Mathematical Epidemiology of Varicella and Herpes Zoster

Designing vaccination programs to mitigate the burden of diseases caused by varicella-zoster virus

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

Outline

- Colleagues within CDC and elsewhere
- Objective predict long-term impact of childhood and adult vaccination
- Process models as hypotheses
- Details assumptions, conceptual model, particular functions, parameters
- Immunity waning at different rates, with and without internal boosting
- Surveillance Antelope Valley, CA, and West Philadelphia, PA, a rural and urban community
- Progress winnowing alternative hypotheses, refining survivors, ...

Collaborators

Herpes virus team:

- Paul Gargiullo
- Dalya Guris

Others:

- Aisha Jumaan
- Scott Schmid
- Jane Seward

Substantive experts:

- Ann Arvin
- Steve Black
- Anne Gershon
- Philip Krause
- Philip LaRussa
- Myron Levin
- Henry Shinefield
- Barbara Watson

Objectives: Determine the Longterm Impacts of ...

- ... childhood vaccination (1 or 2 doses) on varicella, ...
 - a) Has vaccination increased susceptibility to or incidence of varicella among adolescents and adults? Would catch-up or a second dose mitigate this effect?
- b) If the herd immunity threshold cannot be attained via a single dose, what second-dose coverage and effectiveness are required? What is the optimum age?
- 2. ... and herpes zoster (HZ) caused by wild-type and vaccine virus
 - a) Will reduction in varicella increase rates of wild-type HZ temporarily?
 - b) What role, if any, does internal vs. external boosting play in maintaining protection against HZ?
- 3. ... adult vaccination on HZ and varicella

1.

- a) Will adult vaccination affect varicella by reducing opportunities for exposure to adults with HZ?
- b) What is (are) the optimal age(s) for vaccinating adults? Does it depend on their history of disease or vaccination?

Modeling Process

- 1. Formulate answerable questions and devise a suitable conceptual model (states and transition processes)
- 2. Present for review by substantive experts, and revise as invariably (in my experience) is needed
- **3.** Write and encode equations, increasingly explicit representations of our collective understanding
- 4. Estimate parameters from observations insofar as possible, querying experts if necessary
- 5. Attempt to reproduce active surveillance in sentinel site(s), and remedy apparent deficiencies
- 6. Experiment or analyze to answer policy questions

Evaluation

- Insofar as models are hypotheses, failures are informative provided we can diagnose their causes and remedy them
- Our model includes hypothetical contributions to the force of infection from modified disease and zoster, durations of naturally-acquired and artificially-induced immunity, suppositions about the nature and contribution of internal boosting, possible forcing, ...
- Evaluation can not only increase understanding of relevant phenomena, but assures reliable policymaking tools

Assumptions

- Even after two doses, vaccinees may remain wholly or partially susceptible
- People with typical and modified varicella and HZ do not contribute equally to the force of infection
- Everyone is protected on recovery from varicella. Because immunity wanes, people would become "increasingly susceptible to HZ" absent boosting. Until about 45 years of age, we are boosted by controlled reactivations of latent virus (internally) as well as exposure to infectious persons (externally), but we lose our ability to control reactivations, eventually becoming "susceptible to HZ."
 Older people may be boosted by exposure, but develop HZ on reactivation
- Those "susceptible to HZ," who are neither exposed nor reactivate, become "susceptible to modified varicella" and eventually to varicella (i.e., wholly susceptible)
 - Primary and secondary vaccine failures result in typical and relatively mild disease post-vaccination, respectively

Epidemiologic Sub-model





Third National Health and Nutrition Examination Survey (NHANES III), 1988-94



Infection Rates (with epsilon=0.6; slightly assortative mixing)[†]



[†]Hethcote, HW. Modeling heterogeneous mixing in infectious disease dynamics. pp. 215-37 in <u>Models</u> for <u>Infectious Human Diseases</u>: their <u>Structure and Relation to Data</u>, Isham and Medley, 1996, Cambridge Q1: How do People with Typical and Modified Varicella and Herpes Zoster Contribute to the Force of Infection?

