

Mathematical Modeling of Pertussis in Sweden



Evaluating hypothetical mechanisms for the changing epidemiology of pertussis throughout the developed world by analyzing natural experiments in Sweden

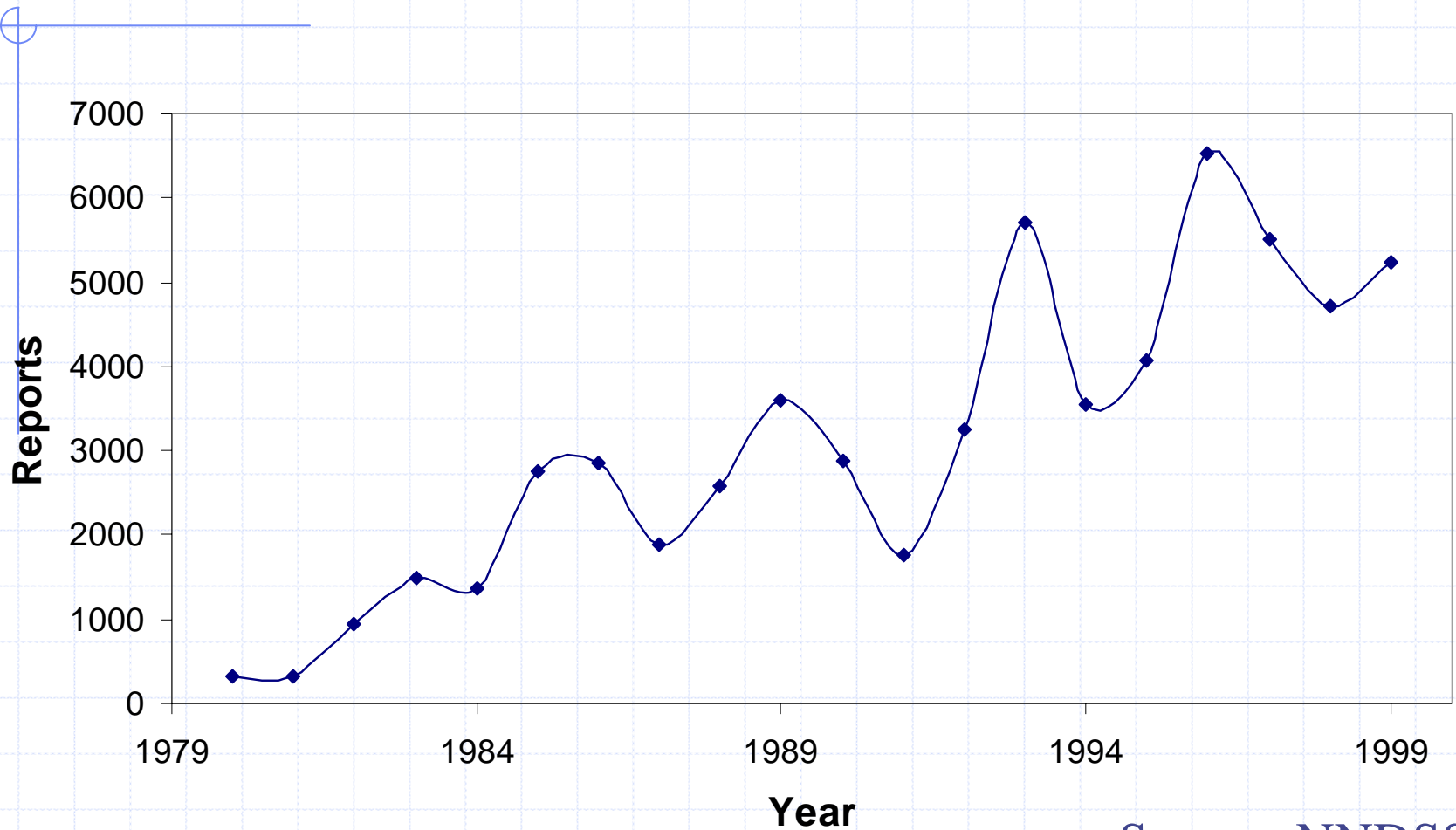


Outline

- Apparent changes in incidence and age-distribution of pertussis
- Hypothetical explanations, unfortunately not mutually-exclusive
- Events in Sweden that permit us to demonstrate the sufficiency of one mechanism by validating ...
- A model of infection, but not necessarily clinically-apparent disease
- Differences between MA and other states that are consistent, or vice-versa
- Proposed research on the biology, epidemiology, ... of pertussis in Sweden



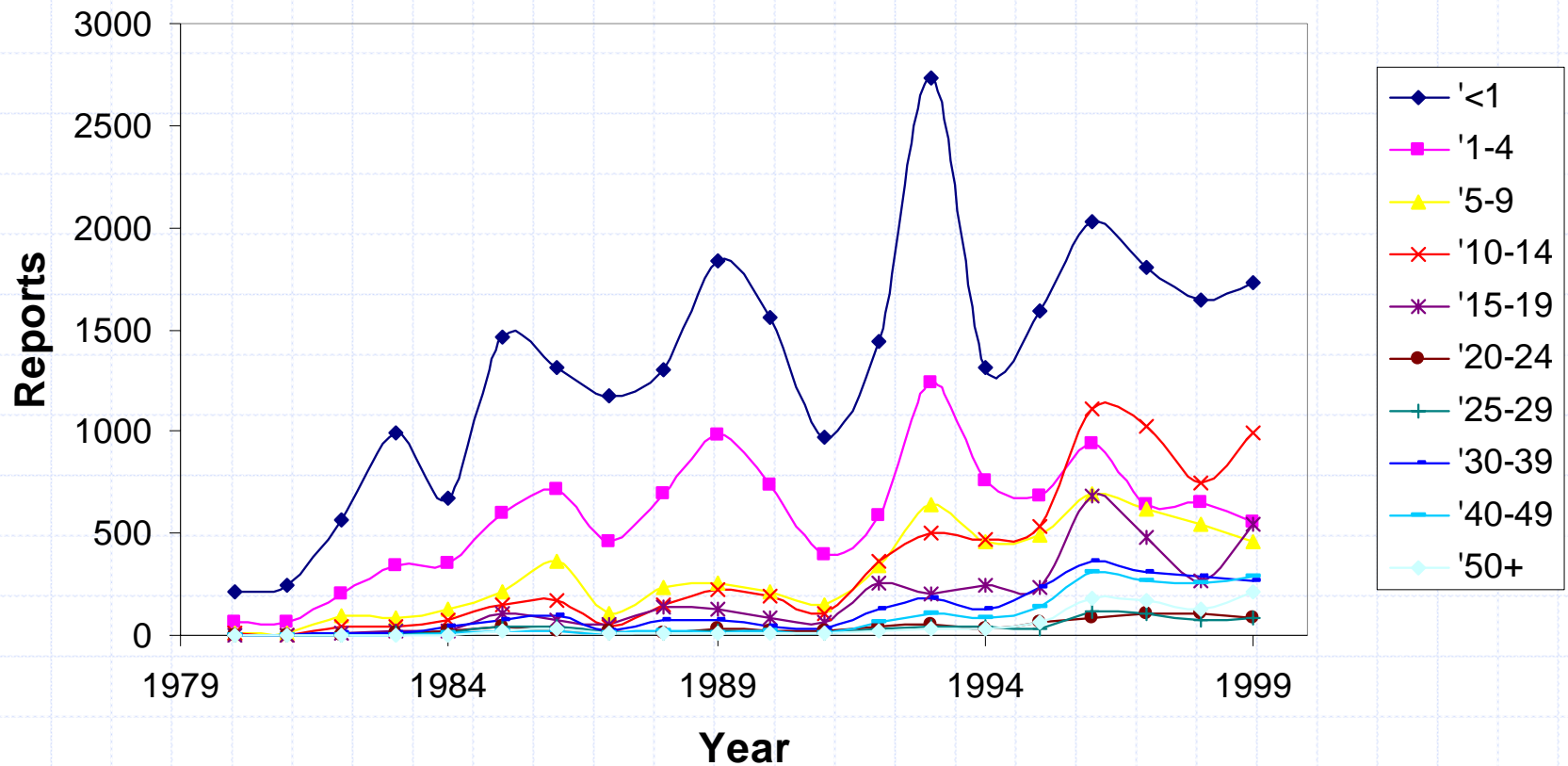
Pertussis in the US, 1976-'99



Source: NNDSS



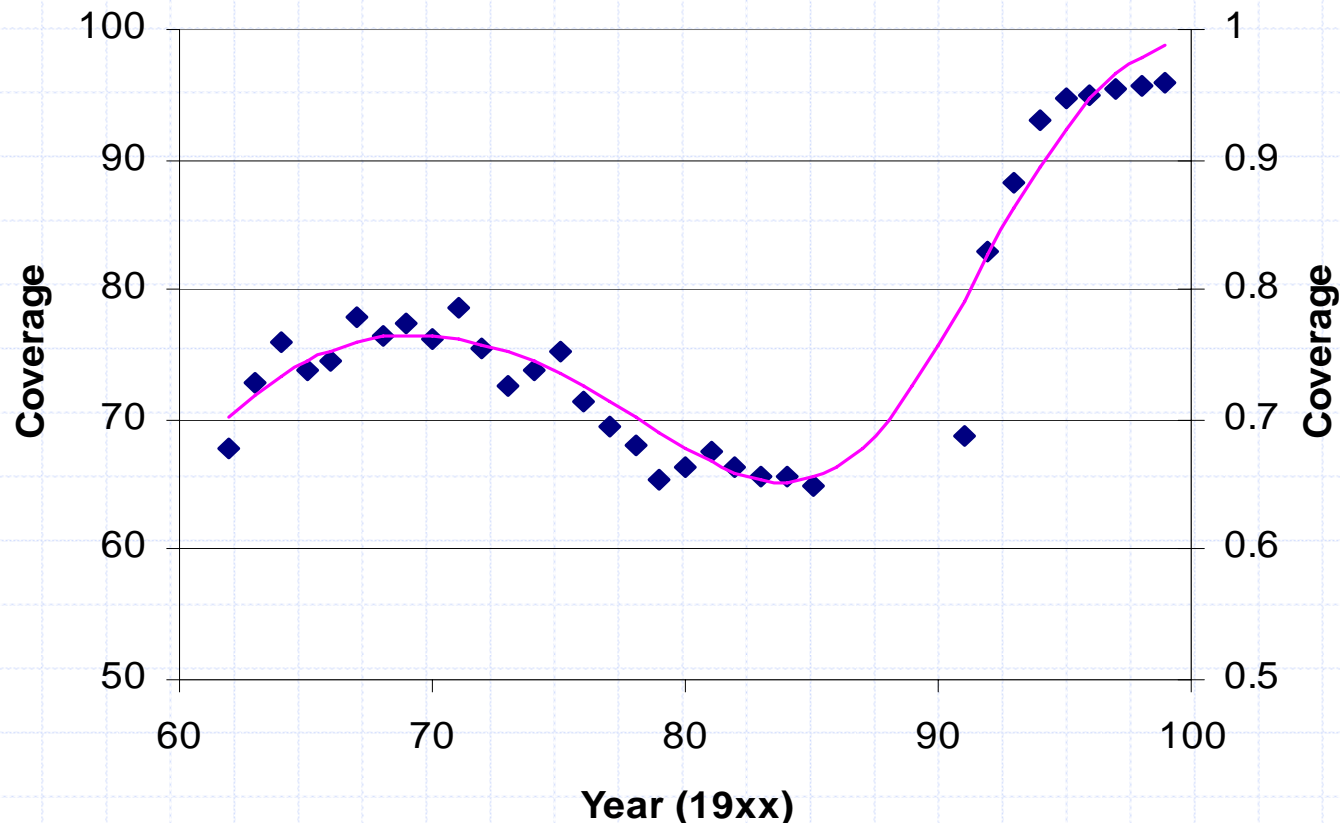
Pertussis in the US, 1980-'99



Source: NNDSS



Despite (because of?) Increased Coverage with Three Doses of DTP



Simpson, D, Ezzati-Rice, T, Zell, E 2001. Forty years and four surveys: How does our measuring measure up? American Journal of Preventive Medicine 20(4S):6-14



Explanations for Changing Epidemiology throughout the Developed World

1. Surveillance artifact – when clinicians learn to recognize immunity-modified disease, they find it among adolescents ...
2. Evolution – selection of antigenic variants against which vaccination is less effective
3. Waning of artificially-induced immunity absent boosting – stay tuned
4. Reduced transmission – when infection rates decline, typical (easily recognized) disease increases among older age groups

