the same probability of being seropositive as an unvaccinated individual of the same birth cohort;
2. Seroconversion to each vaccine component (disease) is independent within an individual and is age-cohort independent;
3. The risk of exposure to infection is homogeneous within a birth cohort and infection with each disease is independent;
4. Each individual receives no more than one dose of the vaccine and the dose is to be given at a fixed age;
5. Upon seroconversion, MMR vaccine confers long-lasting immunity and the immunity is detectable through the presence of IgG antibodies against the diseases in each individual's serum, while the absence of IgG antibodies corresponds to susceptibility i.e., the serological data provide a perfect marker of immunity.

The probability of being seropositive for a vaccinated individual of age cohort j for disease d (q_{jd}) is defined as shown in (2), under assumptions 1 and 5.

$$q_{jd} = \zeta_{jd} + (1 - \zeta_{jd})\, \eta_{jd} \tag{2}$$

The categorization of individuals in the different immunity states was based on the trivariate binary response $\boldsymbol{Y}_{ij} = (Y_{ij1},\ Y_{ij2},\ Y_{ij3})$. The eight immunity states (p_{jk}, for $k = 1,\ldots,8$) – probability that an individual of birth cohort j is classified into category k – are presented in (3), where "+" indicates seropositive and "–" seronegative.

$$\begin{aligned}
p_{j1} &= f_j(+,+,+) = v_j q_{j1} q_{j2} q_{j3} + (1 - v_j)\eta_{j1}\eta_{j2}\eta_{j3} \\
p_{j2} &= f_j(+,+,-) = v_j q_{j1} q_{j2} (1 - q_{j3}) + (1 - v_j)\eta_{j1}\eta_{j2}(1 - \eta_{j3}) \\
p_{j3} &= f_j(+,-,+) = v_j q_{j1} (1 - q_{j2})\, q_{j3} + (1 - v_j)\eta_{j1}(1 - \eta_{j2})\eta_{j3} \\
p_{j4} &= f_j(+,-,-) = v_j q_{j1} (1 - q_{j2})(1 - q_{j3}) + (1 - v_j)\eta_{j1}(1 - \eta_{j2})(1 - \eta_{j3}) \\
p_{j5} &= f_j(-,+,+) = v_j (1 - q_{j1}) q_{j2} q_{j3} + (1 - v_j)(1 - \eta_{j1})\eta_{j2}\eta_{j3} \\
p_{j6} &= f_j(-,+,-) = v_j (1 - q_{j1}) q_{j2} (1 - q_{j3}) + (1 - v_j)(1 - \eta_{j1})\eta_{j2}(1 - \eta_{j3})
\end{aligned} \tag{3}$$

$p_{j7} = f_j(-, -, +) = v_j(1 - q_{j1})(1 - q_{j2})\, q_{j3} + (1 - v_j)(1 - \eta_{j1})(1 - \eta_{j2})\eta_{j3}$

$p_{j8} = f_j(-, -, -) = v_j(1 - q_{j1})(1 - q_{j2})(1 - q_{j3}) + (1 - v_j)(1 - \eta_{j1})(1 - \eta_{j2})(1 - \eta_{j3})$

Here, $f_j(\boldsymbol{y}_{ij})$ denotes the joint probability density function of $\boldsymbol{Y}_{ij}$.

The parameters were estimated by maximizing the multinomial log-likelihood function as defined in (4).

$$\ell(\boldsymbol{v}, \boldsymbol{\zeta}, \boldsymbol{\eta_1}, \boldsymbol{\eta_2}, \boldsymbol{\eta_3} | n_{11}, \dots, n_{18}, n_{21}, \dots, n_{m8}) = \sum_{j=1}^{m} \sum_{k=1}^{8} n_{jk} \log(p_{jk}) \quad (4)$$

Where :

- j represents the number of birth cohorts included in the analysis, where $j = 1, \dots, m$;
- n_{jk} is the number of individuals of birth cohort j classified into category k;
- $\boldsymbol{v} = (v_1, \dots, v_m)$, the vector of vaccination coverage for the m birth cohorts;
- $\boldsymbol{\zeta} = (\zeta_1, \zeta_2, \zeta_3)$, the vector of seroconversion rates, independent of age;
- $\boldsymbol{\eta_1} = (\eta_{11}, \dots, \eta_{m1})$, $\boldsymbol{\eta_2} = (\eta_{12}, \dots, \eta_{m2})$, $\boldsymbol{\eta_3} = (\eta_{13}, \dots, \eta_{m3})$, the vector of exposure probabilities for each disease ($d = 1, 2, 3$) and each birth cohort ($j = 1, \dots, m$);

The total number of estimated parameters from the saturated model is $4m + 3$. In order to obtain biologically relevant estimates for v_j, ζ_d, and η_{jd}, the logit transformation was used to transform probabilities into the real number scale. Although Gay's original model required monotonicity of the exposure probabilities with respect to age, this constraint was not applied in the present analysis, since this assumption seems plausible for populations without MMR vaccination program, which is not the case for the countries in Europe, including Belgium, especially due to the herd immunity effect on the MMR disease dynamics (Goeyvaerts et al., 2012).

4.3. Restricted cubic splines model for the marginal exposure probabilities

A restricted cubic spline (RCS) model was fitted to the marginal exposure probability as a parsimonious alternative to the saturated model, as proposed by Goeyvaerts et al. (2012). Splines are piecewise polynomials within intervals of the explanatory variable that are connected across different intervals of the explanatory variable – used for curve fitting. The endpoints of the intervals in which the explanatory variable is divided are called knots (Harrell, 2001).

The cubic splines model allows the inclusion of an explanatory variable (in this model, age) in a smooth non-linear way, but they present a poor behavior in the tails (before the first knot and after the last knot). Restricted cubic splines add the constraint of linearity in their tails and beyond the boundary knots (by setting the second and third derivatives at the knots to zero), allowing for more parsimonious models (Harrell, 2001). The RCS model for the logit of the exposure probability was defined as shown in (5).

$$logit(\eta_{ja}) = \beta_{0d} + \beta_{1d}j_{1d} + \beta_{2d}j_{2d} + \cdots + \beta_{K-1,d}j_{K-1,d} \quad (5)$$

Where:

- K are the number of knots for the explanatory variable (age);
- $j_{id} = j$ and for $q = 1, \ldots, K-2$:

$$j^*_{q+1,d} = (j-\kappa_{qd})^3_+ - \frac{(j-\kappa_{K-1,d})^3_+(\kappa_{Kd}-\kappa_{qd})}{(\kappa_{Kd}-\kappa_{K-1,d})} + \frac{(j-\kappa_{Kd})^3_+(\kappa_{K-1,d}-\kappa_{qd})}{(\kappa_{Kd}-\kappa_{K-1,d})}$$

where:

- $j_{q+1,d} = \frac{j^*_{q+1,d}}{(\kappa_{Kd}-\kappa_{K-1,d})^2}$ are normalized constants on the original age scale;
- $(j-\kappa_{qd})_+ = j-\kappa_{qd}$, if $j > \kappa_{qd}$;
- $(j-\kappa_{qd})_+ = 0$, if $j \leq \kappa_{qd}$.

RCS models with 3, 4, and 5 knots were fitted to the 2002 and 2006 data from Belgium and the best RCS models were selected based on Akaike's information criterion (AIC) and the Bayesian information criterion (BIC). The knots for the best RCS models were located at equally spaced quantiles, as proposed by Harrell (2001).

4.4. Model including waning and boosting of immunity

An extension of both models previously described, by relaxing assumption 5, thus allowing for loss of immunity was fitted, as proposed by Wood, Goeyvaerts, and Hens (unpublished manuscript). In this model (further referred to as the 'waning model'), the vaccination coverage is estimated from trivariate serological data taking into account waning rates, using serological surveys from at least two different time points. Here, this model was applied to the 2002 and 2006 serological surveys conducted in Belgium. The following assumptions were made to take into account waning and boosting of immunity, as proposed by Wood, Goeyvaerts, and Hens (unpublished manuscript):

1. There are annual probabilities of exposure for each birth cohort and disease;
2. Waning events occur for each antigen, but are age-independent and constant over time;
3. The probability of exposure prior to the age at which MMR vaccination is scheduled is zero;
4. No additional vaccination occurs between the two time points.

