Estimating MMR Vaccine Coverage from Australian Sero-surveillance Data

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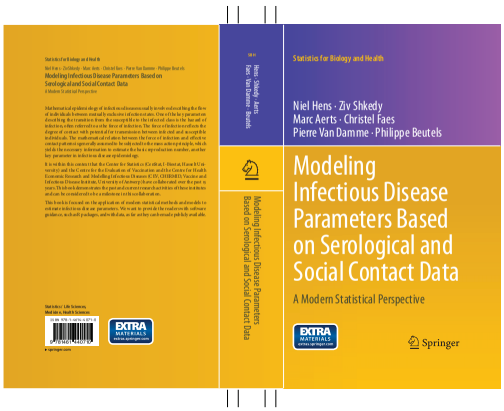
Outline

- Introduction
- Data
- The cohort model
- Simulation study
- Application
- Discussion

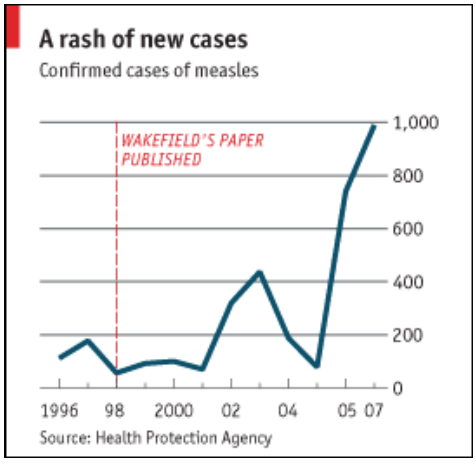
Introduction (1)

- Cross-sectional data:
  - population immunity
  - transmission modelling studies
- Estimates:
  - the force of infection
  - the basic reproduction number
- Goal:
  - getting the most out of available serological data
  - Hens et al. (2012)



Hens, N., Shkedy, Z., Aerts, M., Faes, C., Van Damme, P. and Beutels, P. (2012) Modeling Infectious Disease Parameters Based on Serological and Social Contact Data. Springer-Verlag New York.

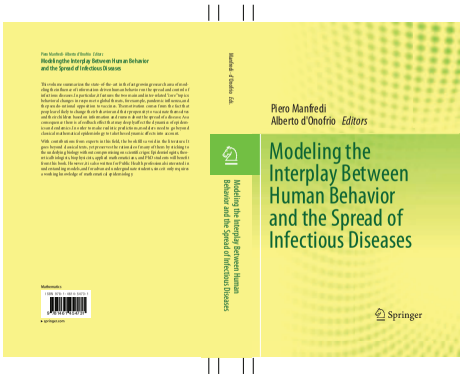
Introduction (2)
Estimating vaccination coverage



Do Vaccines Hurt More Than They Help?

Introduction (3)
Estimating vaccination coverage

- Population surveys
  - e.g. Theeten et al. (2013)



- Trivariate serological data
  - Altmann and Altmann (2000)
  - Nigel Gay (unpub)
  - Goeyvaerts et al. (2012)

