Implications of an Explanation for Secular Patterns in Reported Pertussis in the United States

Mathematical Modeling† of Infectious Diseases: Dynamics and Control

Institute for Mathematical Sciences

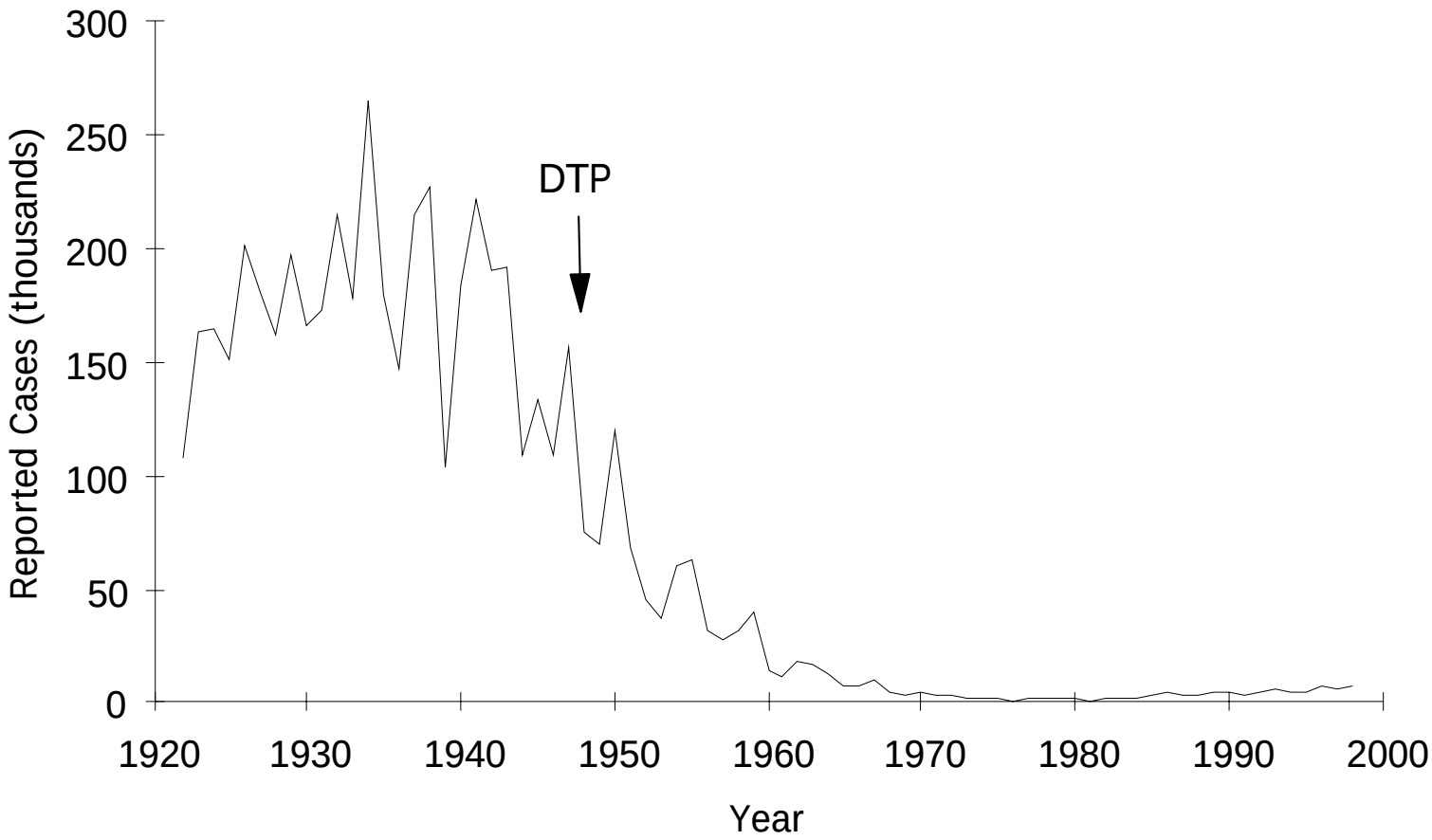
National University of Singapore

†"And the mathematical method of treatment is really nothing but the application of careful reasoning to the problems at hand." Sir Ronald Ross

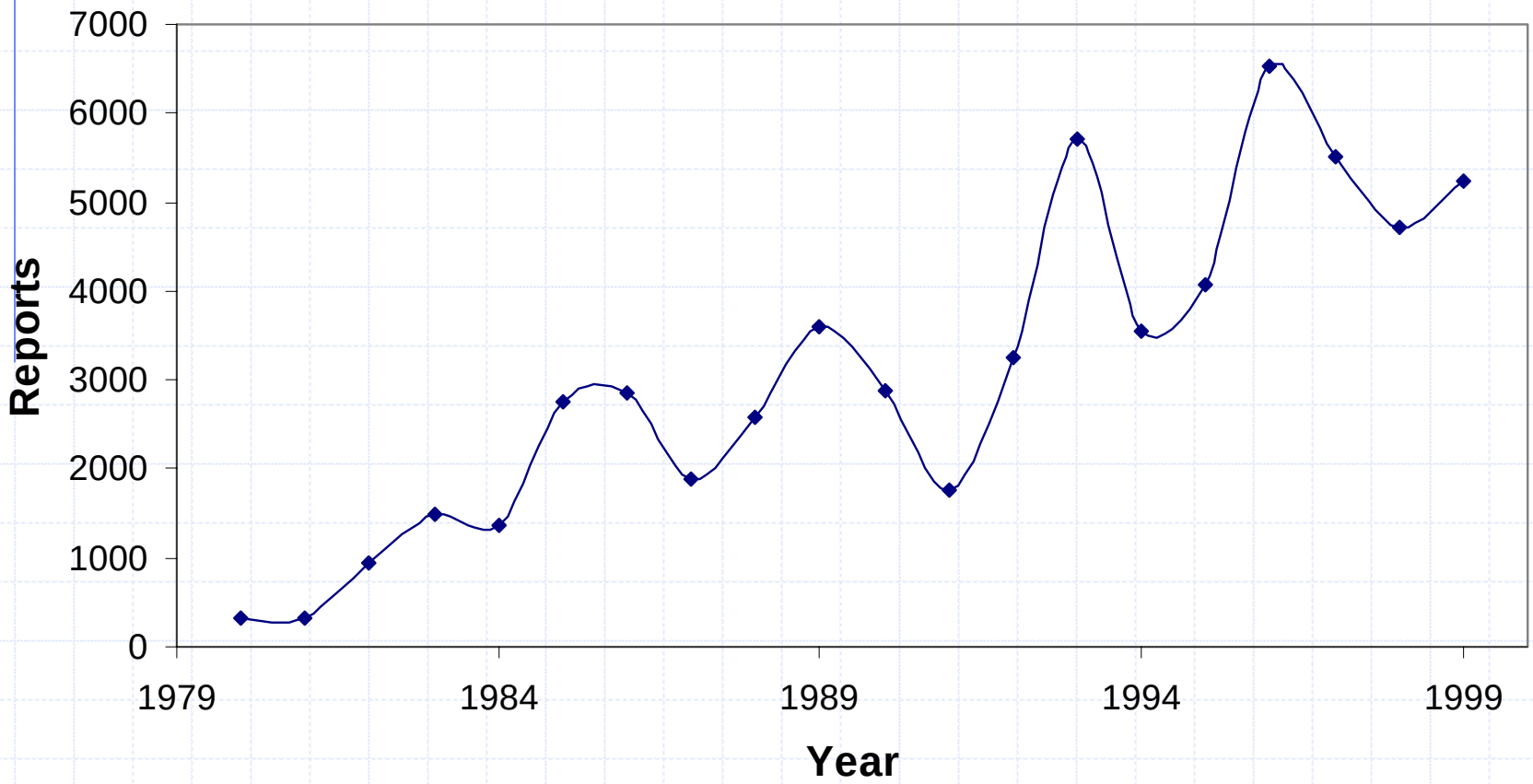
Purpose today

- Unusual use of modeling, possibly because of our practical versus theoretical orientation, …
- … to elucidate as-yet-poorly understood disease against which we've been vaccinating children for more than half a century
- Several of us are interested in models of this sort, if not this model
- Inability to evaluate a key feature to which results are (quantitatively) sensitive diminishes its utility as a policymaking tool
- Yet such a tool is needed, at home as well as abroad