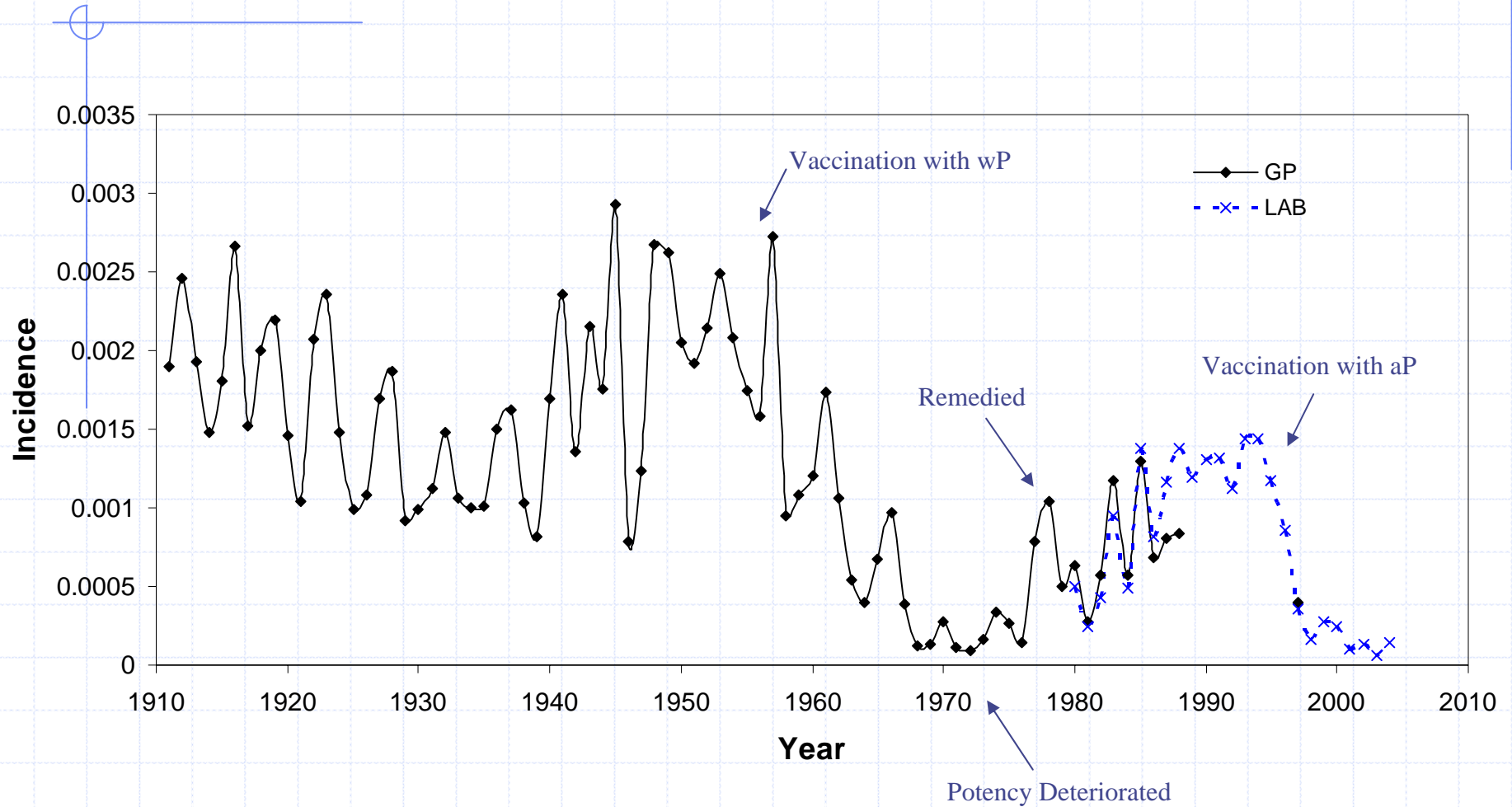


Swedish Collaborators

- Margareta Blennow, Sach's Children's Hospital, Stockholm
- Rose-Marie Carlsson, Smittskyddsinstitutet (SMI)
- Ingela Krantz, Skaraborg Institute for Research & Development, Västra Götaland Region
- Patrick Olin, SMI
- Victoria Romanus, SMI
- Åke Svensson, Stockholm University and SMI
- Birger Trollfors, Sahlgrenska University Hospital, Göteborg
- Peet Tüll, European Centre for Disease Prevention and Control



Pertussis in Sweden



Natural Experiments

- Vaccination with wP began in 1953
- Potency deteriorated 1971-'77
- Remedied 1978-'79
- Hiatus from 1979-'95, during which
- Clinical trials of aP were conducted
- Vaccination resumed in 1996, but
- Counties have used different aPs

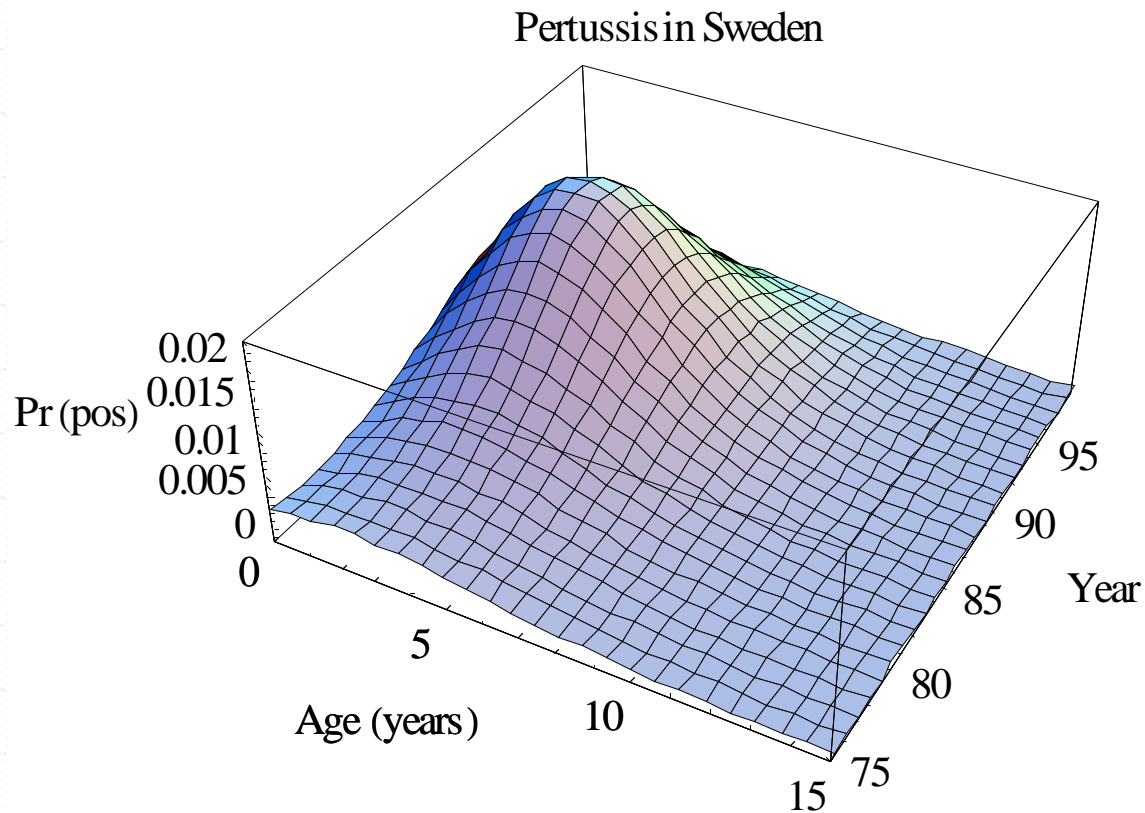


Research Agenda

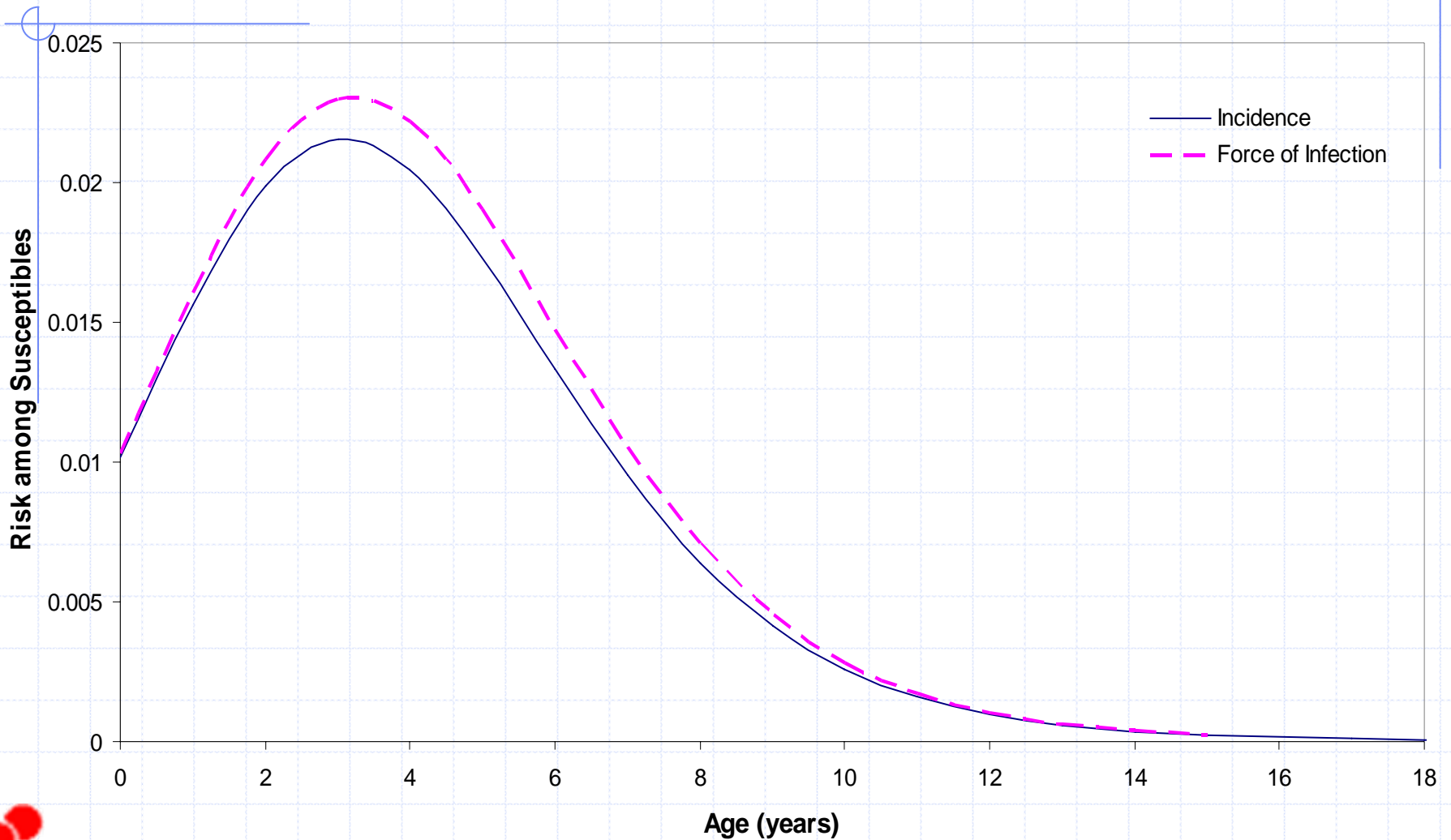
- Estimate contemporary FOI from culture-confirmed cases during 17-year hiatus, and evaluate disposition to submit specimens by comparing to FOI deduced from antibodies to PT soon after vaccination resumed
- Infer age-specific infection rates from FOI, given assumptions about mixing, adjust to fit pre-2000 incidence, compare adjusted to inferred rates to evaluate assumptions, and compare predictions to observations post-2000 to validate model/hypothesis
- Study counties using or having used different aPs to determine their relative effectiveness, predict future incidence and, should booster doses be indicated, determine their optimal timing



Incidence, $\lambda(a,t)S(a,t)/N(a,t)$



As the Hiatus Exceeds the Apparent Period at Risk, $\lambda(a)$ is ...



Switching to Discrete Age, ...

