Rubella in Romania

An Evaluation of Possible Vaccination Strategies via Mathematical Modeling†

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

Contributors

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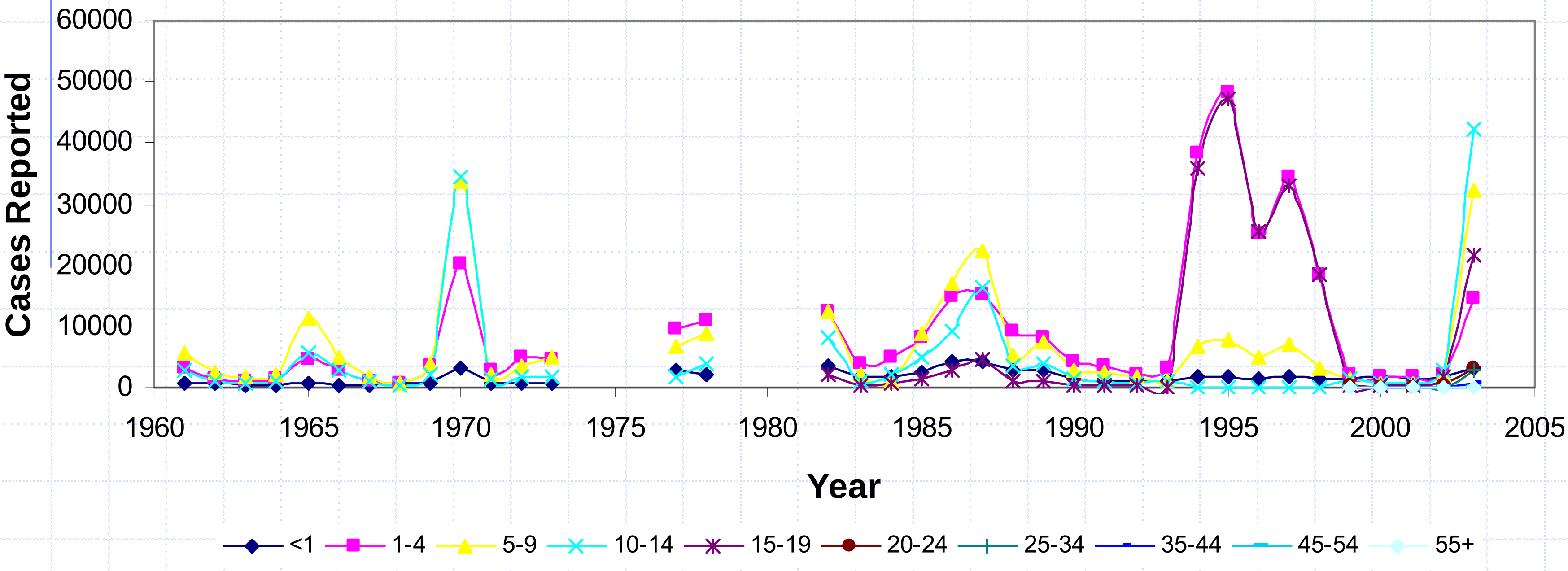
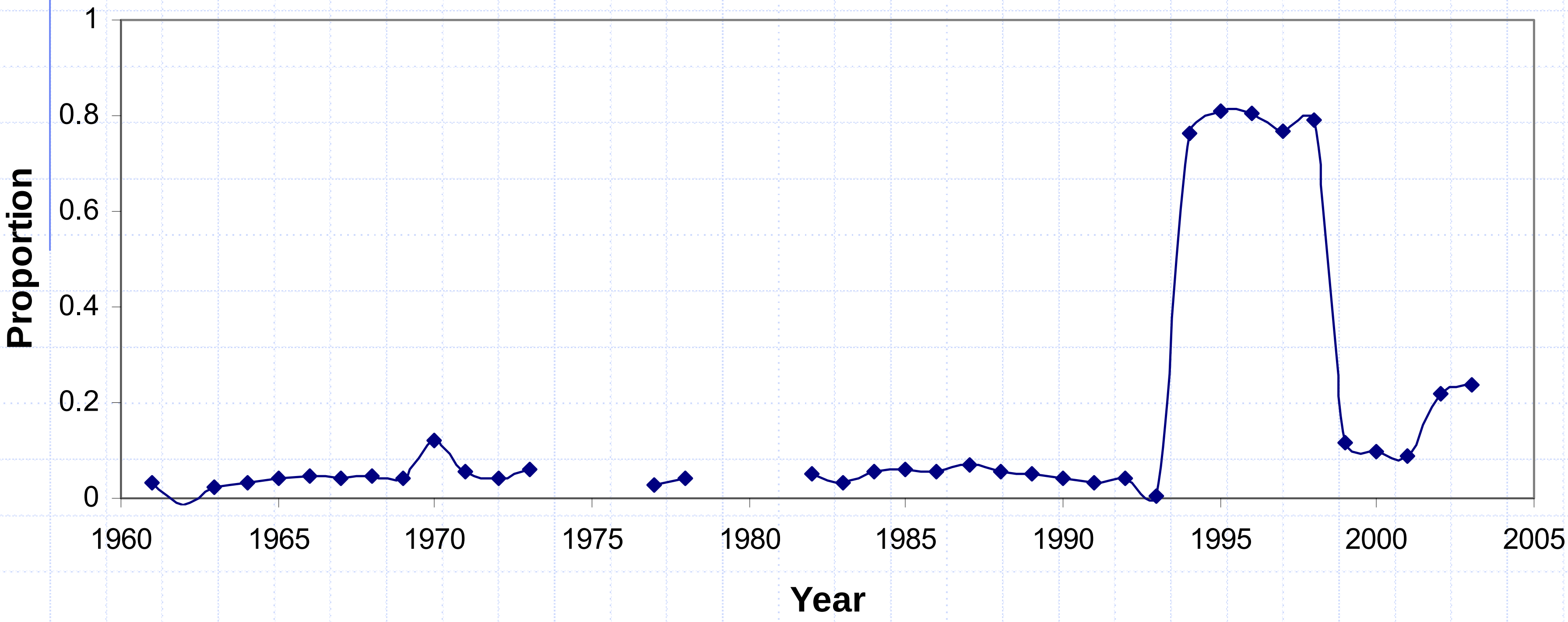
Outline