Pertussis in the United States

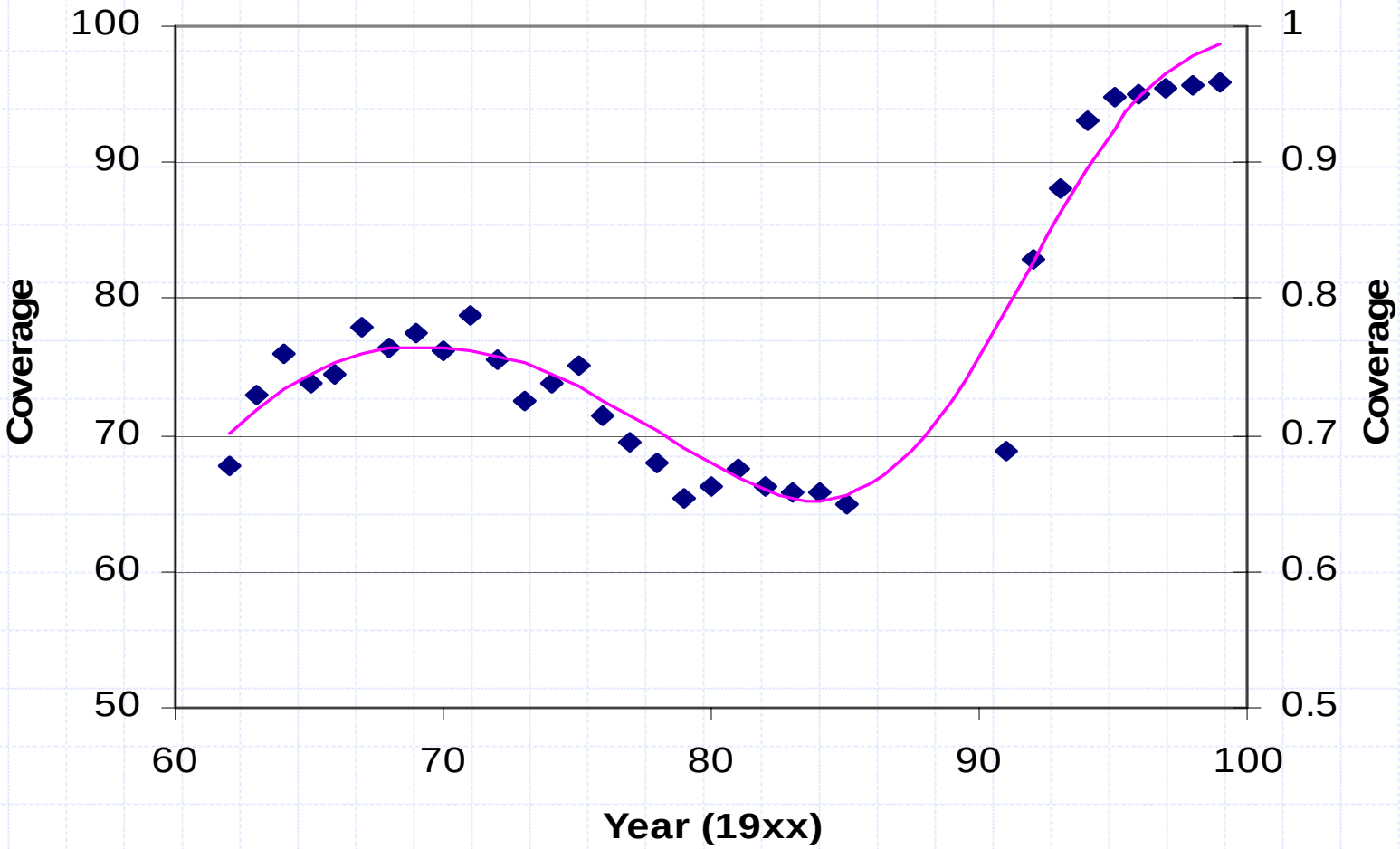


Pertussis in the US, 1976-’99



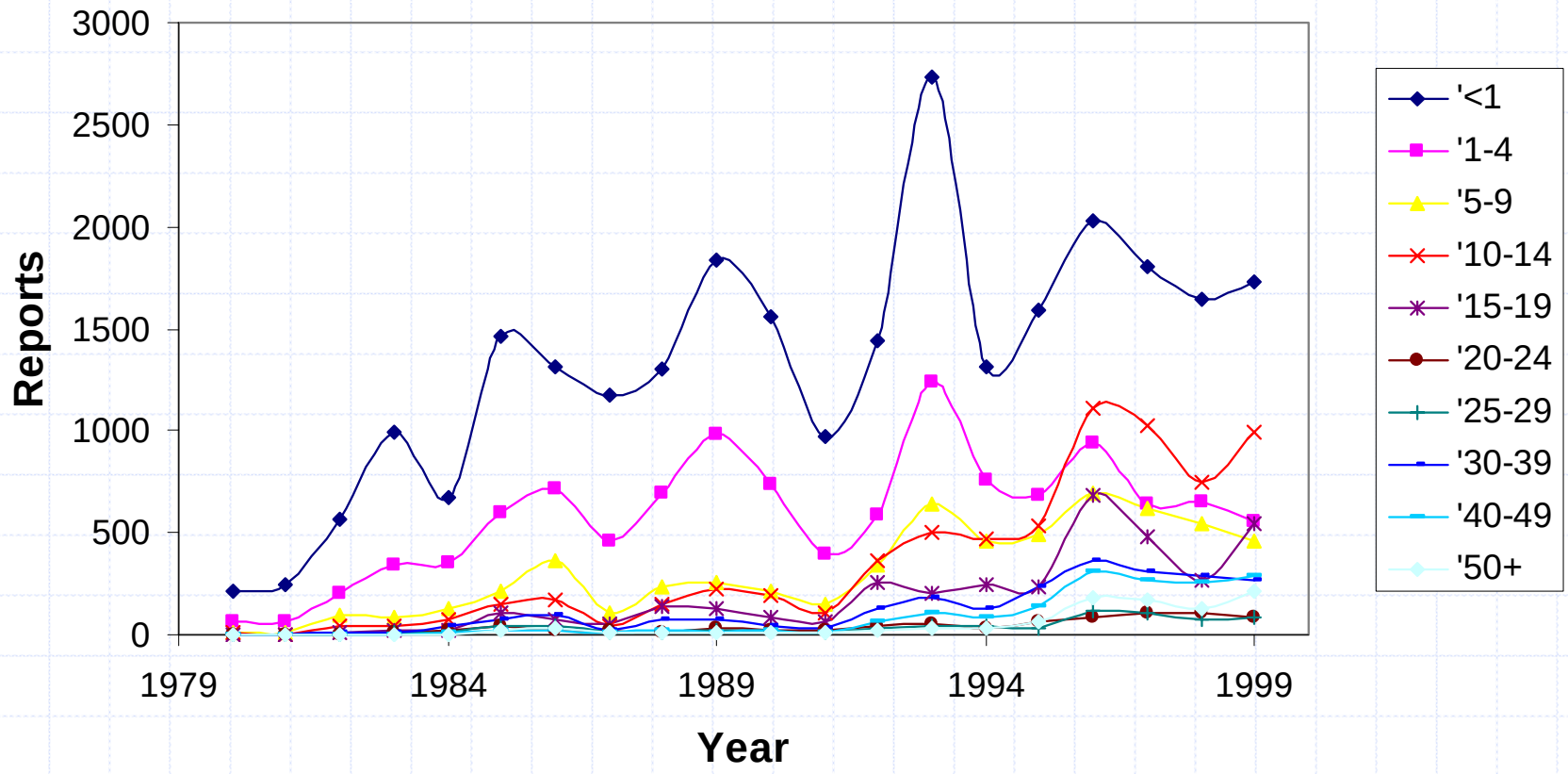
Source: NNDSS

Three Doses of DTP



Simpson, DM, Ezzati-Rice, TM, Zell, ER 2001. Forty years and four surveys: How does our measuring measure up? Am J Prev Med 20(4S):6-14.

Pertussis in the US, 1980-’99



Source: NNDSS

Possible Explanations

1. Surveillance Artifact
2. Consequence of Vaccination (unmasking waning, cohort effect)
3. Deterioration of Vaccine
4. Evolution of Pathogen

NB: These certainly aren't mutually exclusive (and they may not be exhaustive either)

Mathematical models

- Make extraordinary hypotheses (easily evaluated, relatively easily improved, …)
- Eventually inspiring confidence in their reliability as tools for policymaking
- Long used to design, or evaluate and improve, public policy in the UK, …
- Ability to experiment transforms epidemiology from a descriptive to full-fledged science

Ensure that models …

- Are consistent with understanding of disease transmission in human populations
- Have parameters gleaned from literature, estimated from data or opined by experts
- Fit historical observations (settings of interest insofar as possible; disparate otherwise)
- Assist in the design, or evaluation and improvement, of vaccination policy

Pertussis

- To what are the increase in reporting, and older age distribution, attributable?
- Is MA really different from the US as a whole? And if so, why?
- Who infects infants?
- And what could we do about it?

Contributors

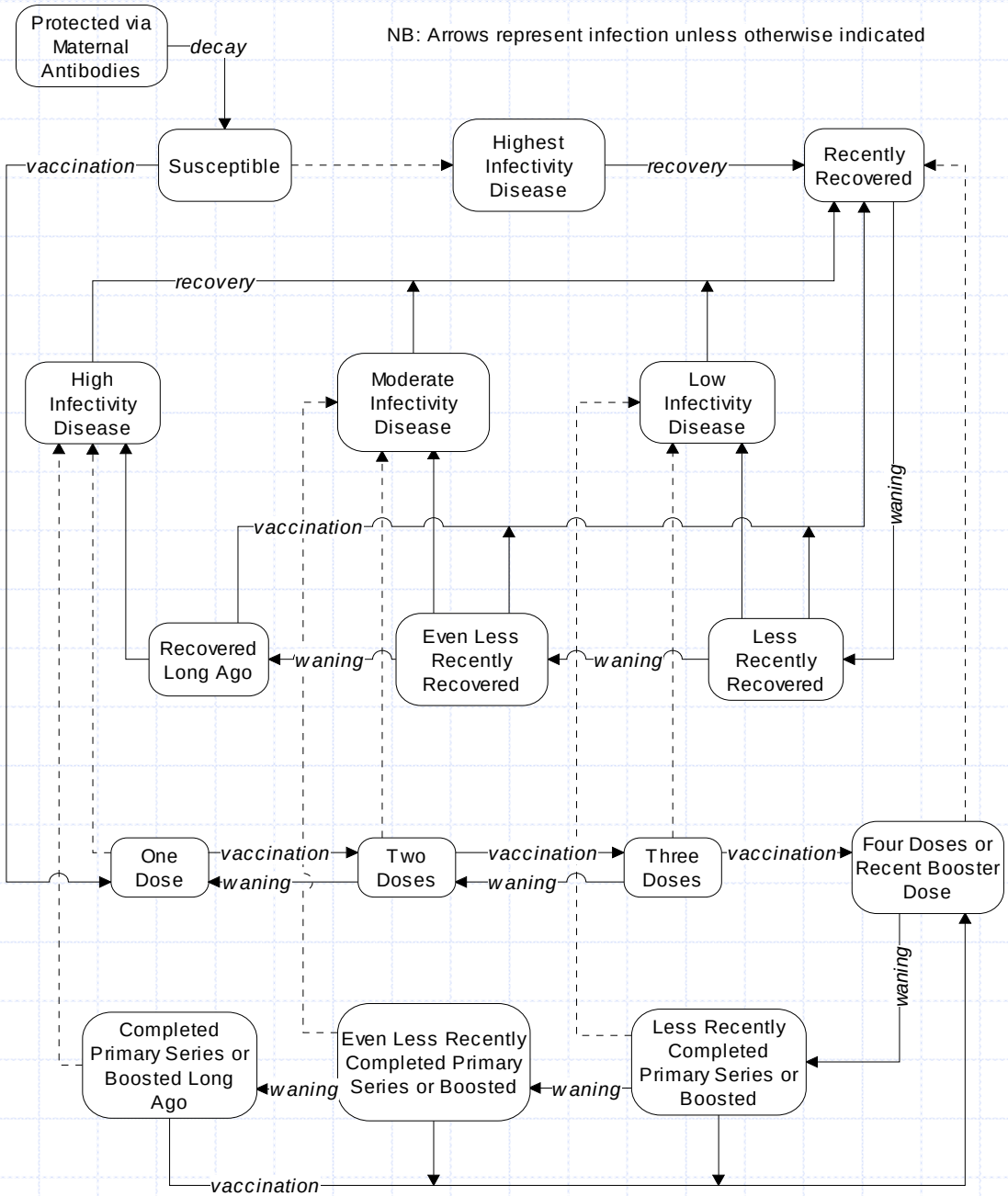
- Melinda Wharton
- Herb Hethcote
- Peter Strebel
- John Glasser
- Patrick Olin
- Peet Tüll
- Masahiro Tanaka

CDC Models (contributors)

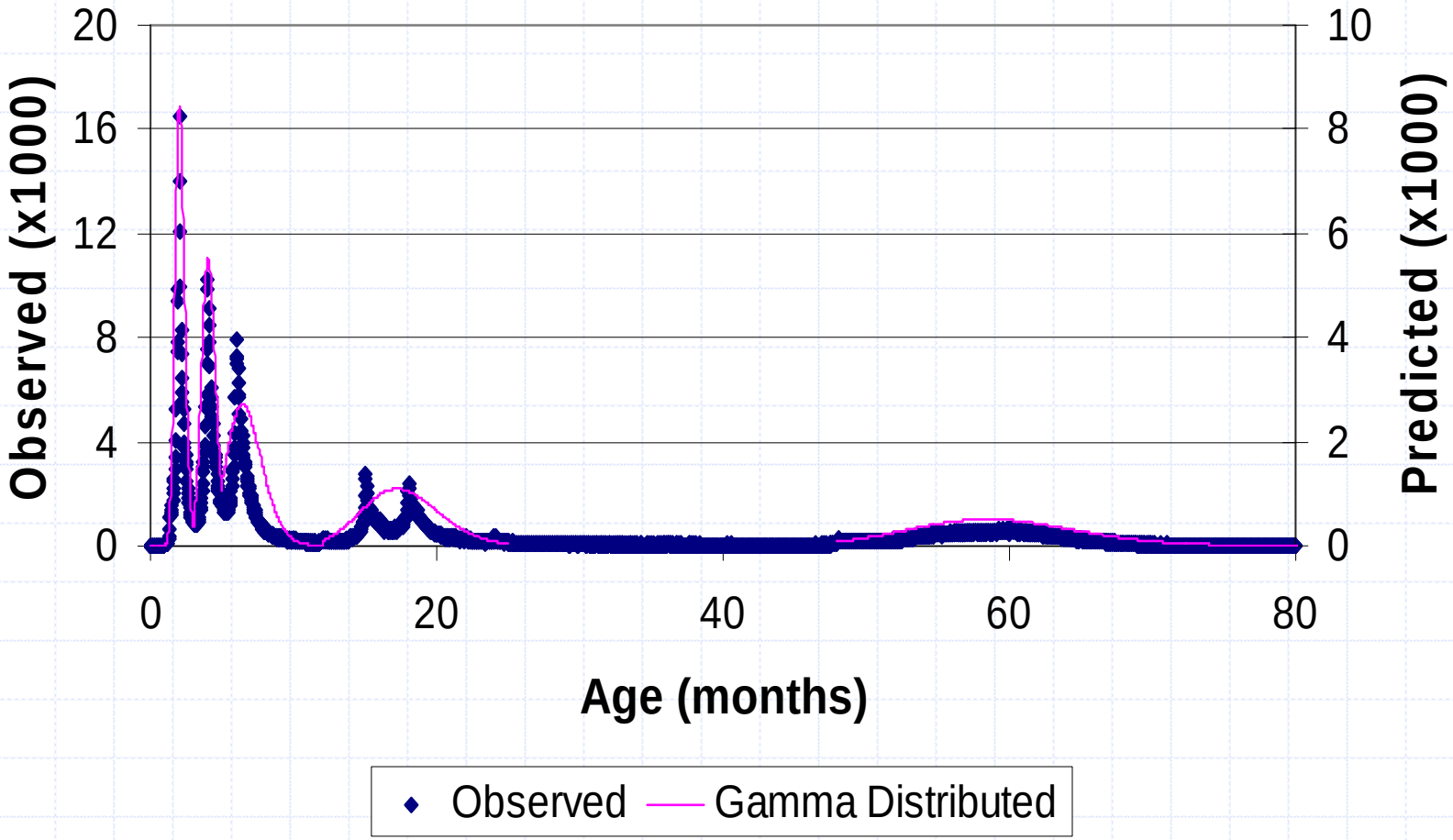
1. No waning (MW, HH)
2. Waning of artificially-induced and naturally-acquired immunity, but asymmetric boosting
3. Symmetric boosting, waning during and post-primary series (…, JG, PS)
4. Population projection, age-distributed vaccinations, refined parameters (…, PO, PT)
5. Age-specific forcing (…,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