For all approaches, either ignoring or taking waning into account, a positive antibody test results from previous exposure to infection or effective vaccination. However, a negative antibody test has different interpretation for the models ignoring and including waning: it represents susceptibility (lack of natural exposure to infection or effective vaccination) in the

models ignoring waning, but may also represent previous exposure followed by antibody level decline below the pre-established threshold in the waning model.
The matrices shown in (6) represent assumptions 1 and 2.

$$\mathrm{E}_{jd}(t) = \begin{pmatrix} 1 & \varepsilon_{jd} \\ 0 & 1-\varepsilon_{jd} \end{pmatrix} \qquad \Omega_d = \begin{pmatrix} 1-\omega_d & 0 \\ \omega_d & 1 \end{pmatrix} \tag{6}$$

Where:

- ε_{jd} are mean annual exposure probabilities for individuals of birth cohort j (j = 1, …, m) and disease d (d = 1, 2, 3) for each serological survey at time t ($t = t_0, t_1$);
- ω_d are the annual waning rates (loss of immunity) for disease d (d = 1, 2, 3), i.e., proportion of children with declining antibody levels following exposure to natural infection or vaccination for disease d per year.

When two serological surveys are available, the trivariate responses $\mathbf{Y_{ij}}$ for each time point, represented by serological surveys at t_0 (2002) and t_1 (2006) in this report, can be modeled with the equations presented in (7).

$$\begin{aligned} g_j(t_0) &= \left(\Omega_1 E_{j1}(t_0) \otimes \Omega_2 E_{j2}(t_0) \otimes \Omega_3 E_{j3}(t_0)\right)^{j-1} V_j \boldsymbol{g}_0 \\ g_{j+t_1-t_0}(t_1, t_0) &= \left(\Omega_1 E_{j1}(t_1) \otimes \Omega_2 E_{j2}(t_1) \otimes \Omega_3 E_{j3}(t_1)\right)^{t_1-t_0} \boldsymbol{g}_j(t_0) \end{aligned} \tag{7}$$

where:

- $g_j(t_0)$ represents the vector of trivariate sera probabilities at t_0, i.e., $\mathbf{Y_{ij}}(t_0)$;
- $g_{j+t_1-t_0}(t_1, t_0)$ represents the vector of trivariate sera probabilities at t_1, i.e., $\mathbf{Y_{ij}}(t_1)$;
- V_j represents the probability of seroconversion due to vaccination and is defined as shown in (8), where the seroconversion rates are disease-specific, but birth cohort-independent;
- $\boldsymbol{g}_0 = [0, \ldots, 0, 1]^T$.

$$V_j = \begin{pmatrix} 1 & v_j\xi_3 & v_j\xi_2 & v_j\xi_1 & v_j\xi_2\xi_3 & v_j\xi_1\xi_3 & v_j\xi_1\xi_2 & v_j\xi_1\xi_2\xi_3 \\ 0 & 1-v_j\xi_3 & 0 & 0 & v_j\xi_2(1-\xi_3) & v_j\xi_1(1-\xi_3) & 0 & v_j\xi_1\xi_2(1-\xi_3) \\ 0 & 0 & 1-v_j\xi_2 & 0 & v_j(1-\xi_2)\xi_3 & 0 & v_j\xi_1(1-\xi_2) & v_j\xi_1(1-\xi_2)\xi_3 \\ 0 & 0 & 0 & 1-v_j\xi_1 & 0 & v_j(1-\xi_1)\xi_3 & v_j(1-\xi_1)\xi_2 & v_j(1-\xi_1)\xi_2\xi_3 \\ 0 & 0 & 0 & 0 & 1-v_j+v_j(1-\xi_2)(1-\xi_3) & 0 & 0 & v_j\xi_1(1-\xi_2)(1-\xi_3) \\ 0 & 0 & 0 & 0 & 0 & 1-v_j+v_j(1-\xi_1)(1-\xi_3) & 0 & v_j(1-\xi_1)\xi_2(1-\xi_3) \\ 0 & 0 & 0 & 0 & 0 & 0 & 1-v_j+v_j(1-\xi_1)(1-\xi_2) & v_j(1-\xi_1)(1-\xi_2)\xi_3 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1-v_j+v_j(1-\xi_1)(1-\xi_2)(1-\xi_3) \end{pmatrix} \tag{8}$$

The parameters were estimated by maximizing the log-likelihood defined in (9).

$$\ell(\boldsymbol{v}, \boldsymbol{\zeta}, \boldsymbol{\varepsilon_1}, \boldsymbol{\varepsilon_2}, \boldsymbol{\varepsilon_3}, \boldsymbol{\omega_1}, \boldsymbol{\omega_2}, \boldsymbol{\omega_3} | n_{11}, \ldots, n_{18}, n_{21}, \ldots, n_{m8}) = \sum_{j=1}^{m}\sum_{k=1}^{8} n_{jk}(t_0)\ \log(g_{jk}(t_0)) + n_{j+t_1-t_0k}(t_1) \log\left(g_{j+t_1-t_0}(t_1, t_0)\right) \tag{9}$$

The standard error for the parameter estimates of all models fitted were obtained by taking the square root of the inverse of the hessian matrix. Again, the probabilities were transformed to the real number scale by using the logit transformation. Thus, the 95% Wald pointwise confidence interval (CI) is presented for each parameter estimate. All analyses were conducted in R (codes available in Appendix 4).

5. Results

When comparing the models fitted without taking loss of immunity into account, the best models were the RCS model with five and three knots for the 2002 and 2006 data, respectively, according to both AIC and BIC (Table 3). Thus, these models were used for further comparisons with the saturated and waning models.

Table 3. AIC, BIC and –2 log-likelihood of the saturated model and RCS models for the joint exposure probabilities, Belgium, 2002 and 2006.

Marginal exposure probability	Number of parameters	AIC	BIC	-2ℓ
2002				
Saturated model	54	2786.247	2792.205	2636.247
Age independence	3	2798.016	2799.923	2750.016
Simple linear predictor	6	2769.343	2771.488	2715.343
RCS with 3 knots	9	2768.161	2770.545	2708.161
RCS with 4 knots	12	2752.494	2755.115	2686.494
RCS with 5 knots	15	2746.977	2749.837	2674.977
2006				
Saturated model	54	3307.177	3313.135	3157.177
Age independence	3	3273.687	3275.593	3225.687
Simple linear predictor	6	3270.344	3272.489	3216.344
RCS with 3 knots	9	3269.481	3271.865	3209.481
RCS with 4 knots	12	3274.495	3277.117	3208.495
RCS with 5 knots	15	3277.056	3279.916	3205.056

Location of the knots: RCS model with 3 knots: 2.7, 9.5, 16.3; RCS model with 4 knots: 1.85, 6.95, 12.05, 17.15; RCS model with 5 knots: 1.85, 5.68, 9.50, 13.33, 17.15

When comparing the 2002 and 2006 vaccination coverage estimated according to the saturated model among the birth cohorts of 1984 to 2001, a similar trend over all the birth cohorts is observed, except for children of the 2001 and 1990 cohorts. Children born in 2001 presented a low MMR vaccination coverage in 2002 (47%, 95%CI=0.35; 0.59), but since they are compared with children with five years of age in 2006, they presented a higher vaccination coverage in 2006 (0.91%, 95%CI=0.84; 0.95), as expected, since the first dose of MMR vaccine was recommended for children during the first year of life (15 months of age). Children born in 1990 were 11 years in 2002, suggesting a possible effect of the second MMR dose, since those children were 15 years in 2006, and the vaccination coverage increased from 0.73% (95%CI=0.55; 0.85) in 2002 to 0.97 (95%CI=0.91; 0.99) in 2006. Finally, it is important to notice that there is a decrease in the vaccination coverage for the

birth cohort of 1993 followed by an increase, which represents the children with 9 years of age in 2002 (one year before the second dose of MMR vaccine is recommended) (Figure 3). The following increase may represent the effect of the second MMR dose.