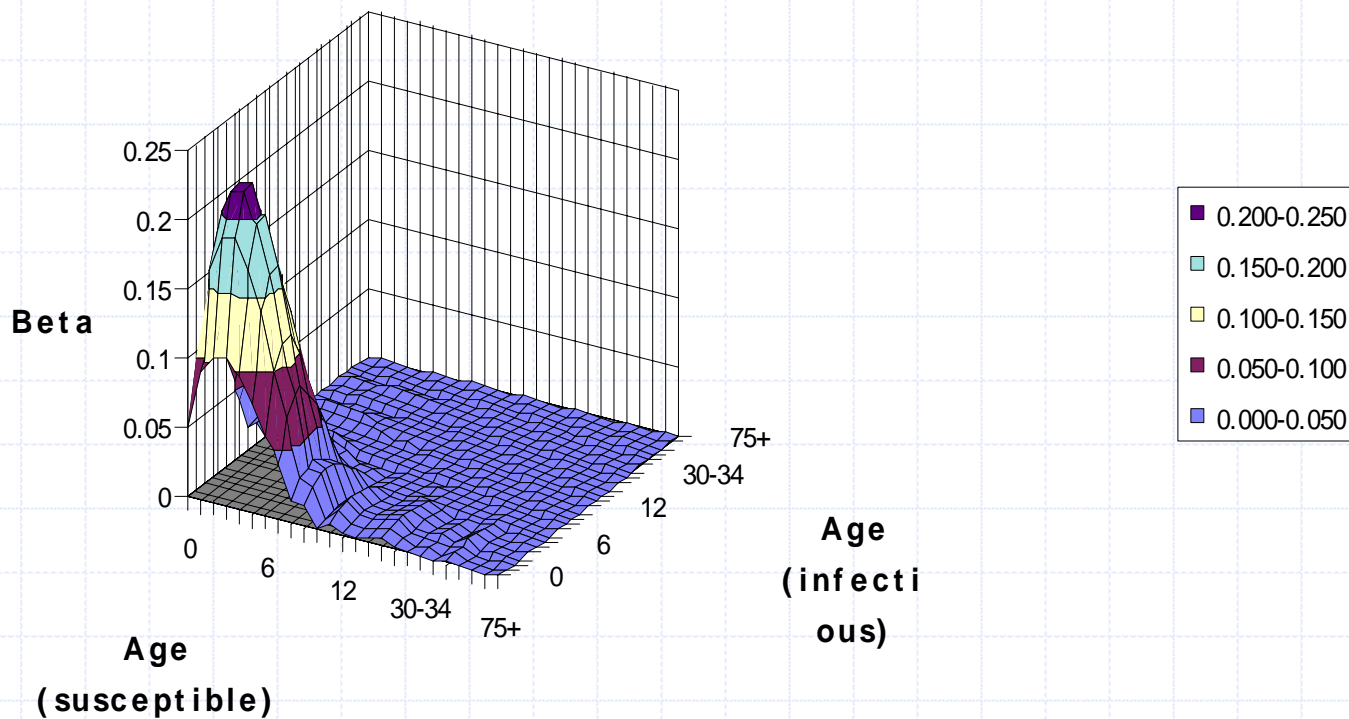
- We can calculate the specific infection rates, β_{ij} , from forces of infection, $\lambda_i(t)$, given assumptions about mixing (i.e., activities and preferences)

$$\lambda_i(t) = \sum_j \beta_{ij} I_j(t),$$

- Or, we can estimate the β_{ij} by modeling infectious, $I_j(t)$, and susceptible people, $S_i(t)$, given suitable time-series, $\lambda_i(t)S_i(t)$
- Doing both, and comparing calculated and adjusted β_{ij} , would evaluate our assumptions about mixing



β_{ij} as Convex Combinations of Activities, b_i given Preference, $0 \leq \varepsilon \leq 1$; here $\varepsilon = 0$



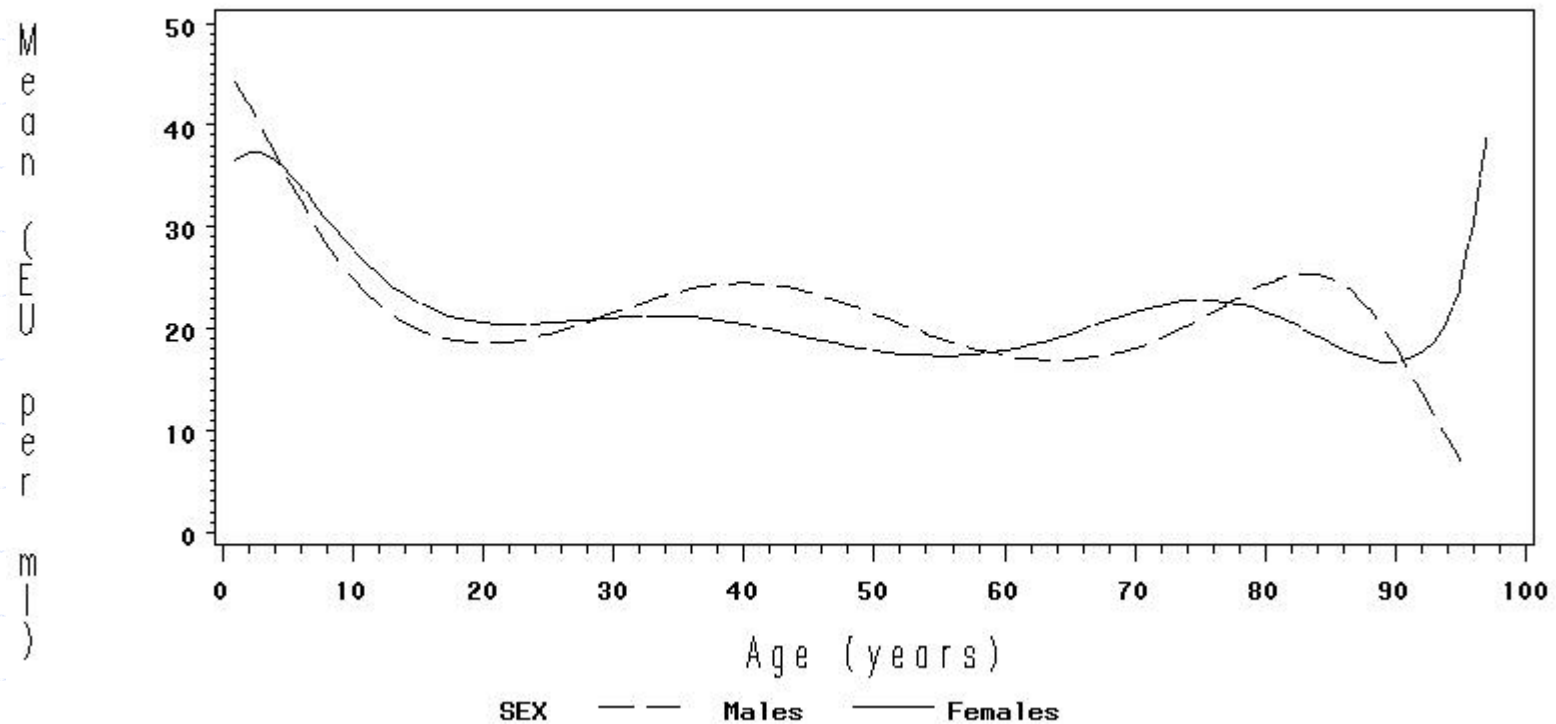
Here $\beta_{ij} = \delta_{ij}\varepsilon b_i + (1-\varepsilon)\sqrt{b_i b_j}$, where $\delta_{ij} = 1$ when $i = j$, but 0 otherwise, ε is preference for others the same age and the b_i are activities.



Swedish Cross-sectional Serosurvey

IgG to Pertussis Toxin

Sweden, 1997



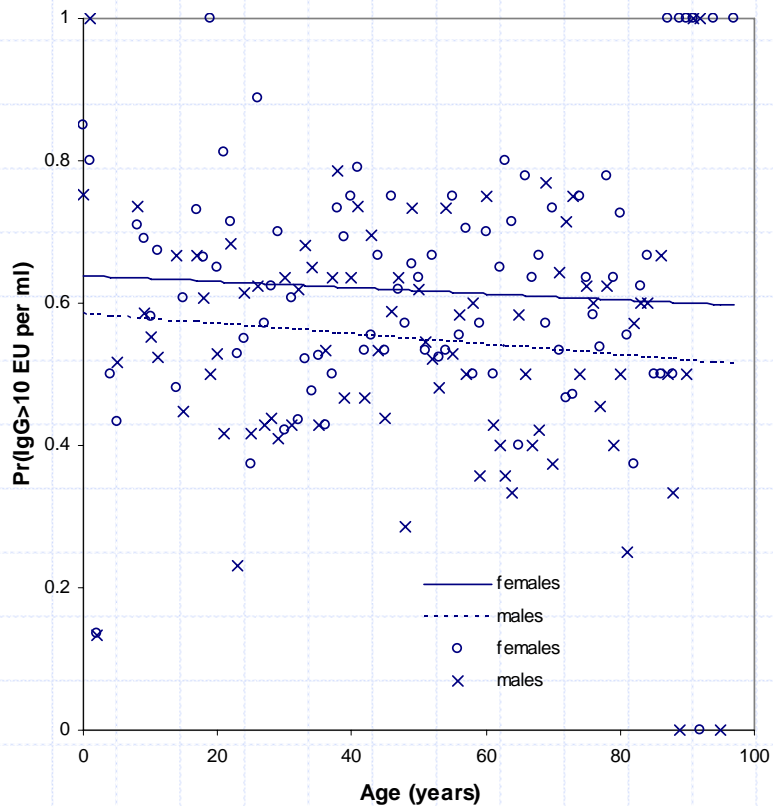
Bias in Disposition to Culture?

- Inferred FOIs consistent with anti-PT soon after resumption of vaccination:
- Most infections occur among young children, but mean at older ages ~2x protective level
- Together with 5-10 year duration of immunity, suggests constant reinfection
- Lack of systematic variation with gender may reflect equal responsibility for child care

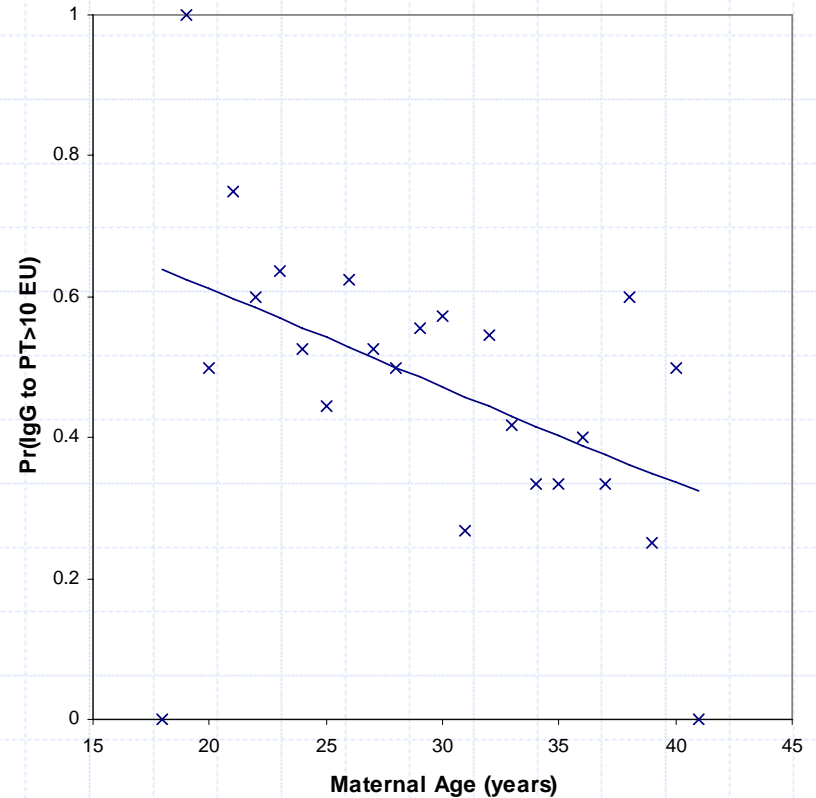


Initial Conditions, 1997

People (N=3241)



