Mathematical Modeling† of Rubella and Congenital Rubella Syndrome

Assessing the Global Burden of CRS, Evaluating Possible Interventions, and Designing Optimal Programs

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

Modeling might assist in …

1. Assessing incidence: congenital rubella syndrome surveillance is unreliable
   - Some lesions are lethal (e.g., spontaneous abortions, stillbirths)
   - Others diagnosed long after birth (e.g., cataracts, hearing deficits, mental retardation)
2. Evaluating potential interventions: approach, strategy
   - Reduce susceptibility or risk of exposure?
   - If susceptibility, adolescent girls, women of child-bearing age, or mothers post-partum?
   - If risk of exposure, routine well-child care, periodic campaigns, or both?
3. Designing hypothetical vaccination programs: tactics
   - Is catch-up necessary? If so, age range and coverage?
   - If routine vaccination, number of doses, age(s) and coverage?
   - If periodic campaigns, frequency, age range and coverage?
4. Incorporating economics and logistics: which program would be optimal?
   - Costs of alternative approaches, strategies, tactics?
   - Opportunity costs (i.e., what other health programs would rubella vaccination preclude)?
   - Feasibility (of, e.g., access to target groups)?
5. Anticipating changes: vaccination alters the epidemiology
   - Indirect effects can produce counter-intuitive, even perverse outcomes
   - Alter course if necessary to ensure that goals are attained

Assessing CRS Burden

- Data: demographic information (equivalent of women by age, births by age of mother) and either disease (rubella among women by age) or sero- (risk of infection by age) surveillance. Absent gender-stratified surveillance, assume …

- Approach: where cases among WCBA are reported[†], multiply by age-specific birth rates (~ Pr[pregnant|age]) to obtain women infected and pregnant the same year, correct for duration of gestation (40/52), and ignore seasonality

[†]account for under-reporting insofar as possible

Rubella during Pregnancy†
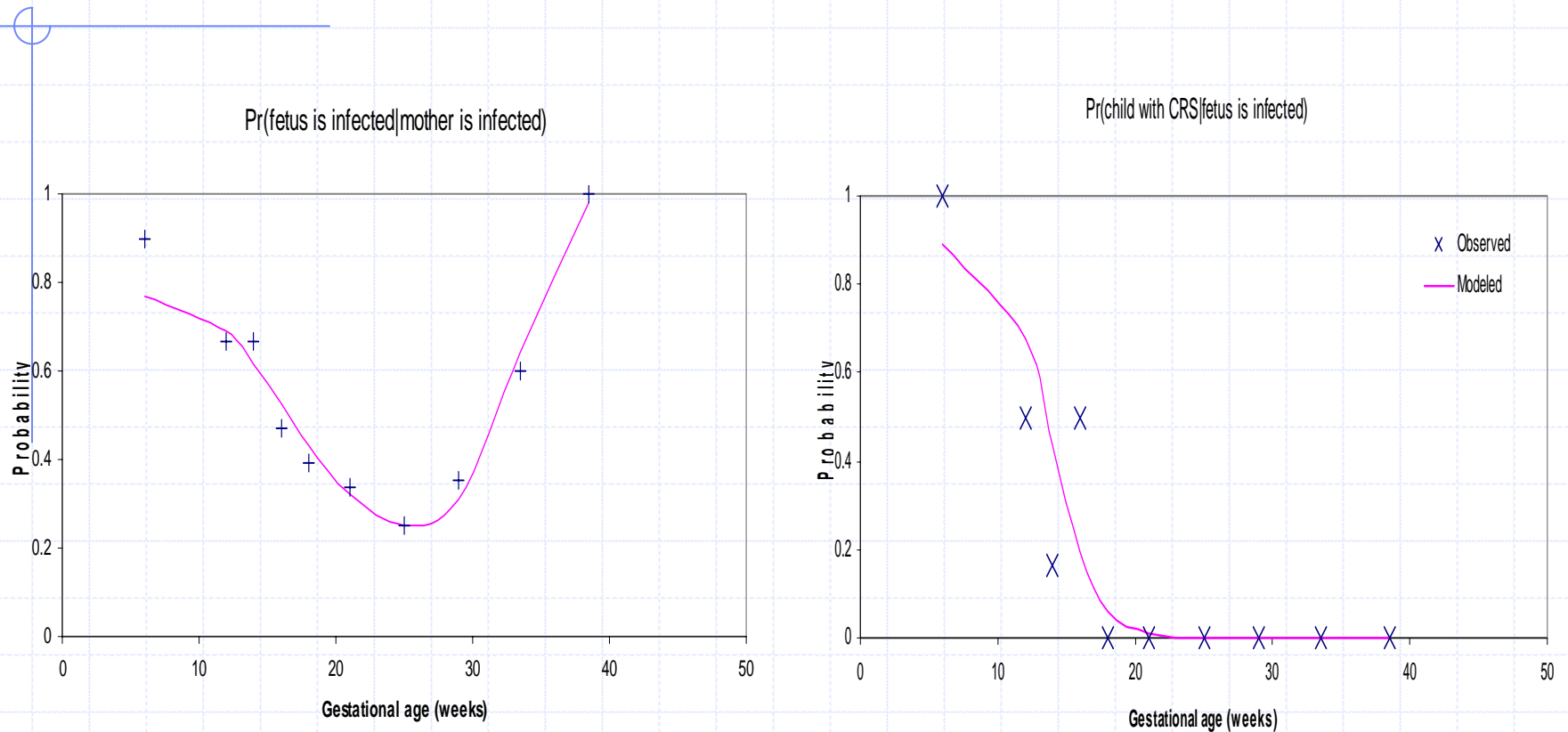
†Miller et al. 1982. Consequences of confirmed maternal rubella at successive stages of pregnancy. The Lancet October 9th, pp. 781-84

Probability of a Child w/CRS given Maternal Infection during Week x

NB: analysis of published summary should be refined via individual observations (e.g., 9 of 10 women infected during the first 10 weeks bore children with CRS, but I don't know exactly when they were infected).

Catalytic Modeling

- If reliable age- and gender-specific disease surveillance isn't available, infer age-specific infections among WCBA from sero-surveillance and demographic data

- Muench named several simple mathematical functions (that can be fit to serological data via maximum likelihood) by analogy with enzyme-catalyzed chemical reactions

- Farrington refined this approach, but Cutts and Vynnycky argued that data available throughout much of the world warrant only the simplest of Muench's expressions
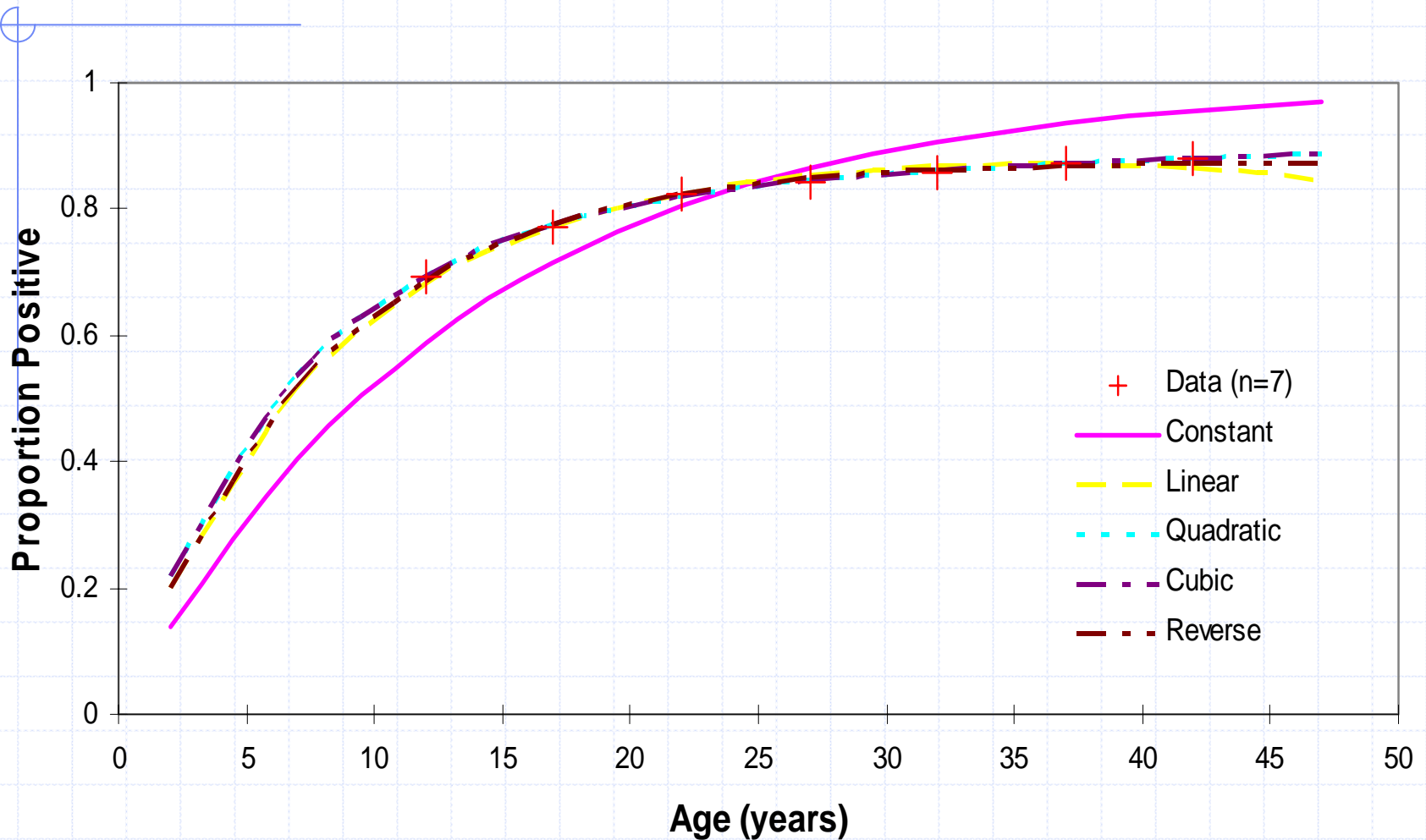
Muench, H 1959. *Catalytic Infection Models in Epidemiology*. Harvard University Press