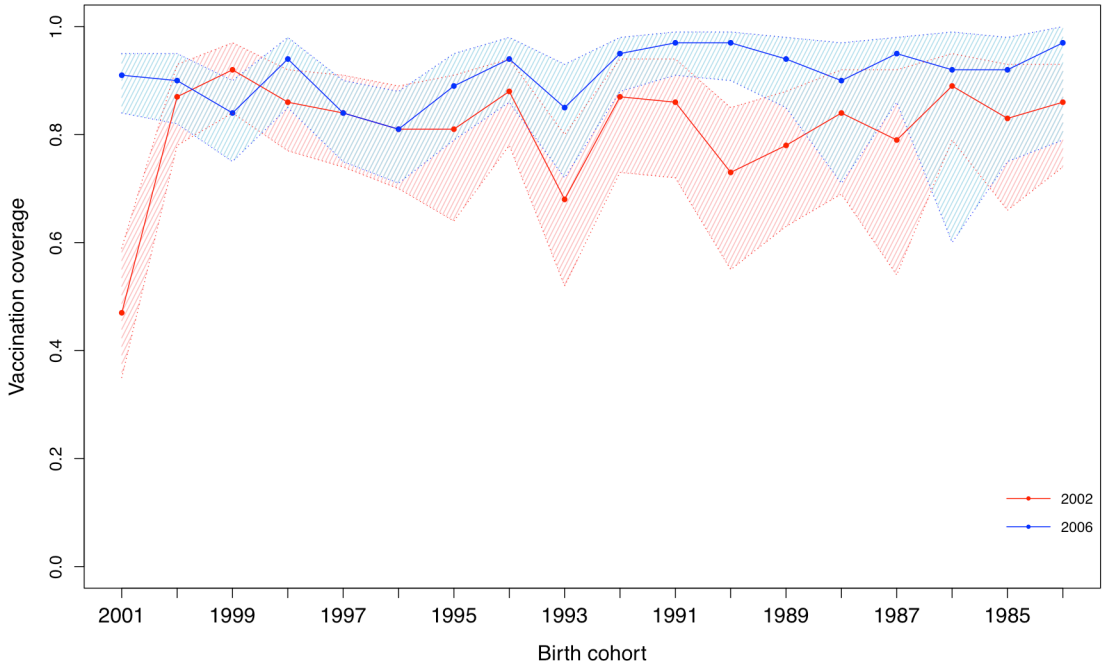


Figure 3. Estimated vaccination coverage for the saturated model (shaded area indicates the 95% pointwise Wald confidence interval). Belgium, 2002 and 2006.

The estimated vaccination coverage for both models ignoring waning – saturated and RCS models – were very similar for both 2002 and 2006 data (Figure 4). However, when taking loss of immunity into account, lower vaccination coverage point estimates for birth cohorts of 1996 to 2000 (2 to 6 years children) and 1988 (14 years) are observed, suggesting a possible overestimation of the vaccination coverage for these birth cohorts when waning is not included in the model. For the other older age groups, the point estimates of vaccination coverage for the waning model were larger than the other two models. However, these results should not be overinterpreted, given the uncertainty in the data (overlap of the pointwise 95% CI of the vaccination coverage estimates).

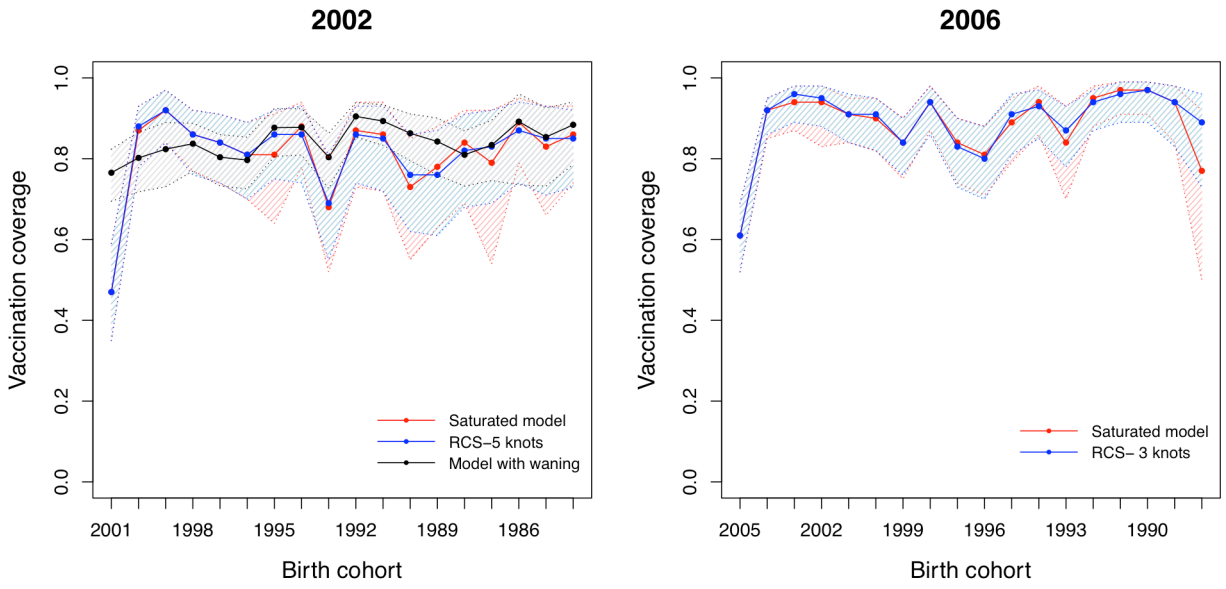


Figure 4. Estimated vaccination coverage for the saturated model, RCS model with five knots and the waning model for the 2002 data (left panel) and for the saturated model and the RCS model with three knots for the 2006 data (right panel). The shaded area indicates the 95% pointwise Wald confidence interval.

Table 4 shows the estimated seroconversion rates according to the saturated, RCS, and waning models for the 2002 and 2006 data from Belgium. No difference in the seroconversion rates for each disease was observed for the saturated and RCS models within the 2002 and 2006 serological surveys. However, a significant decrease in the seroconversion rates for measles and an increase for mumps is observed when comparing 2002 and 2006 data without taking waning into account. According to these models, the lowest seroconversion rate was obtained for mumps in 2002 (85%), but for measles in 2006 (91%). Despite the observed low seroconversion for mumps when loss of immunity is included in the model, in line with the 2002 seroconversion rates estimates, the waning model estimates suggest an underestimation of the seroconversion rates for mumps by the saturated and RCS models for the 2002 data.

Table 4. Seroconversion rates for measles, mumps, and rubella for the saturated, RCS, and waning models, Belgium, 2002 and 2006.

Model	Measles		Mumps		Rubella	
	ζ_1	95% CI	ζ_2	95% CI	ζ_3	95% CI
2002						
Saturated Model	0.99	0.96; 0.99	0.85	0.82; 0.88	0.99	0.97; 1.00
RCS – 5 knots	0.99	0.96; 0.99	0.85	0.82; 0.88	0.99	0.97; 1.00
2006						
Saturated Model	0.91	0.89; 0.92	0.94	0.93; 0.96	0.98	0.97; 0.99
RCS – 3 knots	0.90	0.88; 0.92	0.94	0.92; 0.95	0.98	0.97; 0.99
Waning model	0.98	0.96; 0.99	0.92	0.90; 0.94	0.99	0.98; 1.00

RCS: Restricted cubic splines model; ζ: Seroconversion rates; 95%CI: Pointwise 95% confidence interval

The plots for the exposure probabilities estimated by the saturated and RCS models for the 2002 and 2006 Belgian data are presented in Figure 5. The saturated model for the 2002 data suggests an increasing trend of the exposure probability over age (birth cohort). In the saturated model for the 2006 data, this trend is not very clear, although it seems to be true for mumps and rubella for children born between 1988 and 1990. The comparison between the saturated and the RCS models for both 2002 and 2006 data shows that the fitted profiles from the RCS models are smoother with narrower 95% pointwise CIs than the saturated models. Again, the exposure probabilities seem to be larger in older birth cohorts, with the birth cohort of highest exposure probability varying among the three diseases: 1992 for measles and 1988 for mumps and rubella for the 2002 data, and 1995 for measles and 1988 for mumps and rubella for the 2006 data. The RCS models suggest that the pattern of the exposure probabilities for measles differ from mumps and rubella, i.e., unvaccinated teenagers born from 1985 to 1990 and born from 1988 to 1991 for the 2002 and 2006 data, respectively, are more likely to have acquired past infection with either mumps or rubella than measles.