1. Observations
   - Historical surveillance
   - Explanation for secular patterns, relevance to vaccination
2. Mathematical modeling
   - Measles/rubella model, modeling process
   - Evaluation via comparison of predicted and reported rubella and congenital rubella syndrome
3. Policy assessments
   - Routine childhood vaccination, coverage required for control
   - Marginal benefit of catch-up campaigns
   - Targeted vaccination: adolescent girls and young women or women of childbearing age
   - Composite strategies
4. Summary

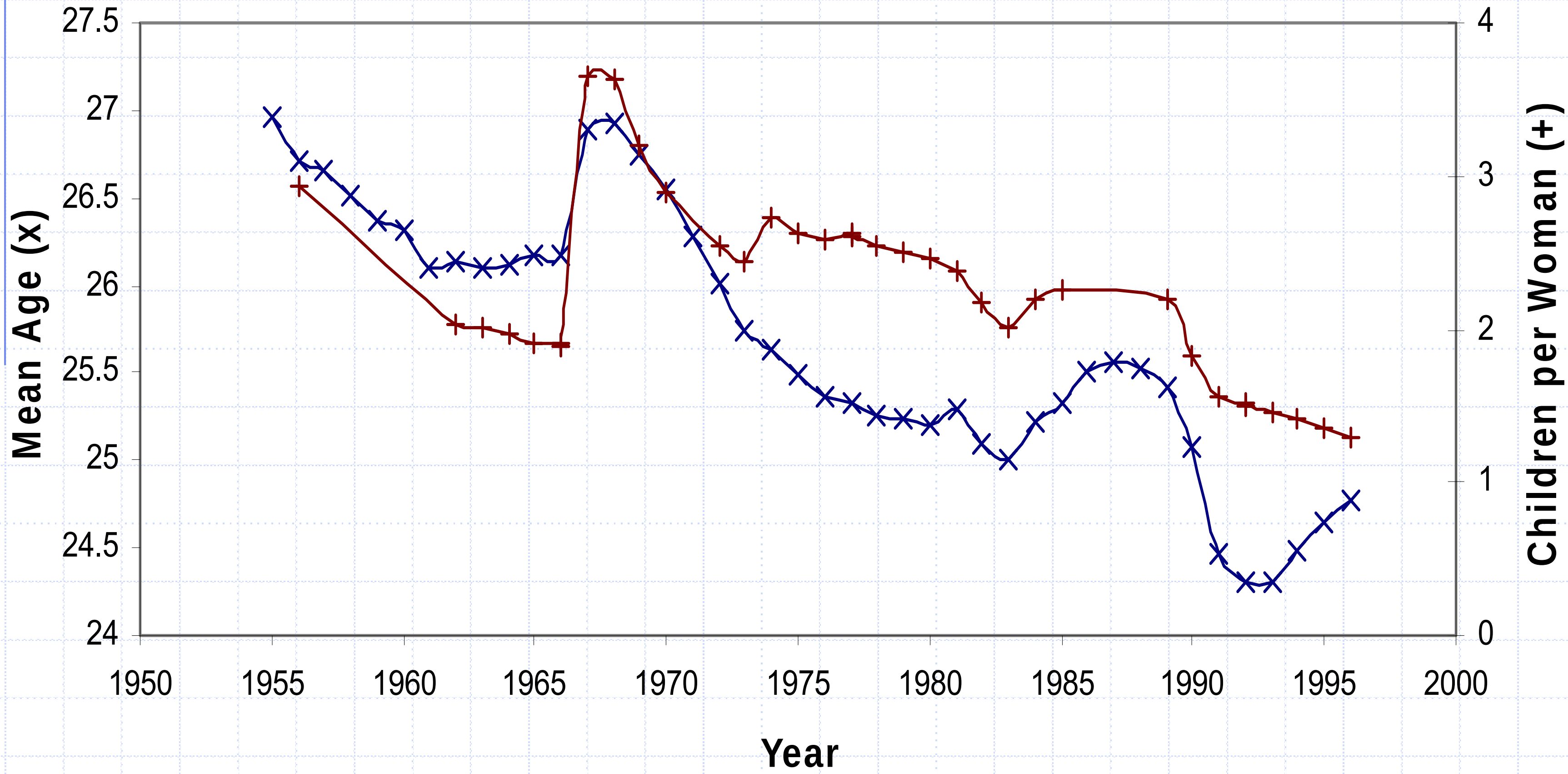