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



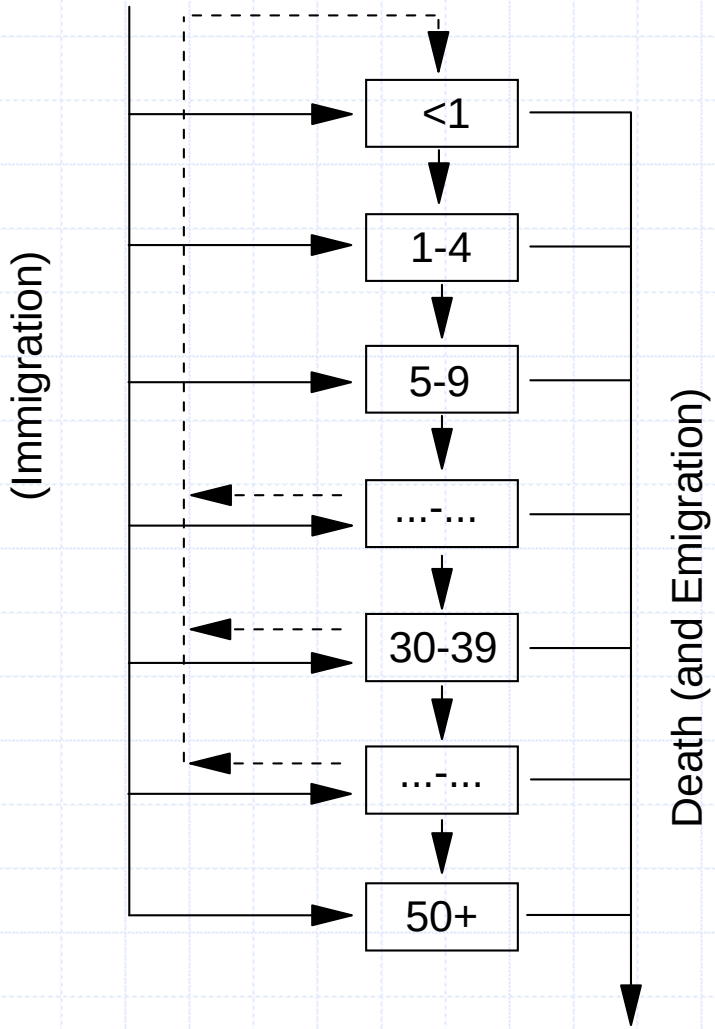
Pertussis Vaccination at NCK



Population Projection

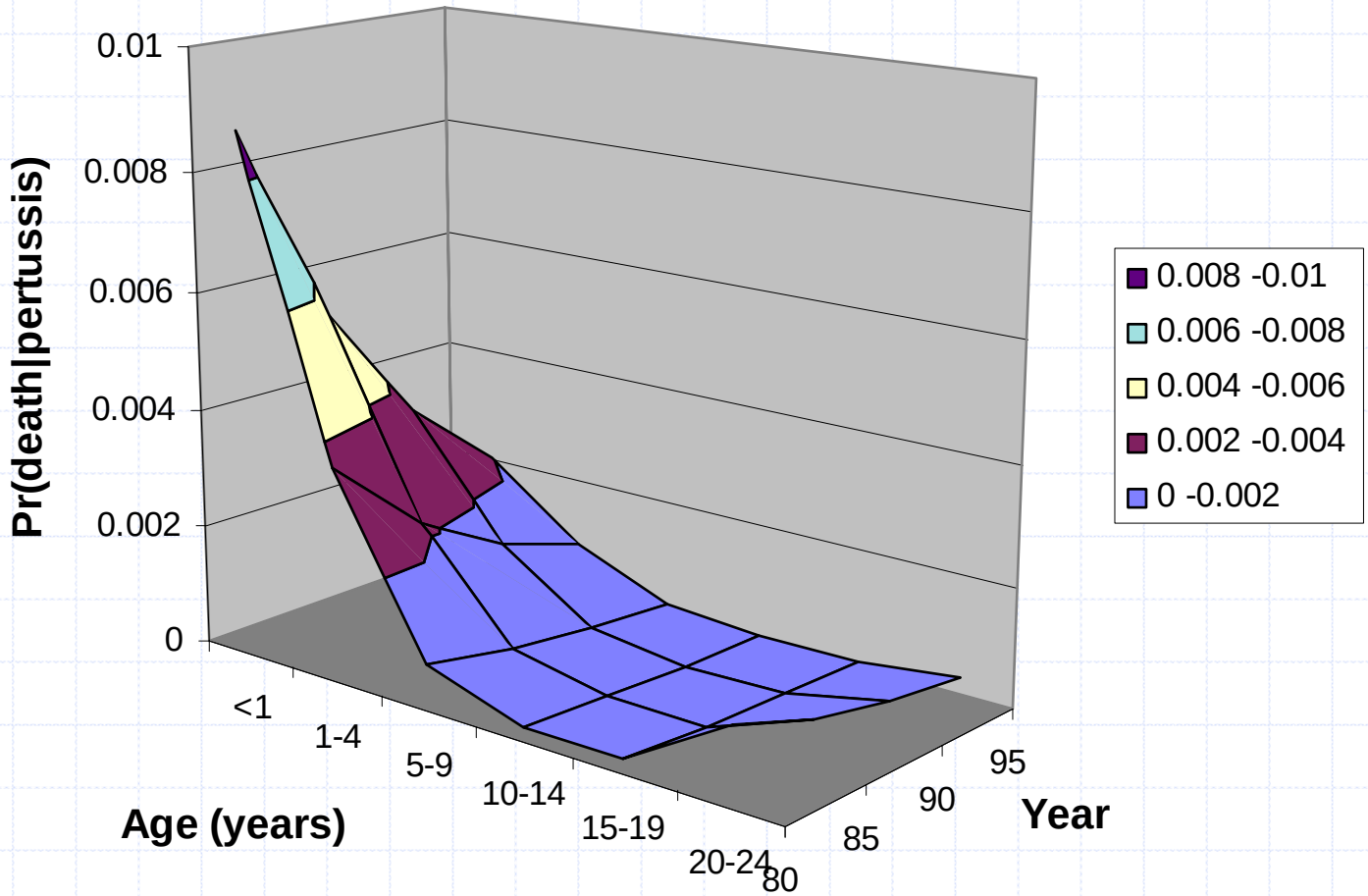
Demographic methods are standard and requisite information is readily available:

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



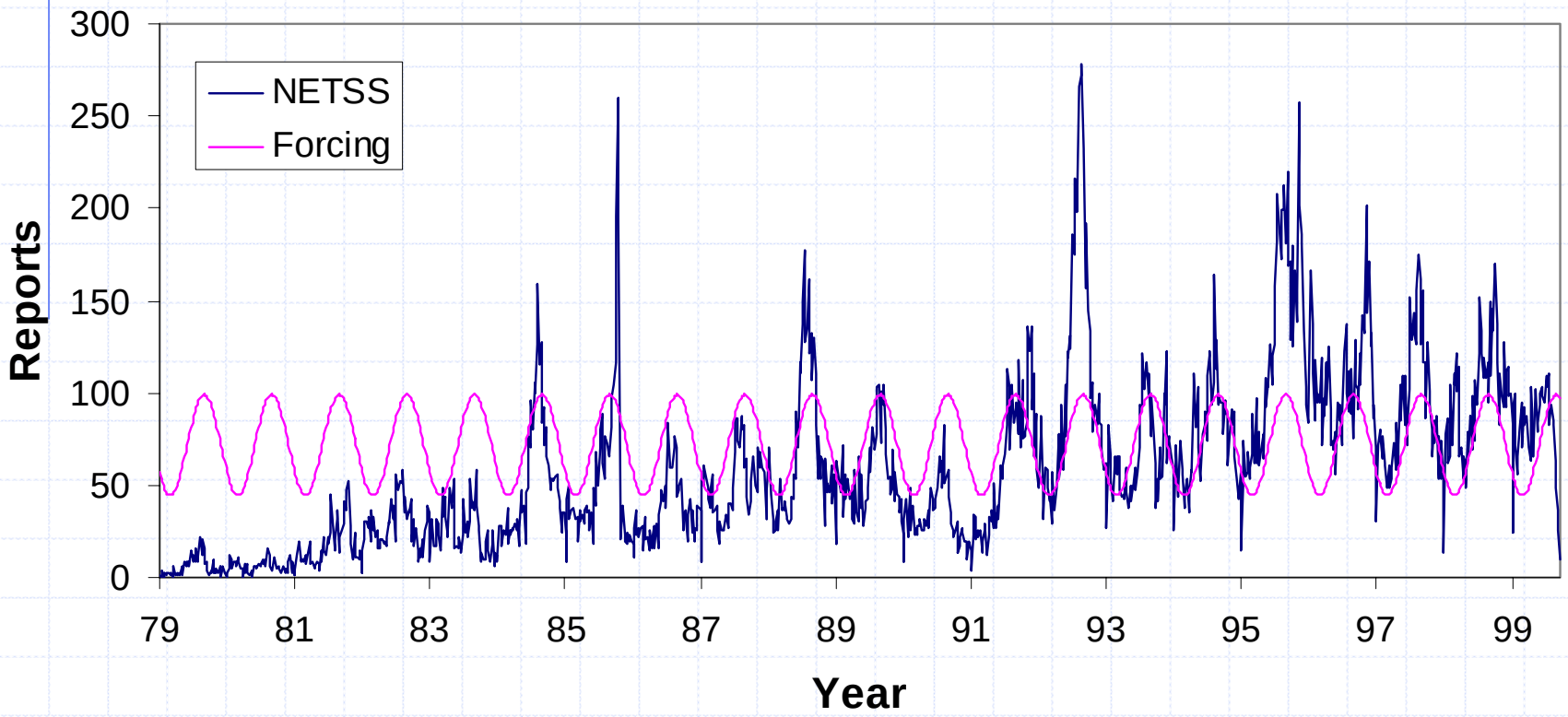
NB: Unlabeled vertical arrows represent aging and dashed ones birth. Migration is not presently modeled.

Pertussis Mortality in the US†

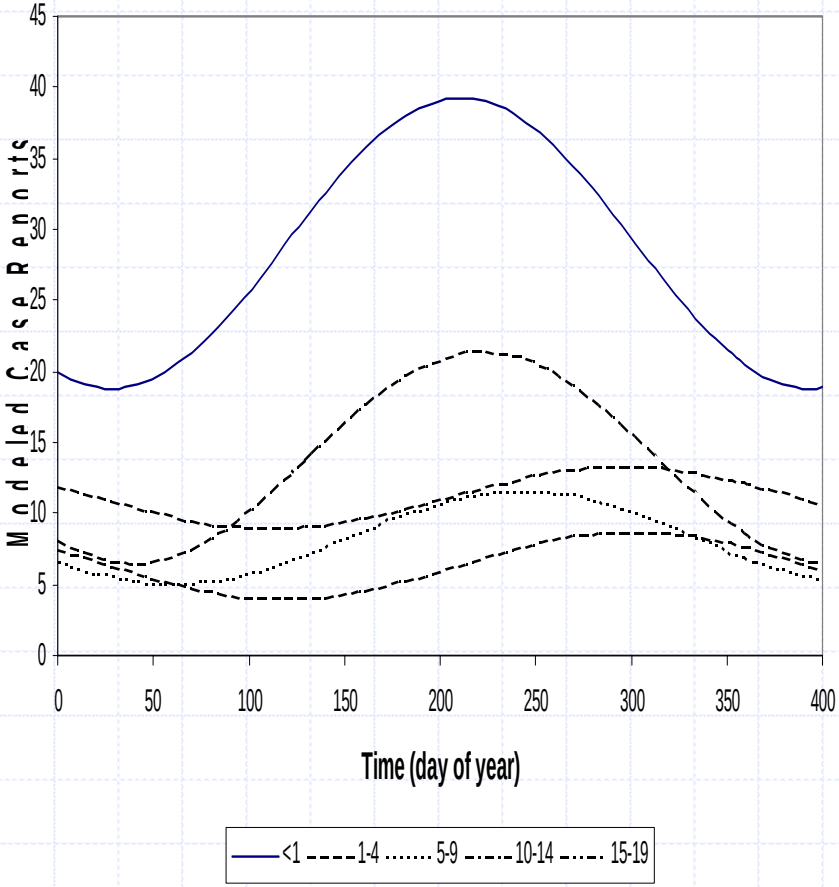


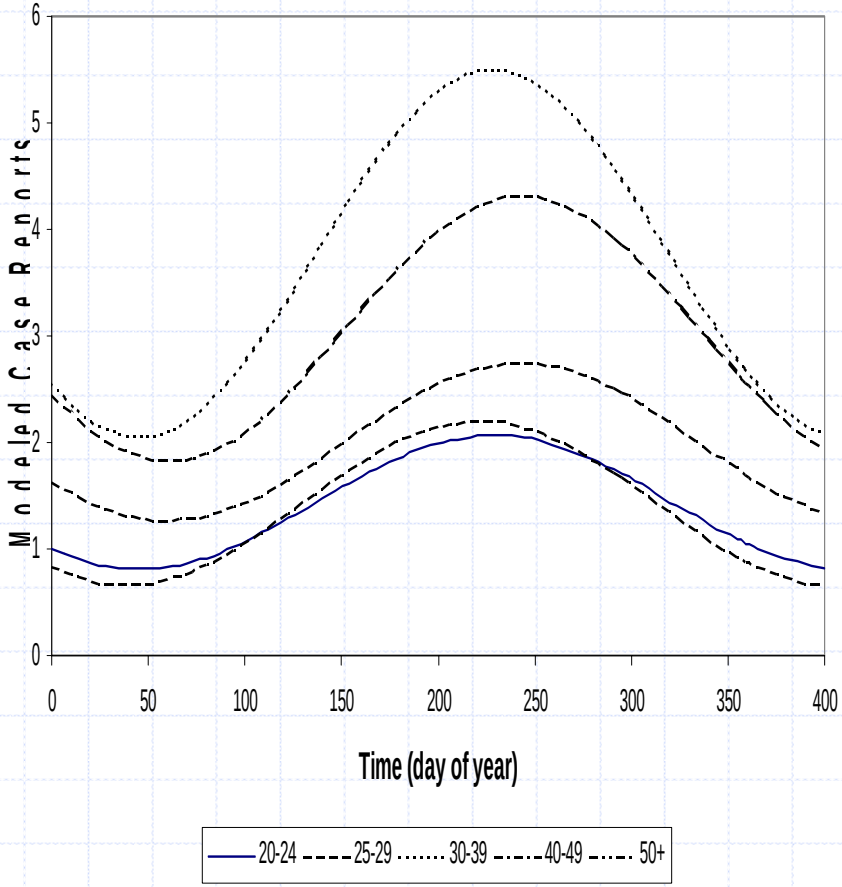
†statistical synthesis via bivariate logistic regression of several articles referenced in model documentation

Seasonal Forcing Apparent in US Pertussis Surveillance



Age-Specificity





Model 5

- Why force? Disease is transmitted among age classes, adolescents are out of phase, affecting their impact on others.
- To what is the seasonality of this disease attributable? If cycles among school-aged children don't predominate, what age-specificity is observed?
- Will the model system resonate? With a 3 to 4 year period? Isn't this yet another opportunity to validate the model?