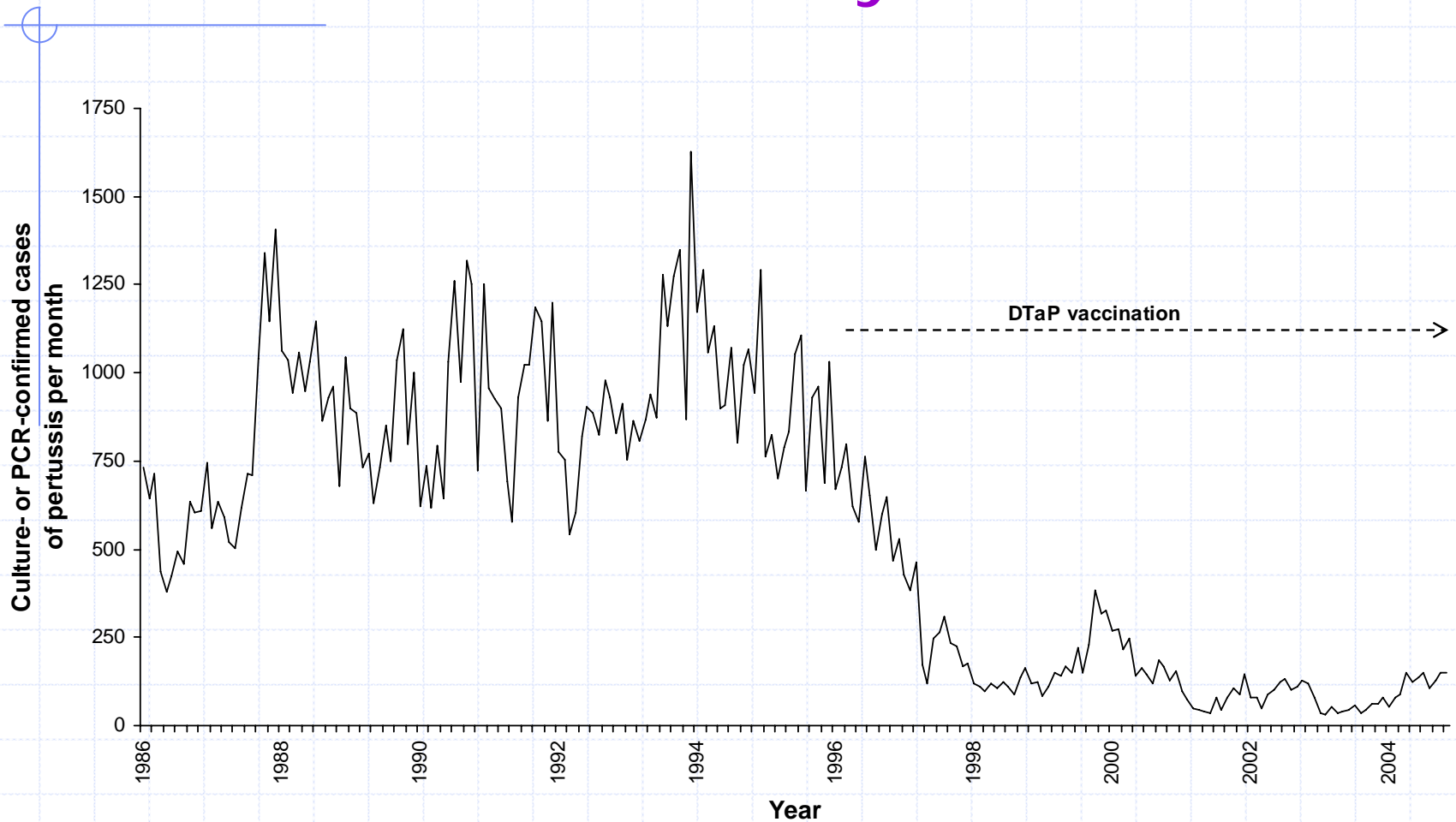
Cord Blood (N=226)



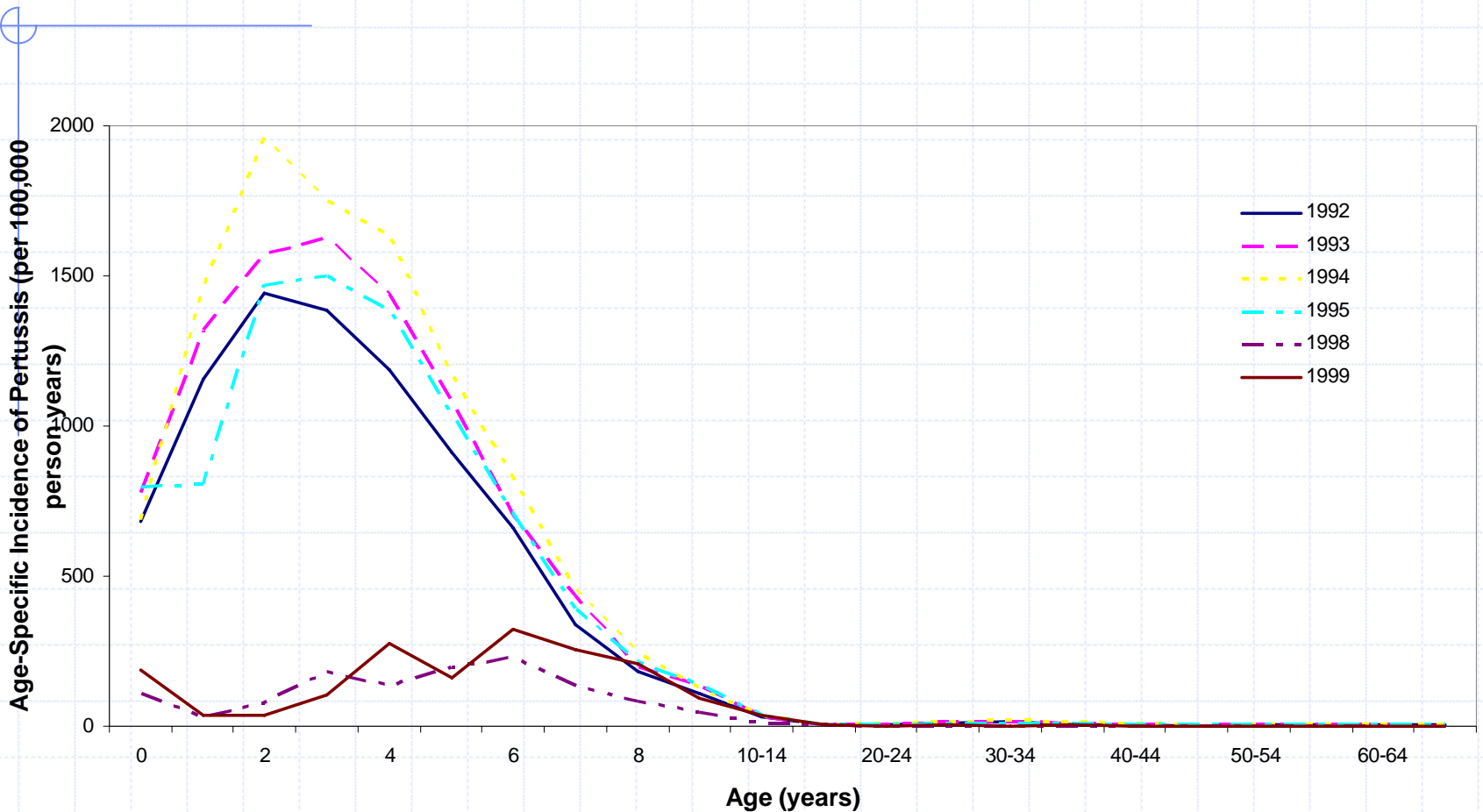
10 EU threshold of protection (personal communication, Joop Schellekens, RIVM)