Farrington, P 1990. Modeling forces of infection for measles, mumps and rubella. Statistics in Medicine 9:953-67

Cutts, F, Vynnycky, E 1999. Modeling the incidence of congenital rubella syndrome in developing countries. International Journal of Epidemiology 28:1176-84

Rubella in Mexico, 1987-88[†]

Legend:
- + Data (n=7)
- Constant
- Linear
- Quadratic
- Cubic
- Reverse
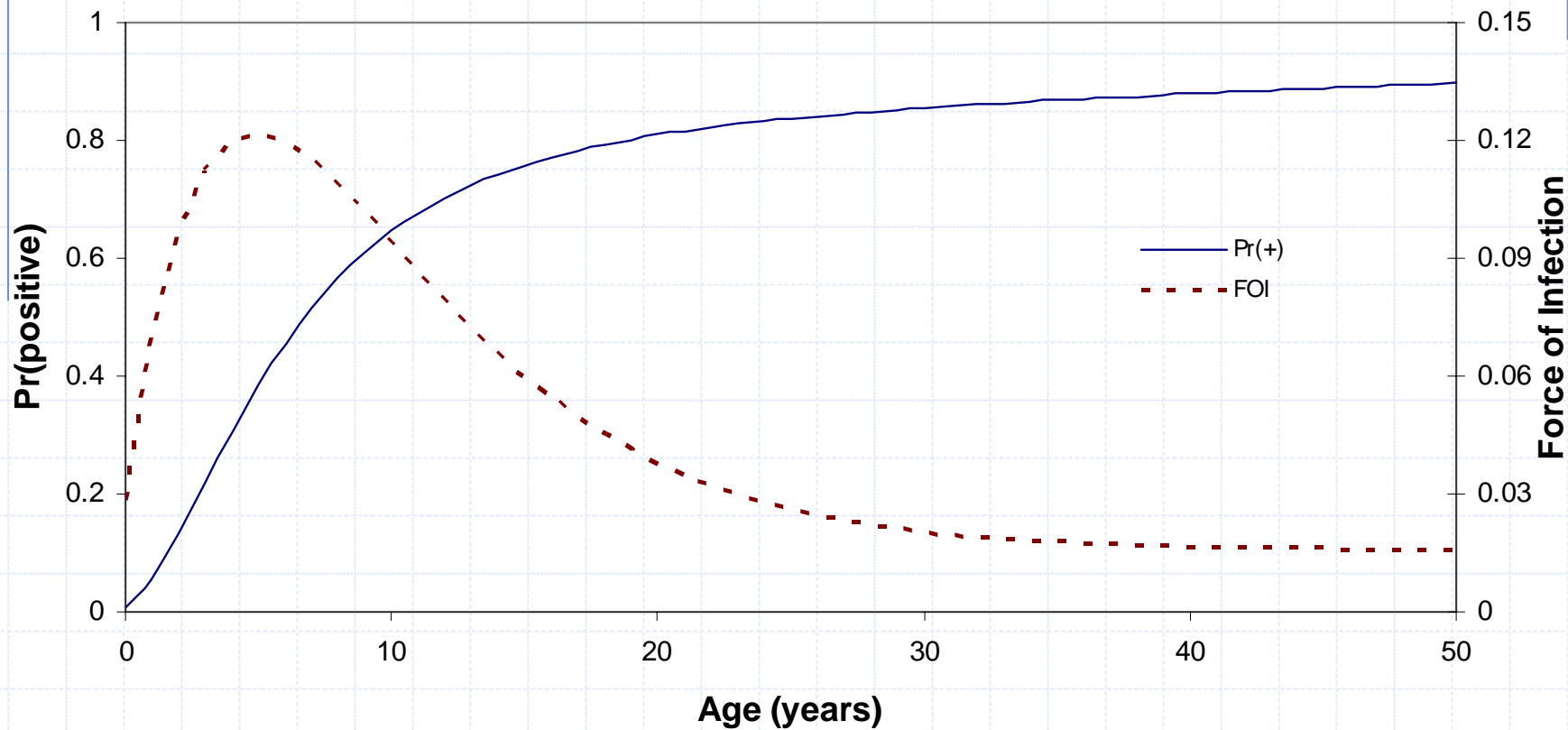
X-axis: Age (years)
Y-axis: Proportion Positive

[†]Gutierrez-Trujillo et al. 1990. Seroepidemiología de la rubéola en mujeres Mexicanas. Encuesta Nacional Probabilística. Salud Pública de México 32:623-31.

Parametric Models
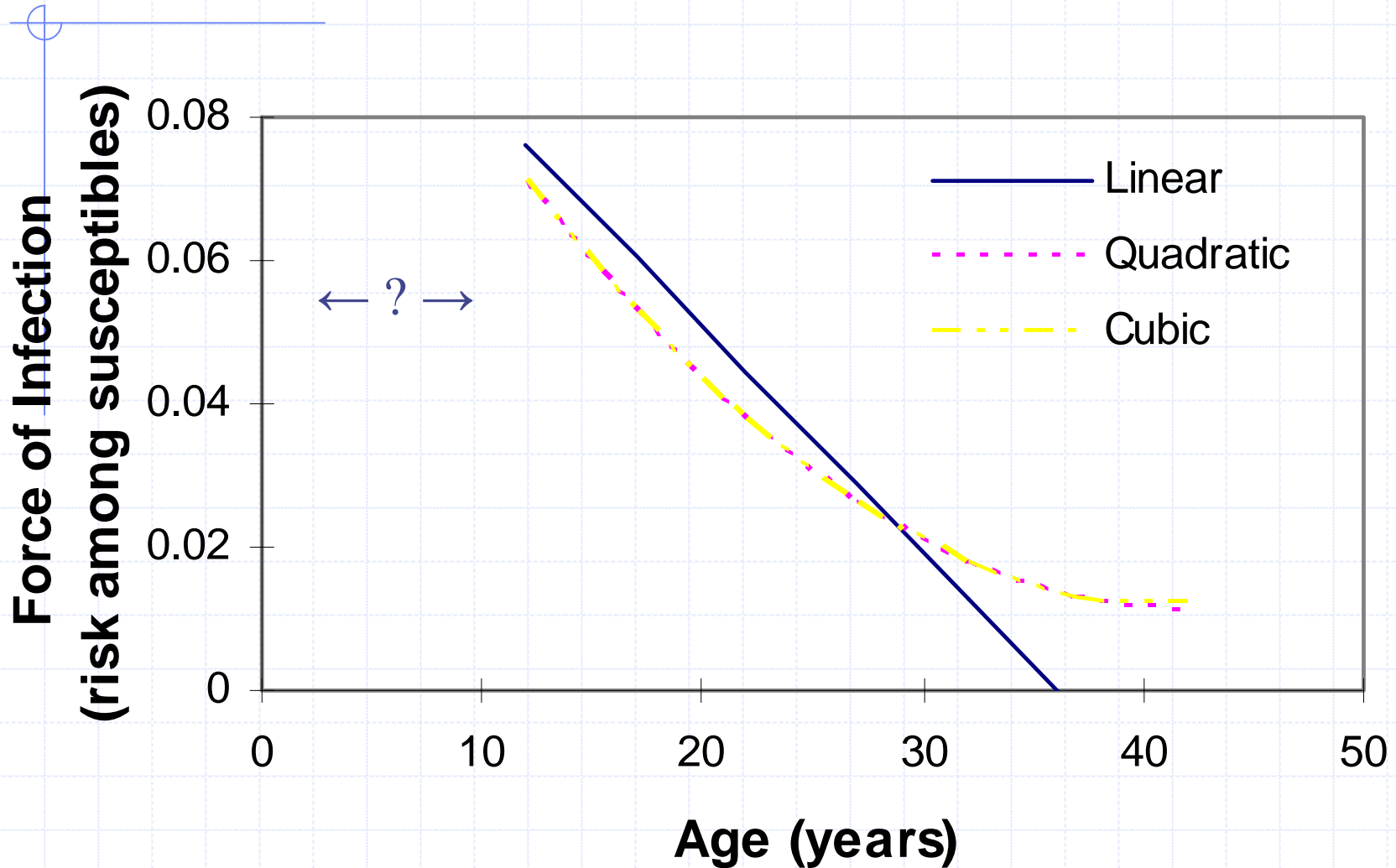
# Farrington's Model, 1987-88 Rubella Serological Survey in Mexico