Seasonal Forcing

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

where e_t is a sequence of uncorrelated $(0, \mathbf{s}^2)$ variates, the amplitude **a** is small relative to the variance of e_t and ω_t is the frequency in radians (e.g., $2\pi/365.25$). Now,

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

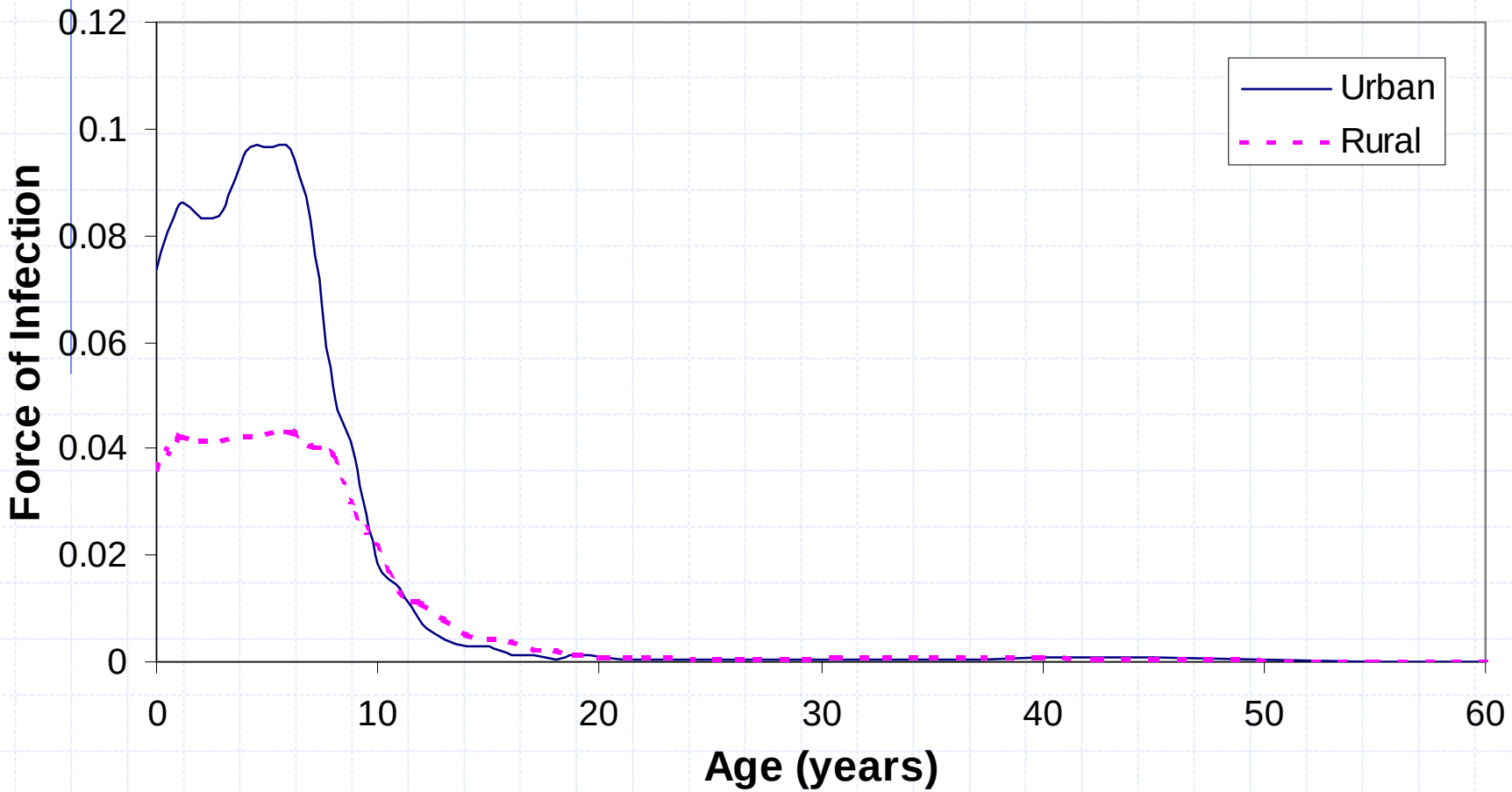
where $A^2+B^2 = \mathbf{a}^2$ and tan (**d**) = B/A. To identify where the forcing occurs, we estimate age-specific $\mathbf{a}_i$ and $\mathbf{b}_i$.

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

Infection Rates

- Calculated age-specific risks of infection from pre-vaccination disease histories in Maryland
- Estimated infection rates via Hethcote's method, *assuming* 0.2 preferential and 0.8 proportionate mixing
- Adjusted rates to minimize disparities between model predictions and historical surveillance via Marquardt's method
- Calculated age-specific risks from adjusted rates, … and compared with contemporary national serological survey

Pertussis in Maryland, 1908-'17†



†Fales, W.T., 1928. The age distribution of whooping cough, measles, chicken pox, scarlet fever and diphtheria in various areas of the United States. Am. J. Hyg. 8:91-8.

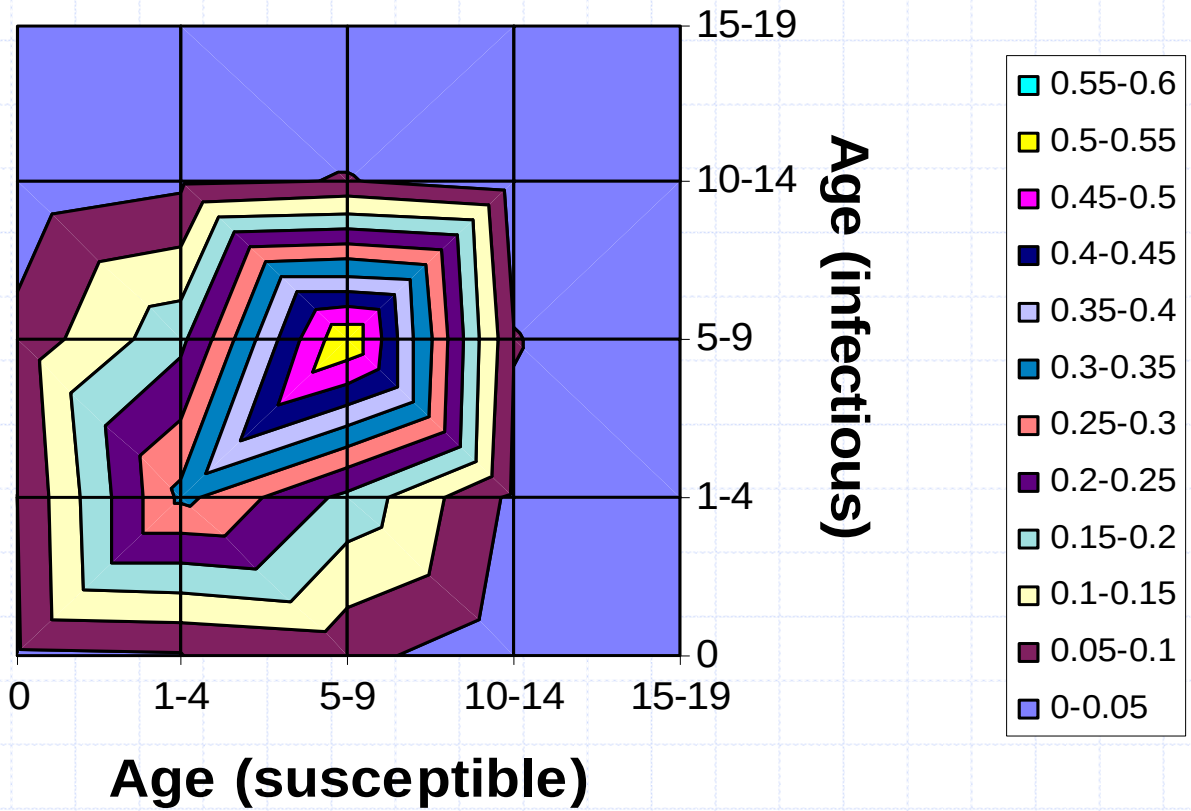
Force of Infection†

$$\boldsymbol{\lambda}_i = \hat{\mathbf{E}}_j \mathbf{b}_{ij} I_j,$$

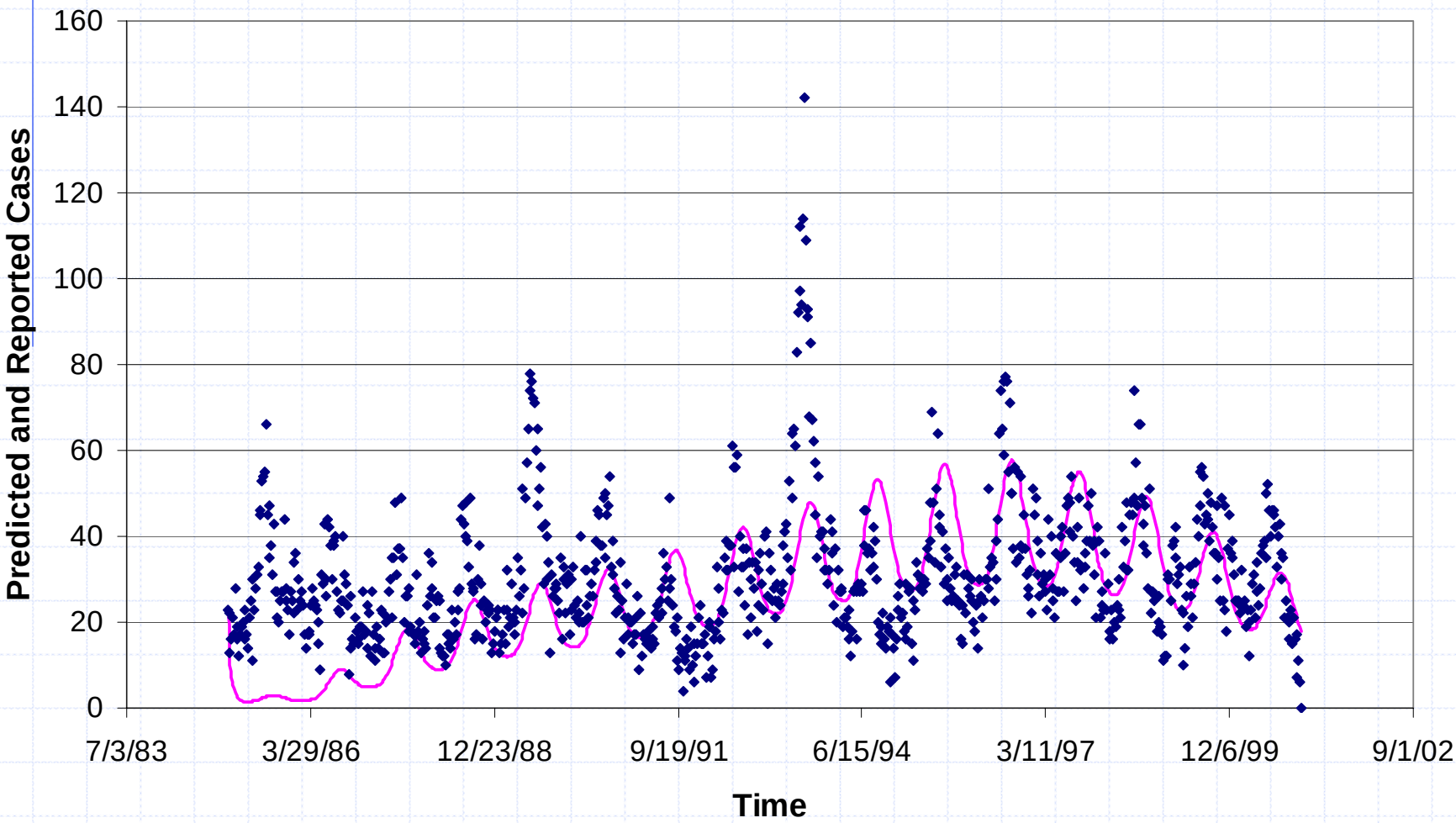
where $\boldsymbol{\lambda}_i$ is the risk of infection experienced by members of age group i, $\mathbf{b}_{ij}$ is the rate at which members of group j infect them and I_j is the number of infectious individuals aged j

†Our force of infection, $\boldsymbol{\lambda}_i = \hat{\mathbf{E}}_j SF_{ij} * \mathbf{b}_{ij} (I4_j + F3I3_j + F2I2_j + F1I1_j)$, where $SF_{ij} = 1 + [\mathbf{a}_i \sin(\mathbf{w}t) + \mathbf{b}_i \cos(\mathbf{w}t)] + [\mathbf{a}_j \sin(\mathbf{w}t) + \mathbf{b}_j \cos(\mathbf{w}t)]$, I1-I4 are disease states and F1-F3 factors by which I1-I3 are less infectious than I4.