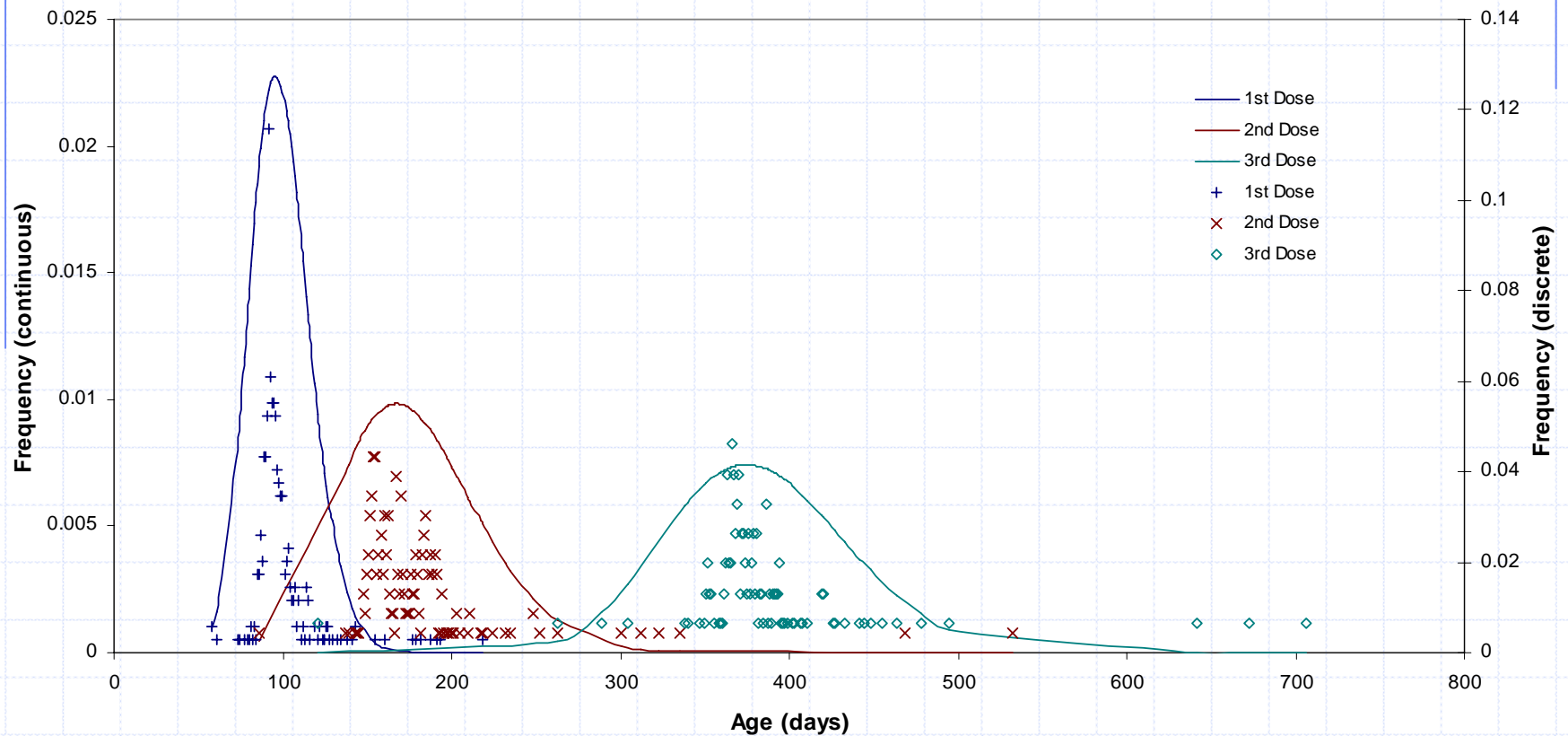
Return to Endemicity in Sweden



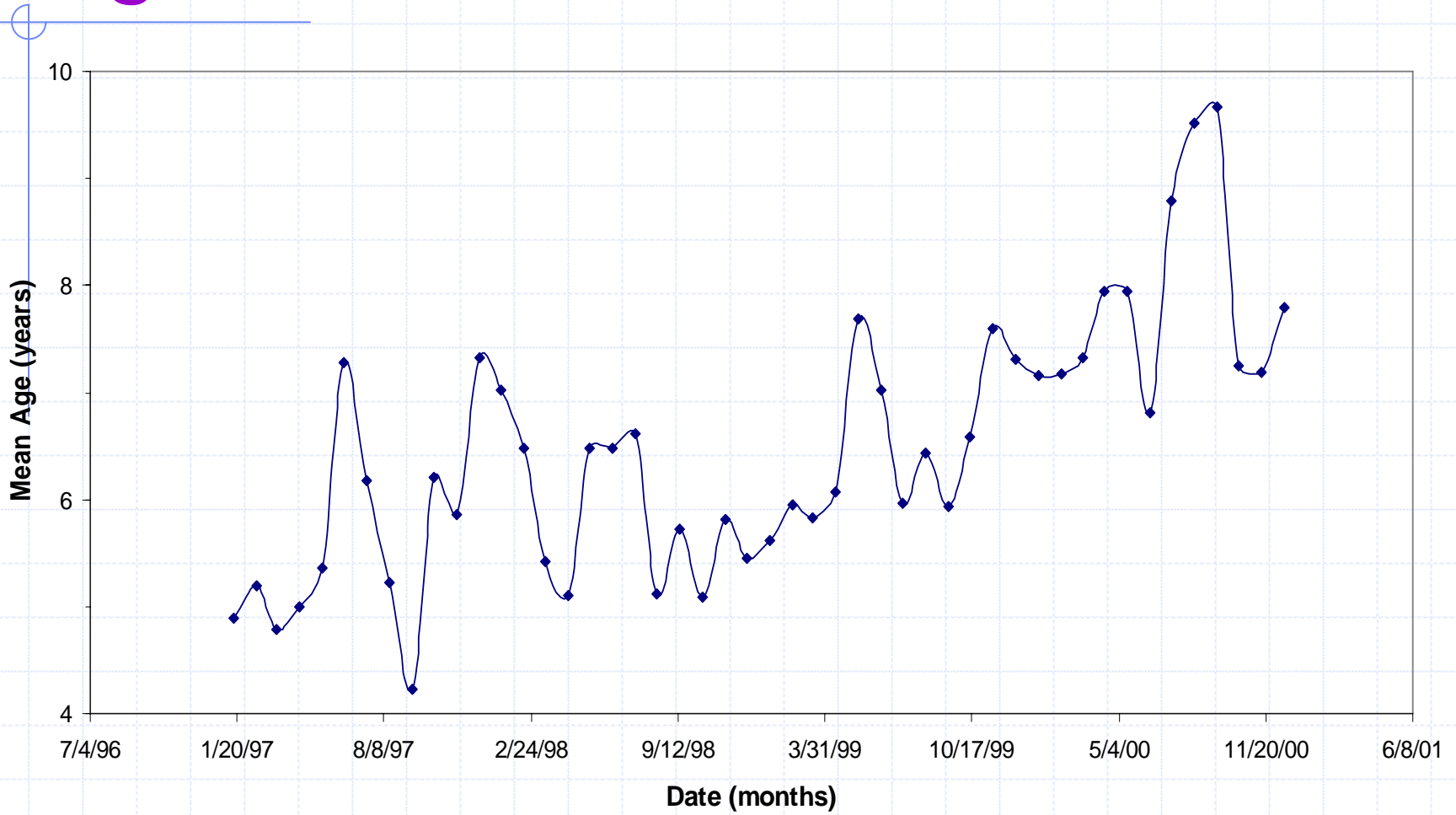
Transition from Pre- to Post-Vaccination Incidence



98% Vaccinated at 3, 5, and 12 Months of Age



Age at Pertussis Infection



Childhood Vaccination ...

- Always increases the mean age of infection, but when immunity wanes and ...
- Coverage is high, immunity declines enough for clinically-apparent disease upon exposure
- If coverage is low, immunity is frequently boosted via exposure to ill children
- So, disease spectrum depends on exposure, which in turn depends on coverage
- Transmission (λS vs β) has indeed been reduced in the developed world, but by vaccination



Serological Analyses (US)

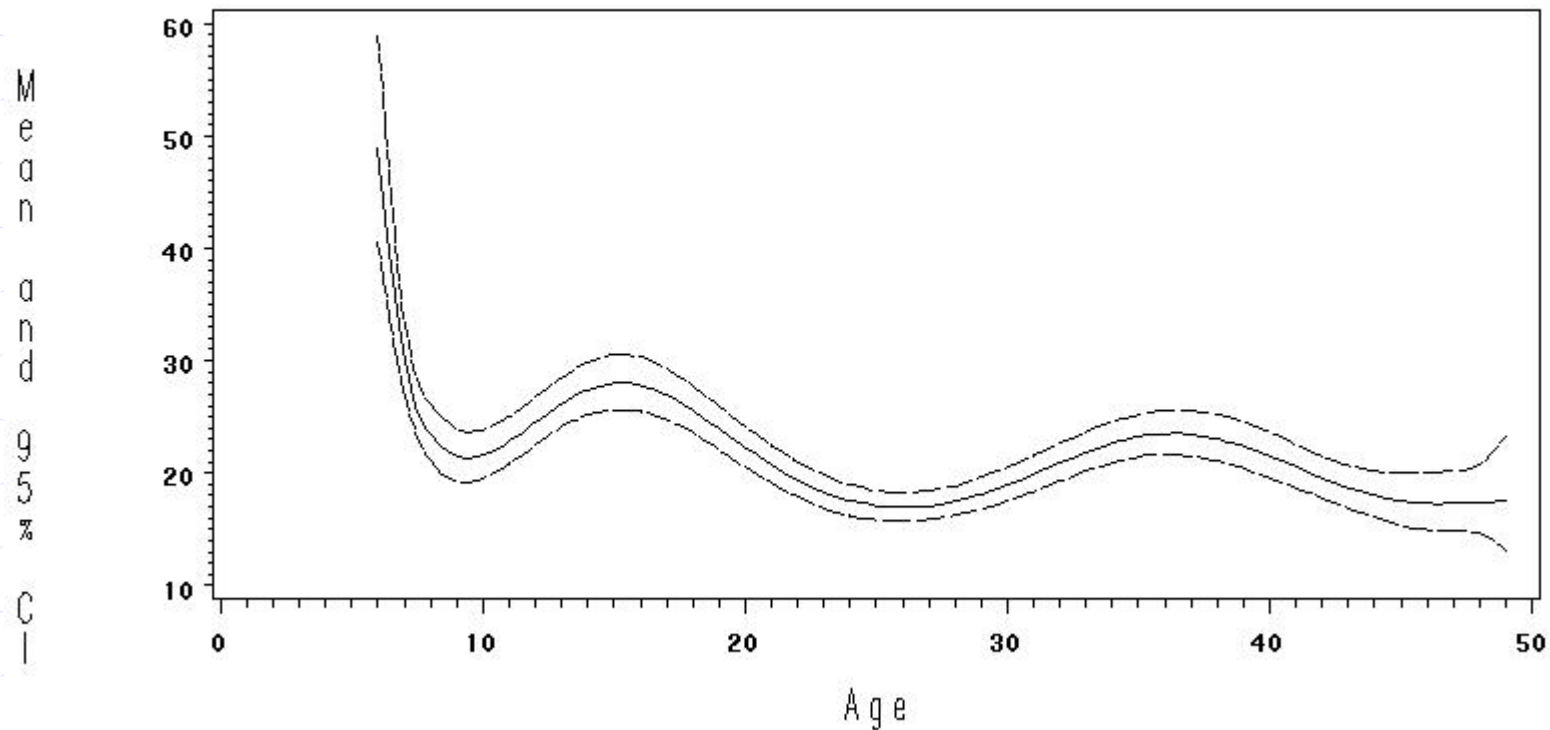
- In NHANES III, 1991-'94, antibodies to PT, FHA and FIM types 2 and 3 were assayed in 6,137 sera from people aged 6-49 years
- Questionnaire includes information about recent respiratory illnesses and prior vaccination, neither controlled in this analysis
- FOIs resemble mean IgG to PT (next slide) or $Pr > 94$ EU per ml ([†]Baughman, et al., figure 2), indicating recent infection or vaccination

[†]Baughman, AL, et al. 2004. Clin Diagn Lab Immunol 11:1045-53.