Rubella in Romania



Rubella among Romanians ≥15 Years Old



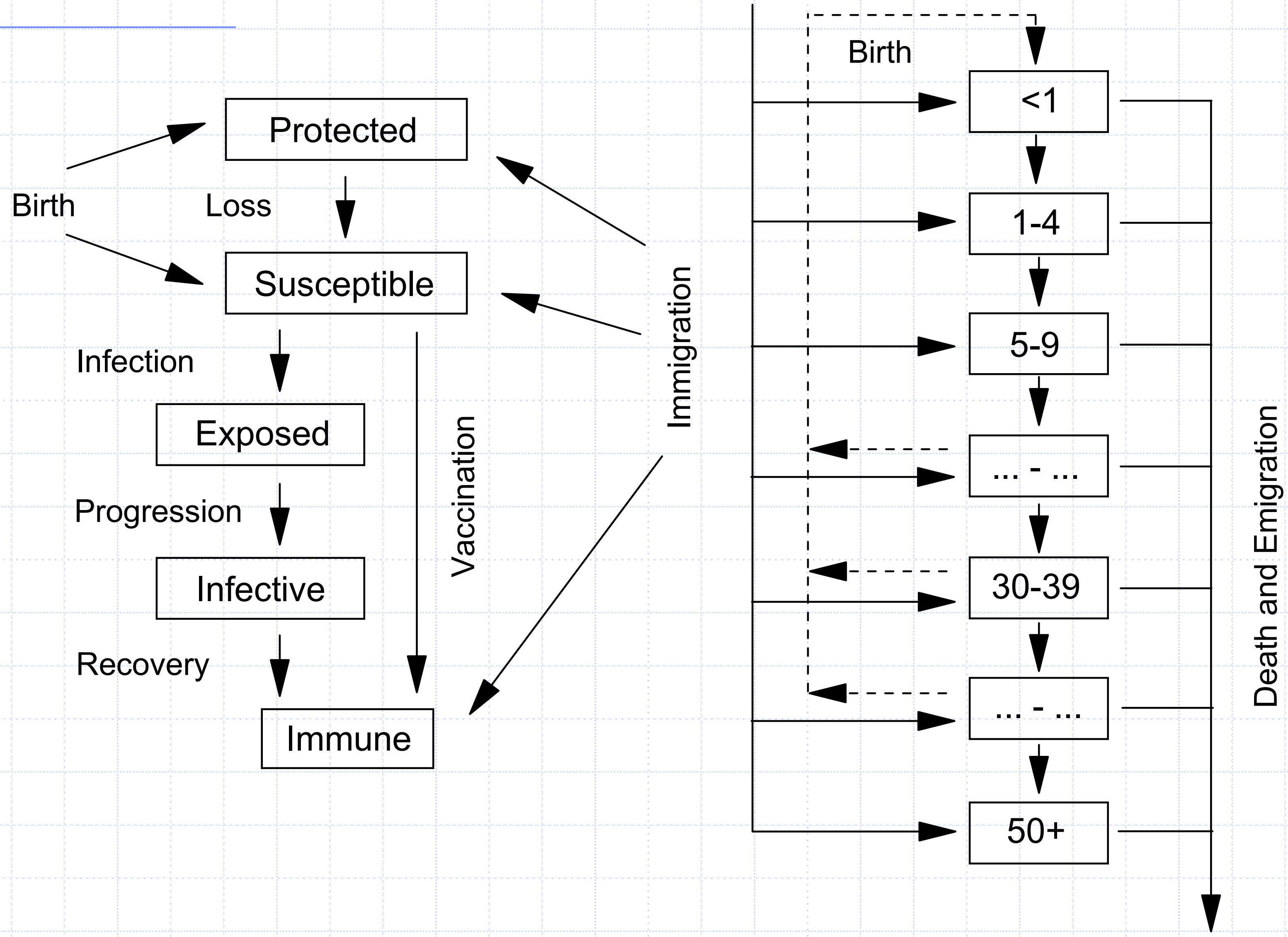
Childbearing in Romania



Pattern and Explanation

- Transition from relatively small 5- to larger 10-year cycles (a period-doubling bifurcation?)
- As births decline, longer periods are required for enough susceptibles to accumulate
- The mean age of infection increases, and with it the incidence of congenital rubella syndrome
- Childhood vaccination can have this effect if coverage is insufficient
- We will ascertain coverage required to preclude it via mathematical modeling