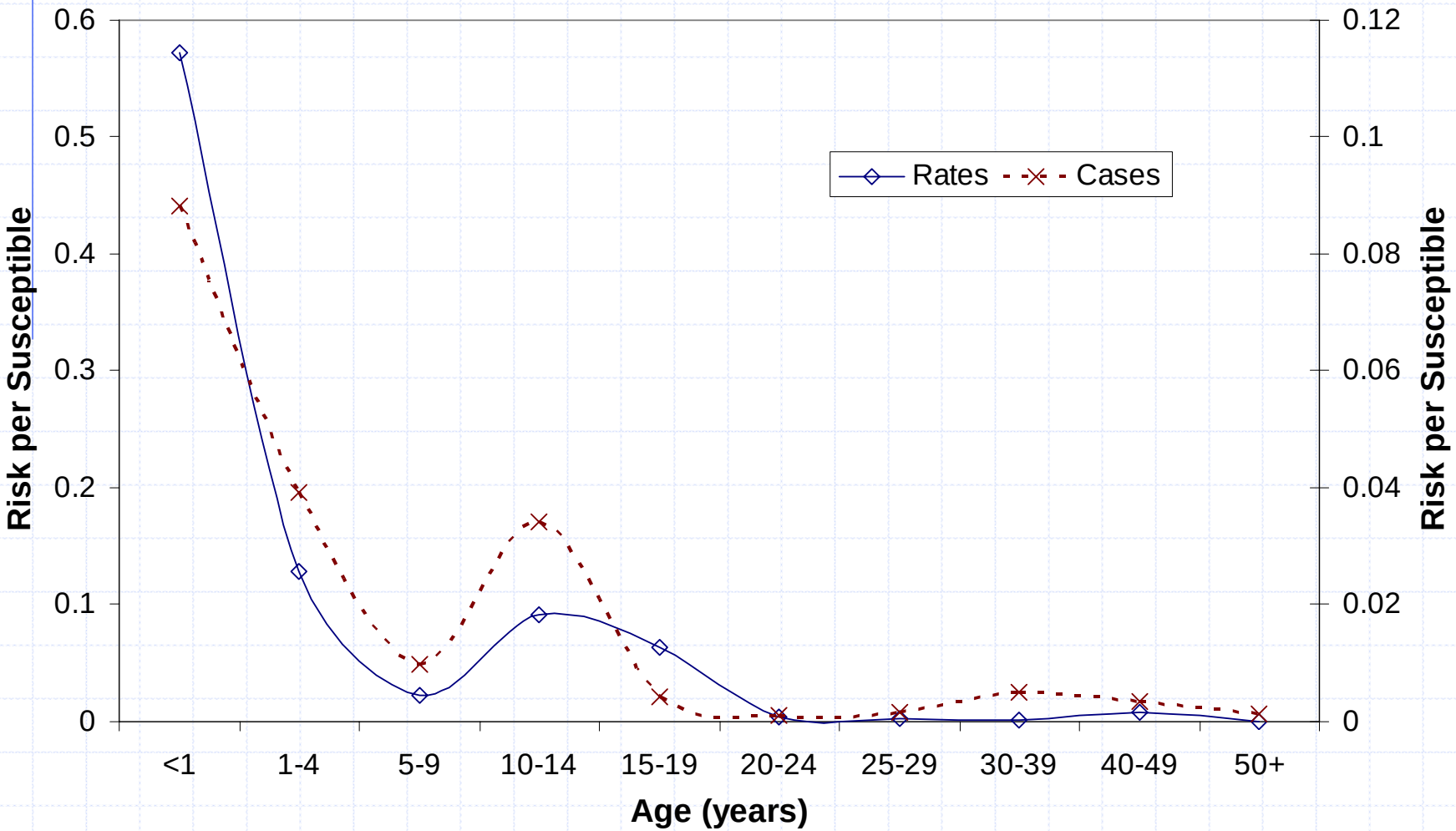
Infection Rate Estimates



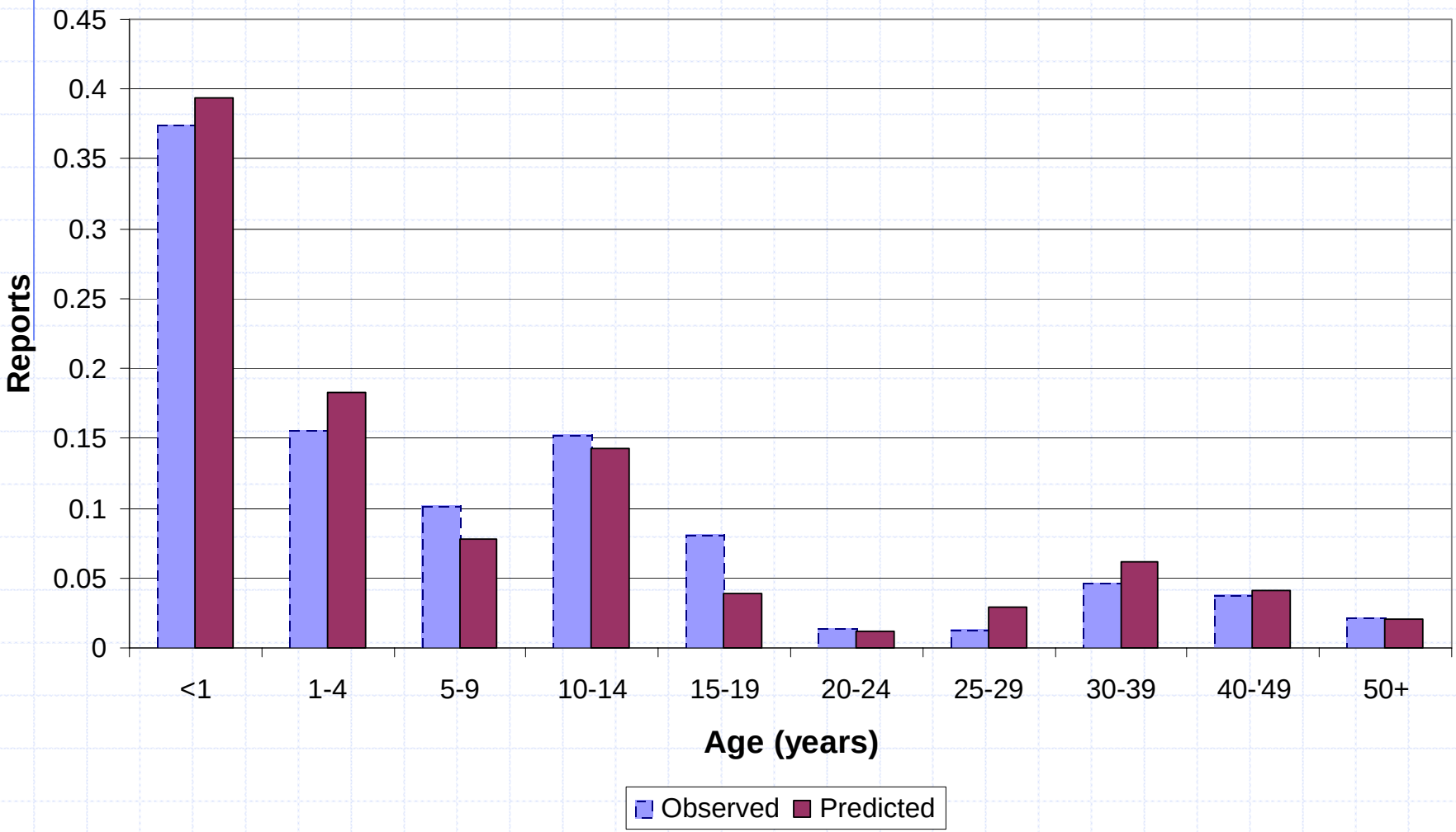
Pertussis among US Infants



Forces of Infection in the US



Pertussis in the US



Serological Analyses (US)

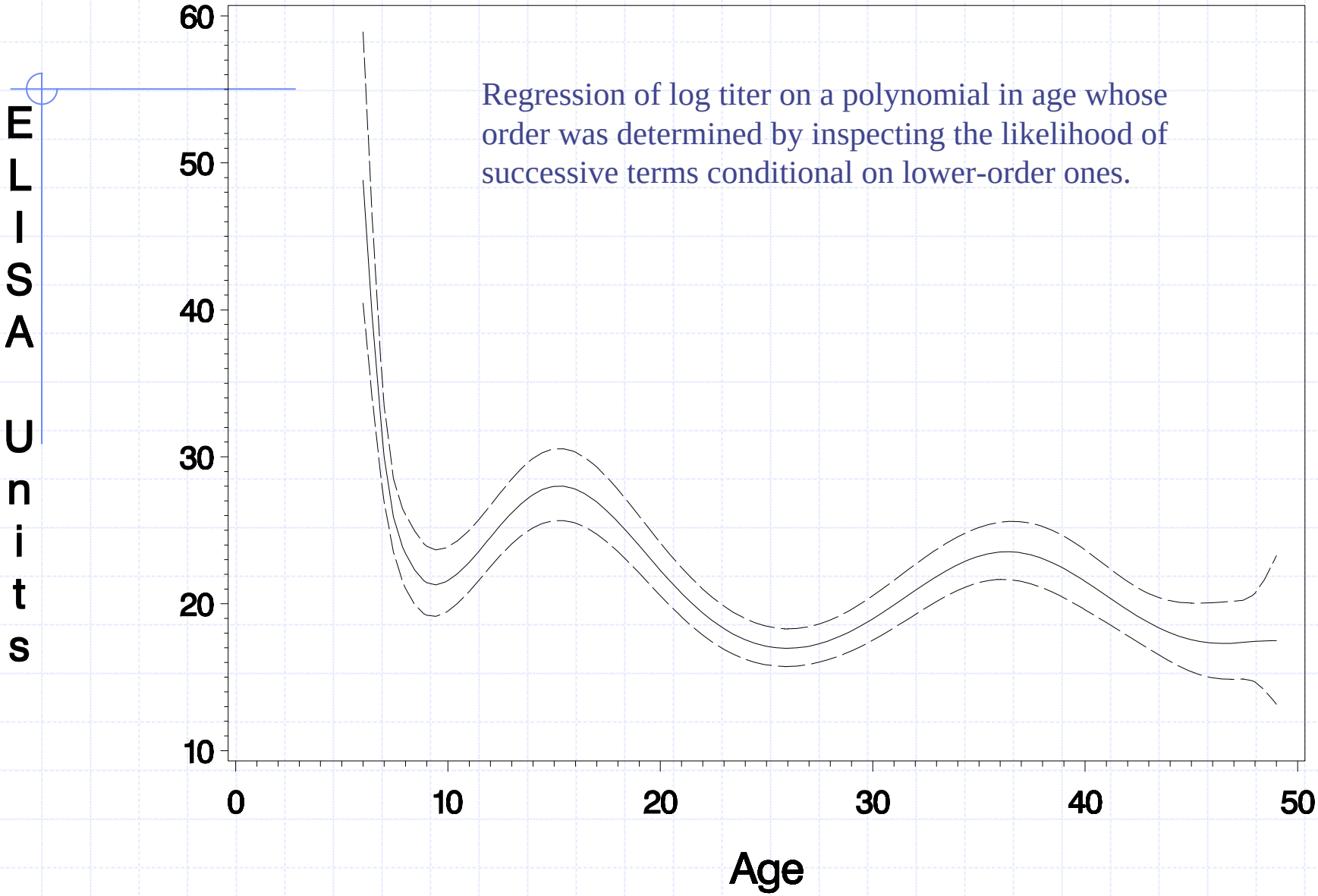
- In NHANES III, antibodies to PT, FHA and FIM types 2 and 3 were assayed in 6,137 sera from people 6-49 years of age during 1991-'94
- Analyzed by Drew Baughman et al., who identified susceptible, distantly infected or vaccinated (distinguishable via questionnaire), and recently infected sub-populations
- Drew's medical colleagues are interested in diagnosis, the cutoff between recently infected and distantly infected or vaccinated

Initial Conditions

- Given a serological correlate of immunity (e.g., PT), can use its presence to determine initial proportions immune
- Used survey of volunteers for an influenza vaccine trial at Vanderbilt – with an arbitrary 10 IU threshold – in modeling to date
- Could use the cutoff between susceptible and immune from Drew's analysis of NHANES, but would lose the first test of this model

IgG to Pertussis Toxin

Pertussis Serology from NHANES III

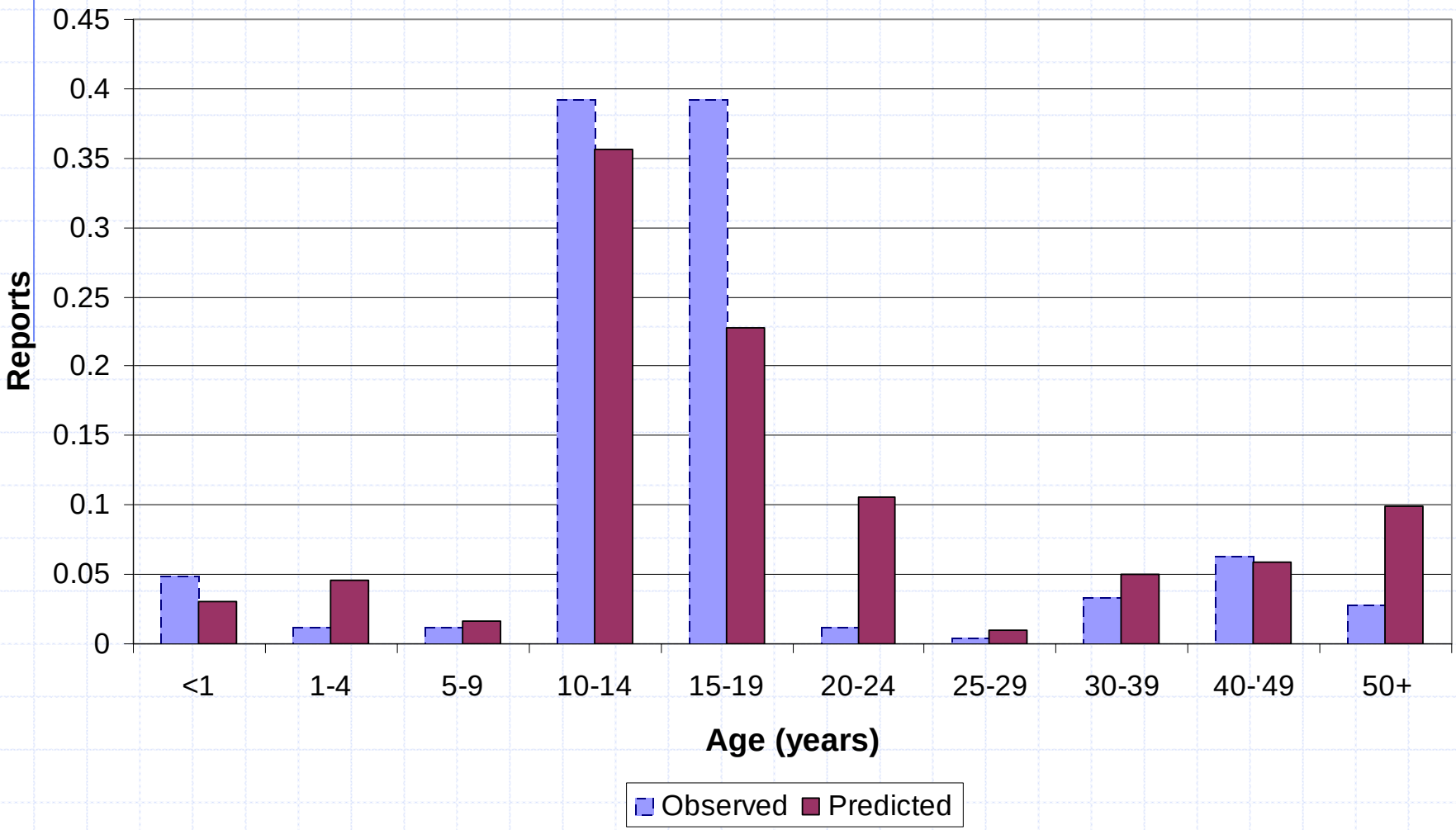


Regression of log titer on a polynomial in age whose order was determined by inspecting the likelihood of successive terms conditional on lower-order ones.