- Risk per Susceptible = Infection rate * probability of encountering an infectious person
- Infection rate ≈ average probability of transmission on contact * rate of contact (either may vary seasonally)
- F_1 is the contribution of people with modified relative to typical varicella (≈ 0.5 , Seward et al. 2004. JAMA 292:704ff), and F_2 and F_3 are the relative contributions of people with wild-type and vaccine-strain zoster, respectively ($F_2 \approx 0.1$, Ferguson et al. 1996. PNAS 93:7231ff; $F_3 \approx 0.01$, guesstimate)

 $\lambda(a,t) = \int_{a'} \beta_0(a,a') \left[SF(a,\tau) + SF(a',\tau) \right] \left\{ I(a',t) + F_1 \left[I_M(a',t) + VI_M(a',t) \right] + F_2 WZ(a',t) + F_3 VZ(a',t) \right\} / N(a',t)$

 $SF(a,\tau) = \beta_1(a)\sin(2\pi\tau) + \beta_2(a)\cos(2\pi\tau)$, where τ is day of year

 $N(a,t) = MA(a,t) + S(a,t) + V_1S(a,t) + S_M(a,t) + VS_M(a,t) + V_1P(a,t) + V_2P(a,t) + L(a,t) + L_M(a,t) + VL_M(a,t) + I(a,t) + I_M(a,t) + VI_M(a,t) + IS_{WZ}(a,t) + IS_{VZ}(a,t) + WZ(a,t) + VZ(a,t)$

Household Contact Study

- Vax Hx: Among unvaccinated contacts, vaccinated primary cases with <50 lesions had much lower (23%) and unvaccinated primaries with 50+ higher (74%) SARs
- But vaccinated primary cases with 50+ lesions (primary failures?) and unvaccinated primaries with <50 (histories?) had similar SARs (65% and 68%, respectively)
- Dis Hx: Among naive contacts, primary cases with histories had lower SARs (44%) than those without histories (72%), but secondary cases had similar lesion distributions

Seward, JF, Zhang, JX, Maupin, TJ, Mascola, L, Jumaan, AO 2004. Contagiousness of varicella in vaccinated cases: a household contact study. JAMA 292:704-08

Seasonal Forcing (external factors possibly affecting Pr(T|C) and C rates)



School Enrollment's effect* on Disease Incidence is Age-Specific, Temperature's ...

| Model | \mathbf{R}^2 | School | р | Temperature | р |
|-------|----------------|--------|-------|-------------|--------|
| 0-1 | 0.6 | -0.09 | 0.93 | -2.502 | 0.01 |
| 2 | 0.55 | 0.59 | 0.56 | -3.003 | 0.003 |
| 3-4 | 0.71 | 2.75 | 0.007 | -3.817 | 0.0002 |
| 5 | 0.73 | 1.066 | 0.29 | -5.108 | 0.001 |
| 6-9 | 0.8 | 2.804 | 0.006 | -4.34 | 0.0001 |
| 10-12 | 0.53 | 2.057 | 0.04 | -2.081 | 0.039 |
| 13-19 | 0.47 | 1.88 | 0.06 | -2.943 | 0.004 |
| 20+ | 0.45 | 1.122 | 0.26 | -3.166 | 0.002 |

*Conditional on vaccination

Q2: Duration of Naturally-Acquired Immunity (absent boosting), and Distribution among 3 States?

- Modelers have assumed 5-20 years
 - Some calculations (with boosting):
 - Difference between mean ages of varicella and HZ is 62 years. This interval is an emergent property (we hypothesize), with boosting to higher levels of immunity forestalling HZ. Without such boosting, immunity would continue waning toward susceptibility to HZ, resulting in a much shorter HZ-free period
 - Cumulating annual estimates (based on NHIS) of proportions infected at successive ages, interpreting the result, 1.07, as 7% experience more than one episode, comparing with age-specific proportions seropositive (based on NHANES), calculating the requisite waning rate and inverting it yields 27 years
- Partition into fully protected, increasingly susceptible to zoster, protected from modified and typical varicella

Conventional Wisdom?