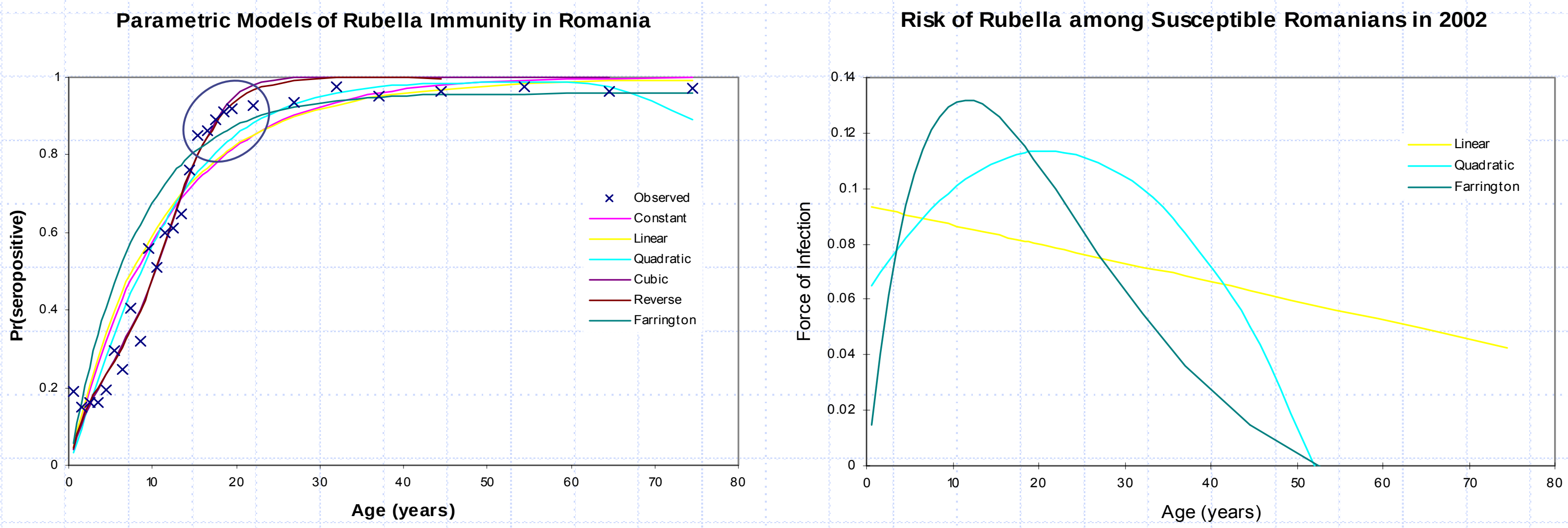
Measles/Rubella Model



Modeling Process

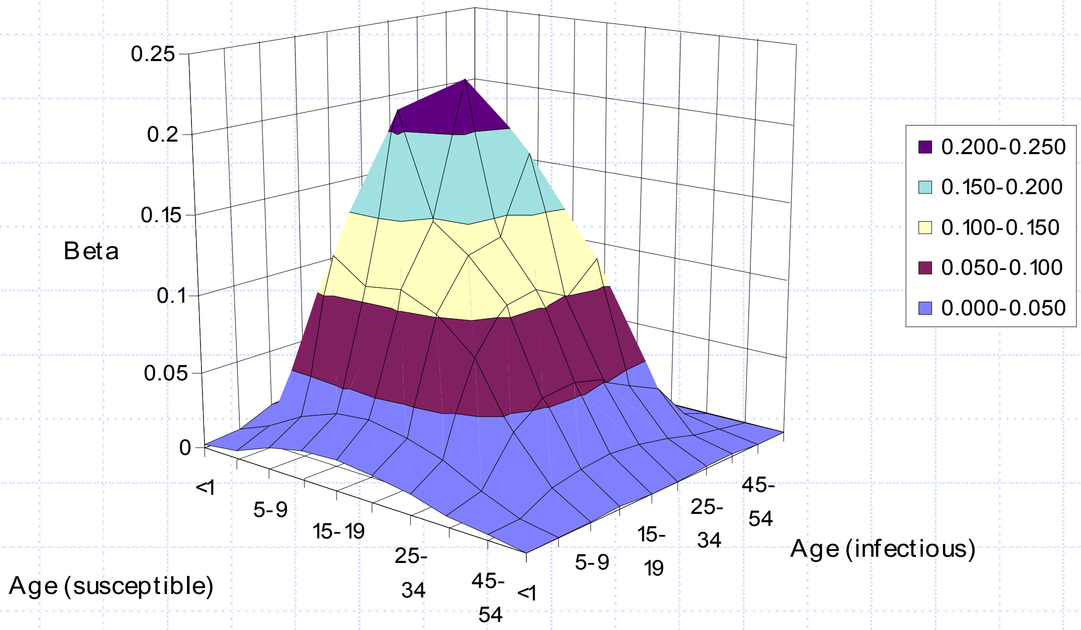
- Estimate parameters from observations insofar as possible (e.g., infection rates from cross-sectional serological survey assuming mixing)
- Adjust infection rates and harmonic coefficients (seasonal forcing) to minimize disparities between predictions and observations
- Evaluate possible vaccination strategies for mitigating the burden of CRS (e.g., routine childhood, w/ and w/o catch-up, targeted female)

Catalytic Modeling



NB: in February of 2002, 37,375 girls 14-18 years of age were vaccinated in Bucharest (ca. 10% of population)

Infection Rates



0.06249	0.00487	-0.000116

Group	x	n	Midpoint	Pr(+)	Population	Susceptible	Immune	Pr(female)	BR	DR	Childbearing proportion	mean	variance	gamma	Infection proportion	mean	variance	gamma
<1	0	1	0.5	0.03135	234,888	227,525	7,363	0.486032		0.020725		0	0	4.78E-27	0.03135	0.01567	0.00784	0.005377
1-4	1	4	3	0.18806	929,487	754,686	174,801	0.486415		0.001051		0	0	8.09E-12	0.15671	0.47014	1.41042	0.166646
5-9	5	5	7.5	0.44527	1,432,890	794,872	638,018	0.489514	0	0.000814		0	0	2.2E-05	0.2572	1.92904	14.4678	0.313125
10-14	10	5	12.5	0.66242	1,702,905	574,864	1,128,041	0.489752	0.000555	0.000517	0.001951	0.024389	0.304866	0.009792	0.21716	2.71444	33.9305	0.239683
15-19	15	5	17.5	0.80446	1,778,748	347,819	1,430,929	0.490311	0.040335	0.000637	0.148245	2.594281	45.39991	0.135002	0.14204	2.48565	43.4989	0.143238
20-24	20	5	22.5	0.88902	1,971,486	218,791	1,752,695	0.486561	0.096879	0.000819	0.391623	8.811521	198.2592	0.340811	0.08456	1.90268	42.8103	0.075854
25-34	25	10	30	0.95135	3,371,755	164,036	3,207,719	0.494026	0.058884	0.001349	0.413343	12.40028	372.0085	0.461008	0.06233	1.86983	56.0949	0.051503
35-44	35	10	40	0.98024	3,070,435	60,666	3,009,769	0.500687	0.00682	0.0038	0.044185	1.767405	70.69622	0.040456	0.02889	1.15568	46.2273	0.010645
45-54	45	10	50	0.98755	2,723,718	33,899	2,689,819	0.510457	0.000111	0.008183	0.000653	0.032659	1.632975	0.000981	0.00731	0.36561	18.2807	0.002008
55+	55	20	65	0.9765	5,286,491	124,256	5,162,235	0.560713	0	0.04162	0	0	0	1.75E-06	-0.0111	-0.7188	-46.723	0.000297
Total					22,502,803						1		688.3017	0.988073	0.976496		210.0058	1.008375