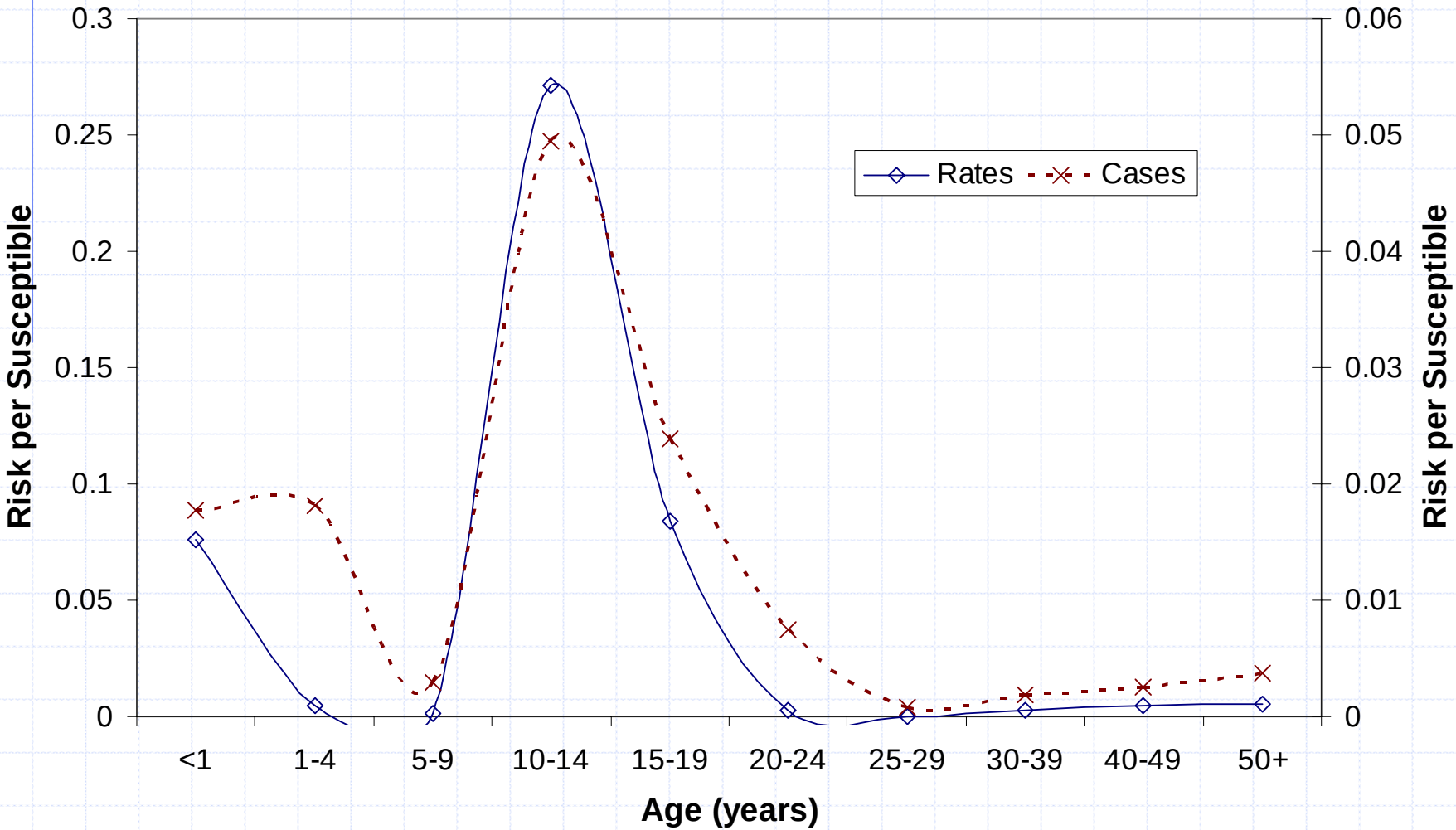
Pertussis in Massachusetts

- MA produced a wP vaccine, attained higher coverage and reported adolescent disease sooner (Marchant et al. 1994 JID 169:1297-305) and more commonly than any other state (Yih et al. 2000 JID 182:1409-16)
- Investigators pioneered diagnosis via anti-PT antibodies in single sera, enabling them to affirm suspicion among adolescents/young adults, which however not only increased case reports, but suspicion, …

Pertussis in MA



Forces of Infection in MA

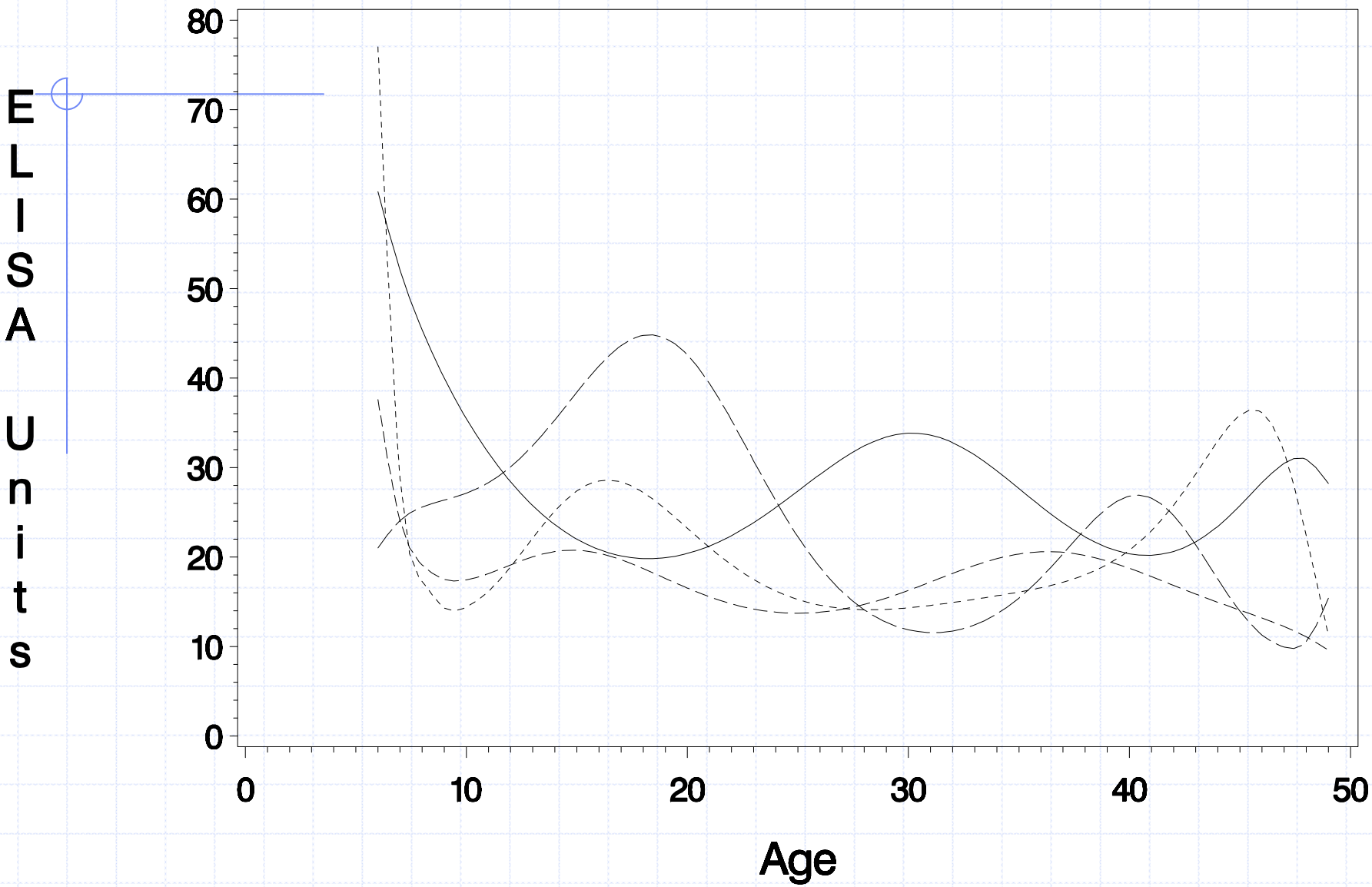


Questions

- Do the FOIs on young children and adolescents in MA really differ that much from the US as a whole, or …
- Could the initial conditions be wrong?
- With what change in initial conditions would the US FOIs work in MA?
- Does this make sense?

IgG to Pertussis Toxin

Pertussis Serology from NHANES III



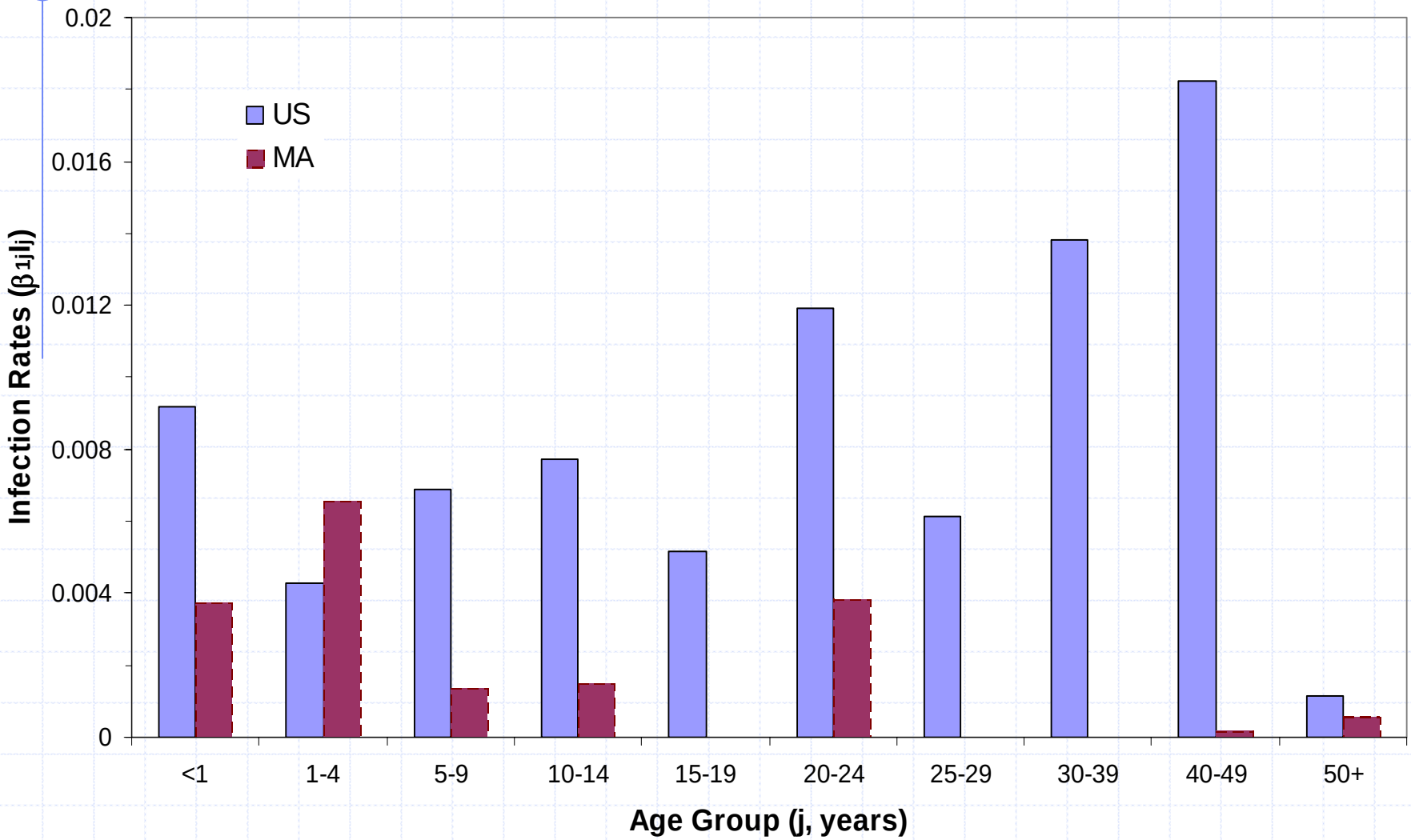
What's the Explanation?