Age-Specific Risks of Infection

- Given a model of the proportion, ideally of women, seropositive at any age, …
- We can calculate the risk of infection in any interval, ages x to x+n say, by subtracting the proportion at age x from that at age x+n
- Multiplying these by the number of women in each age interval yields estimates of the number infected, …
- Which we could observe directly from age- and gender-specific surveillance, if available

Mexico (composite of 1987-88 serosurvey and 1995 demography)

Age	Females	Fertility (children per year)	Pr(infection), 5-year interval	Women Infected per year	Infected while Pregnant
10-14	5,335,001	0.002535	0.104518	111,520	217
15-19	5,023,827	0.095064	0.057123	57,395	4,197
20-24	4,713,373	0.19773	0.032716	30,840	4,691
25-29	4,148,437	0.176597	0.019366	16,068	2,183
30-34	3,504,924	0.128445	0.011947	8,375	827
35-39	2,842,293	0.075837	0.008166	4,642	271
40-44	2,248,455	0.030005	0.006964	3,131	72
45-49	1,763,712	0.006471	0.00776	2,737	14
50+	1,421,656	0.002875	0.010023	2,850	6
					12,479

CRS in Mexico
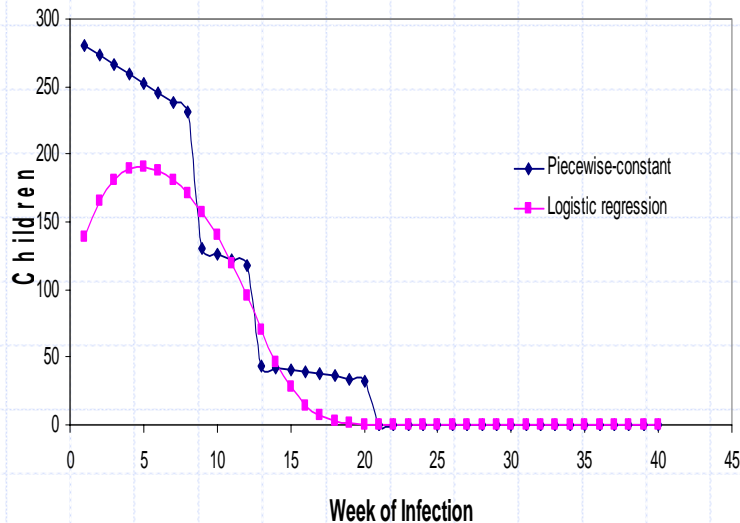
Annual estimates:

- Piecewise-constant risks: 2,850

- Logistic regression (w/ cubic gestational age): 2,088

- Cutts and Vynnycky: 2,324-2,730

Limitations of this Approach

Serosurveillance:

- Naturally-acquired and artificially-induced immunity are indistinguishable, …

- Method assumes that years are alike, but may actually be multi-annual periodicity, …

- … leading to negative risks of infection, as would waning of immunity (or antibody titers)

Either sero- or disease surveillance:

- Demographic and survey data should be contemporary, but rarely are (could project population to align)

- Retrospective, so cannot project impact of (i.e., design, evaluate, or improve) interventions

Rubella in Mexico
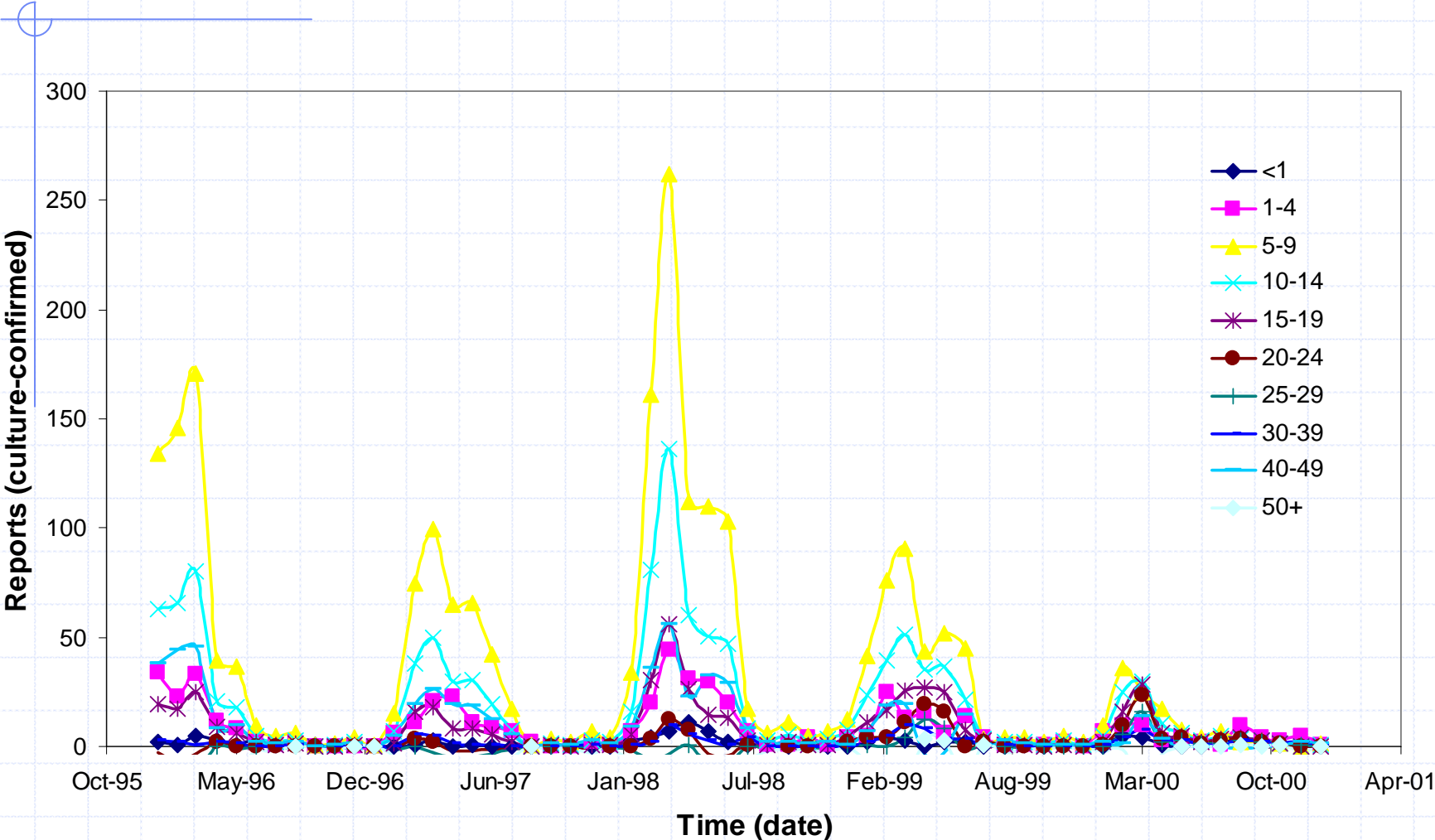
Summary

- CRS incidence is under-ascertained even by careful studies of hospital records, …
- But is estimable from 1) women of childbearing age and births by age of mother, …
- Together with 2) disease or, via catalytic modeling, sero-surveillance
- Surveys sampling ages in proportion to the rate of change in Pr(sero+) would be more valuable …
- In evaluating interventions, which requires dynamic modeling of rubella

Recommendations

1. Fit demographically-realistic dynamic models to surveillance from countries with the most accurate and complete records in each region

2. Others could replace country-specific parameters insofar as possible (or keep those of their neighbor insofar as necessary), and …

3. Depending on whether they had already embarked on, or were just considering a rubella vaccination program, use these tools to:

Recommendations (cont'd)

- Ensure that policy goals were being attained, by projecting future CRS incidence, and if not, to evaluate possible mid-course corrections

- Or, to evaluate their options (i.e., approach, strategy, tactics, economics, logistics, …), enumerated more fully on my second slide