- On recovery from varicella, VZV establishes latency in dorsal root ganglia
- Reactivates (periodically ?), and immune system responds
- Ability to quell reactivation declines with age, certain illnesses, drugs, stress
- Eventually, episodes of zoster may occur

Progression to Herpes Zoster is Unique among Natural History Parameters



Donahue, JG, Manson, JE 1995. The incidence of herpes zoster. Archives of Internal Medicine 155:1605-09.

Q3: Why does Zoster Increase with Age?

- Immunocompetence certainly declines, but evidently immunity can be boosted via vaccination (Oxman et al. 2005. NEJM 352:2271ff)
- Reduced exposure? Incidence is lower among adults exposed to children w/chickenpox (Thomas et al. 2002. Lancet 360:678ff)
- Both (i.e., increased waning and reduced boosting)?

Details

- We model reactivation of latent virus via the harmonic function, $y = a \sin (bx + c) + d$, where |a| is amplitude, $2\pi/|b|$ period, and x age. To simulate diminution in ability to control reactivation, a is an exponential function of age. With the exponent estimated from Donahue et al. (1995), this simulates zoster. With smaller exponents, it also simulates internal boosting
- Assuming that latency evolved as a means of persistence when humans were small scattered bands (Hope-Simpson 1965), we allow the period to be $N(\mu,\sigma^2)$, with $\mu=15$ years (and $\sigma=0.1587*\mu$), the hypothetical mean age of childbearing, or generation time, when HZV evolved. For reference, μ is about 25 years in the developed world now

Here $b = 2*\pi/15$, c = 15, and d = 0. The nature of the increase depends on the coefficient of age



Antelope Valley, CA



Vaccination in Antelope Valley, CA



Varicella in Antelope Valley, CA



Disease Severity



One Previous Episode



Hall, S, Maupin, T, Seward, J, Jumaan, AO, Peterson, C, Goldman, G, Mascola, L, Wharton, M 2002. Second varicella infections: are they more common than previously thought? Pediatrics 109:1068-73.

Timing of Disease



 \rightarrow Modified Vaccinated (n=718) \rightarrow Modified Unvaccinated (n=4,075) \rightarrow Other (n=7,520)

Evaluation Strategy

- Simulating model with 35- and 70-year durations of immunity with and without internal boosting (next slide)
- Will determine how well models reproduce observed time-series, eliminate worst and refine best combination

Parameter Combinations



Combinations "explain" typical (>50 lesions) better than modified disease, suggesting ...



Why Model the Underlying Mechanisms (insofar as possible)?

- Why not just fit a statistical model to these data (next slide)?
- If we want reliable answers to such questions as
 - Is catch-up indicated?
 - What about a second dose?
 - When should adults be vaccinated?
- The system must respond realistically to simulated alternatives (i.e., experiments)
- Only to the extent that we model the relevant processes can we hope for this

Phenomenological Modeling



Q4: Residual Issues

- 1. Duration of artificially-induced immunity and distribution among states?
- 2. Incidence of vaccine-strain HZ, duration of episodes and contribution to FOI?

Acknowledgement

I was privileged to study with Richard Levins, a theoretical population biologist whose applied research concerns Third World agro-ecosystems. Colleagues ranging from mathematicians willing to grapple with biological complexity to medical epidemiologists who eradicated smallpox despite simplistic models have been persuaded to view ours simply as explicit hypotheses. The extent to which they reflect contemporary understanding of relevant phenomena, are structurally sound, and analyzed or simulated properly is a tribute to them. Insofar as progress in science entails remedying errors apparent on evaluating hypotheses ever more rigorously, one must occasionally be wrong. But I alone – not my mentor, colleagues, or employer, the Centers for Disease Control and Prevention - am responsible for any as-yet-uncorrected misconceptions.