- As vaccination intensifies, disease among children declines (as do opportunities for boosting by virtue of exposure to sick children)
- This unmasks waning, which is independent of vaccination except insofar as artificially-induced immunity may not last as long as naturally-acquired
- Coverage increased faster in MA than elsewhere in the US, and has been sustained at levels not yet attained in some states, accelerating the …
- … reduction in childhood disease, and consequent increase in adolescent susceptibility, which led to increased adolescent disease

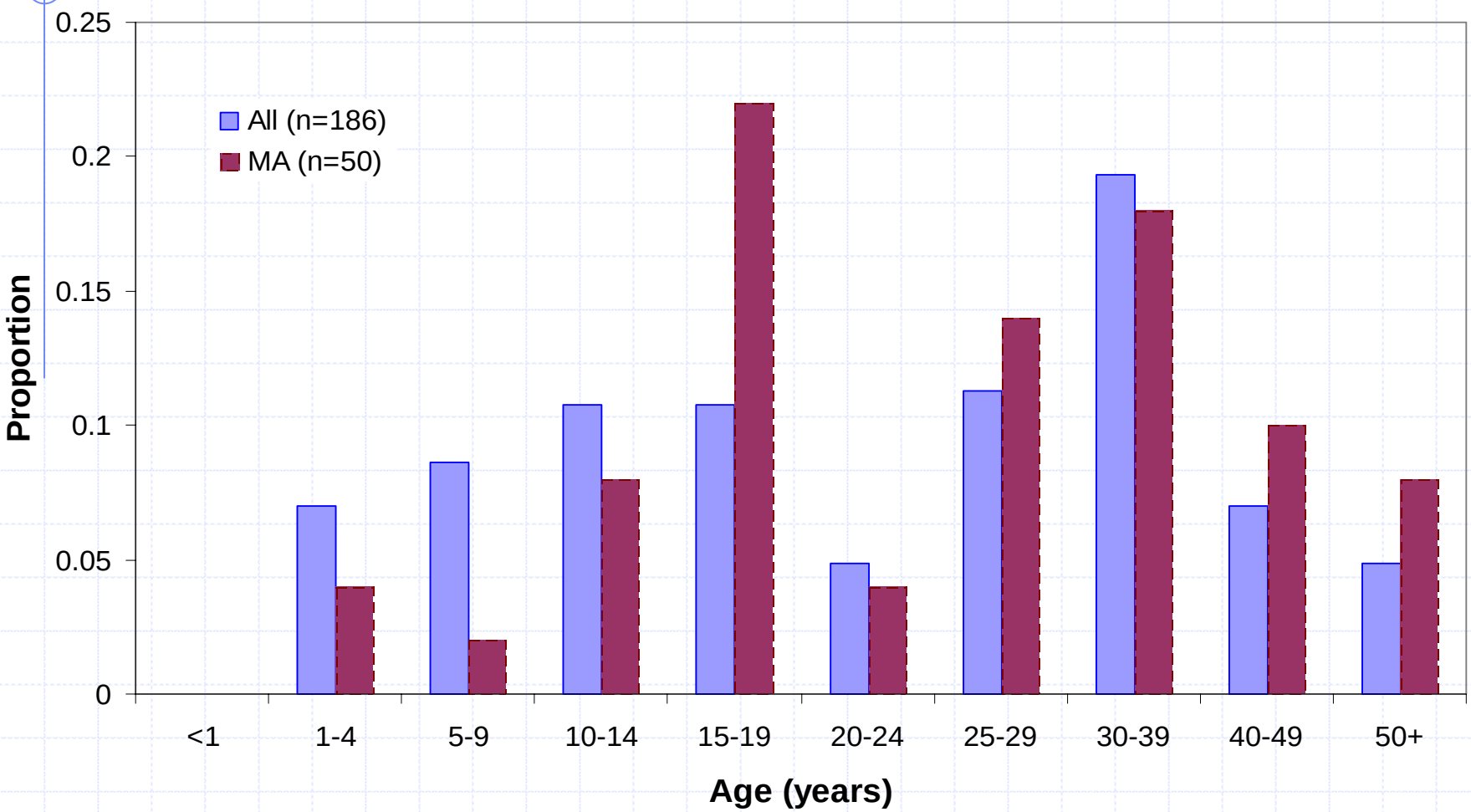
Adolescent Disease

- Young parents who were infected as adolescents are immune, but others risk infection by adolescents
- Adolescents don't infect infants, but they do infect young parents and middle-aged folks (grandmothers?) who do
- Vaccination would yield the benefit (immunize parents-to-be) without the risk (FOI on young parents, grandparents, …)

Source of Infant Infections

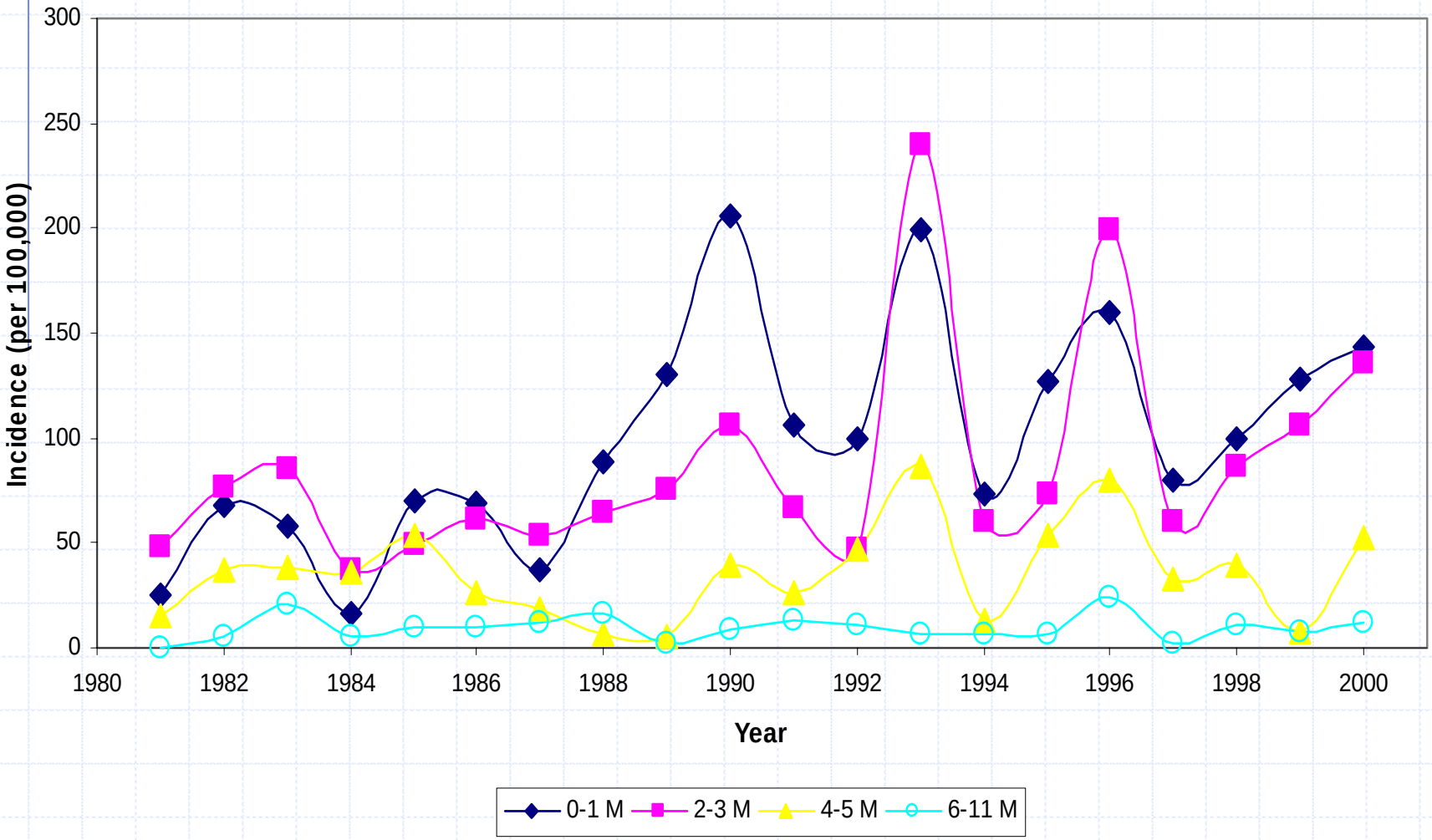


Multi-state Study of Infant Infections†

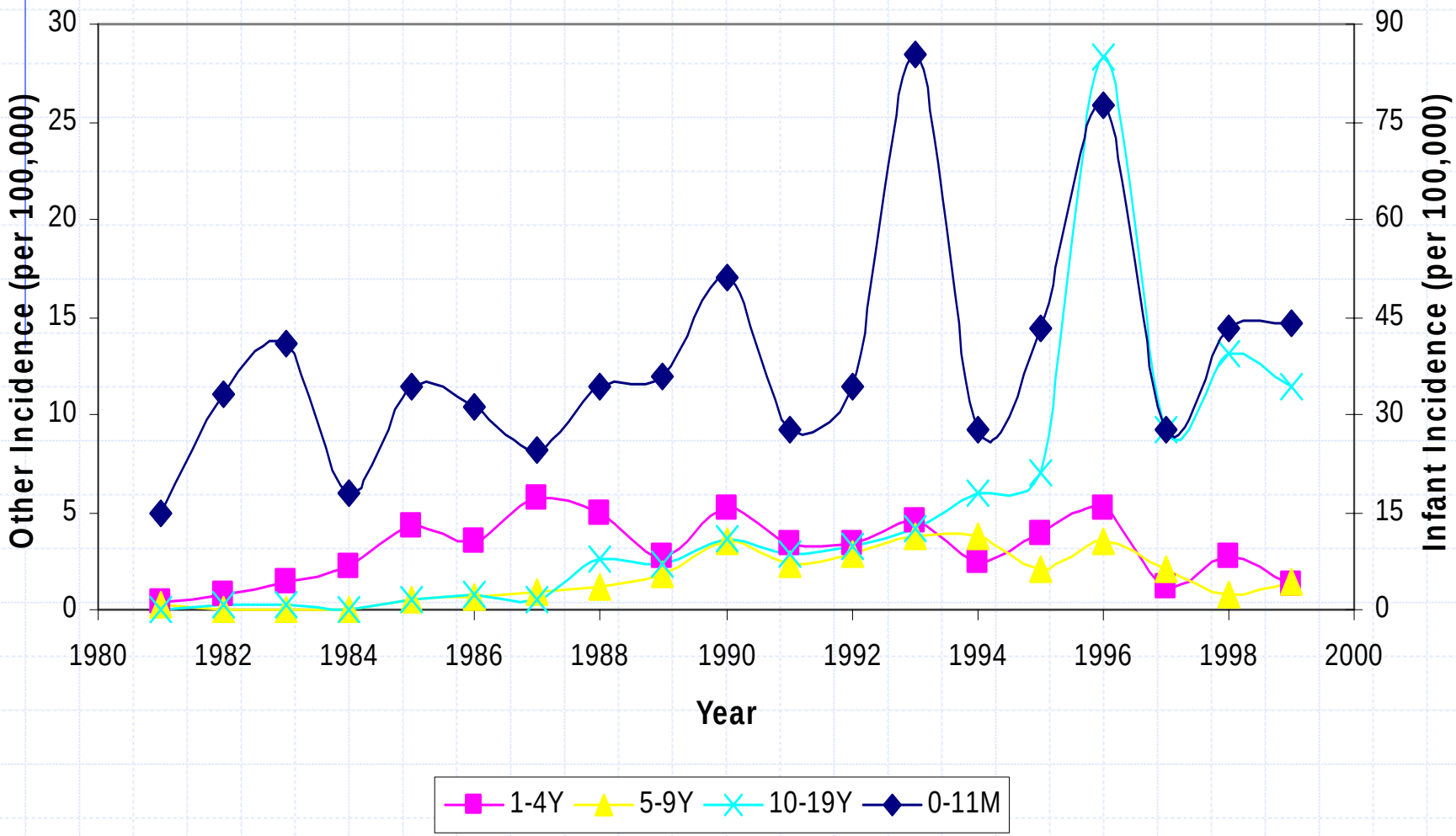


†Bisgard, KM et al. 2001. Infant pertussis: who is the source? Prospective investigation of cases from GA, IL, MN, MA, January 1999-October 2000. Pediatric Research 49:110A.