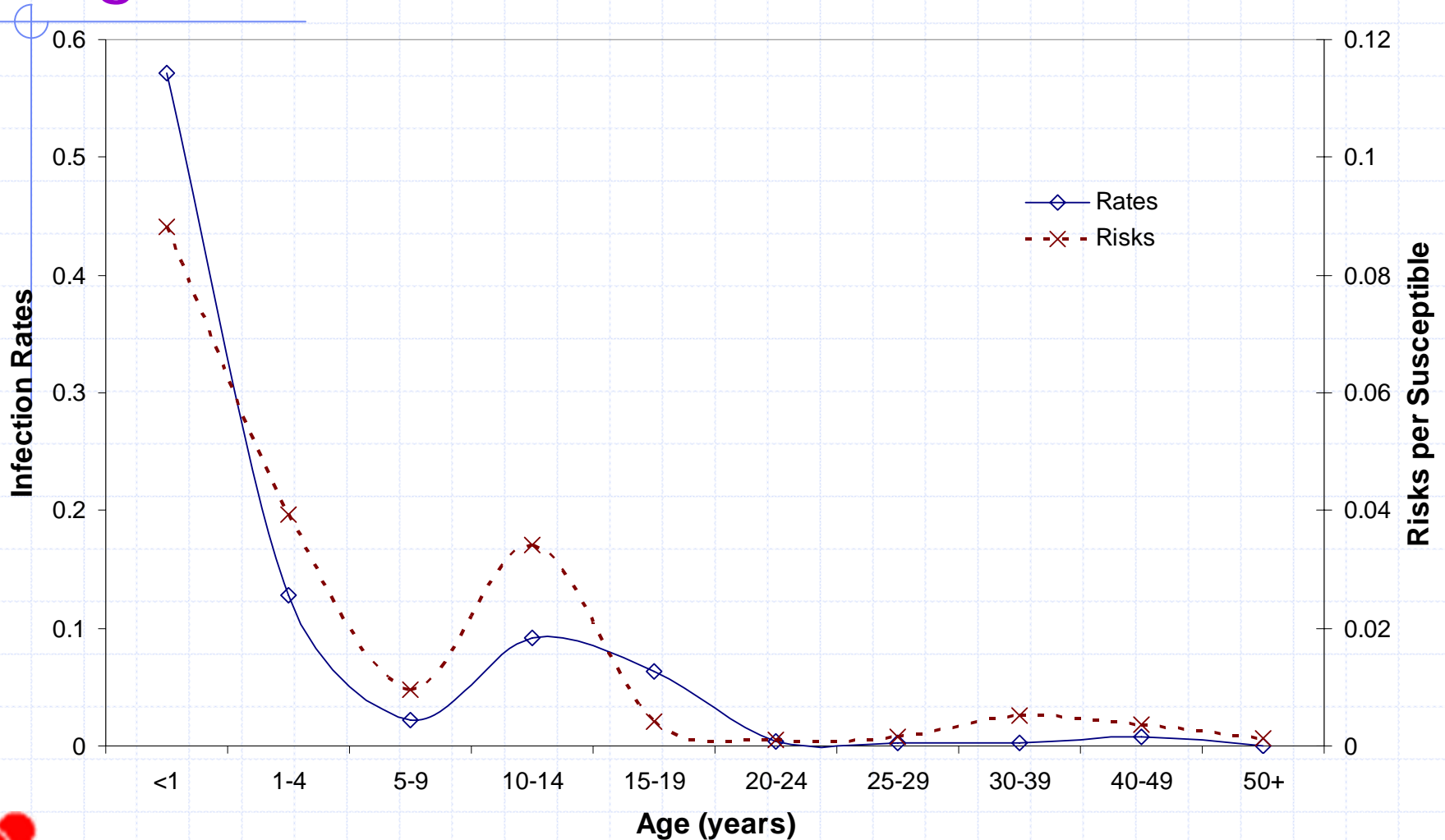


US Cross-sectional Serosurvey

IgG to Pertussis Toxin
Pertussis Serology from NHANES III



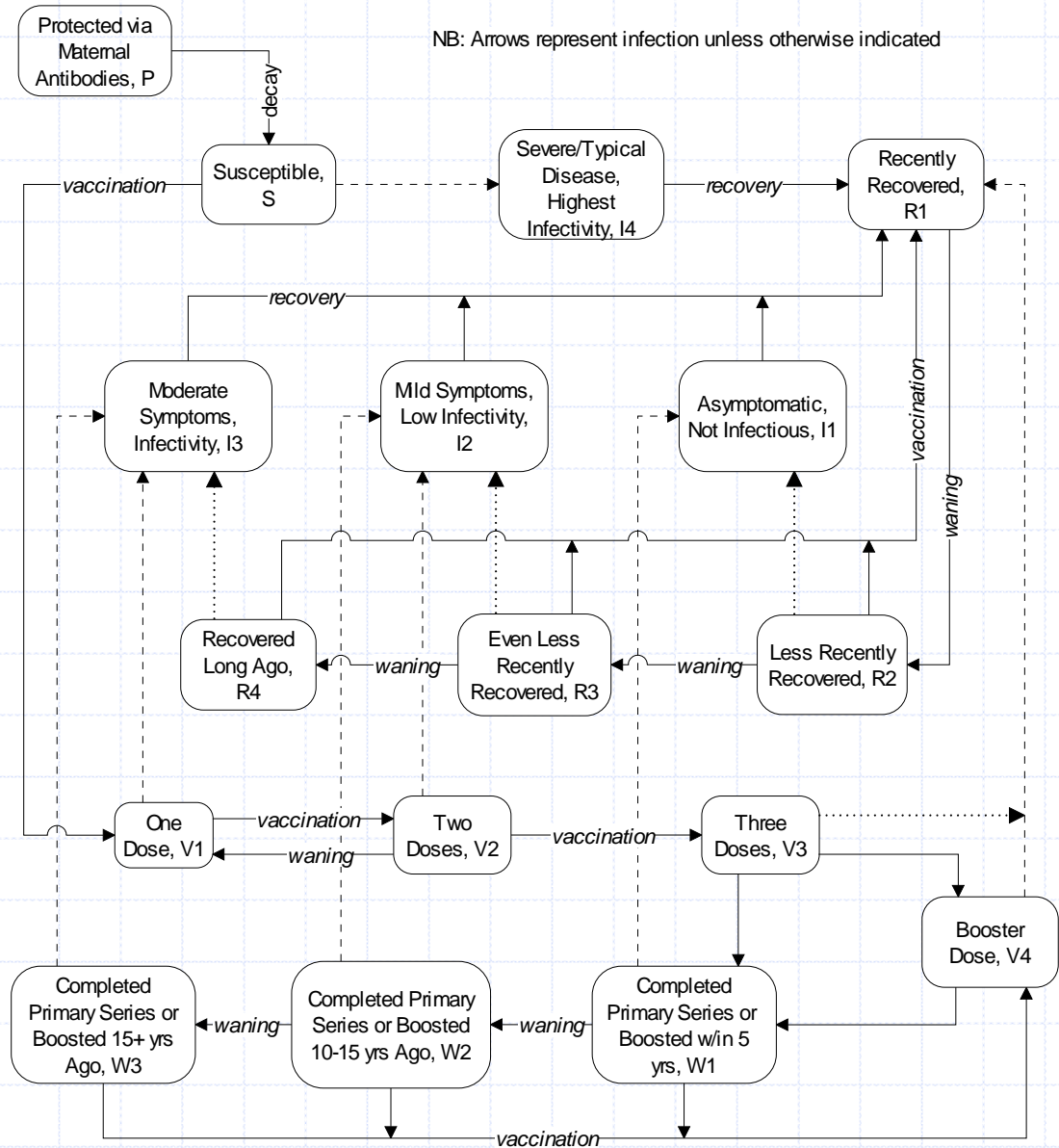
From Adjusted β_{ij} 's and "Equilibrium" Age-Distributions in the US, 1990-99



Model

Features:

- Waning of immunity, artificially-induced and naturally-acquired at different rates
- Incremental protection from successive doses
- Permits additional booster doses (e.g., adolescents or young adults)
- Never regain immunological naïveté



Population Projection

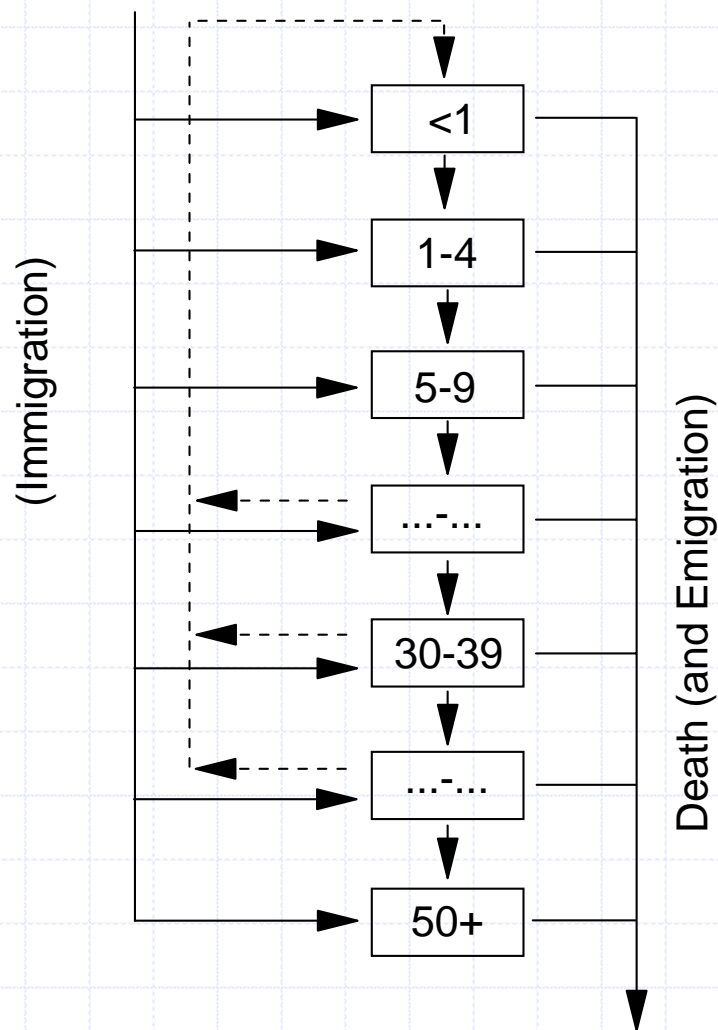
Demographic methods are standard and requisite information is readily available:

- Population by age and gender
- Age-specific deaths
- Births by age of mother
- Age-specific migration (if indicated)



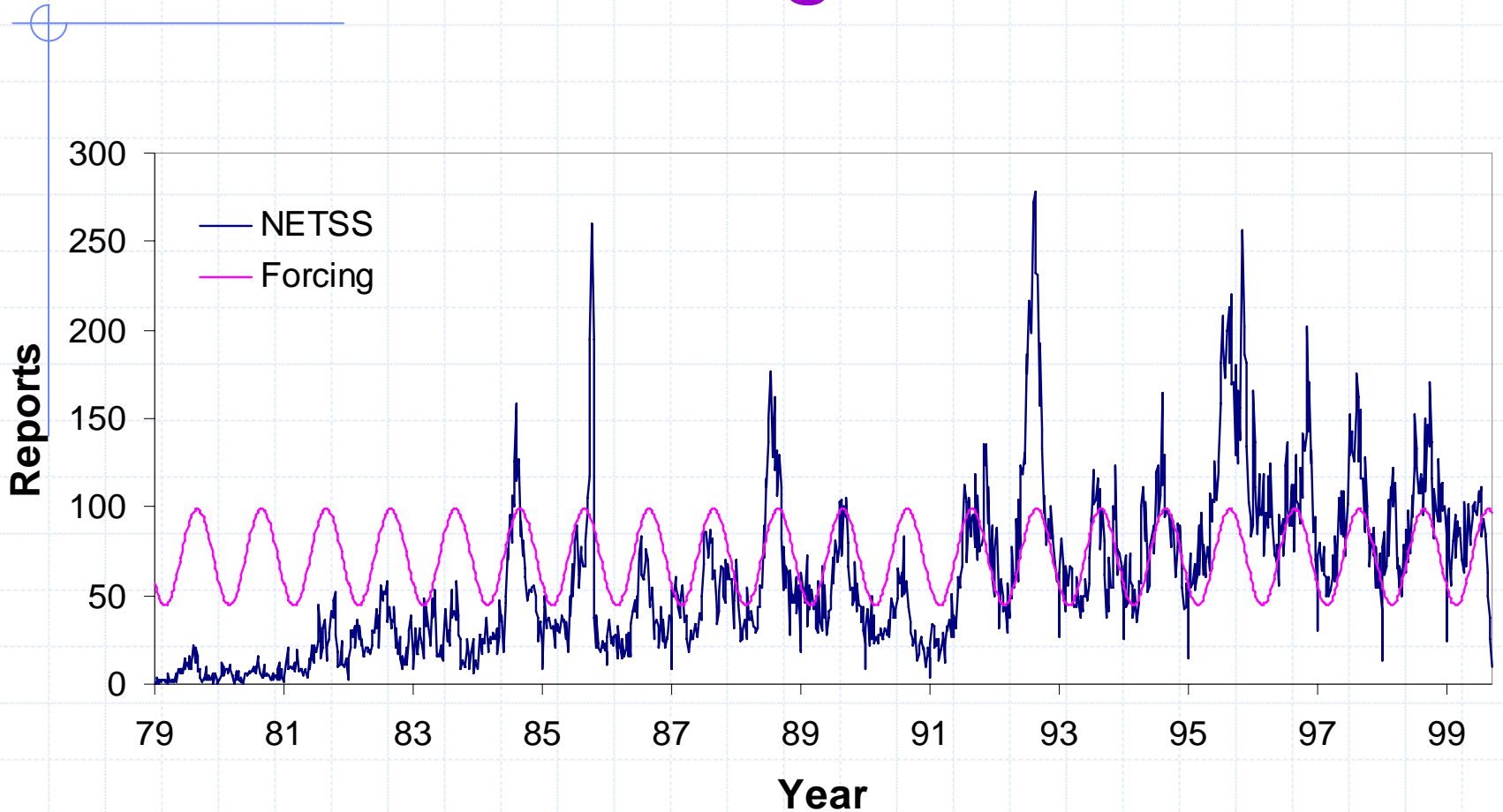
Features:

- Any number and size of age groups
- Dynamic population by virtue of age-specific birth, death, and ...
- If indicated, immigration and emigration rates



NB: Unlabeled vertical arrows represent aging and dashed ones birth. Migration is not presently modeled.

Seasonal Forcing in the US



Harmonic Forcing

$$Y_t = \mu + \alpha \sin(\omega_t t + \delta) + e_t,$$

where e_t is a sequence of uncorrelated $(0, \sigma^2)$ variates, the amplitude α is small relative to the variance of e_t and ω_t is the frequency in radians (i.e., $2\pi/365.25$). Now,