Issue: cross-sectional sample

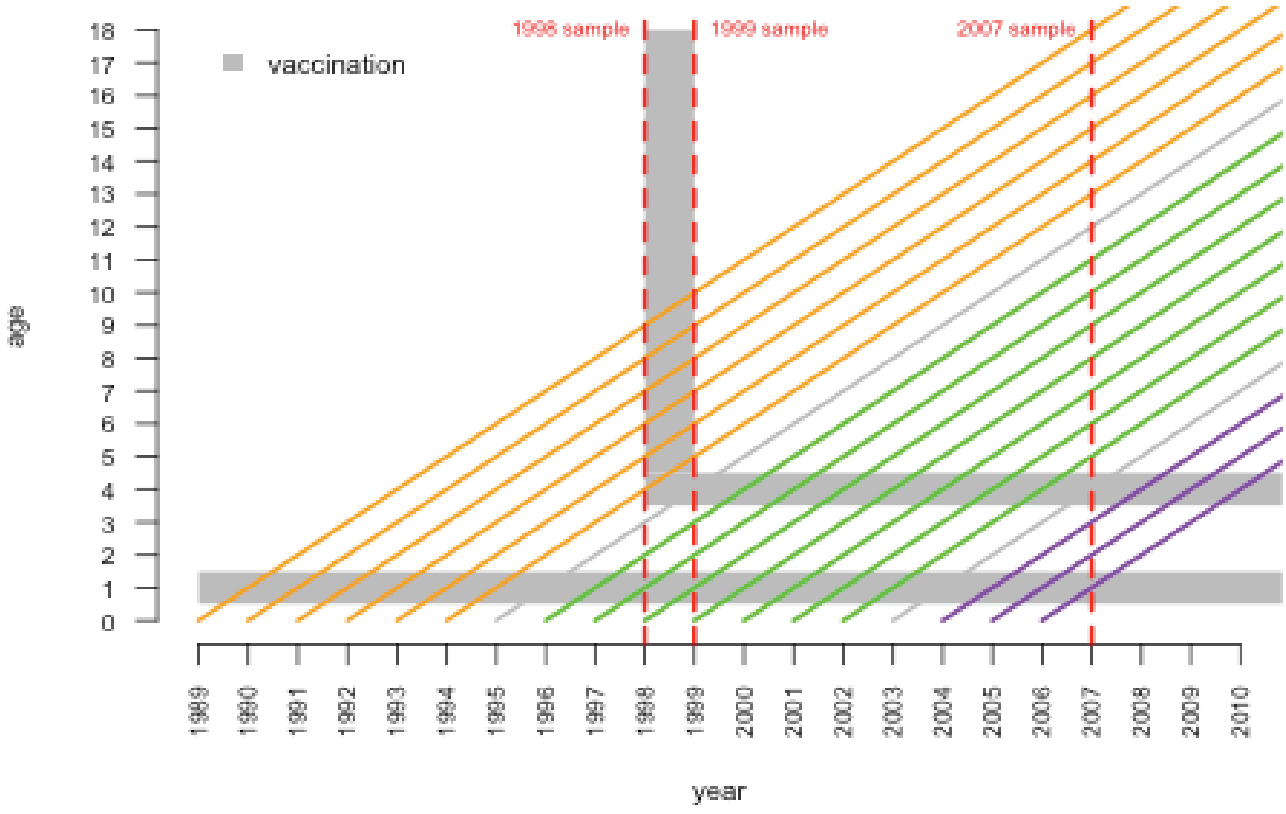
Data (1)
Exploiting serial seroprevalence data

- Goal:

  account for waning and boosting processes while estimating vaccination coverage

- Data:
  - Australia
  - Serological samples 1998, 1999 and 2007
  - MMR vaccination
    - initiation: 1989 – single dose at 12 months of age
    - catch-up campaign: end of 1998
    - since then: vaccination at 12 months and 4 years of age

Data (2): Lexis Diagram



Data(3)

- Positive antibody test:
  - exposure to wild-type or vaccine antigen
- Negative antibody reading:
  - absence of exposure or decline after previous exposure
- Equivocal results:
  - missing data
  - missing at random

Table 1: Trivariate serostatus of complete data (ordered as Measles, Mumps and Rubella results)

