Measles epidemics and vaccination coverage in Germany

Michaela Paul

Biostatistics Unit
Institute for Social and Preventive Medicine
University of Zurich

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Introduction: Measles in Germany

- Measles is a highly contagious disease.
- The introduction of the measles vaccine has considerably lowered the incidence level in Germany to a historical low of 0.2 cases per 100 000 inhabitants in 2004.
- However, large local outbreaks occurred in some of the federal states in recent years.
- The differences in incidence are most likely due to very heterogeneous vaccination coverage rates.

This talk is about:

Empirical investigation of the association between vaccination rates and measles epidemics using routinely collected data.

Herzog et al. (2010)

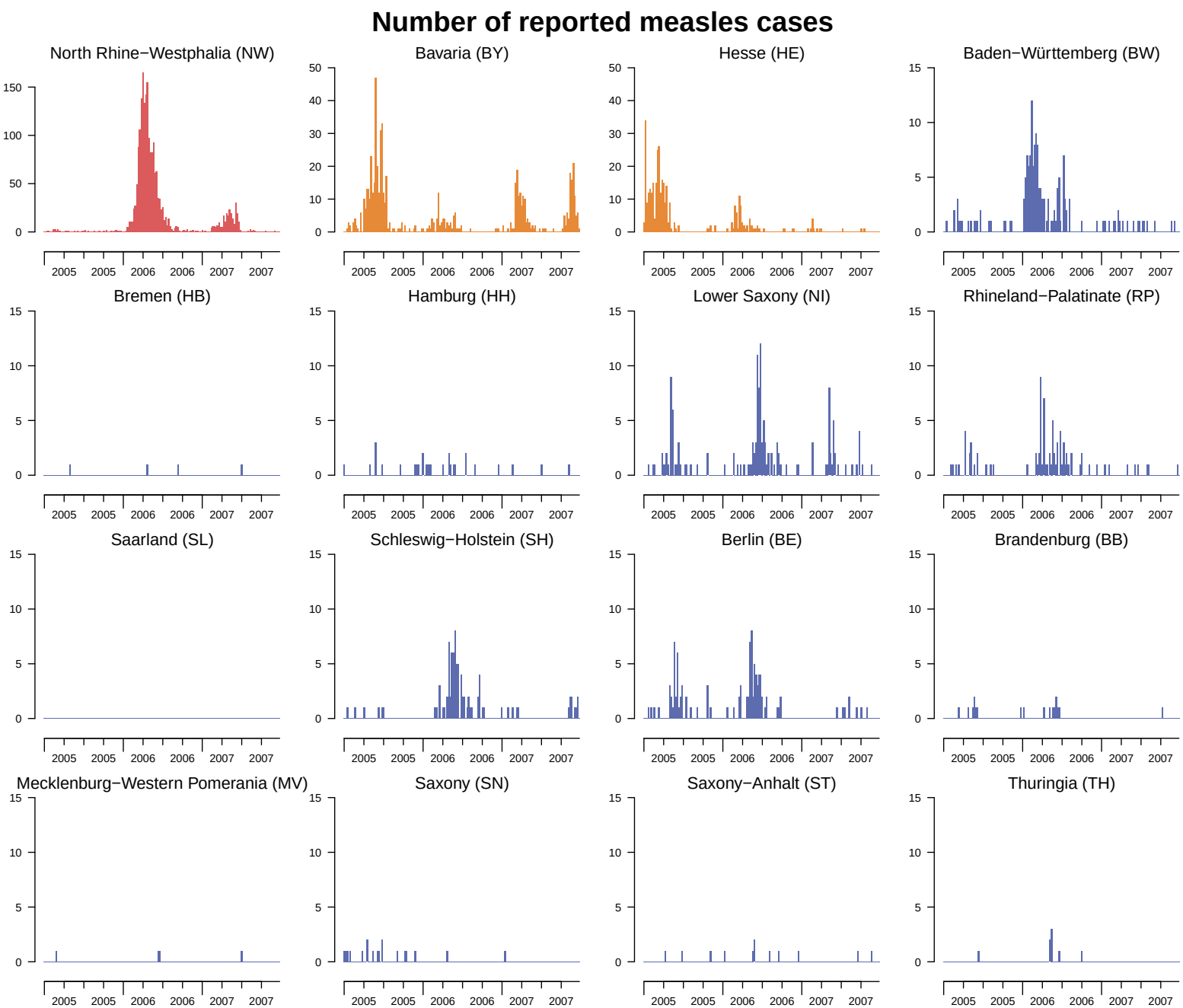
Data on measles incidence and MMR vaccination rates