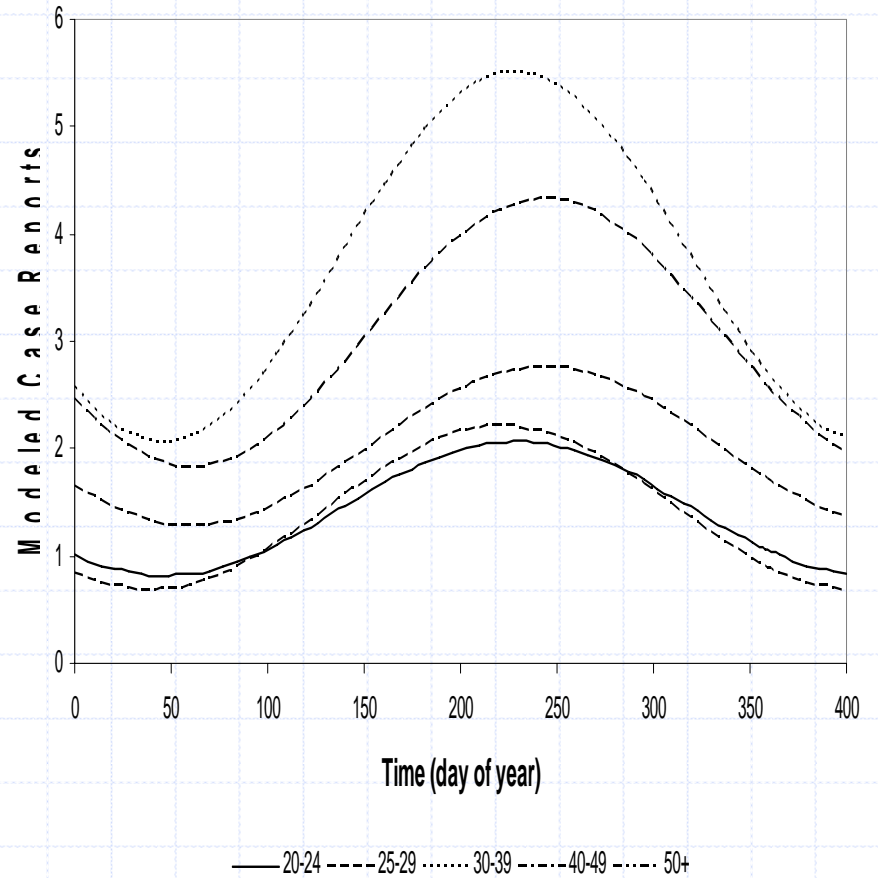
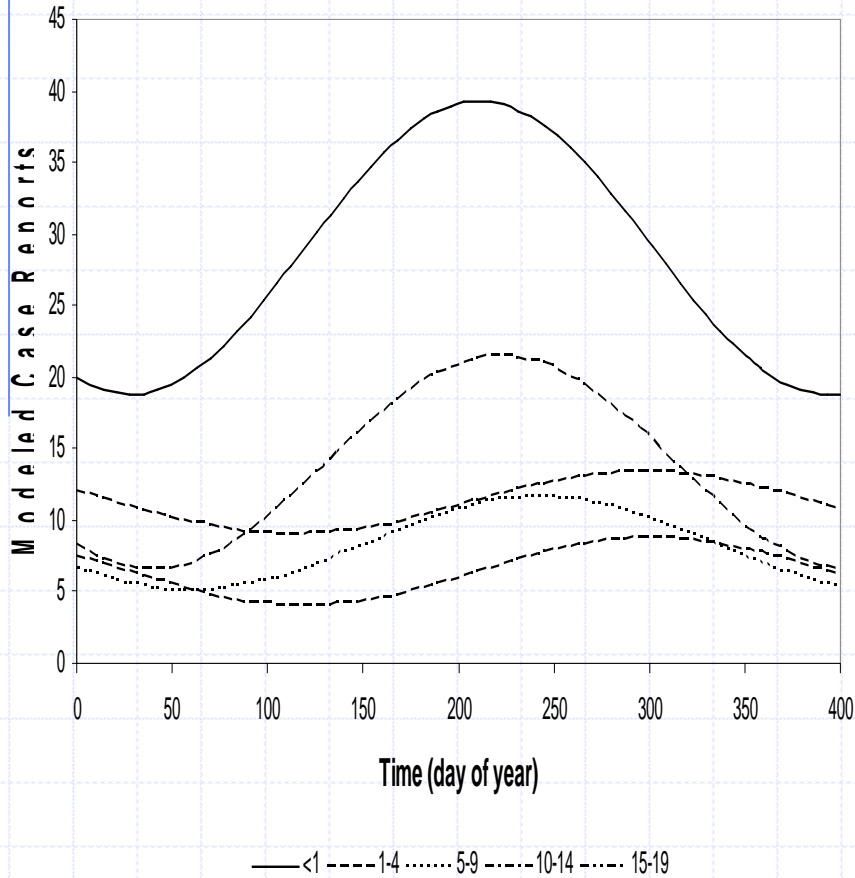
$$\alpha \sin(\omega_t t + \delta) = A \sin(\omega_t t) + B \cos(\omega_t t),$$

where $A^2 + B^2 = \alpha^2$ and $\tan(\delta) = B/A$. To identify where the forcing occurs, we estimate age-specific α_i and β_i .

$$SF_i = 1 + [\alpha_i \sin(\omega_t t) + \beta_i \cos(\omega_t t)].$$



Age-Specificity



CDC Models (contributors)

1. No waning (MW, HH)
2. Waning of artificially-induced and naturally-acquired immunity, but asymmetric boosting
3. Symmetric boosting, waning during and post-primary series (... , JG, PS)
4. Population projection, age-distributed vaccinations, refined parameters (... , PO, PT)
5. Age-specific forcing (... , MT)

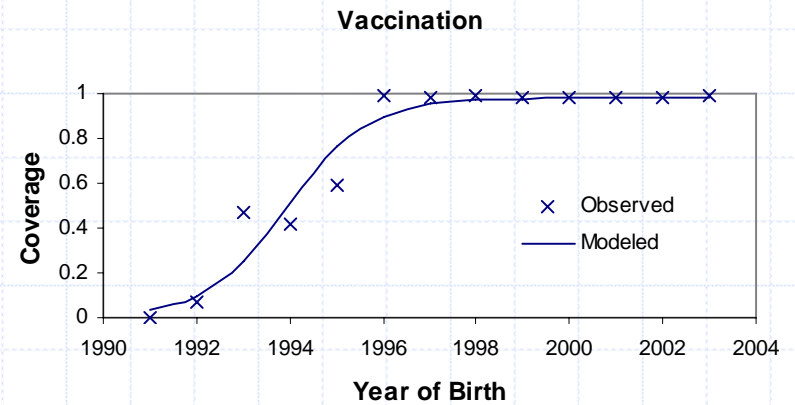
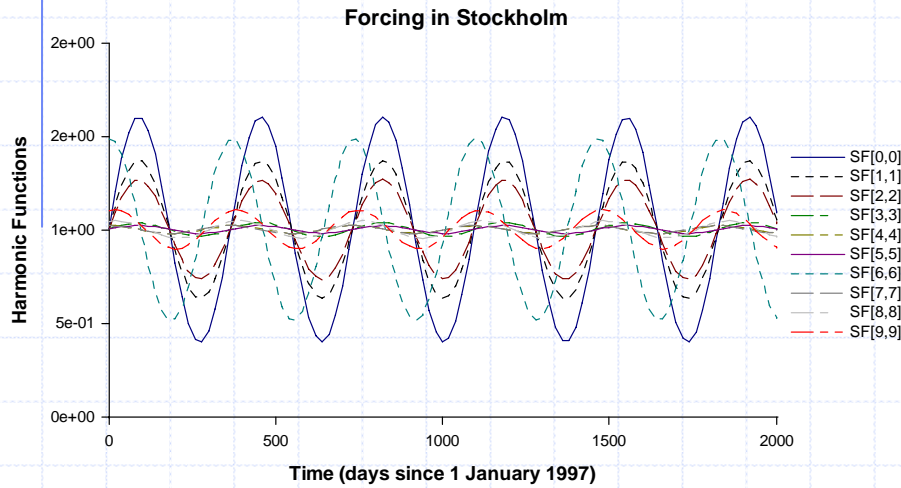


Model 5

- Why force? Disease is transmitted among age-classes, adolescents are out of phase, and policy questions concern adolescents
- Does the school calendar cause this seasonality? If cycles among school-aged children don't predominate, what age-specificity is observed?
- Will the model system resonate with an approximately 3-year period? Isn't this yet another opportunity for validation?



Pertussis in Sweden

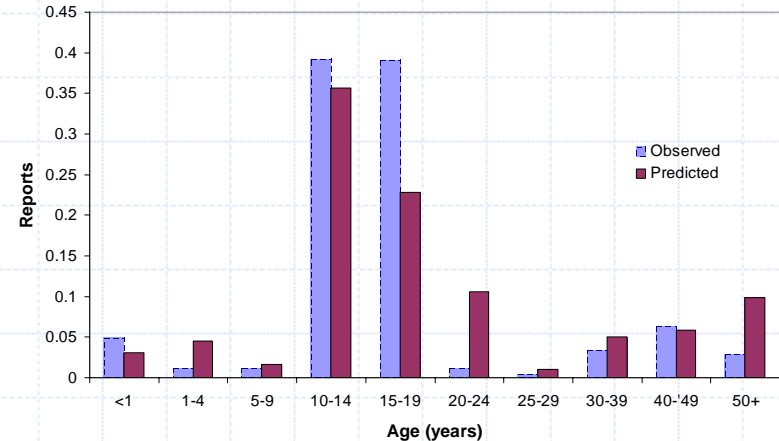
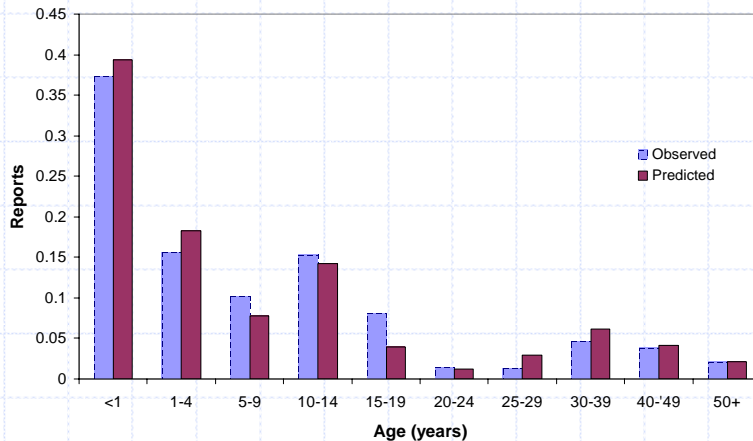


Heterogeneity

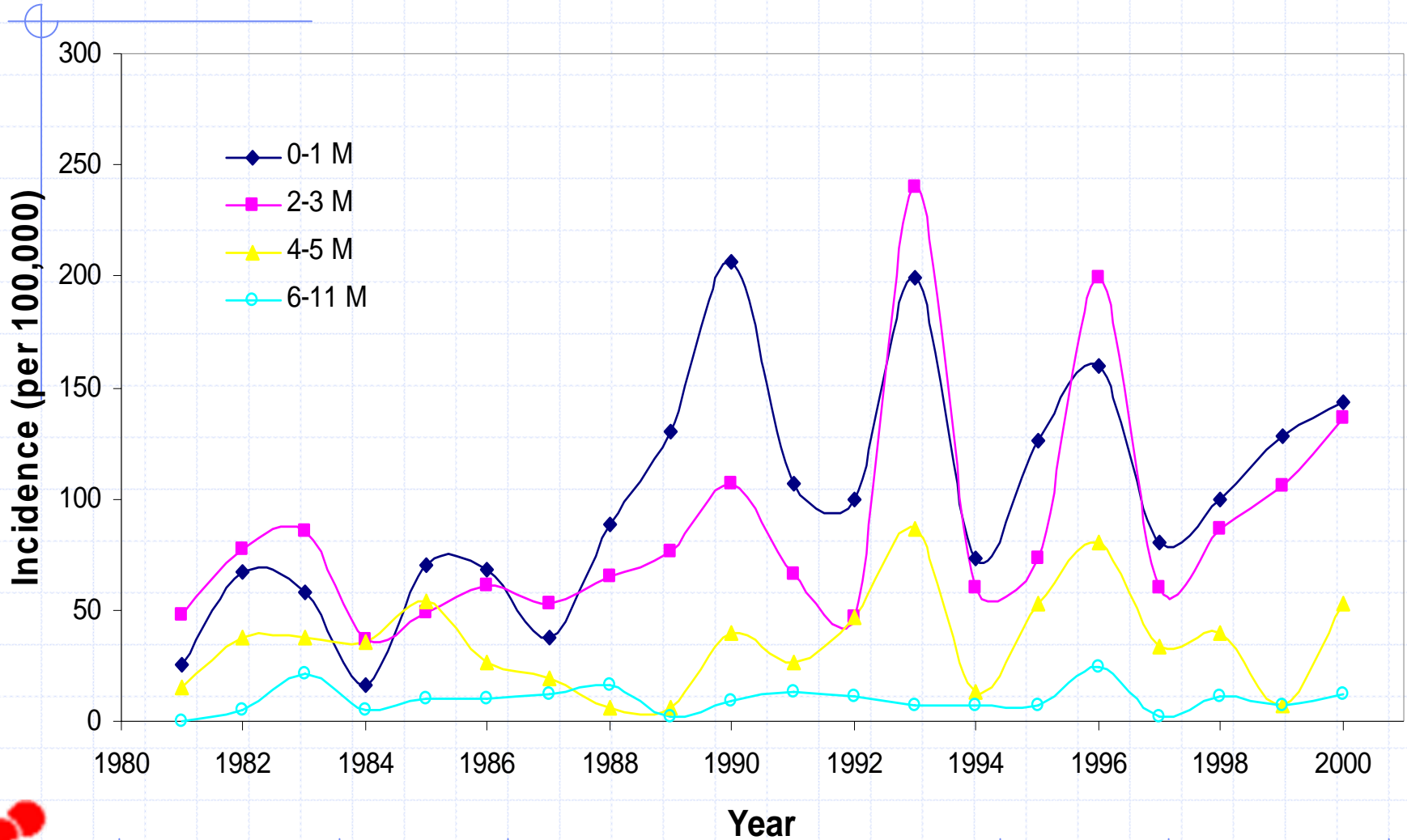
- States attaining higher coverage earlier (and sustaining it longer), ...
- Of which MA is the best example, report more cases among adolescents than young children
- Young infants at risk of serious disease can be infected by older siblings or, in high coverage states
- By caretakers, who may not realize they are infectious, but whose frequent contacts are intimate
- If they, in turn, were infected by adolescents, vaccination would be indicated
- Simulations suggest vaccinating older adolescents is optimal, but only marginally better than younger ones