# Vaccination and Congenital Rubella Syndrome in Costa Rica: Analytical and Mathematical Epidemiology†

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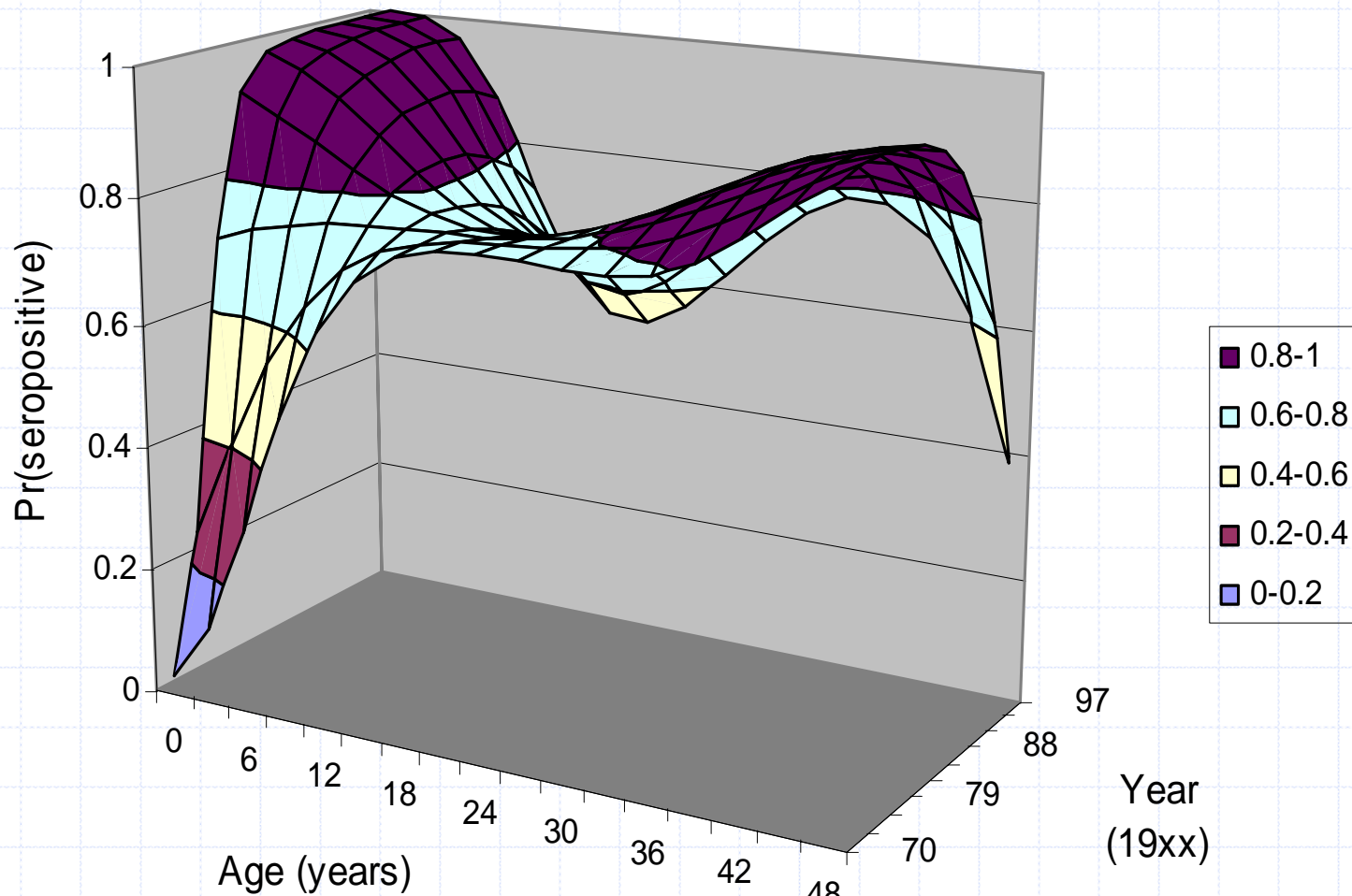
Rubella Vaccination
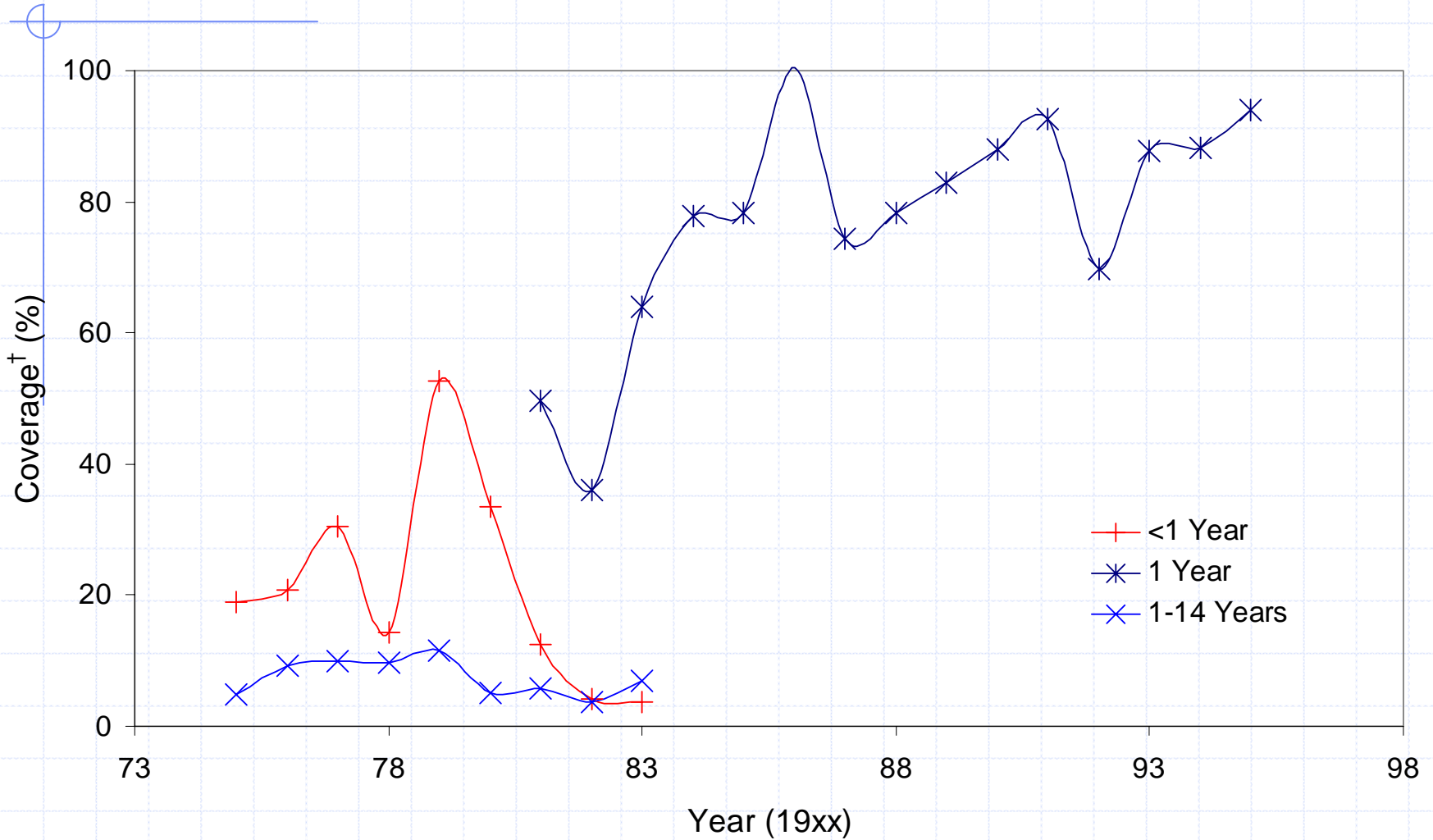
†estimated via the administrative method

Rubella Incidence
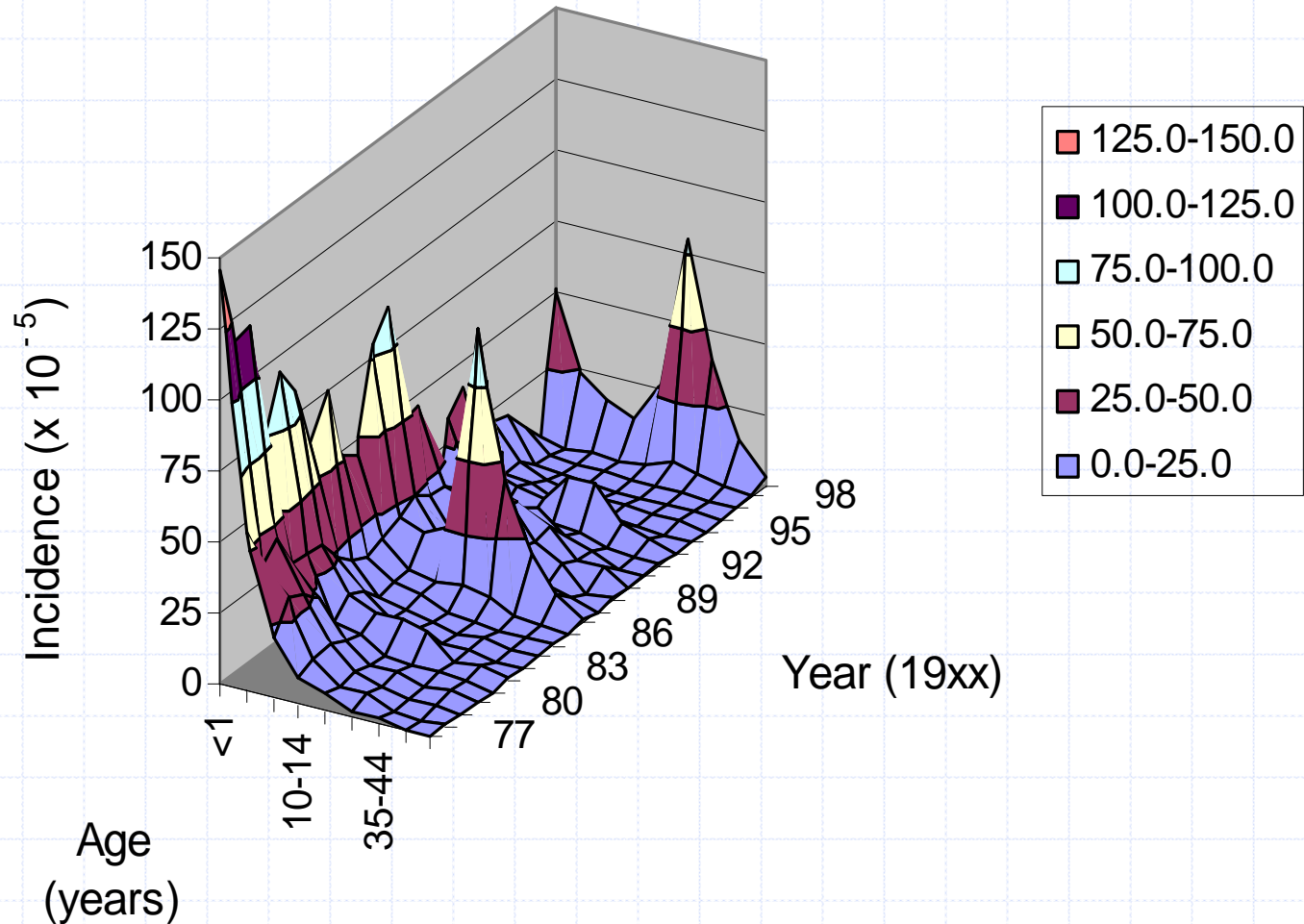
Synthesis of Rubella Serology since before Vaccination Began

