# *Statistical Methods for Infectious Diseases*
# *Household Based Studies I*
# *Lecture 7A*

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# *Household-based studies*

- Studying effects of vaccines
- Effects of influenza antiviral agents
- Transmission studies
- Natural history: transmissibility, the incubation and latent periods, the duration of infectiousness, and the serial interval between cases
- Household exposure as natural challenge studies (surrogates of protection)

# *VE from SAR: Index case identified*

- The secondary attack rate (SAR), the proportion of susceptibles exposed to an infectious person who become infected, has been used to estimate protective effects of vaccination since the 1930's (Kendrick and Eldering 1939).
- SAR is a special case of the transmission probability.
- $SAR_{vs}$ : SAR from a person of vaccine status $v$ to a person of vaccine status $s$, $v, s = 0, 1$

# *VE from SAR: Index case identified*

- The index case in a household is the case that draws attention to the household and leads to ascertainment of the household.
- The index case is also often the first, or primary, case in the household, but not necessarily.
- A case that occurs too soon after the primary case to have resulted from infection by the primary case is called a co-primary case.

# *VE based on nonparametric secondary attack rates (SAR)*

- The three main unstratified vaccine effects are

$$\begin{aligned} VE_{S.1/.0} &= 1 - \frac{SAR_{.1}}{SAR_{.0}}, \\ VE_{I1./0.} &= 1 - \frac{SAR_{1.}}{SAR_{0.}}, \\ VE_{T} &= 1 - \frac{SAR_{11}}{SAR_{00}}. \end{aligned}$$

- The stratified measures of $VE_S$ and $VE_I$ are

$$\begin{aligned} VE_{S01/00} &= 1 - \frac{SAR_{01}}{SAR_{00}}, \quad VE_{S11/10} = 1 - \frac{SAR_{11}}{SAR_{10}}, \\ VE_{I10/00} &= 1 - \frac{SAR_{10}}{SAR_{00}}, \quad VE_{I11/01} = 1 - \frac{SAR_{11}}{SAR_{01}}. \end{aligned}$$

# *Household-based studies*

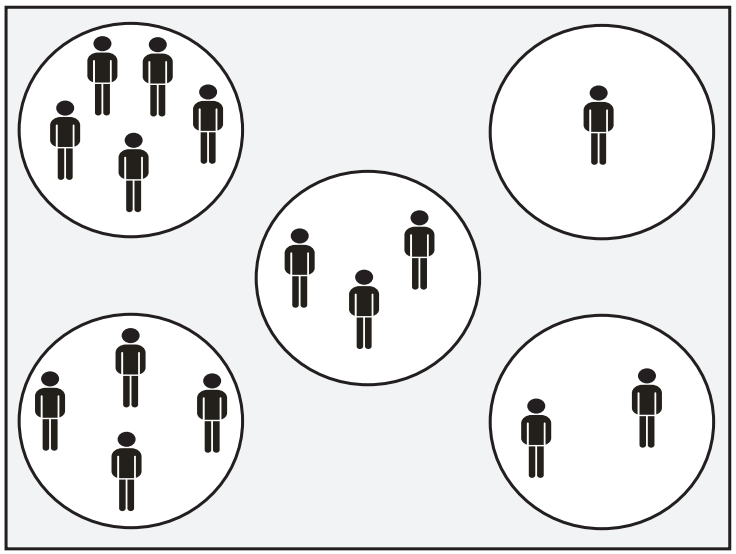
- In observational studies, evaluating vaccine efficacy under conditions of household exposure can help reduce bias generated by unequal exposure in vaccinated and unvaccinated people.
- Often but not always the household exposure studies are nested in a study that has the primary analysis based on one of the unconditional measures of vaccine efficacy, such as $VE_{S,IR}$ or $VE_{S,CI}$.
- In these studies, when an exposure is determined to have occurred, for instance, when a sibling of a vaccine study participant has a case of pertussis, then the outcomes are evaluated in a secondary analysis.