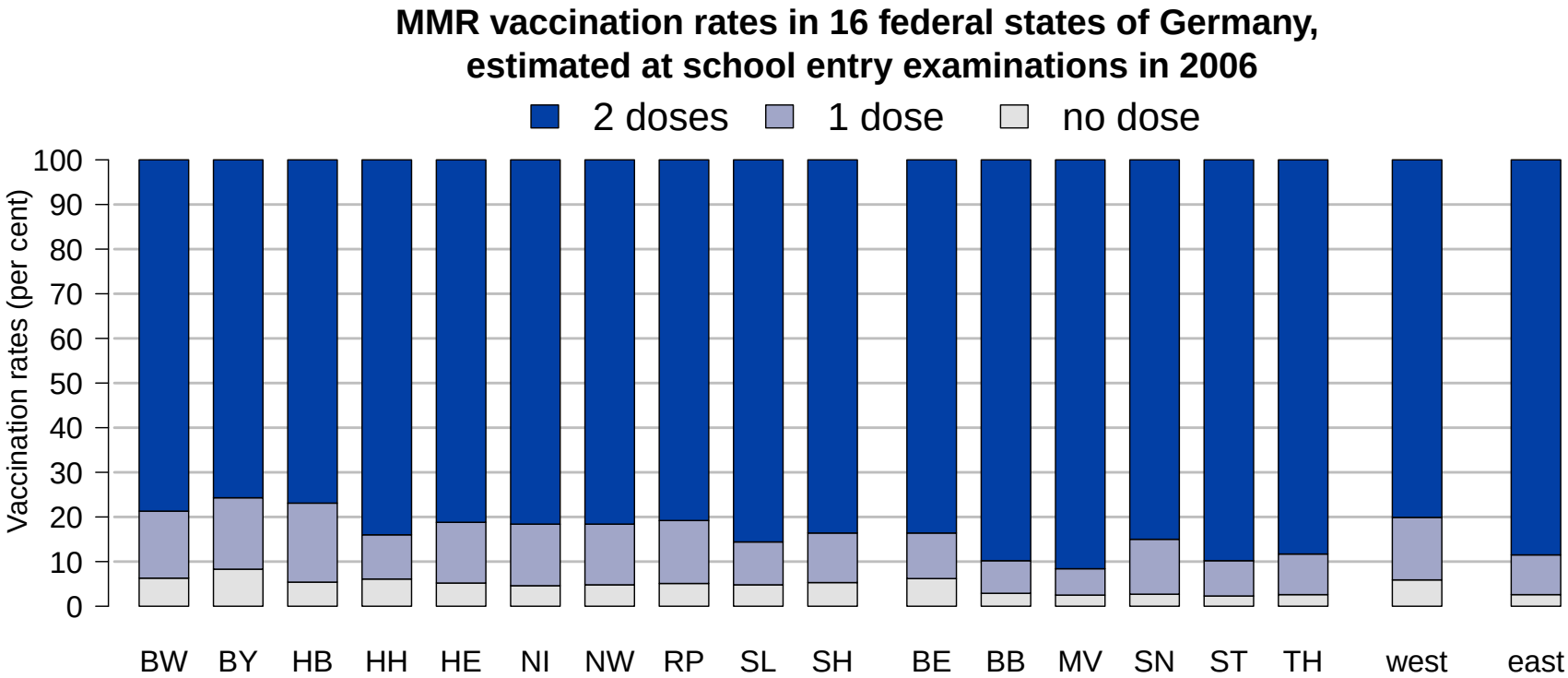
Measles incidence

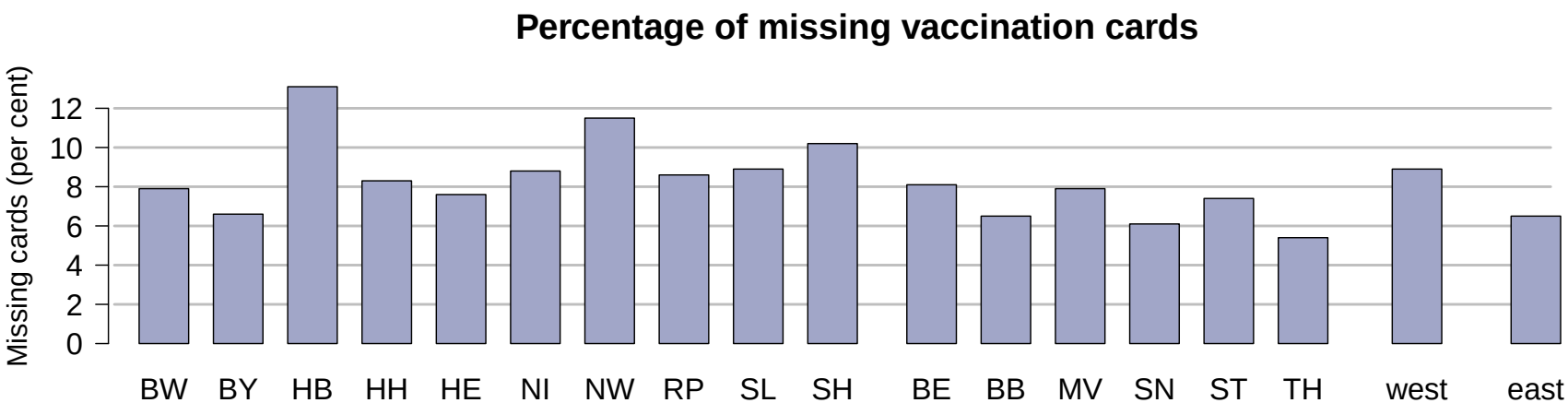
- The Robert-Koch Institute (RKI) provides weekly numbers of reported cases.
- The time series can be further stratified by e.g. region or age.
- We use cases of all ages in 16 federal states for 2005 – 2007.