Estimated Annual Burden of CRS

- Cases among women of childbearing age during year 19xx * children per woman that year * duration of a trimester ([1/3]*[40/52] years) * average risk (0.65) = children w/CRS

- All diseases are under-reported, and 50% of rubella infections may be asymptomatic, for which reason CRS may be estimated via catalytic modeling of sero-prevalence

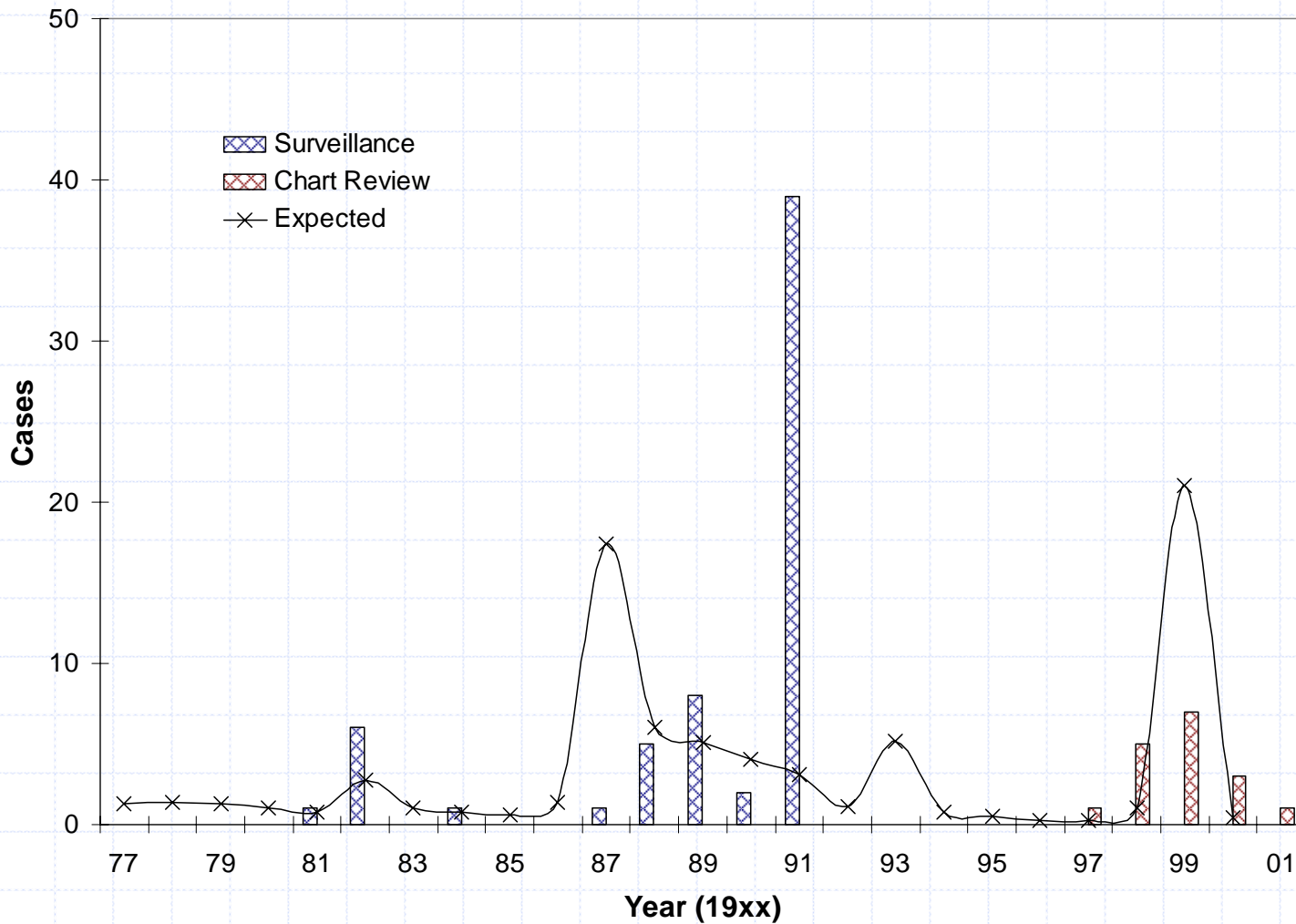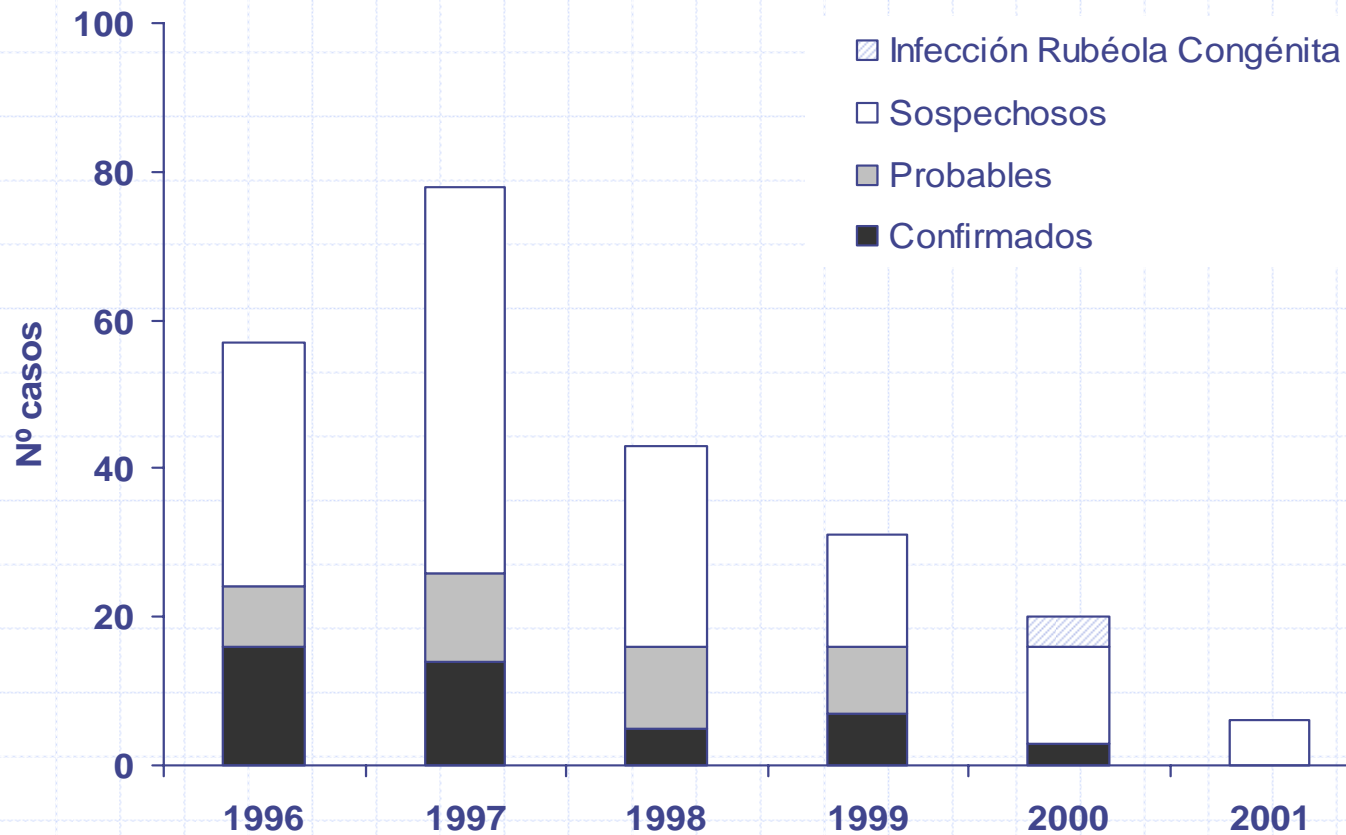# Birth Rates
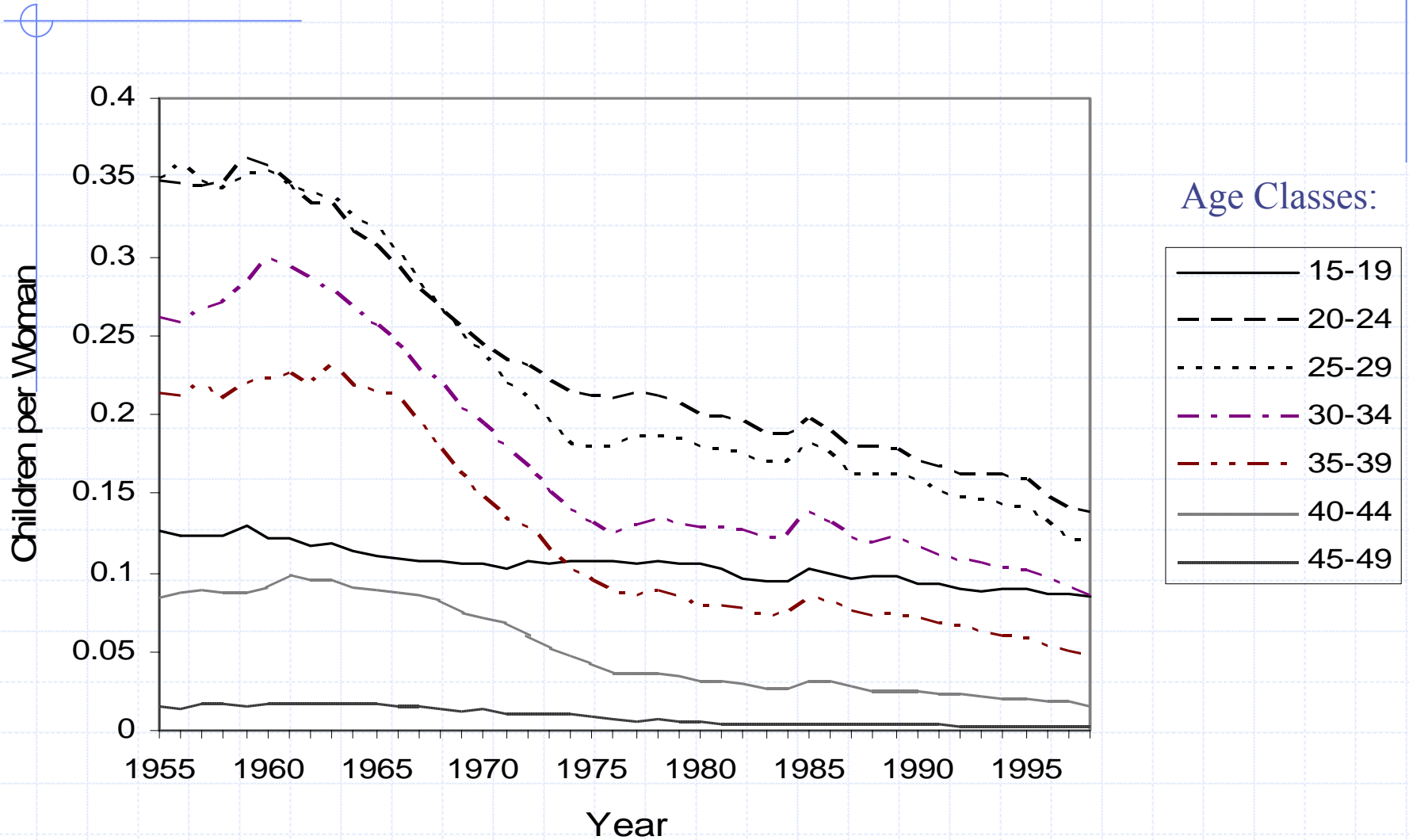
Congenital Rubella Syndrome