	Trivariate sera counts (data shown as 1998,1999, 2007 serosurvey triples)								
Birth Cohort	+++	++-	+-+	-++	+--	-+-	--+	---	Total
1989	19,31,17	0,0,1	7,2,5	0,0,3	3,0,0	0,0,0	0,0,2	0,0,0	29,33,28
1990	19,30,18	1,1,0	11,2,6	0,0,0	1,0,1	1,1,0	1,1,2	0,2,0	34,35,27
1991	19,28,16	0,0,2	9,2,8	3,1,0	0,1,0	0,0,0	0,0,1	2,0,2	33,32,29
1992	26,28,19	0,0,0	11,4,5	3,0,0	1,1,0	1,0,0	0,1,2	0,1,1	42,35,27
1993	43,31,20	0,0,1	13,3,7	3,0,0	4,0,0	0,1,1	2,0,0	5,0,1	70,35,30
1994	47,70,18	1,0,0	14,6,5	5,0,1	1,0,0	2,0,0	2,1,1	3,2,0	75,79,25
1995	52,55,22	4,1,0	18,10,9	3,4,0	0,0,0	2,0,0	4,4,1	7,3,0	90,77,32
1996	53,35,26	0,0,1	13,29,8	5,4,0	2,0,1	1,0,0	2,3,2	12,5,0	88,76,38
1997	61,50,19	1,0,0	14,19,7	3,1,1	2,1,0	0,0,0	1,2,1	28,4,0	110,77,28
1998	-,74,44	-,1,0	-,21,8	-,2,1	-,3,0	-,1,0	-,6,2	-,53,0	-,161,55
1999	-,-,47	-,-,0	-,-,11	-,-,2	-,-,1	-,-,0	-,-,3	-,-,2	-,-,66
2000	-,-,48	-,-,0	-,-,11	-,-,1	-,-,1	-,-,0	-,-,2	-,-,4	-,-,67
2001	-,-,60	-,-,0	-,-,5	-,-,1	-,-,0	-,-,0	-,-,1	-,-,1	-,-,68
2002	-,-,67	-,-,1	-,-,9	-,-,2	-,-,1	-,-,0	-,-,2	-,-,1	-,-,83
2003	-,-,147	-,-,1	-,-,24	-,-,5	-,-,0	-,-,0	-,-,2	-,-,5	-,-,184
2004	-,-,113	-,-,0	-,-,40	-,-,3	-,-,1	-,-,0	-,-,6	-,-,8	-,-,171
2005	-,-,80	-,-,1	-,-,39	-,-,4	-,-,2	-,-,0	-,-,2	-,-,9	-,-,137
2006	-,-,57	-,-,0	-,-,62	-,-,0	-,-,4	-,-,0	-,-,3	-,-,36	-,-,162
Total	342,432,838	7,2,8	110,98,269	25,12,24	14,6,12	7,2,1	12,18,35	57,70,70	571,640,1257

The cohort model (1)

- denote birth cohort: *j*
- denote infection: *d*

$$q_{jd} = s_{jd} + (1 - s_{jd}) e_{jd}$$

probability of pos test result after vaccination

probability of seroconversion

probability of exposure

The cohort model (2)

The trivariate response for an individual in cohort *j:*

$$p_{j1} = f_j(+,+,+) = v_j q_{j1} q_{j2} q_{j3} + (1 - v_j) e_{j1} e_{j2} e_{j3}$$
$$p_{j2} = f_j(+,-,+) = v_j q_{j1} (1 - q_{j2}) q_{j3} + (1 - v_j) e_{j1} (1 - e_{j2}) e_{j3}$$
$$p_{j3} = f_j(-,+,+) = v_j (1 - q_{j1}) q_{j2} q_{j3} + (1 - v_j) (1 - e_{j1}) e_{j2} e_{j3}$$
$$p_{j4} = f_j(-,-,+) = v_j (1 - q_{j1}) (1 - q_{j2}) q_{j3} + (1 - v_j) (1 - e_{j1}) (1 - e_{j2}) e_{j3}$$
$$p_{j5} = f_j(+,+,-) = v_j q_{j1} q_{j2} (1 - q_{j3}) + (1 - v_j) e_{j1} e_{j2} (1 - e_{j3})$$
$$p_{j6} = f_j(+,-,-) = v_j q_{j1} (1 - q_{j2}) (1 - q_{j3}) + (1 - v_j) e_{j1} (1 - e_{j2}) (1 - e_{j3})$$
$$p_{j7} = f_j(-,+,-) = v_j (1 - q_{j1}) q_{j2} (1 - q_{j3}) + (1 - v_j) (1 - e_{j1}) e_{j2} (1 - e_{j3})$$
$$p_{j8} = f_j(-,-,-) = v_j (1 - q_{j1}) (1 - q_{j2}) (1 - q_{j3}) + (1 - v_j) (1 - e_{j1}) (1 - e_{j2}) (1 - e_{j3})$$