Measles-Mumps-Rubella (MMR) vaccination rates

- Coverage rates are estimated based on vaccination cards presented at yearly school entry examinations.
- They yield information about the vaccination status of children aged 4–7.
- We use state-specific rates for the 1st and 2nd dose of MMR for 2006.

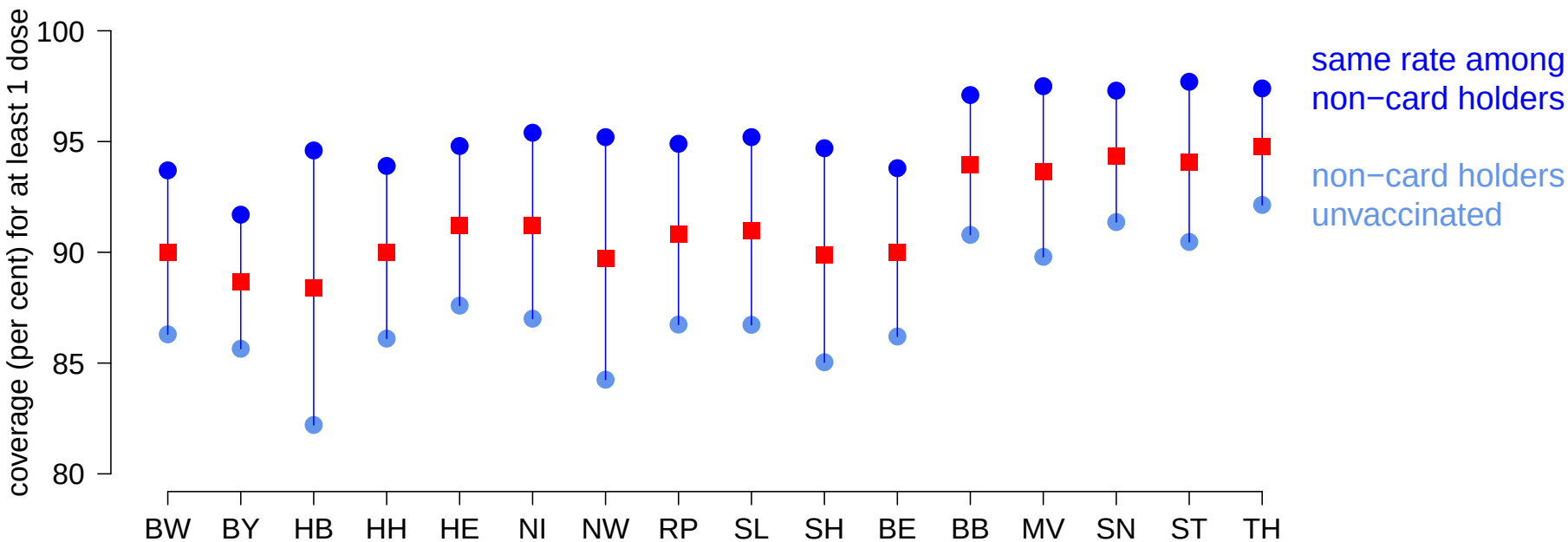

Number of reported measles cases
North Rhine−Westphalia (NW)
Bavaria (BY)
Hesse (HE)
Baden−Württemberg (BW)
Bremen (HB)
Hamburg (HH)
Lower Saxony (NI)
Rhineland−Palatinate (RP)
Saarland (SL)
Schleswig−Holstein (SH)
Berlin (BE)
Brandenburg (BB)
Mecklenburg−Western Pomerania (MV)
Saxony (SN)
Saxony−Anhalt (ST)
Thuringia (TH)
2005 2005 2006 2006 2007 2007