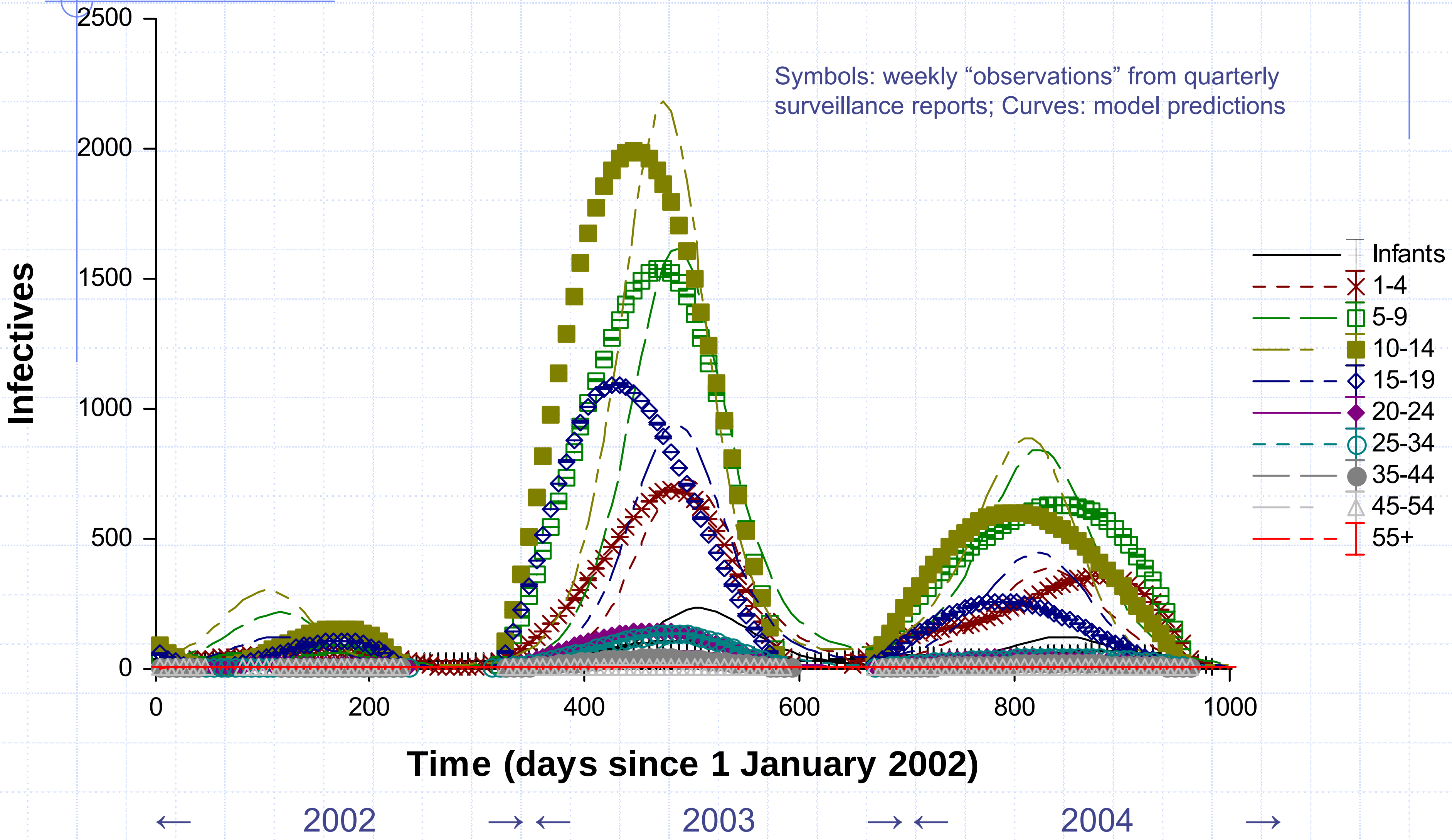
Childbearing		Infection	
mean:	25.63054	mean:	12.1899
variance:	31.37716	variance:	61.41129
std:	5.601532	std:	7.836535
Alpha	20.93639	Alpha	2.419661
Beta	1.22421	Beta	5.037868

Initial conditions:
Pr(+) are probabilities of being seropositive from a catalytic model whose
force of infection is a linear function of age; see FOI_Romania for other models
Multiplying the population by Pr(+) and 1-Pr(+) give immune and susceptible

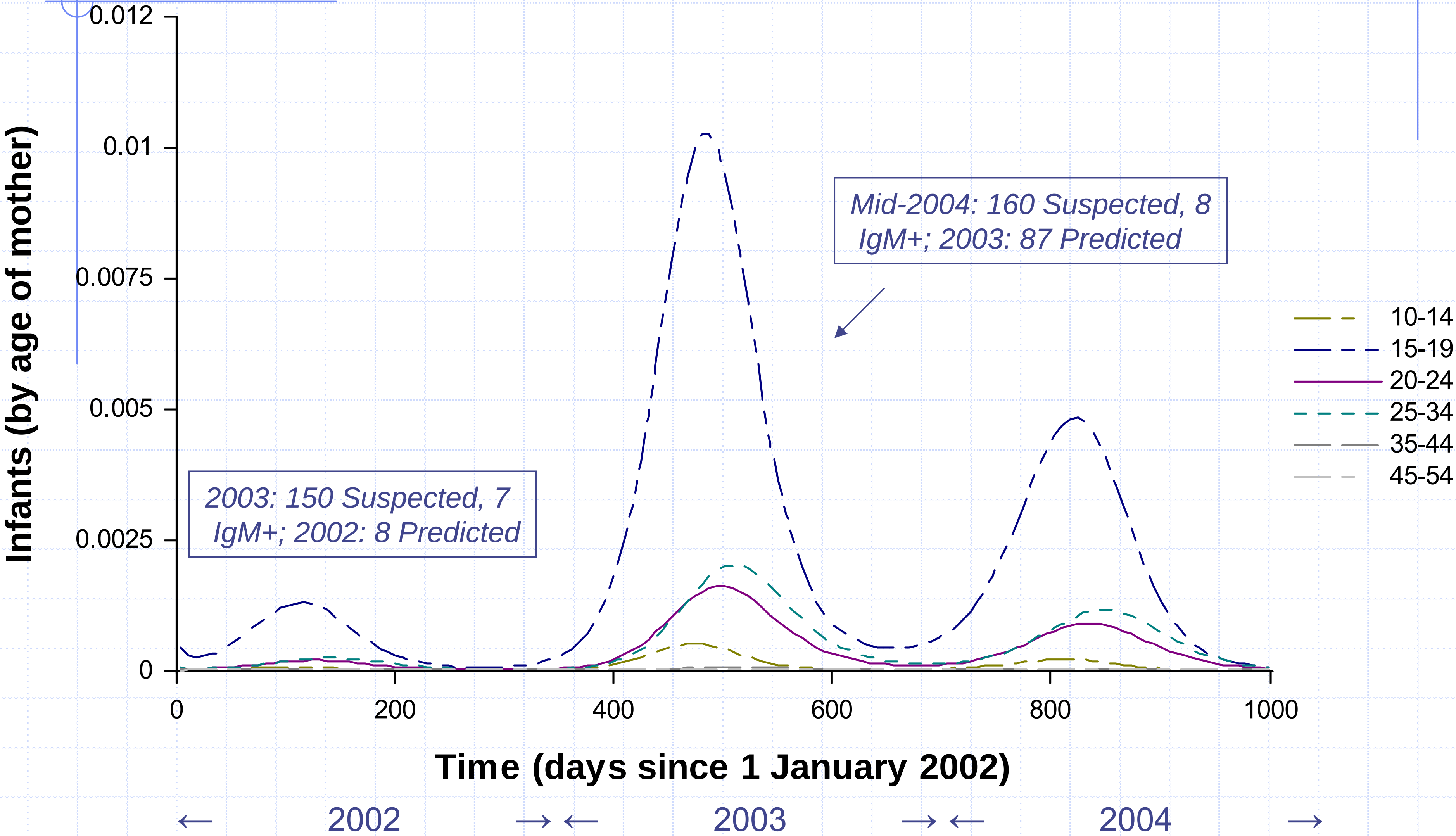
Other demographic parameters:
Pr(female) are proportions (or probabilities that randomly chosen persons are) female
BR and DR are annual birth and death rates