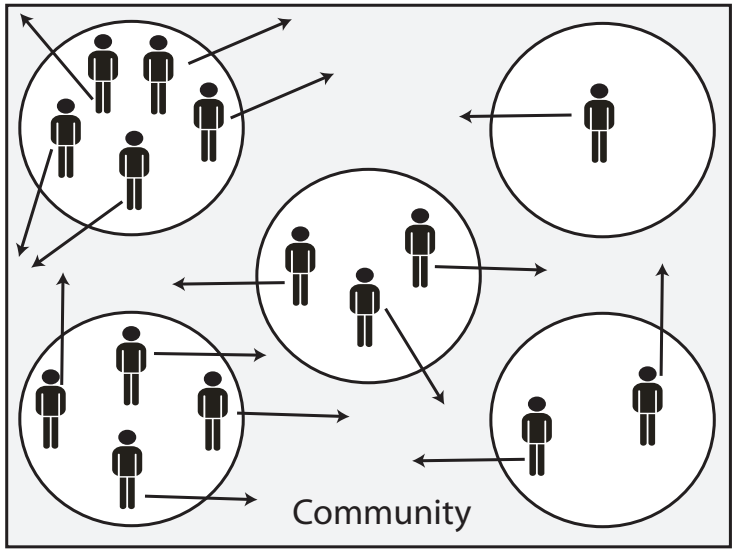
# *Household-based studies*

- The data structure and follow-up period can depend on whether the infection results in immunity that lasts at least as long as the study period, such as in influenza, colds, or measles,
- or whether a person can experience repeated episodes of infection, carriage or disease during the study, such as pneumococcal nasopharyngeal carriage.
- using final value data, time-to-event data, longitudinal studies

# *Household-based studies*

- Households assuming independence of households
- Households within communities




Community

# *Other small transmission units*

- Households allow easy identification of contacts between a case and susceptibles
- Families are convenient units of study.
- Sexual partnerships
- School buses
- Airplanes
- Classrooms
- Day care centers

# *Pertussis*

- Pertussis vaccines developed in the 1920s
- Whole-cell versus acellular vaccines
- Michigan 1930s (Kendrick and Eldering)
- Niakhar, Senegal: trials 1990-1996
- England: why estimates of pertussis vaccine lower in household contact studies than when assessed in cohort analyses (Fine et al 1988); retrospective versus prospective ascertainment

# *Pertussis*

- Sweden
- Vaccination stopped in 1979
- Pertussis became endemic again
- DT versus DTP trials possible

# *Influenza*

- Seattle: Virus Watch intensive surveillance in the 1960's and 1970's (Fox et al):
  $\longrightarrow$ vaccination not indicated for children.
- Cleveland, USA: 1948-1957 (Dingle et al 1964): source of age-distribution of influenza attack rates 1957 Asian influenza pandemic (Table 10.6)
- Influenza Epigrippe, France (Carrat 2002): households recruited by family member going to GP.

# *Influenza*

- Influenza antiviral post-exposure prophylaxis: two oseltamivir and two zanamavir studies (Yang Yang):
  $\longrightarrow$ $AVE_I$ not estimable from any of the four studies

- Tecumseh, Michigan: 1976-1981 (Monto et al 1985)

# *Influenza A(H3N2) infections in 1977-1978 and 1980-1981*

Observed distribution combined epidemics in Tecumseh, Michigan.

| No. infected | No. of susceptibles per household[a] | | | | |
|---|---|---|---|---|---|
| | 1 | 2 | 3 | 4 | 5 |
| 0 | 110 | 149 | 72 | 60 | 13 |
| 1 | 23 | 27 | 23 | 20 | 9 |
| 2 | | 13 | 6 | 16 | 5 |
| 3 | | | 7 | 8 | 2 |
| 4 | | | | 2 | 1 |
| 5 | | | | | 1 |
| Total | 133 | 189 | 108 | 106 | 31 |

[a] The criterion for classifying individuals as susceptible is a preseason hemagglutination inhibition test detecting no antibody in a dilution of 1 in 128 or less. Households with more than five susceptibles are deleted from all analyses. from Addy et al (1991).

# *Measles*

- The clinical efficacy of three measles vaccines was studied in a randomized trial in Niakhar, Senegal.
- Garenne et al (1993) evaluated the efficacy of measles vaccines after controlling for the level of exposure to infection within compounds.
- The analysis controlling for the level of exposure within compound (SAR) was nested in the randomized study.
- Vaccine trial conducted from August 1987 to July 1990 to compare two high-titer vaccines, the Edmonston-Zagreb and the Schwarz, and the standard Schwarz.
- Different levels of exposure within compounds defined using a linear score: 1 = living in a different compound; 2 = living in same compound but eating from a different kitchen; 3 = eating from the same kitchen but sleeping in a different hut; 4 = sleeping in the same hut

# *Pneumococcal carriage studies*

- Preparatory to introducing pneumococcal vaccines
- Asymptomatic carriage
- Finland
- France
- United Kingdom
- Bangladesh
- Upcoming meningococcal carriage studies in Africa