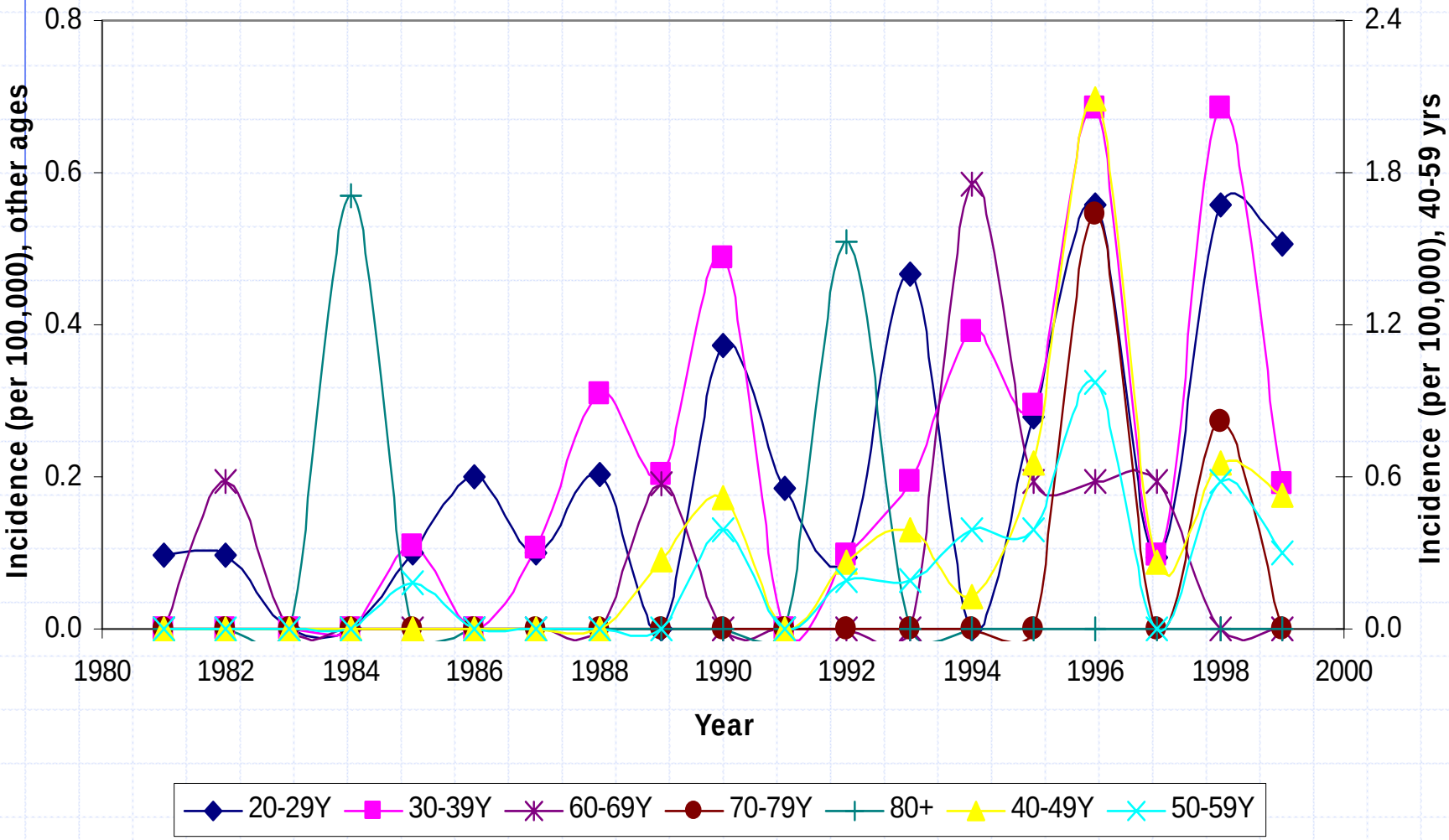
Infant Pertussis in MA



Childhood Pertussis in MA



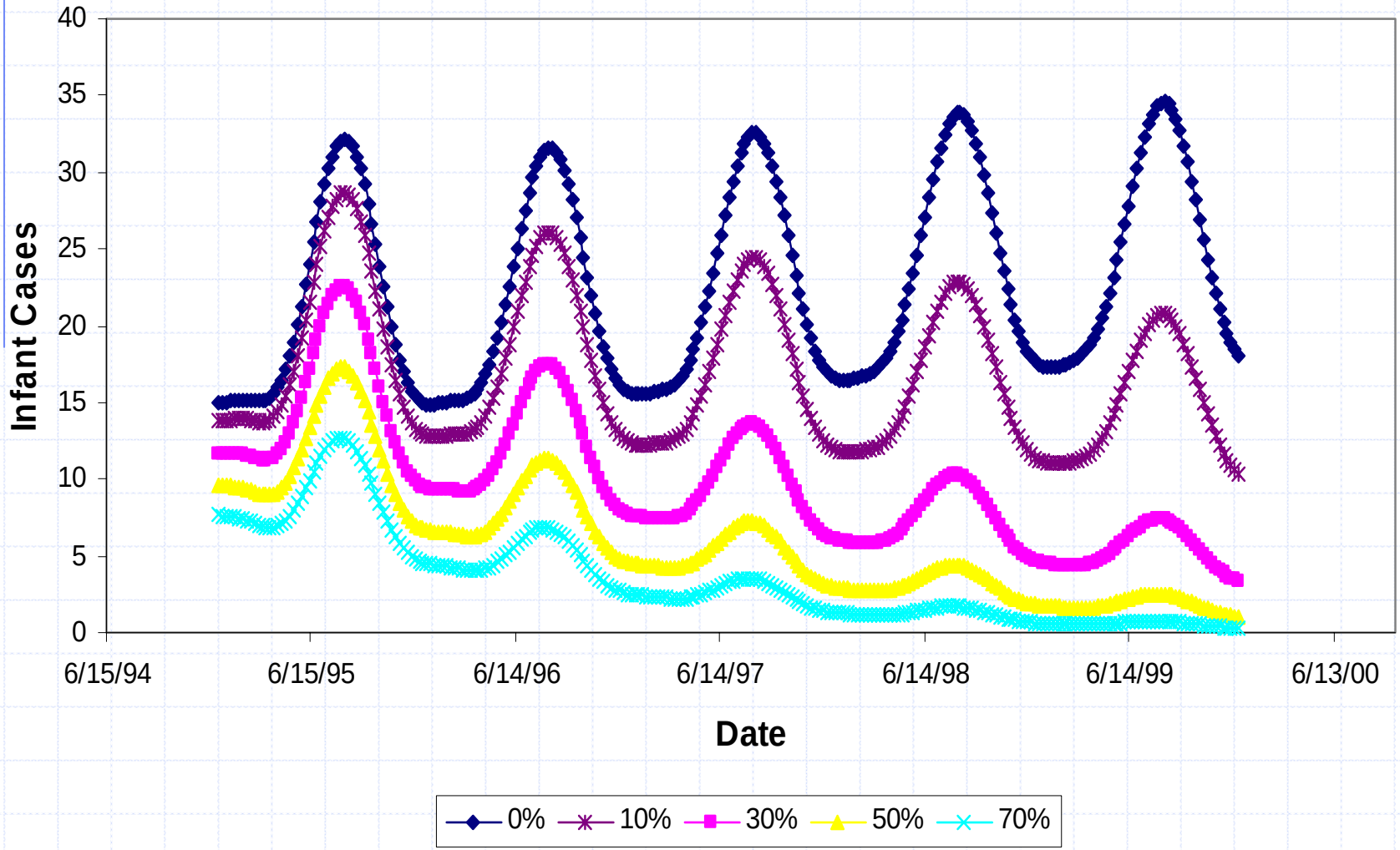
Adult Pertussis in MA



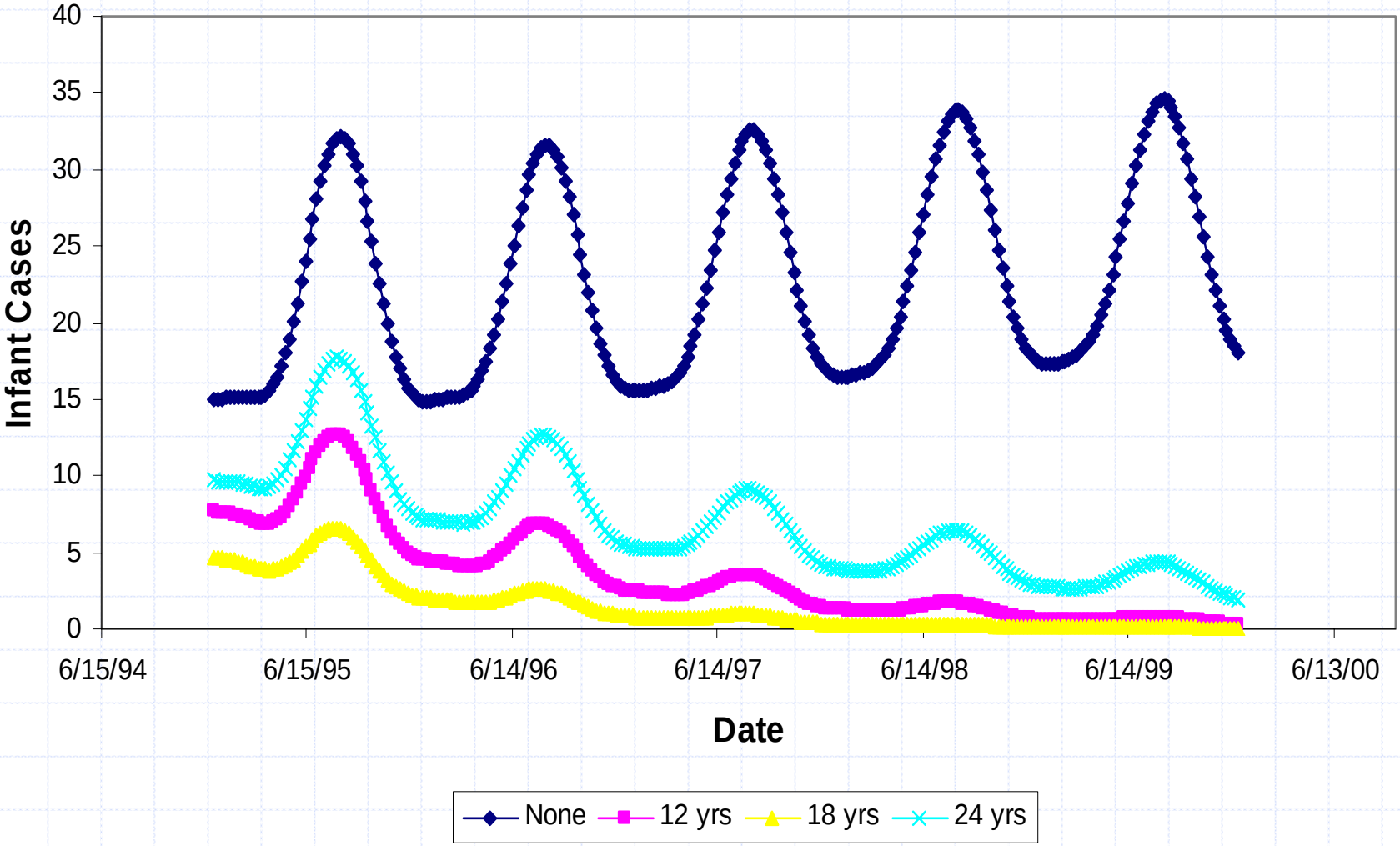
Recipe for Reducing Infant Disease

1. Disease among infants <4 months implicates caretakers, so vaccinate parents and possibly grandparents and other middle-aged adults who care for young children
2. Ensure that older siblings complete primary series on time and vaccinate adolescents. This would reduce both disease where reported and the force of infection on caretakers. Unless scheduled too early, young parents would still be immune
3. Explore a) possible reduction in middle-aged adult susceptibility and b) other indirect effects (i.e., adolescents don't infect infants directly, but do infect parents, …) via modeling?

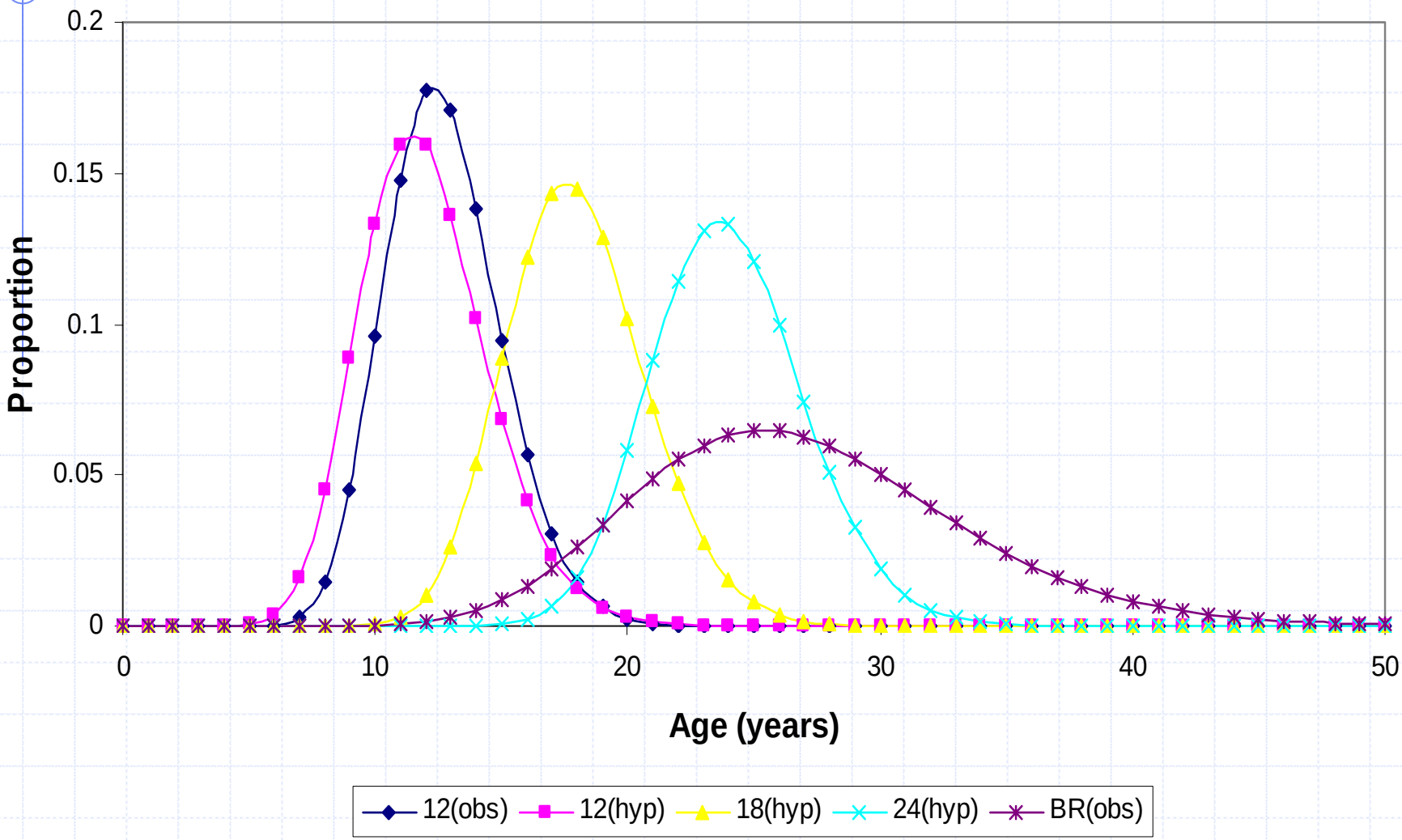
Impact of Re-vaccinating at 12 years on Infant Disease



Impact of Re-vaccinating 70% at different Ages on Infant Disease



Gamma Distributed Ages at Re-vaccination



Summary

- Among the several hypothetical explanations for the changing epidemiology of pertussis, only one explains all key observations:
  - increased infant,
  - and adolescent disease as
  - childhood disease is declining
- Childhood vaccination
  - replaced naturally-acquired with relatively short-duration, artificially-induced immunity, and …
  - reduced opportunities for boosting via exposure to sick children as it controlled childhood disease
- Mathematical models are hypotheses about mechanisms underlying natural phenomena. Pertussis model passes multiple tests:
  - US adjusted FOIs resemble IgG to PT from NHANES III
  - projections and adjusted FOIs are discrepant in MA, suggesting fewer susceptible children and more adolescents than initial conditions from southeastern US
  - this is exactly what 'waning absent boosting' hypothesis would lead one to expect where higher vaccine coverage has been sustained than yet attained in some states
  - regionally-stratified NHANES III also indicates that adolescents were susceptible in NE prior to increased disease
  - US model and multi-state study of infant infections both implicate parents and middle-aged adults (grandmothers?)

Summary (cont'd)

- Adolescent vaccination
  - should replace natural boosting (i.e., immunize parents-to-be)
  - reduce adolescent disease and
  - consequent FOI on caretakers of young infants and others who might infect them
  - reduce infant disease
- Simulations
  - confirm this prediction
  - impact is greater at 18 than 12 or 24 years