In the remaining columns are calculated the mean age of mothers, its standard deviation,
and -- via the method of moments -- the gamma distribution's parameters
To implement childhood and targeted female vaccination, the dynamic model asks users for
mean ages and standard deviations; post-partum mothers are one such strategy

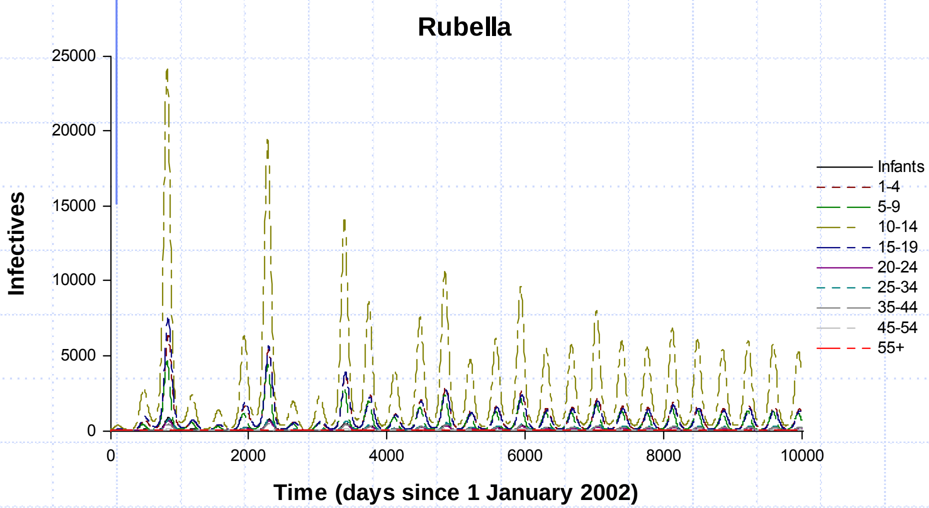
Model fit to 1Q02-1Q04 surveillance predicts 2Q-3Q04 reasonably well (overall $R^2 \approx 0.7$)

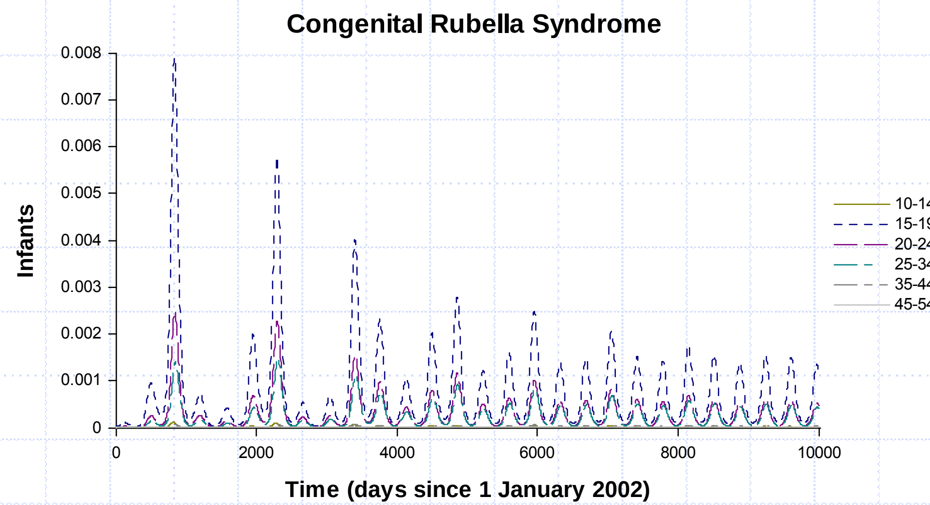


Predictions (annual areas under curves) and Surveillance Reports (the next year)