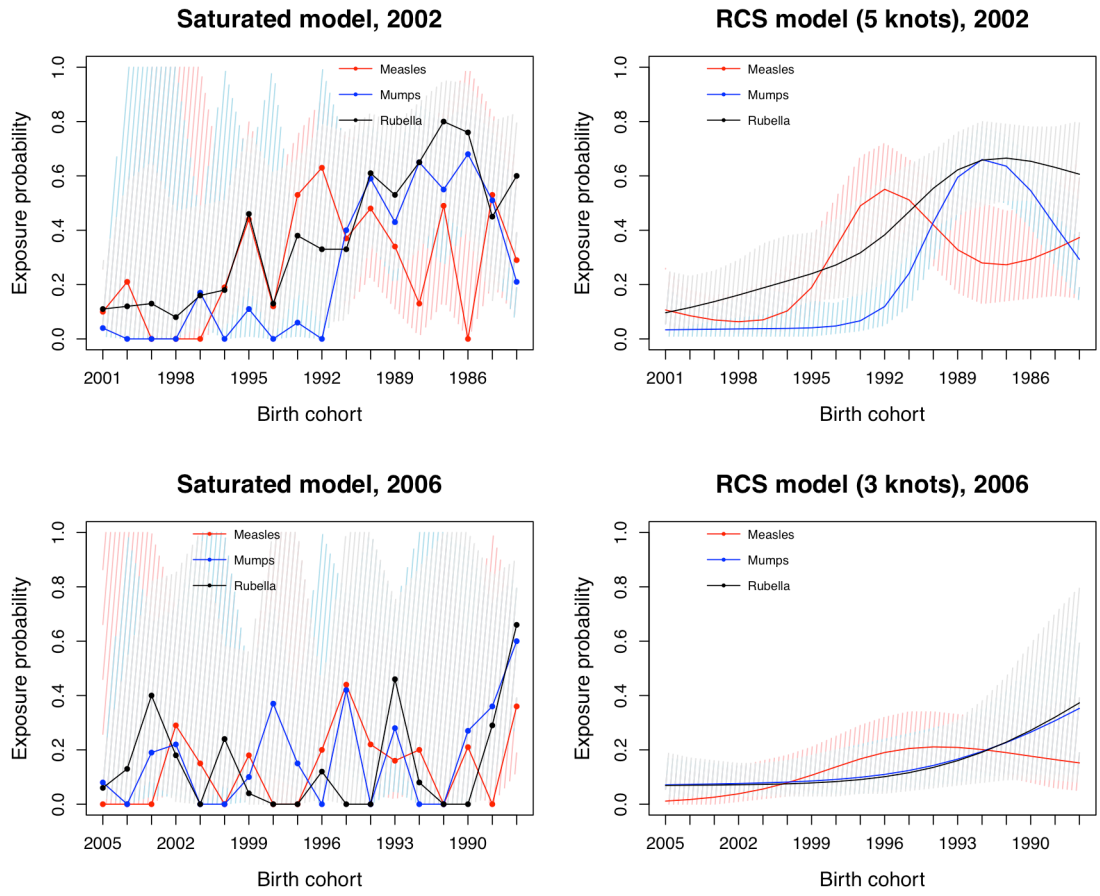


Figure 5. Estimated exposure probability for measles, mumps, and rubella, for the saturated and RCS models with 5 knots for the 2002 data (upper panel) and for the saturated and RCS models with 3 knots for the 2006 data (lower panel). The shaded area indicates the 95% pointwise Wald confidence interval.

The mean annual exposure probabilities estimated by the waning model for each birth cohort is presented in Figure 6. The estimated exposure probabilities for the 2002 and 2006 data show different patterns: while for the 2002 data the exposure probabilities for all birth cohorts are close to zero, except for the 1994 birth cohort for mumps, which presented a mean annual exposure probability close to one, for the 2006 data, an increasing trend over birth cohort is observed, with highest point estimates for the 1986 birth cohort.

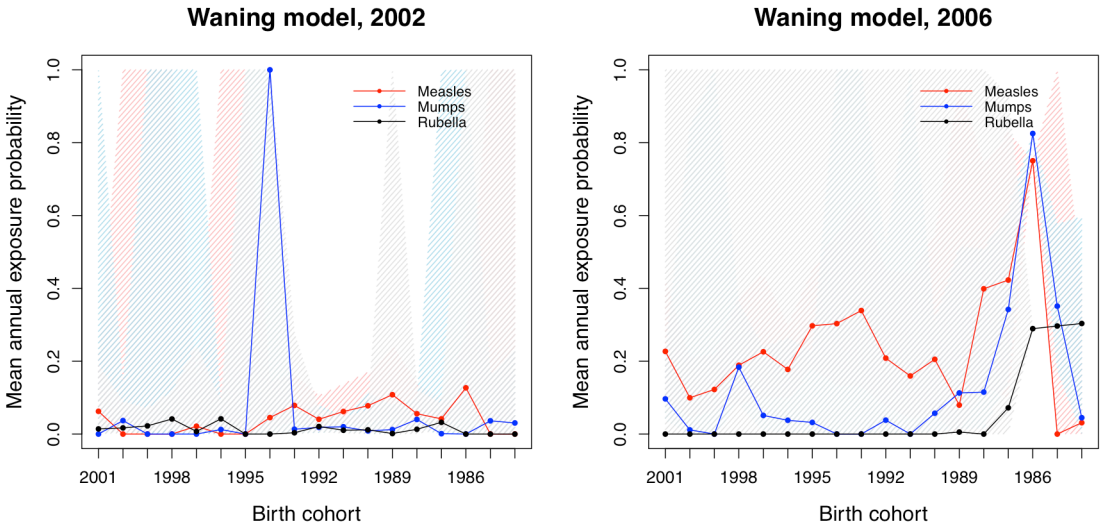


Figure 6. Estimated mean annual exposure probability since vaccination for measles, mumps, and rubella, for the waning model for 2002 (left panel) and 2006 (right panel) data. The shaded area indicates the 95% pointwise Wald confidence interval.

The estimated mean annual waning rates were ω_1=0.0050 (95%CI=0.0036; 0.0071), ω_2=0.0045 (95%CI=0.0032; 0.0064), ω_3=0 for measles, mumps, and rubella, respectively. Given the low estimates for the mumps waning rate obtained as compared to waning rates found in the literature (ω_2=0.035, 95%CI=0.022;0.056) (see e.g. Wood, Goeyvaerts, and Hens, unpublished manuscript), a sensitivity analysis with fixed waning rates was conducted in the next section.

6. Sensitivity analysis

By ignoring waning, the vaccination coverage is expected to be underestimated by the saturated and RCS models (Goeyvaerts et al., 2012). However, this was not systematically observed (i.e., not observed for the 1996 to 2000 birth cohorts), although the difference was not statistically significant.

Also, the estimated annual waning rates were lower than expected. As a sensitivity analysis, the waning model with fixed waning rates and seroconversion rates, as estimated by the model applied to the Australian data (ω_1= 0.005; ω_2= 0.035; ω_3=0.002; ζ_1=0.95; ζ_2=0.90; ζ_3=0.99) (Wood, Goeyvaerts, and Hens, unpublished manuscript), was fitted and the estimated vaccination coverage is presented in Figure 7 (the point estimates for all the

parameters for the fixed waning model is presented in the Appendix 1). By fixing the seroconversion rates and mean annual waning rates, the vaccination coverage point estimates of the waning model were larger or closer to the estimates of the saturated model as compared to the waning model with free parameters, except for the birth cohort of 1999.
Also, the estimates for both the saturated and waning models are close to the vaccination coverage estimates for the first MMR dose for the corresponding birth cohorts of 2000, 1994, and 1988 from retrospective Epi-surveys conducted in Flanders (Belgium) in 2005 and 2008 (Vandermeulen et al., 2008; Theeten et al., 2009; Theeten et al., 2007).