The cohort model (3)

- Maximize loglikelihood:
  (Goeyvaerts et al. 2012)

$$LL = \sum_{j,k} F_{jk} \log(p_{jk})$$

observed frequency

model-based probability

The cohort model (4)

- Let's assume there are annual probabilities of exposure and waning for each antigen
- Let's assume a constant waning rate in time and with age
- Let's assume that exposure depends on the birth cohort only

The cohort model (5)

- Mathematically:

$$E_{jd} = \begin{pmatrix} 1 & e_{jd} \\ 0 & 1-e_{jd} \end{pmatrix} \text{ and } W_d = \begin{pmatrix} 1-w_d & 0 \\ w_d & 1 \end{pmatrix}$$

exposure probability

waning probability

- How do we use this in our model?

The cohort model (5)

- First we rewrite the vaccination model:

$$V_j = \begin{pmatrix}
1 & v_j s_2 & v_j s_1 & v_j s_1 s_2 & v_j s_3 & v_j s_2 s_3 & v_j s_1 s_3 & v_j s_1 s_2 s_3 \\
0 & 1-v_j s_2 & 0 & v_j s_1 (1-s_2) & 0 & v_j s_3 (1-s_2) & 0 & v_j s_1 s_3 (1-s_2) \\
0 & 0 & 1-v_j s_1 & v_j s_2 (1-s_1) & 0 & 0 & v_j s_3 (1-s_1) & v_j (1-s_1) s_2 s_3 \\
0 & 0 & 0 & 1-v_j (1-s_1)(1-s_2) & 0 & 0 & 0 & v_j (1-s_1)(1-s_2) s_3 \\
0 & 0 & 0 & 0 & 1-v_j s_3 & v_j s_2 (1-s_3) & v_j s_1 (1-s_3) & v_j s_1 s_2 (1-s_3) \\
0 & 0 & 0 & 0 & 0 & 1-v_j + v_j (1-s_2)(1-s_3) & 0 & v_j s_1 (1-s_2)(1-s_3) \\
0 & 0 & 0 & 0 & 0 & 0 & 1-v_j + v_j (1-s_1)(1-s_3) & v_j (1-s_1) s_2 (1-s_3) \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1-v_j + v_j (1-s_1)(1-s_2)(1-s_3)
\end{pmatrix}$$

- Now we have all components

The cohort model (6)

Tensor products:

– For one time point:

$$\mathbf{g}_j(t) = (W_1 E_{j1}(t) \otimes W_2 E_{j2}(t) \otimes W_3 E_{j3}(t))^j V_j \mathbf{g}_0, \quad \mathbf{g}_0 = [0,\ldots 0,1]^T$$

– For two time points:

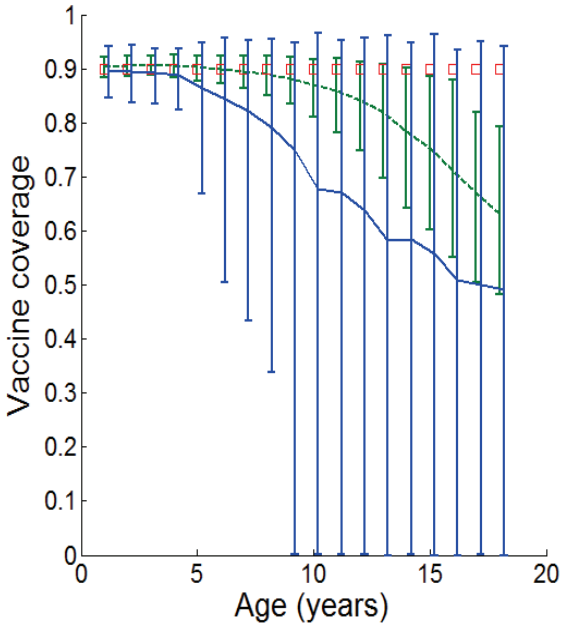
$$\mathbf{g}_{j+t_1-t_0}(t_1,t_0) = (W_1 E_{j1}(t_1) \otimes W_2 E_{j2}(t_1) \otimes W_3 E_{j3}(t_1))^{t_1-t_0} \mathbf{g}_j(t_0),$$