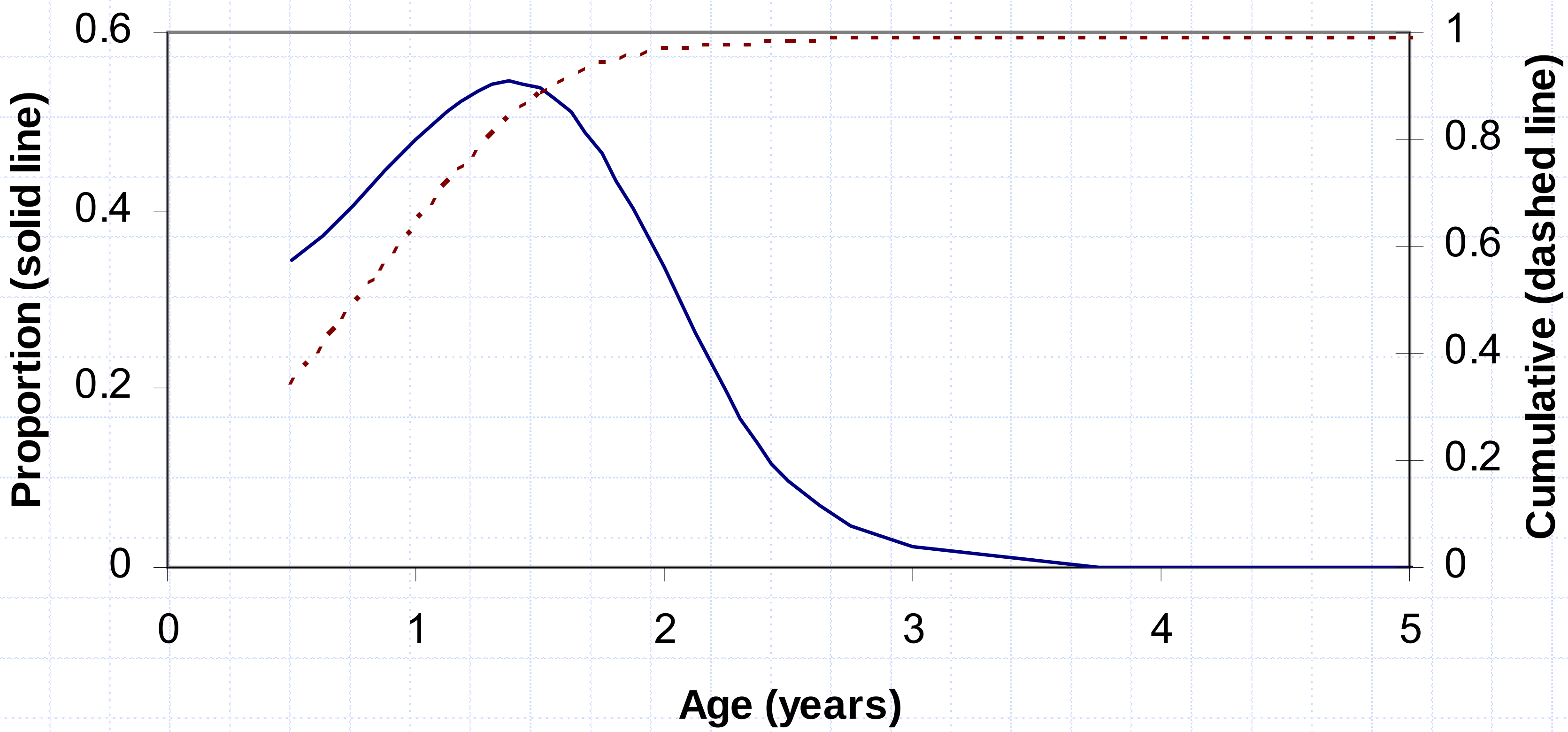
No Vaccination (left: rubella by age; right: CRS by age of mother)



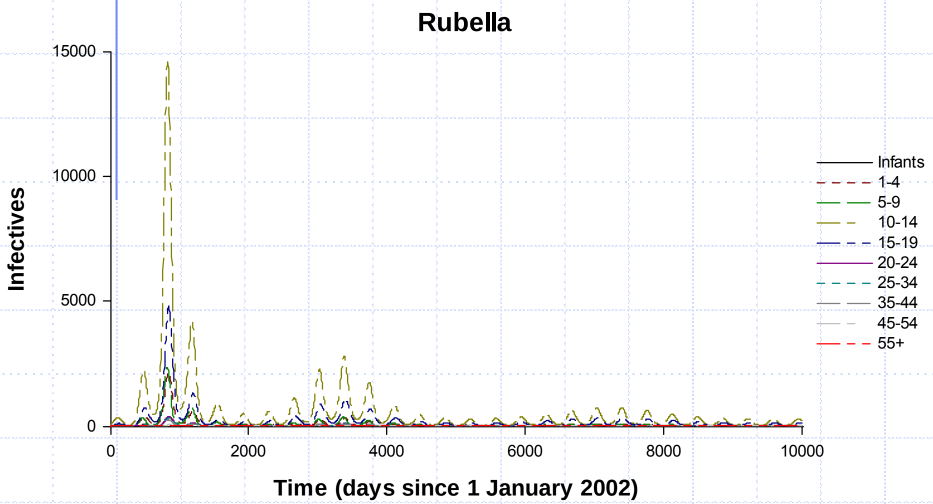


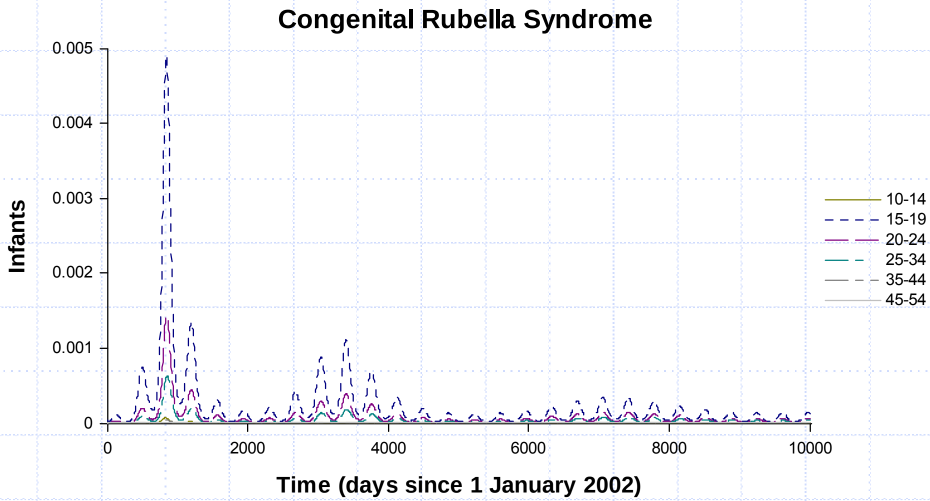
NB: the mean age of childbearing is 25.6 years, so 10,000 days is roughly a generation