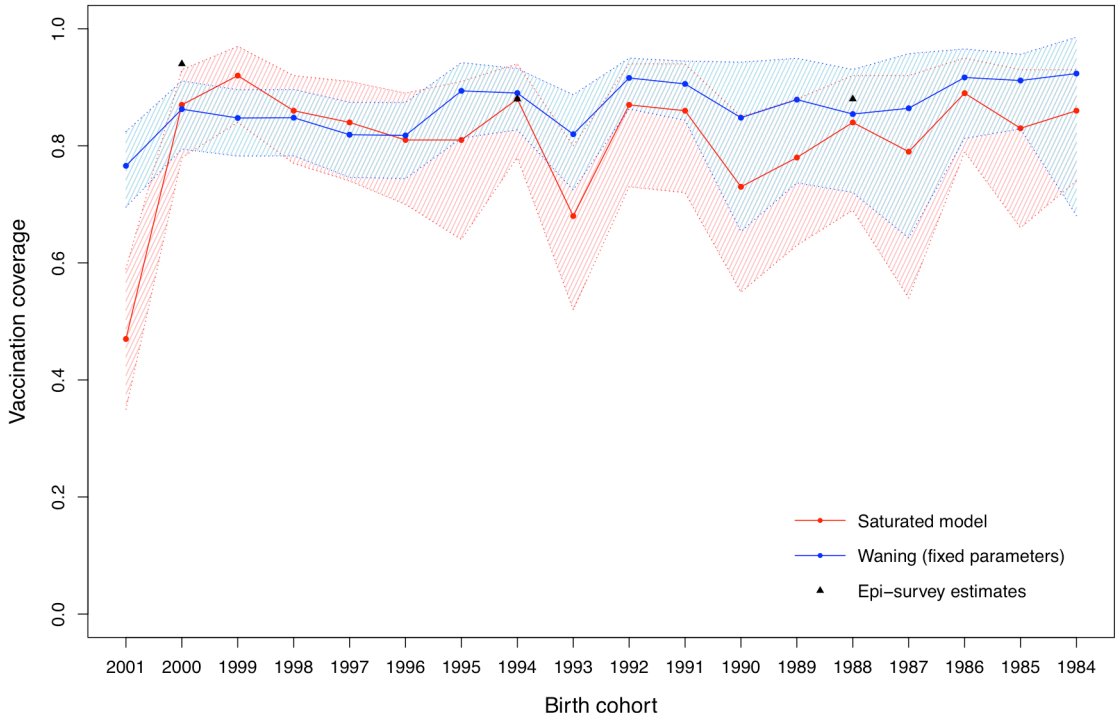


Figure 7. Estimated vaccination coverage for the 2002 saturated model (red line) and waning model (blue line) with fixed seroconversion rates (ζ_1=0.95; ζ_2=0.90; ζ_3=0.99) and waning parameters (ω_1= 0.005; ω_2= 0.035; ω_3=0.002). The black triangles indicate the Epi-survey estimates for the first MMR dose from the Flanders region and the shaded area indicates the pointwise 95% Wald confidence interval.

7. Discussion

In this report, the existing methods for estimating the vaccination coverage from serological surveys were applied to the 2002 and 2006 serological data from Belgium. First, the original saturated model proposed by Gay was fitted, with 75 parameters estimated in total. More parsimonious models for the exposure probabilities as proposed by Goeyvaerts et al. (2012) were also fitted, with 36 and 30 parameters for the 2002 (RCS model with 5 knots) and 2006 (RCS model with 3 knots) data, respectively, showing a smoother and better fit according to AIC and BIC as compared to the saturated models. Finally, since two serological surveys were available for Belgium, these models were extended by relaxing the assumption that the

MMR vaccine confers long-lasting immunity, which is known not to be true for the MMR diseases (Rouderfer, Becker, and Hethcote, 1994; Wood et al., 2009; Brockhoff et al., 2010; Johnson et al., 1996). The model proposed by Wood, Goeyvaerts, and Hens (unpublished manuscript) additionally allowed the estimation of disease-specific waning parameters, representing the loss of immunity over time.

The 2002 and 2006 serological results differ with respect to some immunity states. While in the 2002 data a high proportion of children with seronegative results for mumps, but seropositive for measles and rubella was observed, in the 2006 data, a high proportion of individuals with seronegative results for measles, but seropositive for mumps and rubella was found. These results are contradictory, since no change in the MMR vaccine composition was reported during the period (Theeten, 2011). The difference in the serological results of the two data can explain the difference in the estimated seroconversion rates for 2002 and 2006: lowest seroconversion rates for mumps in 2002 but for measles in 2006.

Furthermore, the waning model suggests an underestimation of the seroconversion rate for mumps by the models fitted to the 2002 data. In other words, while by taking waning immunity into account the seroconversion rates for measles and rubella are not affected, an increase of the seroconversion for mumps is observed. Again, this difference may reflect the difference of the response variables (immunity states) in the 2002 and 2006 data, since in 2006 a larger seroconversion rate for mumps was observed as compared to 2002.

The higher vaccination coverage estimates for most of the older birth cohorts according to the waning model as compared to the saturated and RCS models suggests the presence of waning, i.e., ignoring waning results in an underestimation of the true vaccination coverage. However, this was not the case for the birth cohorts of 1997 to 2000, even after fixing the waning rates and the seroconversion rates in the sensitivity analysis. A possible explanation of these unexpected results may be the difference in some immunity states, as previously pointed out. Moreover, all models suggest insufficient vaccination coverage – lower than the 2015 WHO target of at least 90% coverage for children with one year of age to eliminate measles (WHO, 2012).

The estimated vaccination coverage obtained from all models was close to the estimated immunization coverage for the first MMR dose obtained by face-to-face Epi-surveys conducted in the region of Flanders in 2005 and 2008 for the birth cohorts of 1989, 1995, and 2001, representing children with 14 (Vandermeulen et al., 2008), 7 (Theeten et al., 2009), and 2 (Theeten et al., 2007) years of age. This similarity suggests that the fitted models might be valid to estimate the vaccination coverage, even with some strong assumptions made to improve convergence and restrict the complexity of the model, such as excluding other covariates from the models and assuming independency between the exposure probabilities.

For the models ignoring waning, the exposure probabilities seem to increase over age for both 2002 and 2006 data. The higher exposure probabilities observed for the older age cohorts may be because of the accumulating risk of exposure with age (Goeyvaerts et al.,

2012). The difference in the behavior of the exposure probabilities estimated by the models including and ignoring waning can be explained by the difference in the definition of the exposure probabilities in the models, since the in the waning model we referred to the mean annual exposure probability after vaccination and in the models ignoring waning the exposure probability represent the cumulative exposure probability from birth.

An extension of Gay's saturated model, relaxing the assumption of disease-independent exposure to infection was also proposed by Goeyvaerts et al. (2012), since the three diseases share the same transmission (airborne route). They also allowed for the dependency between seroconversion rates, applying the method to the data from serological surveys conducted in Ireland (2003) and Belgium (2002). The Bahadur model was fitted to assess the correlations between the trivariate response variables. Nonetheless, the Bahadur model was not fitted in this report, since the results obtained from Goeyvaerts et al. (2012) showed only small positive pairwise between-disease correlation with several difficulties to achieve convergence, due to the large number of parameters estimated. This difficulty could be even worse for the waning model fitted here, given the larger number of parameters (132 parameters) estimated compared to the saturated model (75 parameters).

As probably another consequence of the difference in the immunity states results for the two serological surveys, the estimated mean waning rate for mumps was lower than the rate estimated for the Australian data. One could argue that the 2006 data results may not be reliable, since these serological results were different than expected. However, the inspection of the disease-specific proportion of seropositive results for each birth cohort shows a substantial increase in the point estimates for the 1988 to 1994 birth cohorts in the 2006 data, although not statistically significant (see plot in the Appendix 2). As indicated in the Lexis diagram (Figure 2), these cohorts correspond to the children who are eligible to receive the second dose of MMR vaccine in the year of the 2002 serological survey (1988 to 1991 birth cohorts) or in the year of the 2006 serological survey (1992 to 1995 birth cohorts). Thus, this increase is expected and the decrease observed for the other age cohorts is suggestive of waning immunity, indicating no reliability problem with the 2006 data.

Another possible explanation for the difference observed in the results of the two serological surveys is the degree of comparability between the two surveys, since they were conducted in different time points. In order to assess it, the proportion of subjects according to gender, region, and birth cohort were compared by the Pearson chi-square test (see Appendix 3). Indeed, there was a difference in the proportion of subjects sampled by region and birth cohorts in the two serological surveys.

Finally, the MATLAB codes used for the estimation of vaccination coverage by the waning model in Australia were provided by the authors (Wood, Goeyvaerts, and Hens, unpublished manuscript) and adapted to the Belgian data and written in R language. The codes used for both analyses, including three and two serological surveys for Australian and Belgian data, respectively, are readily available for public use in free software.

8. Conclusions and recommendations

The vaccination coverage estimated by the three models for the two serological surveys suggest insufficient immunization coverage for the MMR vaccine to achieve the WHO target of measles elimination (WHO, 2012). Thus, the results can be useful to guide the public health strategies to achieve the WHO target by 2015.

