Statistical Methods for Infectious Diseases
Household Based Studies II
Lecture 11A

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Background

Pneumococcal Studies

- Data structure
- Models and analysis
- Bayesian latent variable model
- Hidden Markov model

Studies conditioning on exposure to infection: VE_S (VE_{col}), VE_I, VE_T

- Households, partnerships, or other small transmission units
- $\longrightarrow$ Households assuming independence of households
- $\longrightarrow$ Households assumed within communities
- Data structure:
- $\longrightarrow$ final-value data
- $\longrightarrow$ time-to-event data
- $\longrightarrow$ longitudinal panel data over time (pneumococcal carriage)

Table: Parameters used for measuring various effects of vaccination∗

Level Parameter choice	Comparison groups and effect: Susceptibility	Infectiousness	Combined change in susceptibility and infectiousness
Conditional on exposure: I Transmission probability	$VE_{S,p}\dagger = 1 - \frac{p_{\cdot 1}}{p_{\cdot 0}}$	$VE_{I,p} = 1 - \frac{p_{1\cdot}}{p_{0\cdot}}$	$VE_{T,p} = 1 - \frac{p_{11}}{p_{00}}$

Study design: I direct	IIA indirect	IIB total	III overall
Unconditional: II Incidence or hazard rate, IR, λ	$VE_{S,IR} = 1 - \frac{IR_{A1}}{IR_{A0}}$	$VE_{IIA,IR} = 1 - \frac{IR_{A0}}{IR_{B0}}$	$VE_{IIB,IR} = 1 - \frac{IR_{A1}}{IR_{B0}}$	$VE_{III,IR} = 1 - \frac{IR_{A\cdot}}{IR_{B\cdot}}$
	$VE_{S,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{A0}}$	$VE_{IIA,\lambda} = 1 - \frac{\lambda_{A0}}{\lambda_{B0}}$	$VE_{IIB,\lambda} = 1 - \frac{\lambda_{A1}}{\lambda_{B0}}$	$VE_{III,\lambda} = 1 - \frac{\lambda_{A\cdot}}{\lambda_{B\cdot}}$
III Proport. hazards, PH	$VE_{S,PH} = 1 - e^{\beta_1}$	NA	NA	NA
IV Cumulative incidence	$VE_{S,CI} = 1 - \frac{CI_{A1}}{CI_{A0}}$	$VE_{IIA,CI} = 1 - \frac{CI_{A0}}{CI_{B0}}$	$VE_{IIB,CI} = 1 - \frac{CI_{A1}}{CI_{B0}}$	$VE_{III,CI} = 1 - \frac{CI_{A\cdot}}{CI_{B\cdot}}$

∗ From Halloran, Struchiner, Longini, Am. J. Epidemiol 1997; 146;789–803.

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Longitudinal (panel) carriage data

- Collection of transmission units, such as households or schools
- Carriage data at certain time intervals
- Relevant covariates, such as age or vaccine status
- Choice of analyses