Figura 1. Número de casos sospechosos, probables y confirmados de Síndrome de rubéola congénita e Infección por rubéola congénita* según año. Hospital Nacional de Niños, Costa Rica, 1996 a 2001

* Casos de SRC identificados por búsqueda retrospectiva en el Hospital Nacional de Niños

Figura 2. Combinación de manifestaciones clínicas de casos probables de Síndrome de rubéola congénita*. Hospital Nacional de Niños.
Costa Rica, 1996-2001
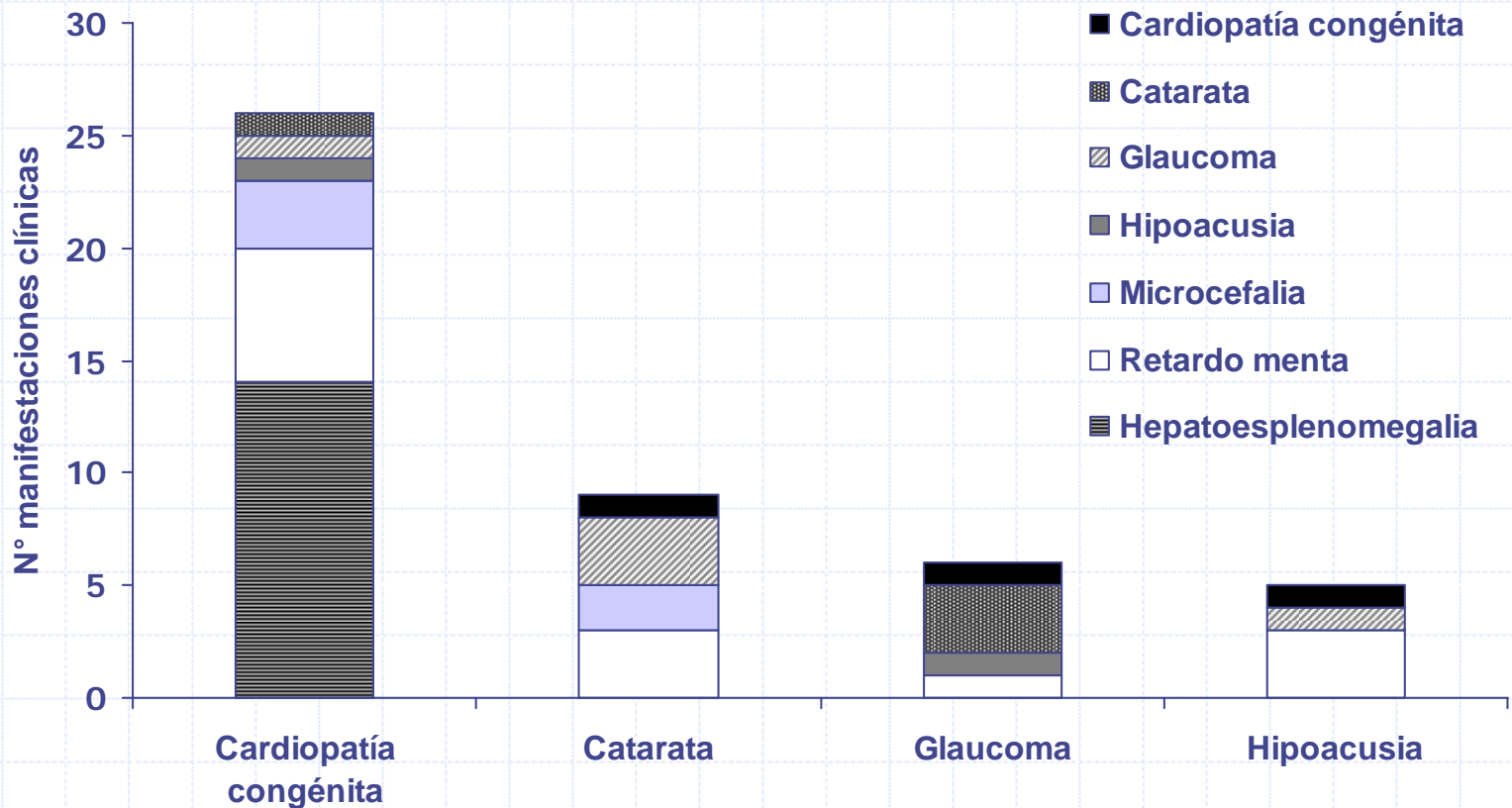
* Incluye manifestaciones clínicas compatibles de los casos clasificados como SRC probables según definiciones de CDC/CSTD