Given the low mean annual waning rate estimates for mumps for Belgium, the inclusion of the second MMR dose, relaxing the assumption that the individuals receive no more than one dose of the vaccine, and other covariates that are potential confounders, such as region, is recommended. The effect of the second dose of the MMR vaccine may have lead to overestimated vaccination coverage estimates, but this is limited to birth cohorts before 1992 (higher than 10 years old – lower bound age recommended for the second dose of MMR vaccine).

Another extension of the models fitted is the inclusion of the equivocal results in the analysis under the assumption of missing at random as performed for the analysis of the Australia data (Wood, Goeyvaerts, and Hens, unpublished manuscript), which can lead to more precise estimates, especially for the waning rates. Although several extensions are possible, the estimation of new parameters increases the complexity of the model, which may also lead to sparseness and consequently to convergence problems. Thus, an alternative to the likelihood approach would be the use of Bayesian methodology. Finally, the model can be applied to the estimation of vaccination coverage of other multistrain vaccines, such as the human papillomavirus and the MMR vaccine with the varicella component.

9. References

Altmann, D., and Altmann, K. (2000). Estimating vaccine coverage by using computer algebra. *The Institute of Mathematics and its Applications Journal of Mathematics Applied in Medicine and Biology*, **17**: 137-146.

Brockhoff, H., J., Mollema, L., Sonder, G., J., B., Postema, C., A., Binnendijk, R., S., Kohl, R., et al. (2010). Mumps outbreak in a highly vaccinated student population, The Netherlands, 2004. *Vaccine*, **28**: 2932-2936.

Dannetun, E., Tegnell, A., Hermansson, G., Torner, A., Giesecke, J. (2004). Timeliness of MMR vaccination—influence on vaccination coverage. *Vaccine*, **24**: 4228-4232.

Demicheli V., Jefferson T., Rivetti A., Price D. (2005). Vaccines for measles, mumps and rubella in children. *Cochrane Database of Systematic Reviews*, **4**:1-45.

Goeyvaerts, N., Hens, N., Theeten, H., Aerts, M., Van Damme, P., Beutels, P. (2012). Estimating vaccination coverage for the trivalent measles-mumps-rubella vaccine from trivariate serological data. *Statistics on Medicine*, **31**: 1432-1449.

Harrell, F. E. (2001). *Regression modeling strategies with applications to linear models, logistic regression, and survival analysis*. Springer Series in Statistics. New York: Springer.

Johnson, C., E., Kumar, M., L., Whitwell, J., K., Staehle, B., O., Rome, L., P., Dinakar, C., et al. (1996). Antibody persistence after primary measles-mumps-rubella vaccine and response to a second dose given at four to six vs. eleven to thirteen years. *Pediatric Infectious Disease Journal*, **15** (8): 687-692.

Kafatos, G., Andrews, N., Nardone, A. (2005). Model selection methodology for inter-laboratory standardisation of antibody titres. *Vaccine*, **23**: 5022-5027.

Omer, S.B., Salmon, D.A., Orenstein, W.A., deHart, M.P., Halsey, N. (2009). Vaccine Refusal, Mandatory Immunization, and the Risks of Vaccine-Preventable Diseases. *The New England Journal of Medicine*, **360**: 1981-1988.

Rouderfer, V., Becker, N., G., and Hethcote, H., W. (1994). Waning immunity and its effect on vaccination schedules. *Mathematical Biosciences*, **194**:59-82.

Theeten, H. (2011). *Assessment of immunization programs through serological surveys and immunization coverage studies - Implications for vaccination policy in Flanders, Belgium*. Dissertation for the degree of doctor in Medical Science, University of Antwerp, Belgium.

Theeten, H., Hens, N., Vandermeulen, C., Depoorter, A.M., Roelants, M., Aerts, M., Hoppenbrouwers, K., Van Damme, P. (2007). Infant vaccination coverage in 2005 and predictive factors for complete or valid vaccination in Flanders, Belgium: an EPI-survey. *Vaccine*, **25**: 4940-4948.

Theeten, H., Hutse, V., Hens, N., Yavuz, Y., Hoppenbrouwers, K., Beutel, P., et al. (2011). Are we hitting immunity targets? The 2006 age-specific seroprevalence of measles, mumps, rubella, diphtheria and tetanus in Belgium. *Epidemiology and Infection*, **139** (4): 494-504.

Theeten, H., Vandermeulen, C., Roelants, M., Hoppenbrouwers, K., Depoorter, A.M., Van Damme, P. (2009). Coverage of recommended vaccines in children at 7–8 years of age in Flanders, Belgium. *Acta Pædiatrica*, **98**: 1307–1312.

Vandermeulen, C., Roelants, M., Theeten, H., Depoorter, A.M., Van Damme, P. Hoppenbrouwers, K. (2008). Vaccination Coverage in 14-Year-Old Adolescents: Documentation, Timeliness, and Sociodemographic Determinants. *Pediatrics*, **121**: e428-e434.

Vellinga, A., Depoorter, A.M., and Van Damme, P. (2002). Vaccination coverage estimates by EPI cluster sampling survey of children (18–24 months) in Flanders, Belgium. *Acta Paediatrica*, **91**: 599-603.

Vyse, A.J., Gay, N.J., White, J.M., Ramsay, M.E., Brown, D.W.G., Cohen, B. J., , et al. (2002). *Epidemiologic Reviews*, **24**: 125-136.

Wood, J., Gidding, H., F., Heywood, A., Macartney, K., McIntire, P., B., MacIntire, C., R. (2009). Potential impacts of schedule changes, waning immunity and vaccine uptake on measles elimination in Australia. *Vaccine*, **27**: 313-318.

Wood, J., Goeyvaerts, N., and Hens, N. (Unpublished manuscript). *Estimating vaccination coverage from Australian serological data.*

World Health Organization. (2005). *Immunization coverage cluster survey – Reference Manual*. Geneva, Switzerland. Accessed on 28/07/2013. Available at <http://whqlibdoc.who.int/hq/2005/WHO_IVB_04.23.pdf>

World Health Organization. (2012). Global measles and rubella strategic plan: 2012-2020. Assessed on 03/09/2013. Available at < http://www.who.int/immunization/newsroom/Measles_Rubella_StrategicPlan_2012_2020.pdf >.

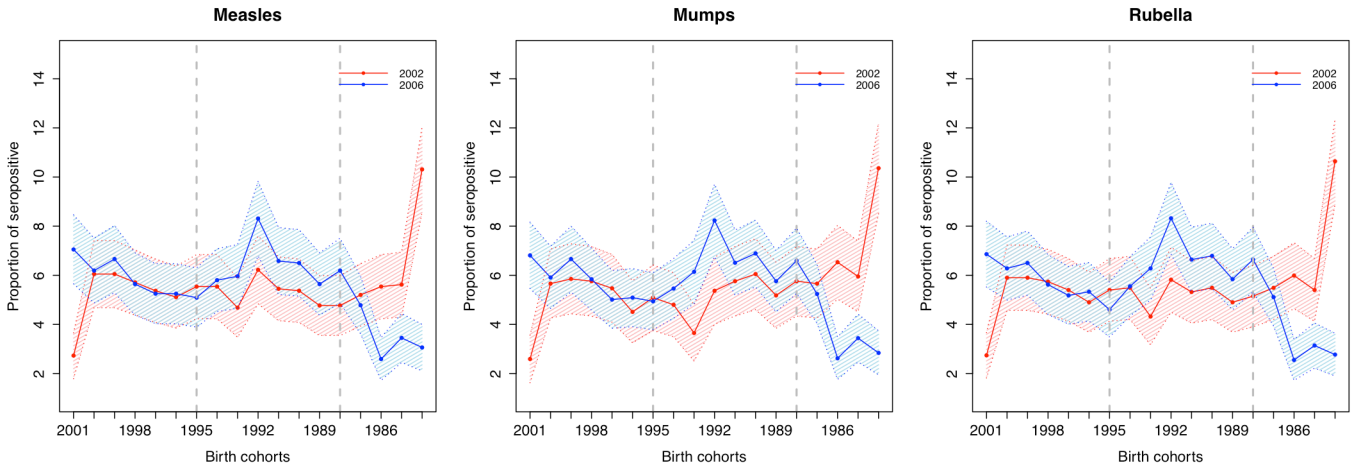
10. Appendix

Appendix 1. Maximum likelihood estimates for the vaccination coverage (ν), seroconversion rate (ζ), exposure probability (η), mean annual exposure probability (ε), and waning rates (ω) according to the saturated and waning models. Belgium, 2002 and 2006.