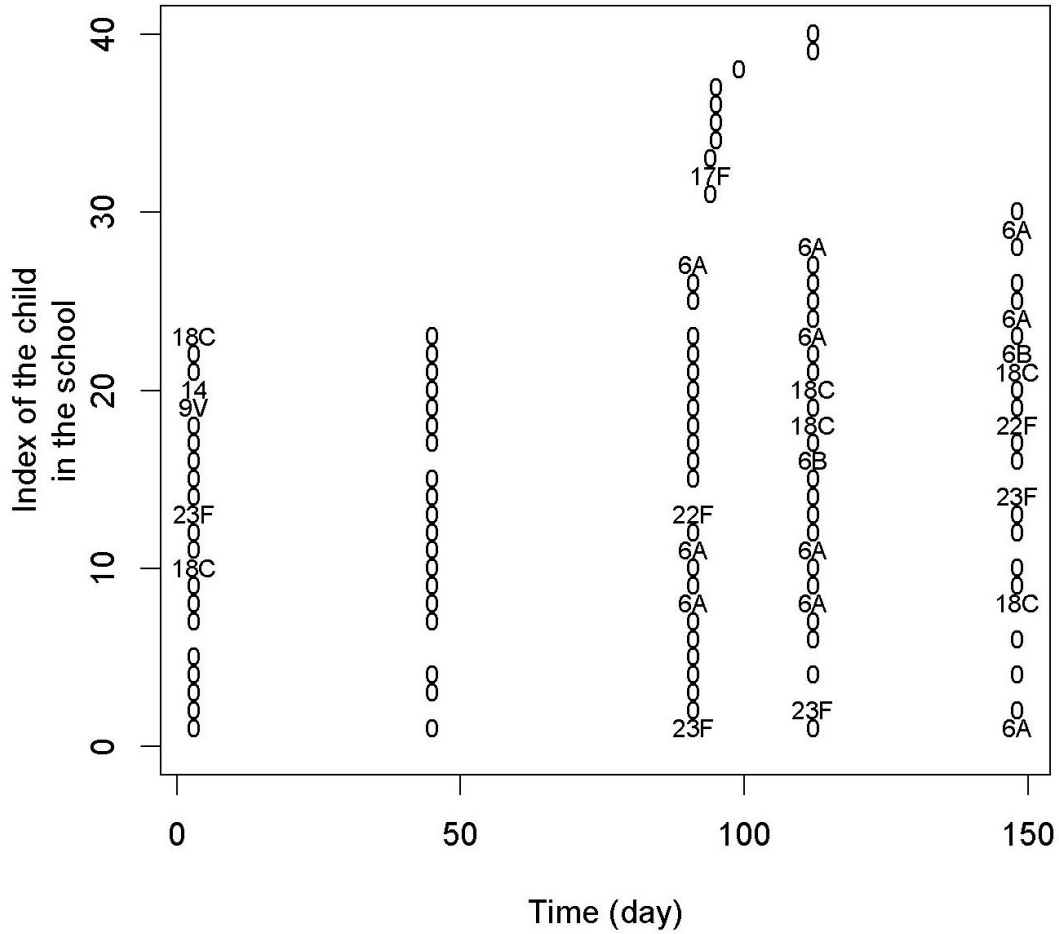

Figure 1
Swabs collected in a school participating in the study. "0" indicates that the sample was taken but no serotype was detected; otherwise, serotype number is given.

Cauchemez et al (2006)

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Statistical Models

- Models of transmission within units such as households or schools assumed within communities.
- Two types of parameters:
  $\longrightarrow$ rate of acquisition from the community (unconditional)
  $\longrightarrow$ rate of acquisition from infective within transmission unit (conditional).
- Covariate (vaccine) effects are modeled affecting these parameters.
- Vaccine effect on duration of carriage (clearance rate) can be modeled directly.

Longitudinal data on pneumococcal carriage

- Problem: neither the acquisition or clearance times are observed.
- Different approaches to statistical models can deal with this problem making a variety of assumptions.
- Other problems: combining multiple serotype data, missing data, competition, errors in diagnosis.

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- Auranen, Arjas, Leino, Takala (2000)

$$\begin{aligned}\tilde{\lambda}_i^{(s)} &= \left[\alpha(t-T_i)+\beta(t-T_i)\sum_{k=1}^{n} C_k^{(s)}(t)\right] \\ &\quad \times\{1-C_i(t)\} \\ \tilde{\mu}_i(t) &= \mu C_i(t)\end{aligned}$$

- α is rate to acquire carriage of serotype s from community
- β is rate of transmission from infective in family to susceptible
- μ is the clearance rate (no serotype specific rates)
- n is size of family, $C_i^{(s)}(t)$ is 0,1 indicator if individual is carrier of serotype s at time t, $C_i(t)$ is indicator of any of the three serotypes
- Problem solved: data augmented by unobserved event times of acquiring and clearing carriage (latent variables) using MCMC methods.