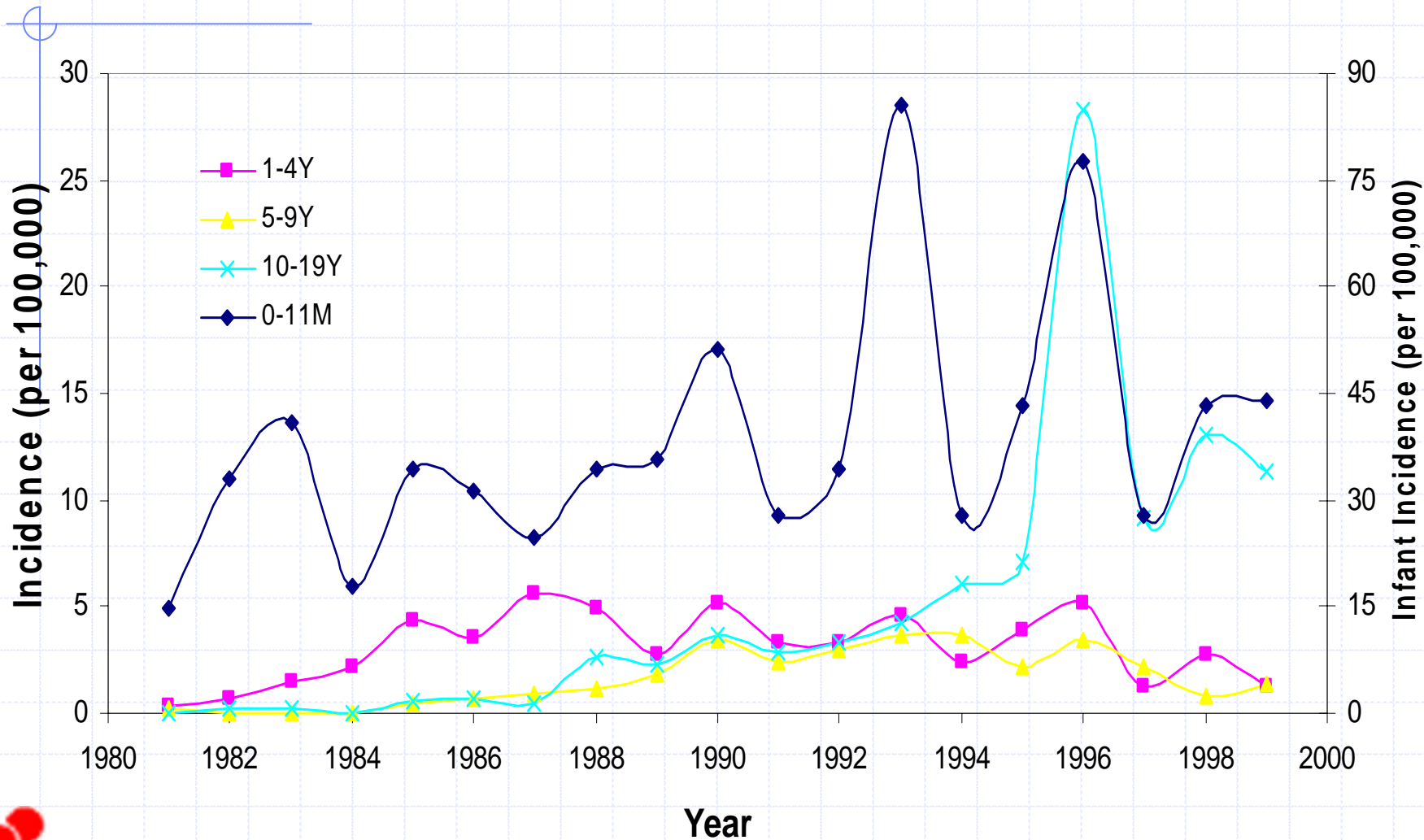
Pertussis in MA (right) and Other States (left), 1990-99



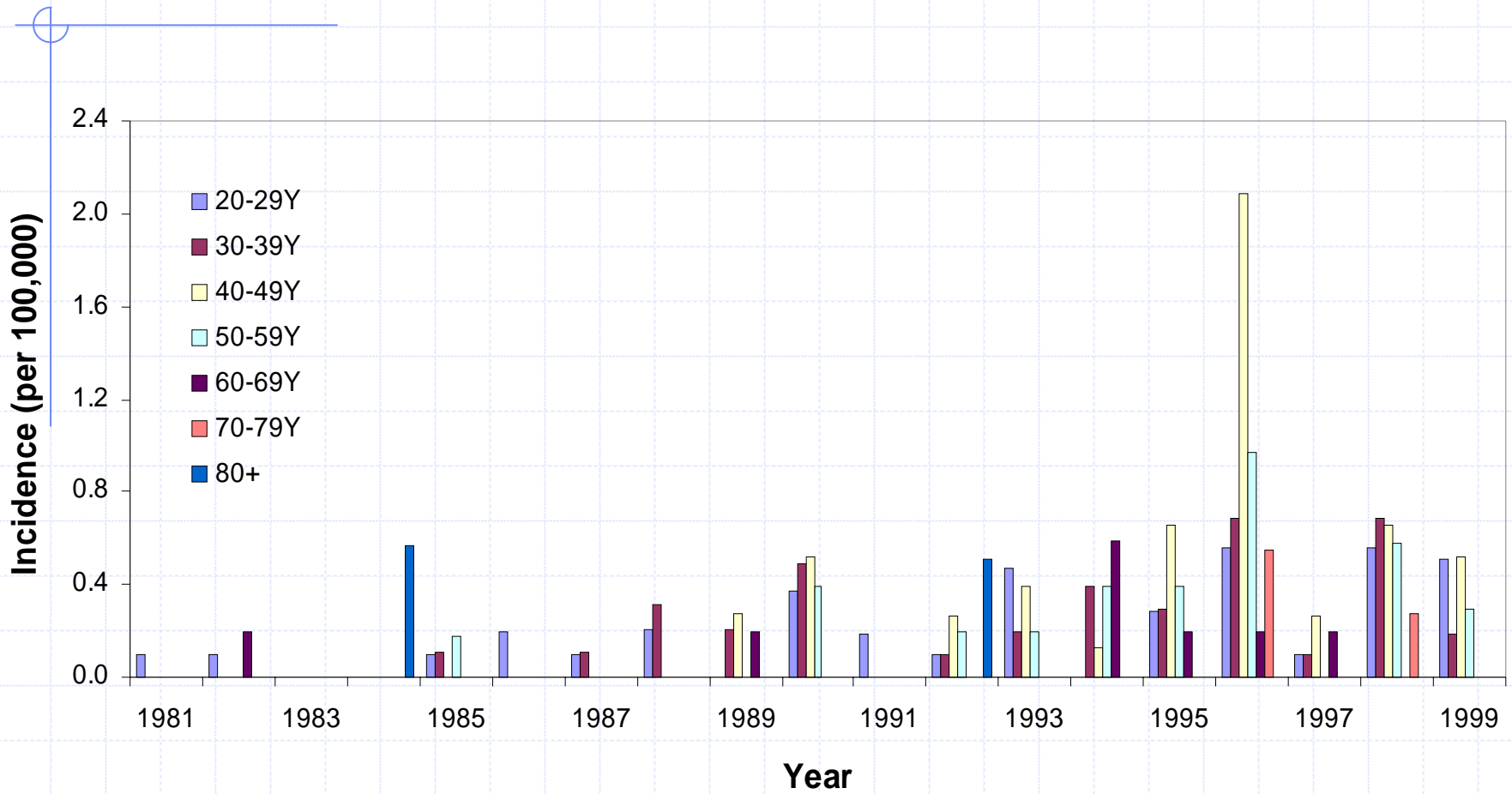
Infant Pertussis in MA



Childhood Pertussis in MA



Adult Pertussis in MA



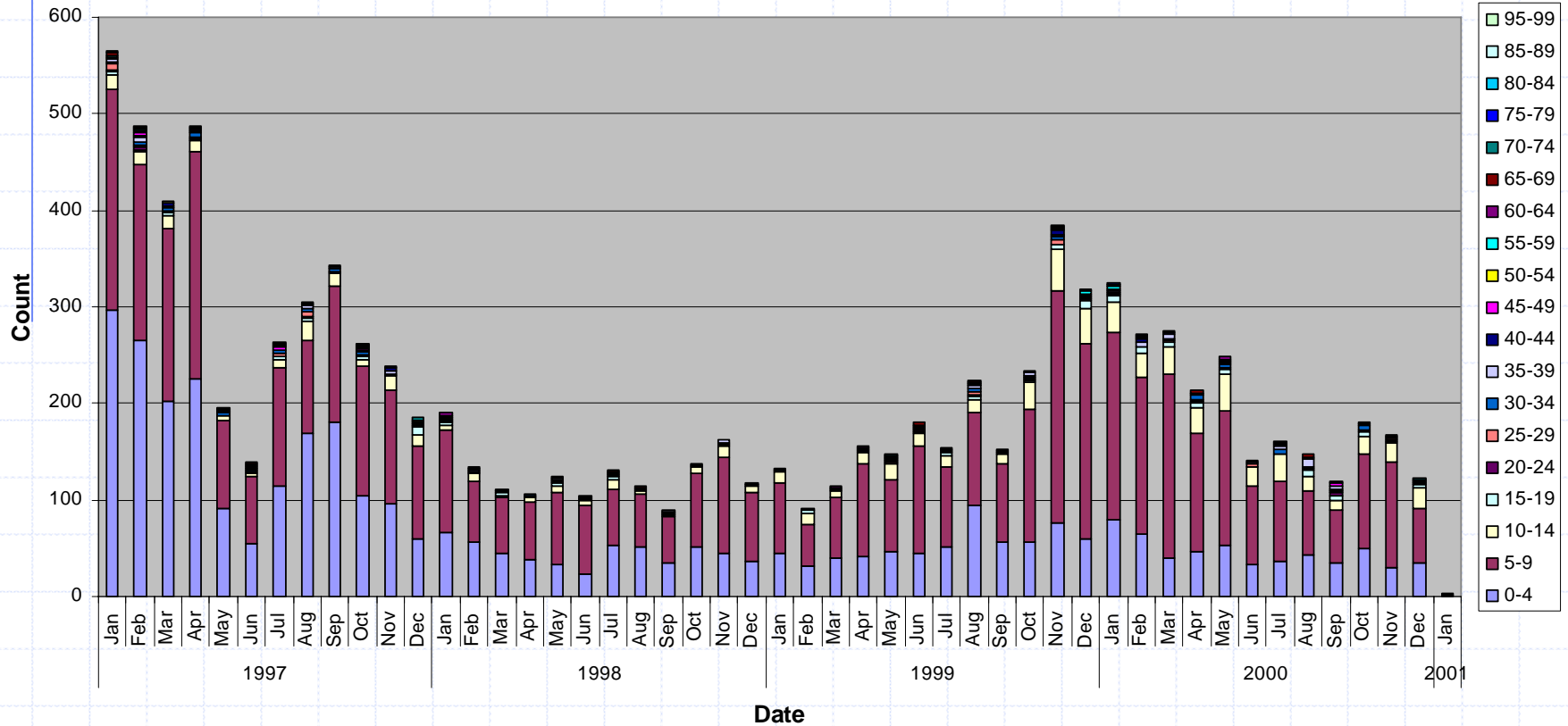
Enhanced Pertussis Surveillance in Sweden

- Colleagues at SIIDC have collected national data on age-specific incidence of culture-confirmed *Bordetella pertussis* since 1986, ...
- And, to document the effect of acellular pertussis vaccines given at 3, 5 and 12 months of age on pertussis in Sweden, ...
- CHC nurses have conducted follow-up interviews of culture-confirmed cases among children born since 1996 via telephone



Déjà vu?

Pertussis in Sweden



Research Opportunities

- Biology – what factors predispose to severe disease?
- Epidemiology – what is responsible for secular pattern?
- Methodology – how do age groups mix?
- Serology – comparison of profiles and laboratory-based incidence
- Vaccinology – comparison of counties or regions using different products



Sources

Sweden

- Rose-Marie Carlsson
- Patrick Olin
- Victoria Romanus

Massachusetts

- Susan Lett
- Stephanie Schauer