Birth cohort	2002 (Saturated model)				2006 (Saturated model)				2002 (Waning model)				2002 (Waning - fixed ζ and ω)			
	ν	η_1	η_2	η_3	ν	η_1	η_2	η_3	ν	ε_1	ε_2	ε_3	ν	ε_1	ε_2	ε_3
2001	0.47	0.10	0.04	0.11	0.91	0.23	0.00	0.00	0.77	0.06	0.00	0.01	0.77	0.04	0.05	0.01
2000	0.87	0.21	0.00	0.12	0.85	0.31	0.19	0.36	0.80	0.00	0.04	0.02	0.86	0.14	0.00	0.11
1999	0.92	0.00	0.00	0.13	0.81	0.29	0.22	0.05	0.82	0.00	0.00	0.02	0.85	0.00	0.00	0.00
1998	0.86	0.00	0.00	0.08	0.92	0.29	0.51	0.00	0.84	0.00	0.00	0.04	0.85	0.07	0.00	0.00
1997	0.84	0.00	0.17	0.16	0.83	0.09	0.20	0.00	0.80	0.02	0.00	0.01	0.82	0.00	0.05	0.00
1996	0.81	0.19	0.00	0.18	0.79	0.26	0.07	0.13	0.80	0.00	0.01	0.04	0.82	0.00	0.00	0.01
1995	0.81	0.44	0.11	0.46	0.88	0.55	0.50	0.00	0.88	0.00	0.00	0.00	0.89	0.00	0.00	0.03
1994	0.88	0.12	0.00	0.13	0.92	0.45	0.23	0.00	0.88	0.05	1.00	0.00	0.89	0.02	0.00	0.00
1993	0.68	0.53	0.06	0.38	0.82	0.28	0.36	0.47	0.80	0.08	0.01	0.00	0.82	0.00	0.03	0.04
1992	0.87	0.63	0.00	0.33	0.92	0.38	0.26	0.16	0.90	0.04	0.02	0.02	0.92	0.00	0.03	0.00
1991	0.86	0.37	0.40	0.33	0.96	0.28	0.21	0.00	0.89	0.06	0.02	0.01	0.91	0.05	0.10	0.00
1990	0.73	0.48	0.59	0.61	0.97	0.29	0.00	0.00	0.86	0.08	0.01	0.01	0.85	0.08	0.09	0.02
1989	0.78	0.34	0.43	0.53	0.94	0.00	0.35	0.15	0.84	0.11	0.01	0.00	0.88	0.04	0.09	0.01
1988	0.84	0.13	0.65	0.65	0.88	0.25	0.38	0.30	0.81	0.06	0.04	0.01	0.85	0.07	0.09	0.00
1987	0.79	0.49	0.55	0.80	0.8	0.41	0.74	0.67	0.83	0.04	0.00	0.03	0.86	0.09	0.09	0.01
1986	0.89	0.00	0.68	0.76	0.89	0.48	0.62	0.49	0.89	0.13	0.00	0.00	0.92	0.11	0.15	0.00
1985	0.83	0.53	0.51	0.45	0.76	0.76	0.85	0.57	0.85	0.00	0.04	0.00	0.91	0.05	0.21	0.00
1984	0.86	0.29	0.21	0.60	0.95	0.86	0.52	0.00	0.88	0.00	0.03	0.00	0.92	0.05	0.11	0.02

Seroconversion rates:
2002: ζ_1=0.99, ζ_2=0.85, ζ_3=0.99;
2006: ζ_1=0.87, ζ_2=0.94, ζ_3=1.00;
Waning model: ζ_1=0.98, ζ_2=0.92, ζ_3=0.99;
Waning (fixed): ζ_1=0.95, ζ_2=0.90, ζ_3=0.99;
Waning rates:
Waning model: ω_1=0.0050, ω_2=0.0045, ω_3=0
Waning (fixed): ω_1=0.005, ω_2=0.035, ω_3=0.002

Appendix 2. Proportion of disease-specific seropositive results (gray dashed lines indicates the birth cohorts eligible to receive the second MMR dose between the 2002 and 2006 serological surveys). Belgium, 2002 and 2006.



Appendix 3. Demographic characteristics of the study participants. Belgium, 2002 and 2006.

Characteristic	2002		2006		χ^2	p-value
	n	%	n	%		
Gender						
Male	687	50.4	725	48.0	1.59	0.2078
Female	676	49.6	786	52.0		
Region						
Flanders	892	65.4	867	57.4	19.86	<0.0001
Wallonia	375	27.6	505	33.4		
Brussels	96	7.0	139	9.2		
Birth cohort						
1984	136	10.0	40	2.6	112.81	<0.0001
1985	72	5.3	48	3.2		
1986	74	5.4	37	2.4		
1987	69	5.1	75	5.0		
1988	66	4.8	99	6.6		
1989	66	4.8	84	5.6		
1990	74	5.4	96	6.4		
1991	71	5.2	95	6.3		
1992	77	5.6	122	8.1		
1993	65	4.8	95	6.3		
1994	74	5.4	83	5.5		
1995	73	5.4	72	4.8		
1996	71	5.2	89	5.9		
1997	75	5.5	86	5.7		
1998	80	5.9	84	5.6		
1999	77	5.6	108	7.1		
2000	80	5.9	95	6.3		
2001	63	4.6	103	6.8		