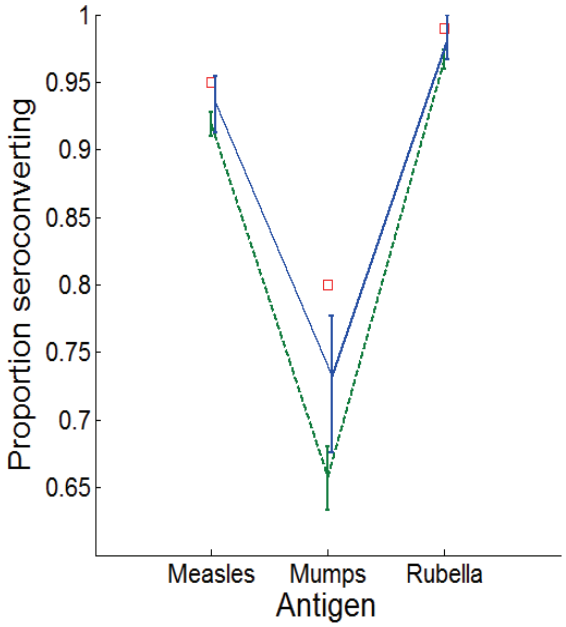
– For m>2 time points:

$$\mathbf{g}_{j+t_m-t_{m-1}}(t_m,t_{m-1},\ldots,t_1,t_0) = (W_1 E_{j1}(t_m) \otimes W_2 E_{j2}(t_m) \otimes W_3 E_{j3}(t_m))^{t_m-t_{m-1}} \mathbf{g}_j(t_{m-1},\ldots,t_1,t_0),$$

Simulation study (1)

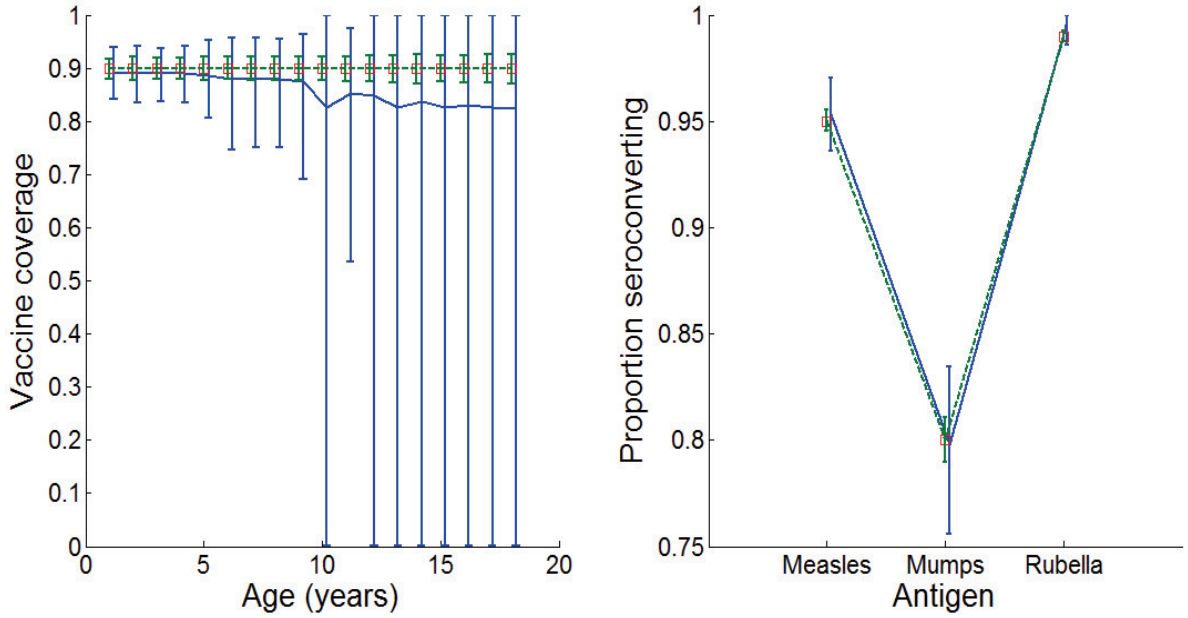
Misspecified model ignoring waning & boosting:





Simulation study (2)

Cohort model:



Application (1)

- Restriction to subset of serodata
  - Born in 1989 or later
    - 1998: <10 years of age
    - 1999: <11 years of age
  - Pulse vaccination program
    - 5-9 years of age in 1998
- Matlab routine *fminunc*
- 95% confidence intervals using a nonparametric bootstrap

Application (2)

- Application to the Australian data:

  3 time points, two vaccination moments

$$\mathbf{h}_{j+t_2-t_0}(t_2,t_1,t_0) = (W_1E_{j1}(t_2)\otimes W_2E_{j2}(t_2)\otimes W_3E_{j3}(t_2))^{t_2-t_1}\,\mathbf{h}_{j+t_1-t_0}(t_1,t_0),$$

$$\mathbf{h}_{j+t_1-t_0}(t_1,t_0) = (W_1E_{j1}(t_1)\otimes W_2E_{j2}(t_1)\otimes W_3E_{j3}(t_1))^{t_1-t_0}\,V_{2j}\mathbf{g}_j(t_0)$$

as before

second vaccination moment

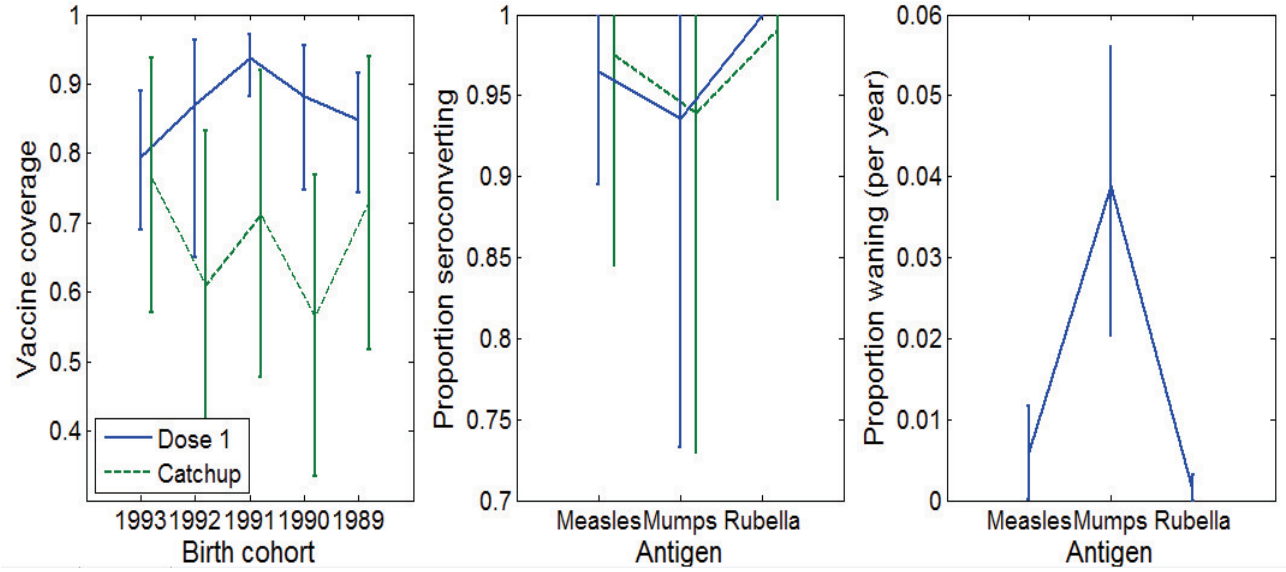
- and the loglikelihood:

$$LL = \sum_{k=1}^{8}\sum_{j=j_0}^{j_1}\left(F_{jk}(t_0)\log(g_{jk}(t_0)) + F_{j+t_1-t_0k}(t_1)\log(h_{j+t_1-t_0k}(t_1,t_0)) + F_{j+t_2-t_0k}(t_2)\log(h_{j+t_2-t_0k}(t_2,t_1,t_0))\right)$$

sero 1998 sero 1999 sero 2007

Application (3)

Resulting estimates:



Discussion (1)

- Using a cohort model we can estimate
  - vaccination coverage
  - seroconversion
  - waning
- Estimates are line with results from
  - vaccination coverage surveys
  - literature on waning and seroconversion
- Exposure (not shown) cannot be estimated accurately

  → requires further research

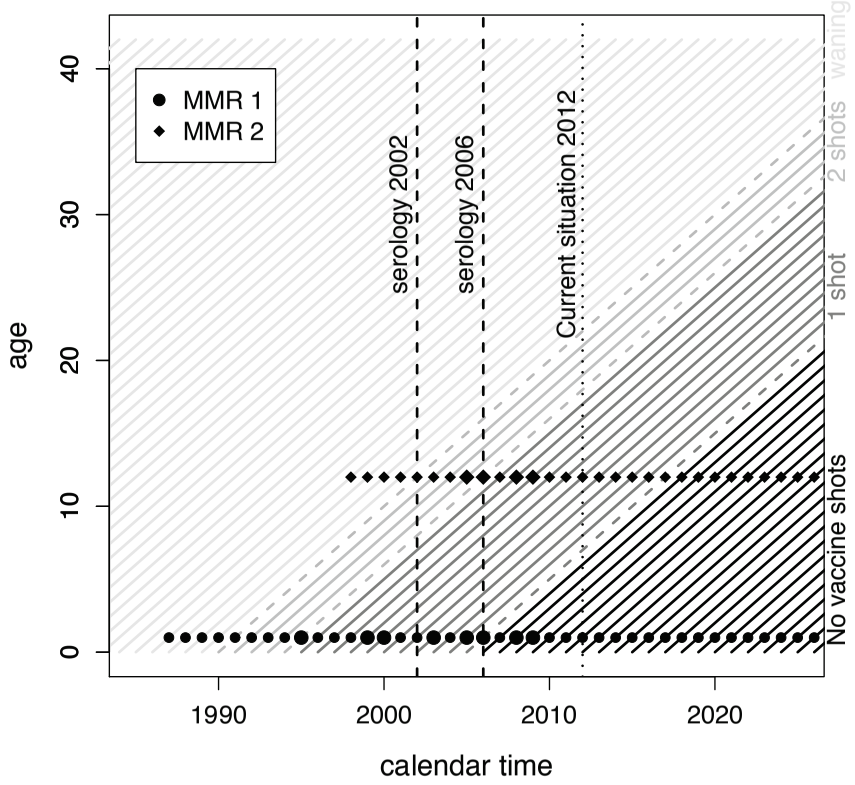
  → possibility to combine these results with incidence data using methodology as presented in Hens et al. (2008) and Azmon et al. (In Press.)