MMR vaccination rates in 16 federal states of Germany,
estimated at school entry examinations in 2006
2 doses
1 dose
no dose
Vaccination rates (per cent)
100
90
80
70
60
50
40
30
20
10
0
BW BY HB HH HE NI NW RP SL SH BE BB MV SN ST TH west east


Percentage of missing vaccination cards
Missing cards (per cent)
12
10
8
6
4
2
0
BW BY HB HH HE NI NW RP SL SH BE BB MV SN ST TH west east

Adjustment of vaccination rates

- True rates are most likely overestimated by the available data as the vaccination status of card-holders is generally better. (Wichmann et al.; 2007)
- Nation-wide information about the degree of overestimation is not available.
- We thus assume that coverage among children without cards is half as high as among those with cards.



Possible modelling approaches

- A simple approach is log-linear Poisson regression accounting for temporal and seasonal trends, and vaccination coverage as explanatory variable.
- However, outbreaks can thus not be captured.
- Temporal dependence beyond regular variation can be addressed by including an autoregression on past cases.
- Held et al. (2005) propose a model formulation where the disease incidence is additively decomposed into an epidemic and an endemic component.

Model formulation

$$y_{s,t}|y_{s,t-1} \sim \text{Po}(\lambda_s y_{s,t-1} + \nu_{s,t})$$

$$\log(\lambda_s) = \beta_0 + \beta_1 \cdot (\text{vaccination rate in state } s)$$

$$\log(\nu_{s,t}) = \alpha + \gamma \cdot (\text{seasonal trend}) + \text{offset}$$

$y_{s,t}$: number of cases in state s at time t
offset : log population fraction in state s

- Model can be fitted by Maximum-Likelihood.
- The model choice criterion AIC is used for model comparison.
- Considered model formulations:
  - A: vaccination rates enter into epidemic component.
  - B: vaccination rates enter into endemic component.
  - C: vaccination rates are not included.

Specification of response and explanatory variables

- For measles the average time between the onset of symptoms in a primary case and a secondary case, the generation time, is about 10 days (Anderson and May; 1991).

$\longrightarrow$ We therefore aggregate measles cases in successive biweekly periods (Finkenstädt and Grenfell; 2000).

- The mass action principle assumes that:

$$\text{Rate of disease spread} \propto \begin{matrix}\text{Susceptibles} \\ \text{(unvaccinated)}\end{matrix} \times \begin{matrix}\text{Infected} \\ \text{(cases)}\end{matrix}$$

$\longrightarrow$ Taking the logarithm of the proportion of unvaccinated students produces this multiplicative relation (model A_0).

Parameter estimates and AIC

model		epidemic component		endemic component	
	AIC	β_0 (se)	β_1 (se)	α (se)	β_1 (se)
log proportion of unvaccinated students					
A_0	3566.1	3.01 (0.52)	1.38 (0.23)	1.78 (0.06)	-
B_0	3576.8	-0.17 (0.02)	-	5.43 (0.69)	1.52 (0.29)
log proportion of students who received at most 1 dose of MMR vaccine					
A_1	3584.1	1.34 (0.31)	1.02 (0.21)	1.76 (0.06)	-
B_1	3591.4	-0.17 (0.02)	-	3.59 (0.45)	1.17 (0.29)
no covariates					
C	3606.8	-0.16 (0.02)	-	1.76 (0.06)	-
D	10433.8	-	-	3.25 (0.03)	-

Summary of results

- The ML estimate of $\lambda = \exp(\beta_0)$ in model C is quite high, $\hat{\lambda} = 0.85$ with standard error se $= 0.02$.
- This indicates a strong dependence on the number of counts at the previous time point after adjustment for seasonal effects.
- The effect of vaccination coverage is significant.
- The incidence pattern of all ages is best described by including the log proportion of unvaccinated students in the epidemic component.
- This is plausible since the proportion of unvaccinated students acts as a surrogate for the population of susceptibles and the number of future cases depends both on the number of cases at present and on the number of susceptible persons.

Discussion

- For the analysis of infectious disease counts, statistical methods for multivariate time series of counts are needed.
- These methods have to be able to cope with occasional outbreaks.
- Vaccination rates can account for regional heterogeneity.
- Although the data on measles incidence and vaccination have some limitations, a clear significant association was observed.
- It would be interesting to analyse age-specific data, possibly on a finer spatial resolution.

References

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Sensitivity of assumed coverage for non-card holders

- We have assumed that coverage among non-card holders is 0.5 times as high as among card holders.
- We computed the AIC for several values ranging from 1 (same coverage) to 0 (all unvaccinated).