Appendix 4. R codes

```
################################
# 1. Saturated and RCS models #
################################

# Trivariate probabilities ------------------------------------------------
pjvec<-function(vj,pij1,pij2,pij3,etaj1,etaj2,etaj3)
{
  pj1=vj*pij1*pij2*pij3+(1-vj)*etaj1*etaj2*etaj3
  pj2=vj*pij1*pij2*(1-pij3)+(1-vj)*etaj1*etaj2*(1-etaj3)
  pj3=vj*pij1*(1-pij2)*pij3+(1-vj)*etaj1*(1-etaj2)*etaj3
  pj4=vj*pij1*(1-pij2)*(1-pij3)+(1-vj)*etaj1*(1-etaj2)*(1-etaj3)
  pj5=vj*(1-pij1)*pij2*pij3+(1-vj)*(1-etaj1)*etaj2*etaj3
  pj6=vj*(1-pij1)*pij2*(1-pij3)+(1-vj)*(1-etaj1)*etaj2*(1-etaj3)
  pj7=vj*(1-pij1)*(1-pij2)*pij3+(1-vj)*(1-etaj1)*(1-etaj2)*etaj3
  pj8=vj*(1-pij1)*(1-pij2)*(1-pij3)+(1-vj)*(1-etaj1)*(1-etaj2)*(1-etaj3)
  return(list(pj1=pj1,pj2=pj2,pj3=pj3,pj4=pj4,pj5=pj5,pj6=pj6,pj7=pj7,pj8=pj8))
}

# Probability for a vaccinated individual in age class j of being seropositive for
disease d ---------------------------------------------
pijd<-function(xijd,etajd){return(xijd+(1-xijd)*etajd)}

# Transformations: canonical link functions -------------------------------
logit<-function(p){return(log(1e-5+p/(1-p)))}
expit<-function(eta){return(exp(eta)/(1+exp(eta)))}

# Log-likelihood for the saturated model ----------------------------------
loglik.gay<-function(data.matrix,allpars){
alpha<- allpars[1:18]
beta1<- allpars[19:36]
beta2<- allpars[37:54]
beta3<- allpars[55:72]
delta1<-allpars[73]
delta2<-allpars[74]
delta3<-allpars[75]
m<-dim(data.matrix)[1]
ll<-rep(NA,m)
for (j in 1:m){
njvec<-as.vector(data.matrix[j,])
vj<-expit(alpha[j])
pij1<-pijd(expit(delta1),expit(beta1[j]))
pij2<-pijd(expit(delta2),expit(beta2[j]))
pij3<-pijd(expit(delta3),expit(beta3[j]))
etaj1<-expit(beta1[j])
etaj2<-expit(beta2[j])
etaj3<-expit(beta3[j])
ll[j]<- sum(njvec*log(1e7+as.vector(unlist(pjvec(vj,pij1,pij2,pij3,etaj1,etaj2,etaj3)))))
}
  return(-sum(ll))
}

# RCS model with 5 knots (2002 data) --------------------------------------
library(splines)
loglik.gay.spline <- function(data.matrix,allpars){
alpha<-allpars[1:18]
m<-dim(data.matrix)[1]
beta1<-approx(seq(1,m,0.1),ns(seq(1,m,0.1),int   =   T,   knots=c(5.68,   9.50,   13.33),
Boundary.knots=c(1.85, 17.15)) %*%matrix (allpars[19:23],ncol=1), seq(1,m,1))$y
beta2<-approx(seq(1,m,0.1),ns(seq(1,m,0.1),int=T,knots=c(5.68,                          9.50,
13.33),Boundary.knots=c(1.85, 17.15))%*%matrix(allpars[24:28],ncol=1),seq(1,m,1))$y
```

```
beta3<-approx(seq(1,m,0.1),ns(seq(1,m,0.1),int=T,knots=c(5.68,                    9.50,
13.33),Boundary.knots=c(1.85,17.15))%*%matrix(allpars[29:33],ncol=1),seq(1,m,1))$y
delta1<-allpars[34]
delta2<-allpars[35]
delta3<-allpars[36]
ll<-rep(NA,m)
for (j in 1:m){
njvec<-as.vector(data.matrix[j,])
vj<-expit(alpha[j])
pij1<-pijd(expit(delta1),expit(beta1[j]))
pij2<-pijd(expit(delta2),expit(beta2[j]))
pij3<-pijd(expit(delta3),expit(beta3[j]))
etaj1<-expit(beta1[j])
etaj2<-expit(beta2[j])
etaj3<-expit(beta3[j])
ll[j]<-sum(njvec*log(1e7+as.vector(unlist(pjvec(vj,pij1,pij2,pij3,etaj1,etaj2,etaj3)))))
}
return(-sum(ll))
}

# RCS model with 3 knots (2006 data) ------------------------------------
library(splines)
loglik.gay.spline <- function(data.matrix,allpars){
alpha<-allpars[1:18]
m<-dim(data.matrix)[1]
beta1<-approx(seq(1,m,0.1),ns(seq(1,m,0.1),int=T,knots=c(5.68,                    9.50,
13.33),Boundary.knots=c(1.85,17.15))%*%matrix(allpars[19:23],ncol=1),seq(1,m,1))$y
beta2<-approx(seq(1,m,0.1),ns(seq(1,m,0.1),int=T,knots=c(5.68,                    9.50,
13.33),Boundary.knots=c(1.85,17.15))%*%matrix(allpars[24:28],ncol=1),seq(1,m,1))$y
beta3<-approx(seq(1,m,0.1),ns(seq(1,m,0.1),int=T,knots=c(5.68,                    9.50,
13.33),Boundary.knots=c(1.85,17.15))%*%matrix(allpars[29:33],ncol=1),seq(1,m,1))$y
delta1<-allpars[34]
delta2<-allpars[35]
delta3<-allpars[36]
ll<-rep(NA,m)
for (j in 1:m){
njvec<-as.vector(data.matrix[j,])
vj<-expit(alpha[j])
pij1<-pijd(expit(delta1),expit(beta1[j]))
pij2<-pijd(expit(delta2),expit(beta2[j]))
pij3<-pijd(expit(delta3),expit(beta3[j]))
etaj1<-expit(beta1[j])
etaj2<-expit(beta2[j])
etaj3<-expit(beta3[j])
ll[j]<-sum(njvec*log(1e-7+as.vector(unlist(pjvec(vj,pij1,pij2,pij3,etaj1,etaj2,etaj3)))))
}
return(-sum(ll))
}

###################
# 2. Waning model #
###################

# Vj matrix ------------------------------------------------------------
trans.mat <- function(x,mu){
x1 = x[1]
x2 = x[2]
x3 = x[3]
r1 = c(1, mu*x3, mu*x2, mu*x1, mu*x2*x3, mu*x1*x3, mu*x1*x2, mu*x1*x2*x3)
r2 = c(0, 1-mu*x3, 0, 0, mu*x2*(1-x3), mu*x1*(1-x3), 0, mu*x1*x2*(1-x3))
r3 = c(0, 0, 1-mu*x2, 0, mu*x3*(1-x2), 0, mu*x1*(1-x2), mu*x1*x3*(1-x2))
r4 = c(0, 0, 0, 1-mu*x1, 0, mu*x3*(1-x1), mu*x2*(1-x1), mu*x2*x3*(1-x1))
r5 = c(0, 0, 0, 0, 1-mu*(x2+x3-x2*x3), 0, 0, mu*x1*(1-x2)*(1-x3))
```

```
r6 = c(0, 0, 0, 0, 0, 1-mu*(x1+x3-x1*x3), 0, mu*x2*(1-x1)*(1-x3))
r7 = c(0, 0, 0, 0, 0, 0, 1-mu*(x1+x2-x1*x2), mu*x3*(1-x1)*(1-x2))
r8 = c(0,0,0,0,0,0,0,1-mu+mu*(1-x1)*(1-x2)*(1-x3))
A = matrix(rbind(r1, r2, r3, r4, r5, r6, r7, r8), nrow = 8, ncol = 8)
return(A)
}

# Log-likelihood ------------------------------------------------------
library(expm)
LogLik <- function(Sdata, param){
const <- c(54,4,0:17)
m = const[1]
Tgap = const[2]
Ind0 = const[3:length(const)]
v1 = exp(param[1:(m/3)])/(1 + exp(param[1:(m/3)]))
v1[is.na(v1)] = 1
vv = rep(v1,2)
s = exp(param[m/3 + (1:3)])/(1 + exp(param[m/3 + (1:3)]))
s[is.na(s)] = 1
e1 = exp(param[(m/3 + 3) + (1:(2*m))])/(1 + exp(param[(m/3 + 3) + (1:(2*m))]))
e = t(matrix(e1, 2*m/3, 3))
e[is.na(e)] = 1
w = exp(param[(7*m/3 + 3) + (1:3)])/(1 + exp(param[(7*m/3 + 3) + (1:3)]))
w[is.na(w)] = 1

# Multinomial probabilities -------------------------------------------
w.90 <- t(trans.mat(w,1))[nrow(trans.mat(w,1)):1,]
W = t(w.90)[nrow(w.90):1,]
X0 = matrix(c(rep(0,7),1), ncol=1, nrow=8)
M = matrix(0, nrow = 8,ncol = 2*m/3) #
In = length(Ind0)
for (i in 1:In){
G = (W %*% trans.mat(e[,i], 1)) %^% Ind0[i]
G1 = (W %*% trans.mat(e[,(In + i)], 1)) %^% Tgap
M[,i] = G %*% trans.mat(s, vv[i]) %*% X0
M[,(i + In)] = G1 %*% M[,i]
}
LL = sum(Sdata * log (M))
return (-sum(LL))
}
```

Auteursrechtelijke overeenkomst

Ik/wij verlenen het wereldwijde auteursrecht voor de ingediende eindverhandeling:
Estimation of vaccination coverage and waning immunity for measles, mumps, and rubella from serological surveys in Belgium, 2002 and 2006

Richting: **Master of Statistics-Biostatistics**
Jaar: **2013**

in alle mogelijke mediaformaten, - bestaande en in de toekomst te ontwikkelen - , aan de Universiteit Hasselt.

Niet tegenstaand deze toekenning van het auteursrecht aan de Universiteit Hasselt behoud ik als auteur het recht om de eindverhandeling, - in zijn geheel of gedeeltelijk -, vrij te reproduceren, (her)publiceren of distribueren zonder de toelating te moeten verkrijgen van de Universiteit Hasselt.

Ik bevestig dat de eindverhandeling mijn origineel werk is, en dat ik het recht heb om de rechten te verlenen die in deze overeenkomst worden beschreven. Ik verklaar tevens dat de eindverhandeling, naar mijn weten, het auteursrecht van anderen niet overtreedt.

Ik verklaar tevens dat ik voor het materiaal in de eindverhandeling dat beschermd wordt door het auteursrecht, de nodige toelatingen heb verkregen zodat ik deze ook aan de Universiteit Hasselt kan overdragen en dat dit duidelijk in de tekst en inhoud van de eindverhandeling werd genotificeerd.

Universiteit Hasselt zal mij als auteur(s) van de eindverhandeling identificeren en zal geen wijzigingen aanbrengen aan de eindverhandeling, uitgezonderd deze toegelaten door deze overeenkomst.

Voor akkoord,

De Carvalho Yokota, Renata Tiene

Datum: **18/09/2013**