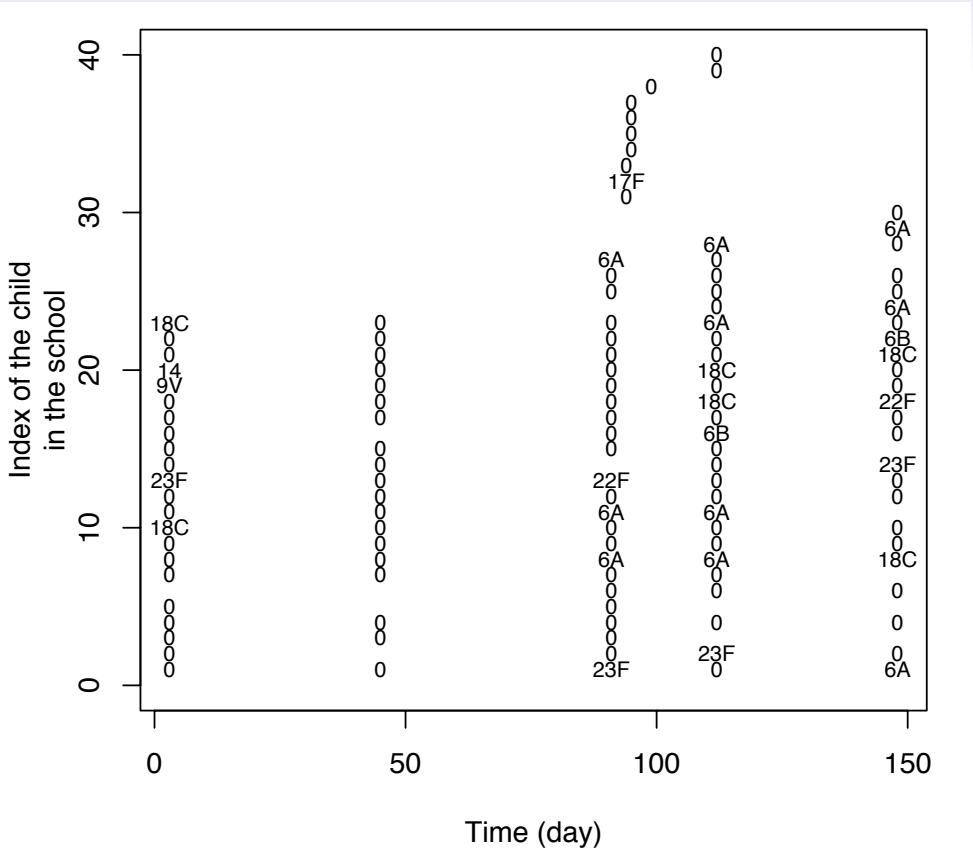



*Figure:* Longitudinal data in a school participating in a pneumococcal carriage study in France (Guillemot et al 2005). A "0" represents a sample in which no pneumococcal serotypes was detected. The other symbols represent the pneumococcal serotype abbreviation of the detected bacteria. (from Cauchemez et al 2006d)

# *Transmission units and contacts*

- Contact must be defined within each study.
- The individuals in a small transmission unit exposed to an infectious case can be thought of as a *minicohort* (Orenstein et al 1988) that has its own reference date for exposure to infection.
- An advantage is that vaccination status is less likely to change over the time of follow-up.
- A small transmission unit can also be thought of as a *minicommunity* if the indirect effects of vaccination of a fraction of the people in the transmission unit are of interest.

# *Ascertainment*

- Ideally, random sample of households
- Prospective enrollment, say population-based surveillance as in Niakhar, Senegal.
- Ascertainment often on index case
- Potential for bias based on size of household
- Following a large number of households prospectively could be expensive
- In an individually randomized vaccine trial, the households of the individuals in the vaccine study can be included in a further study.

# *Other issues*

- Case definition
- Assignment mechanism: household versus individual randomization
- Usually observational

# *Other related designs*

- Case-contact design: an index case is identified, then the people who have made contact with the index case are identified.
- Cluster design: identify a case, then do something around that case defined by location: dengue intervention and immunopathogenesis, vaccine efficacy studies
- Susceptibles exposed to infective contacts: say, HIV vaccine study, per-contact vaccine efficacy (Yang et al 2009).
- Augmented study designs: recruit partnerships or household of RCT participants into study.
- Mini-community designs: households of individual study participants are recruited into the study, regardless of whether a case has developed in the household.

# Thank you!