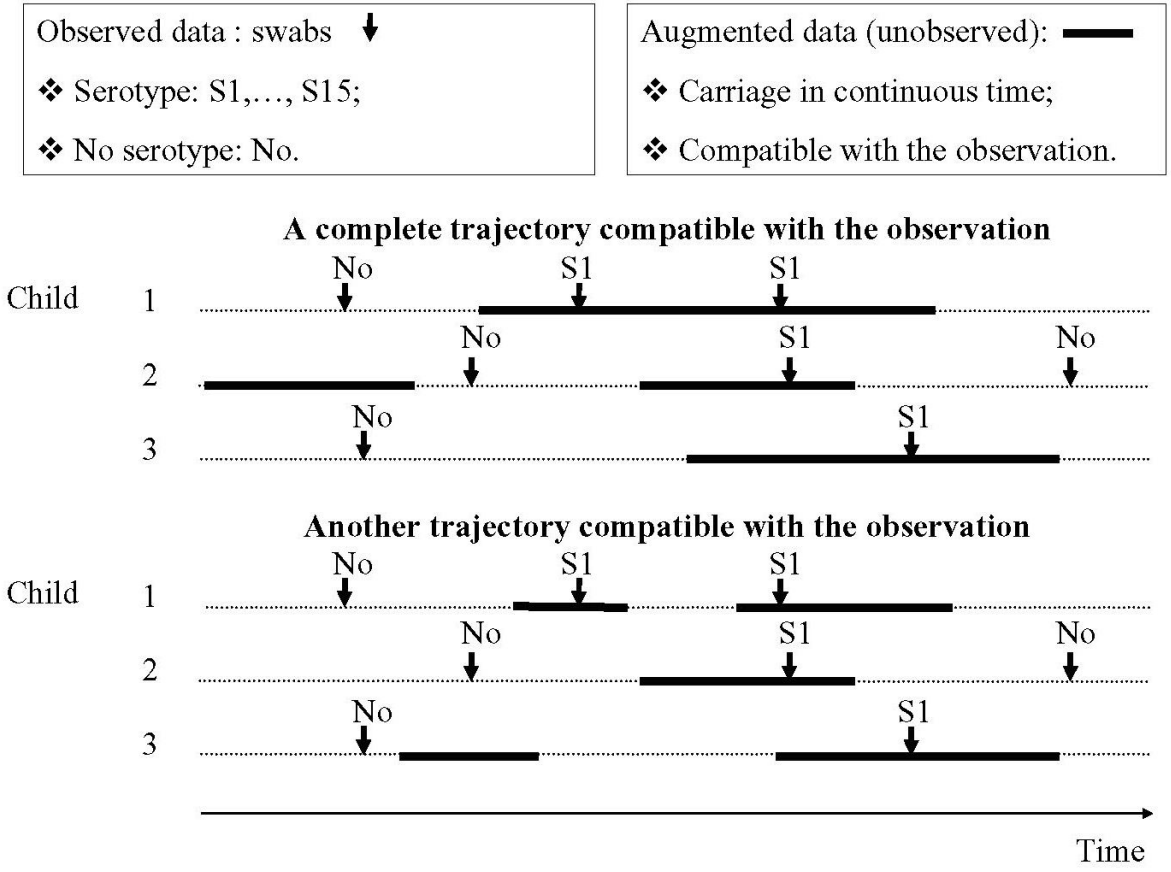

Figure 2
Data augmentation strategy to estimate transmission parameters of *S. pneumoniae* from the longitudinal follow-up of pneumococcal carriage in schools. The observed data consist of the times when swabs are collected in the school. The data are augmented with the times of colonization/decolonization. In the MCMC algorithm, augmented periods of carriage may be added/suppressed, split/combined; and the times of colonization/decolonization may change.

Cauchemez et al (2006)

- Cauchemez, Temime, Valleron, Varon, Thomas, Guillemot, Boëlle (2006)
- similar approach to Auranen et al (2000), school data rather than household
- included serotype data, clustered by community acquisition of infection into two groups
- used same model for influenza household studies

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- Auranen et al (1996) (Hib), Melegaro, et al (2004), Melegaro, et al (2007)

$$\begin{aligned} \Pr_i(S \to C)_{\delta t} &= \left(\alpha_i + \frac{\beta_{1i} I_1(t) + \beta_{2i} I_2(t)}{(z-1)^w}\right) \cdot \delta t \\ \Pr_i(C \to S)_{\delta t} &= \mu_i \cdot \delta t \end{aligned}$$

- $I_1(t)$ and $I_2(t)$ are number of infected children (< 5 yrs) and adults in household, i is age group.

- Problem solved: use a Markov model with 1 day intervals to analyze 28-day interval data assuming only one person can change in household per day.

- Vaccine parameters for susceptibility and infectiousness, also vaccine-dependent clearance rates can be added.

Intensity matrix Q

	000	001	010	011	100	101	110	111
000	q_{11}	$\alpha^{(3)}$	$\alpha^{(2)}$	0	$\alpha^{(1)}$	0	0	0
001	$\mu^{(3)}$	q_{22}	0	$\alpha^{(2)}+\beta^{(2)}$	0	$\alpha^{(1)}+\beta^{(1)}$	0	0
010	$\mu^{(2)}$	0	q_{33}	$\alpha^{(3)}+\beta^{(3)}$	0	0	$\alpha^{(1)}+\beta^{(1)}$	0
011	0	$\mu^{(2)}$	$\mu^{(3)}$	q_{44}	0	0	0	$\alpha^{(1)}+2\beta^{(1)}$
100	$\mu^{(1)}$	0	0	0	q_{55}	$\alpha^{(3)}+2\beta^{(3)}$	$\alpha^{(2)}+\beta^{(2)}$	0
101	0	$\mu^{(1)}$	0	0	$\mu^{(3)}$	q_{66}	0	$\alpha^{(2)}+2\beta^{(2)}$
110	0	0	$\mu^{(1)}$	0	$\mu^{(2)}$	0	q_{77}	$\alpha^{(3)}+2\beta^{(3)}$
111	0	0	0	$\mu^{(1)}$	0	$\mu^{(2)}$	$\mu^{(3)}$	q_{88}

- The elements on the diagonals represent the intensity of staying in the same state.
- The $q_{ii} = 1 - \sum_{j \neq i} q_{ij}$ (Karlin and Taylor 1975).
- The element (4,8) represents the transition from state 011 to state 111.

Unconditional acquisition rates

- Smith et al (1993)
- Data did not include transmission units
- Statistical model included unconditional acquisition rates and and clearance rates

Summary

- Pneumococcal carriage studies fit well within the context of a general framework of vaccine effects.
- Transmission models with parameters conditional on exposure are important for understanding a range of effects.
- Not all effects rely on transmission models.
- The relation to pivotal trials for licensure is open.

Thank You!