Figura 3. Número de casos de Síndrome de rubéola congénita esperados* y observados**. Costa Rica, 1996 a 2001
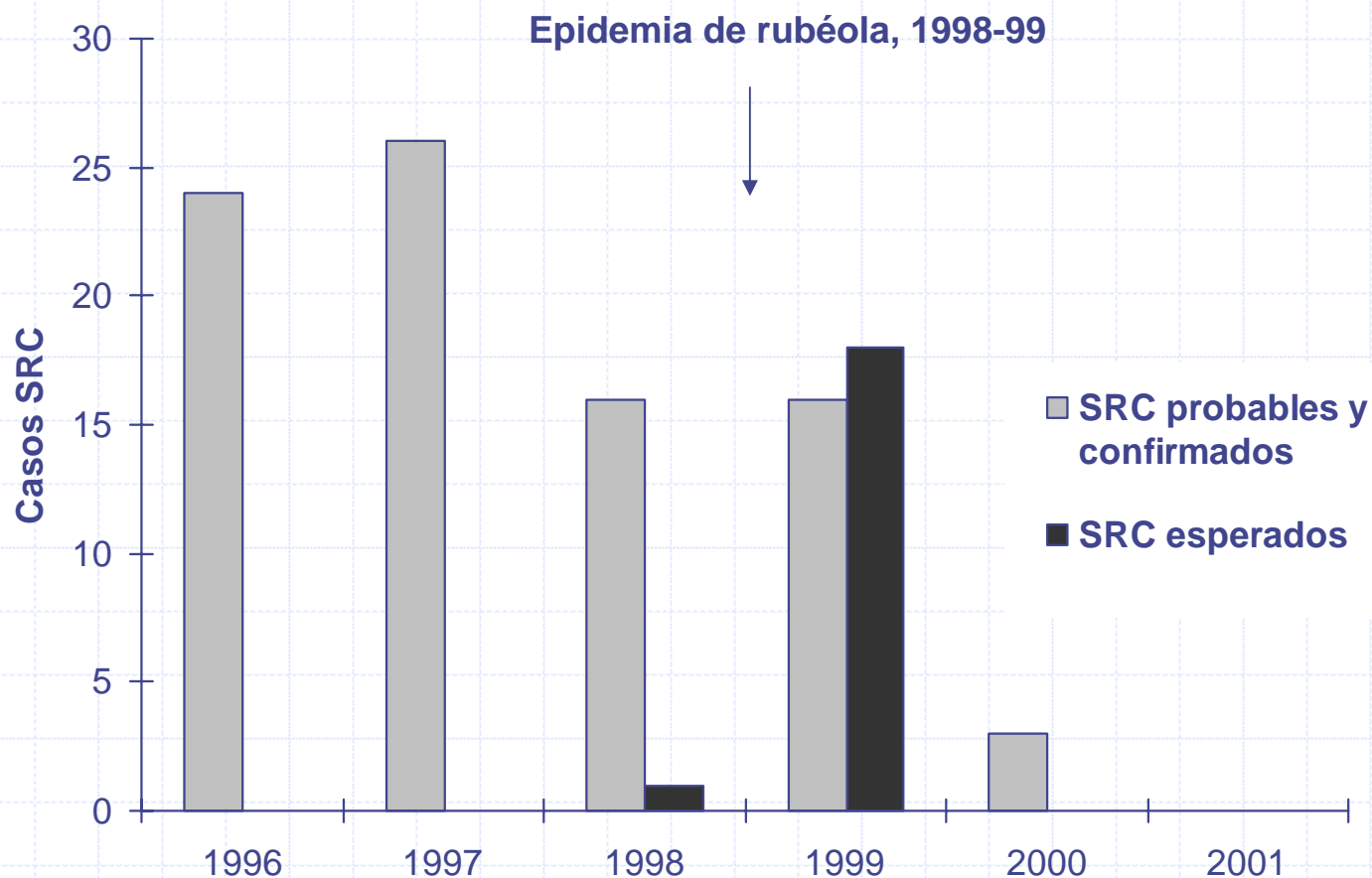
* Casos estimados en base a casos de rubéola en mujeres de edad fértil, tasas específicas de fecundidad y probabilidad de SRC durante el primer trimestre de embarazo
** Incluye casos de SRC probables y confirmados identificados mediante búsqueda retrospectiva en el Hospital Nacional de Niños

Policy Options

1. Increase coverage, possibly via a second opportunity (e.g., a follow-up campaign)
2. One-time mass campaign among adolescent girls and women of childbearing age (WCBA)
3. Composites of routine and targeted vaccination strategies

Why the Benefit of Vaccinating adolescent Girls and young Woman depends on Age

- Direct Effect: her progeny (Fisher's Reproductive Value)

- Indirect Effect: others whom she might infect (age-specific contribution to R_0)

NB: direct effect is greater for women at risk of pregnancy than not, for parous than nulliparous ones, … regardless of age

1995 Value of a Woman's Future Reproduction Relative to a Neonate
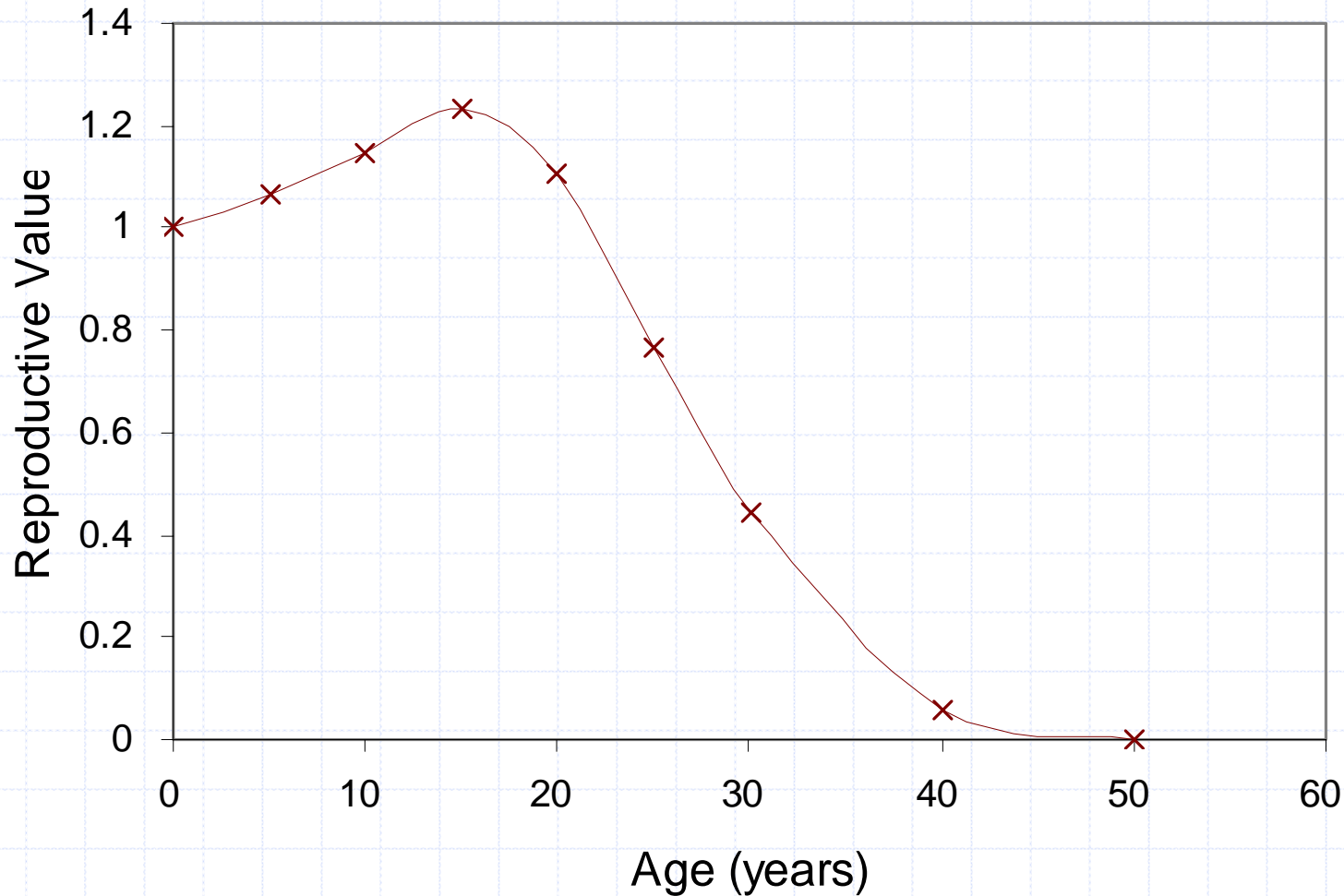
Effective Contacts (inferred from measles in São Paulo)

- If Infection$_{i\ j}$ = Contact$_{i\ j}$ * Pr(susceptible|age i) * Pr(infectious|age j), Contact$_{i\ j}$ = Infection$_{i\ j}$ / [Pr(susceptible|age i)*Pr(infectious|age j)]

- Infection$_{i\ j}$ is from querying cases about the people who infected them, they infected, or both

- Pr(susceptible|age i) are from a statistical synthesis of five serological surveys, and

- Pr(infectious|age j) are quotients of laboratory-confirmed case reports and mid-1997 populations