Discussion (2)

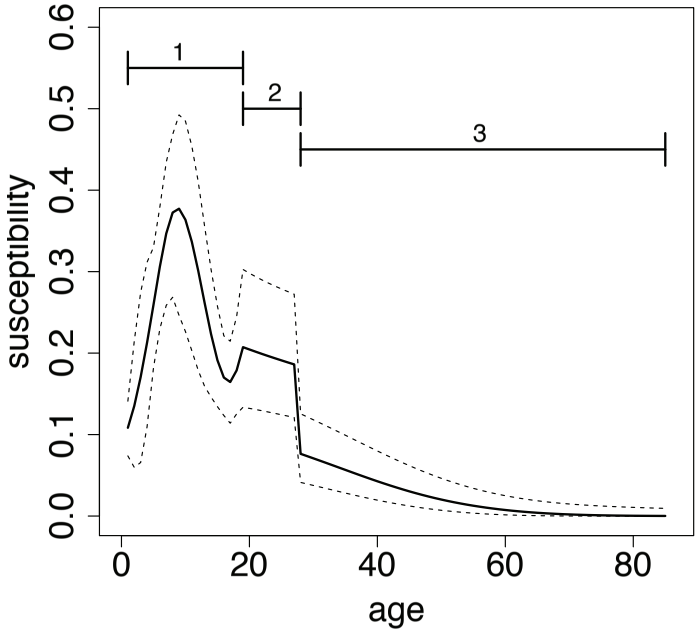
- Assumptions
  - Exponential distributions versus more complex distributions
  - Vaccinees are equally likely to be exposed as non-vaccinees
  - There is no exposure prior to vaccination (first dose)
- Validity of the model
  - highly vaccinated population
  - relatively low incidence
  - Other infections: time resolution

Thank you

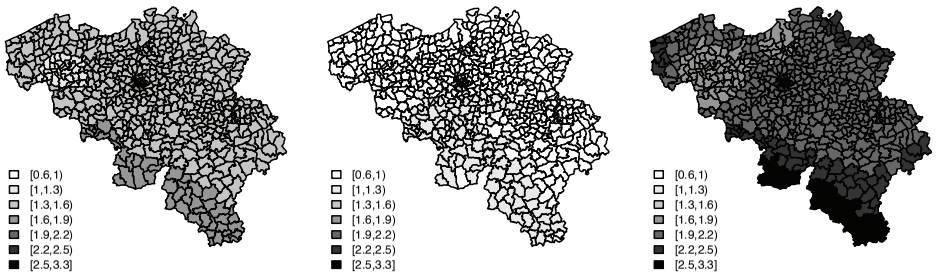
Epilogue
a mumps risk map for Belgium

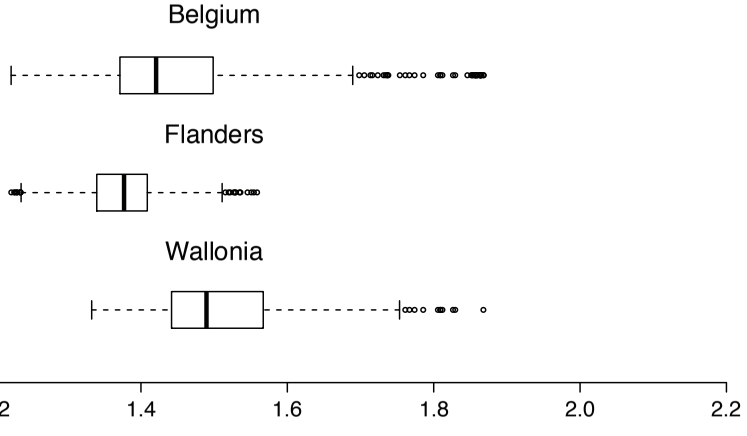


Epilogue (2)



Epilogue (3)





Epilogue
Discussion

- Risk of mumps outbreaks increases over time
- Even with catch-up campaigns it will be difficult/impossible to avoid future outbreaks
- Due to vaccine failure and waning immunity
- A similar result has been obtained for measles in Belgium