Contacts by/of Individuals Aged x
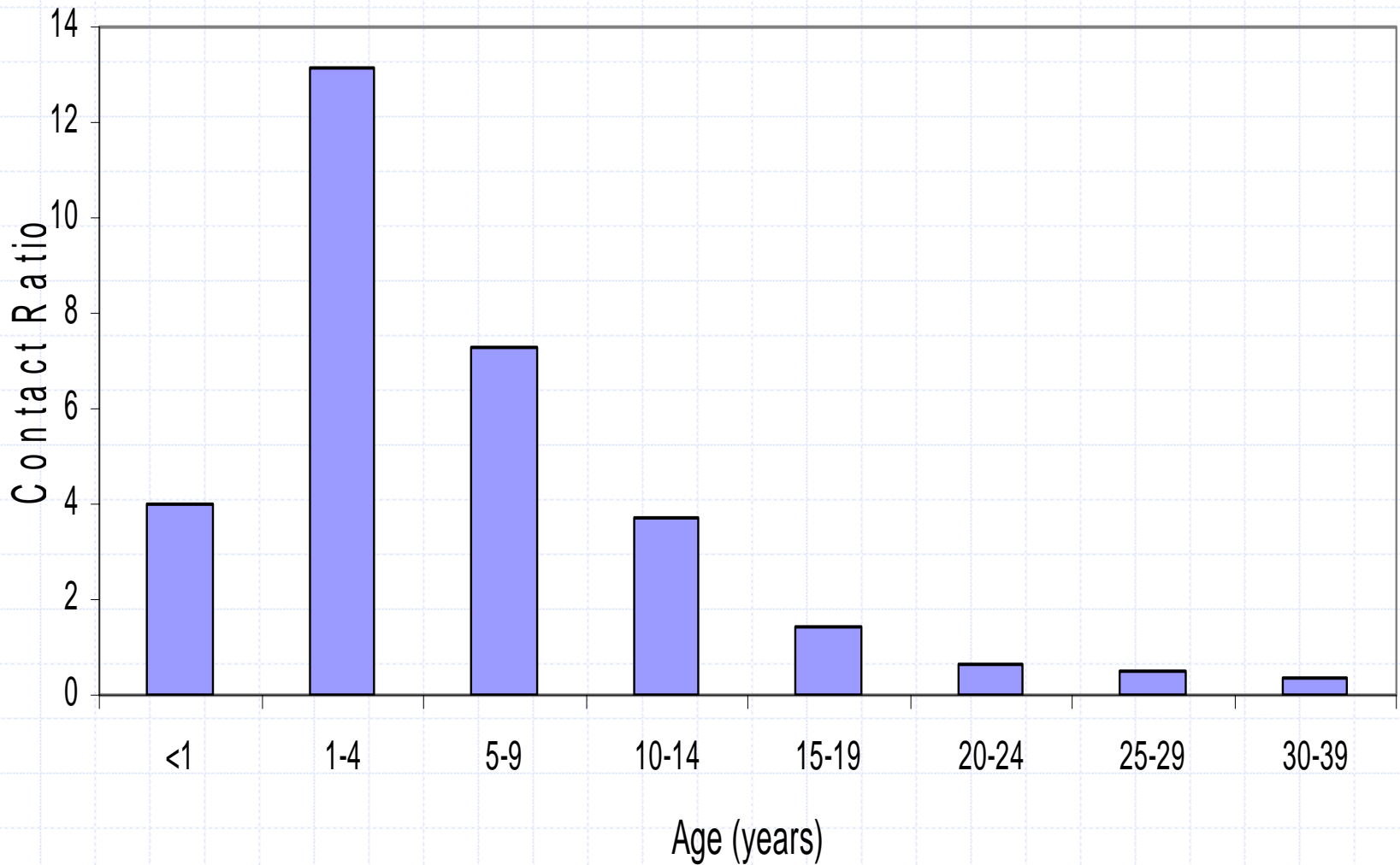
Why the Cost of Targeted Vaccination depends on Age

- Because accessibility (via school, if not well-child care) varies inversely with age
- Can vaccinate adolescents before they leave high school (e.g., catch-up females)
- May be able to vaccinate postpartum women, health-care professionals, teachers
- Other women more difficult, but easier than men, who are most inaccessible

Optimal Resource Allocation?

- If the benefit of vaccination declines and cost increases with age, the net benefit must decline. Moreover, …

- One can show that catch-up campaigns among WCBA are necessary only if coverage among children is insufficient

Devil's Advocacy

- Vaccination has reduced the incidence of rubella and changed its age-specific dynamics, …

- And hence the temporal distribution of CRS, but are there fewer cases?

- How much money has been spent on rubella vaccination since the mid-70s?

- Given other public health needs, have those resources been well spent?

Impact of Vaccination on CRS?
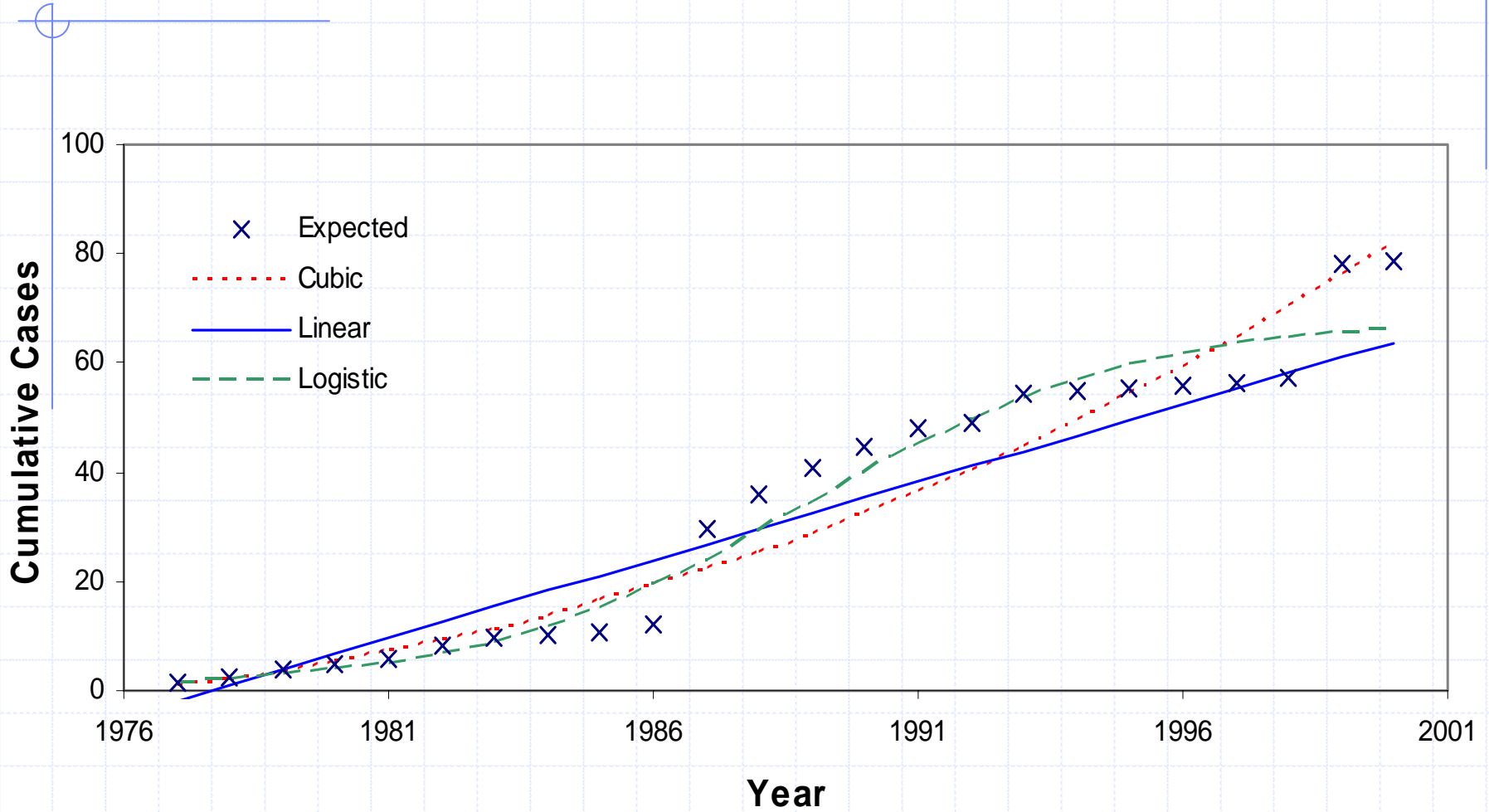
Did Modelers Have Anything to Offer Costa Rican Health Policymakers?

- Could have advised on need for catch-up campaign, its age range, coverage goals, …

- Identified number and timing of routine doses, coverage, … required to achieve any goal (e.g., maintain reduction in CRS attained via recent mass campaign, eliminate rubella), determine if MMR need be used in follow-up campaigns, …

- Determined which of alternative strategies for dealing with immigration was most cost-effective

Postscript

- Mass campaign during 2000 attained very high coverage through 39 years of age
- Currently collecting economic information for cost-benefit studies