Age Distribution, Single Dose

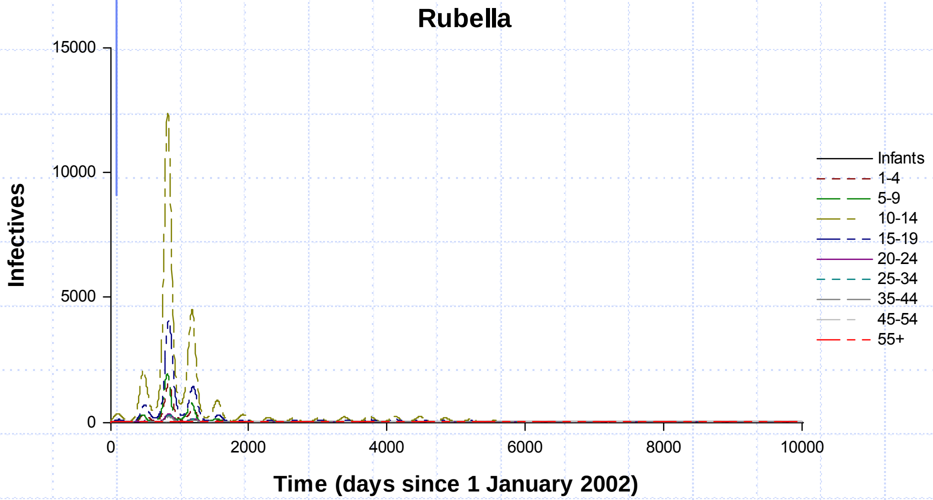


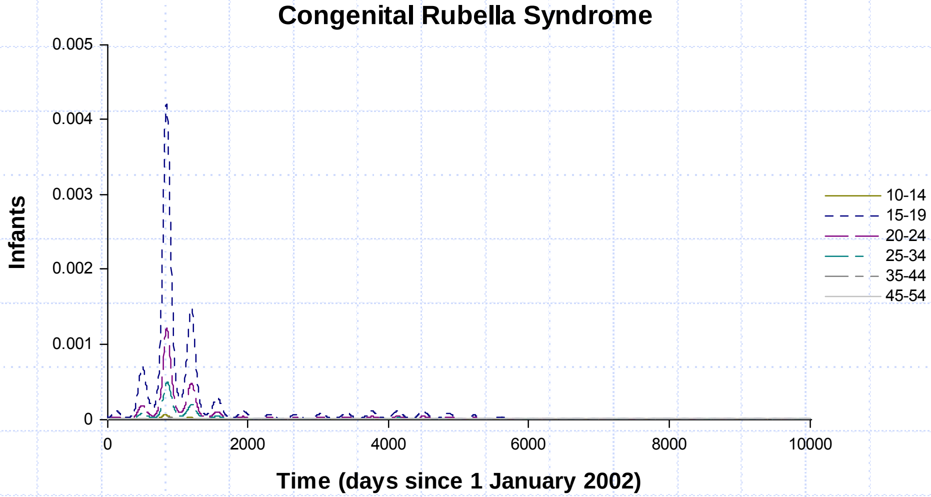
70% Coverage, 1 Dose



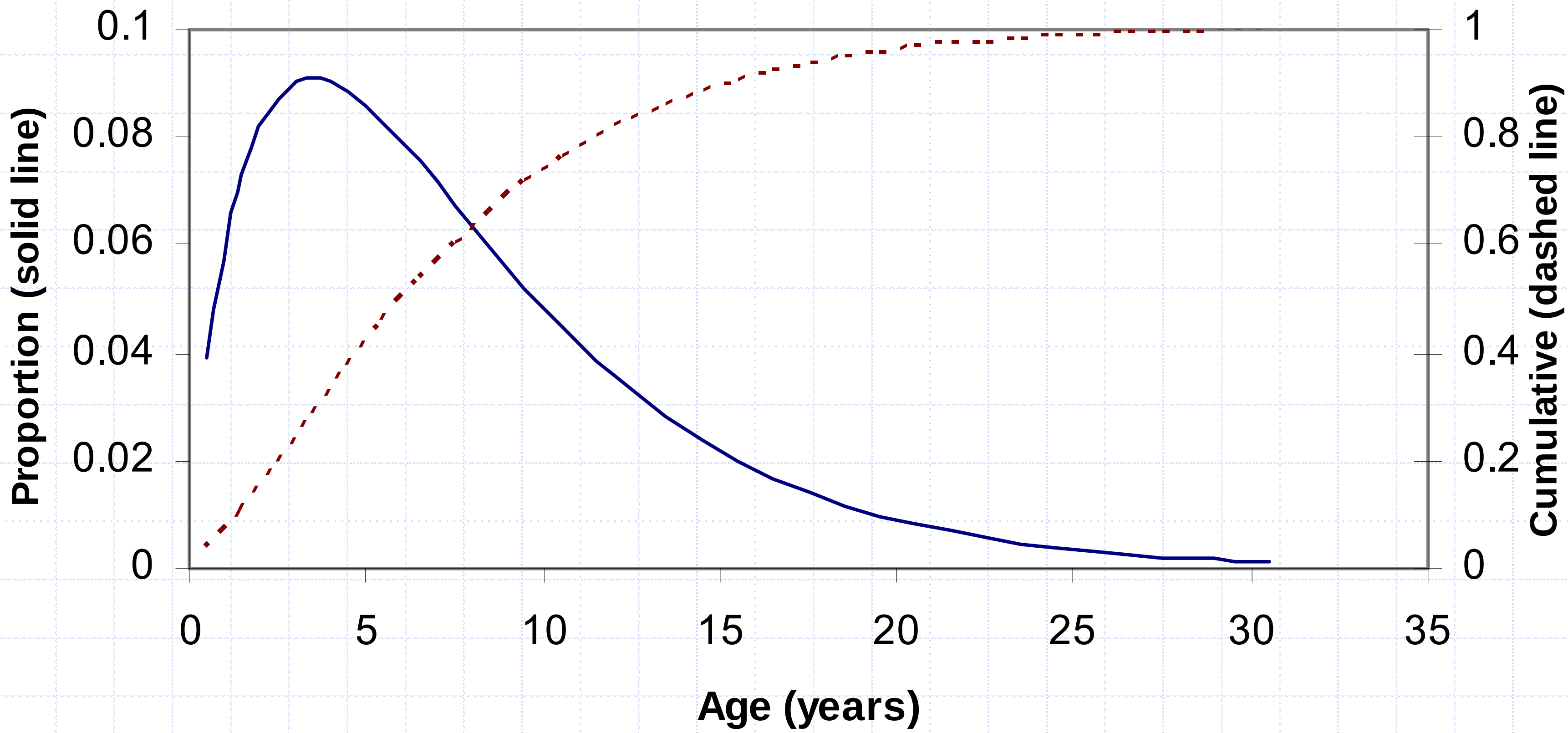


80% Coverage, 1 Dose

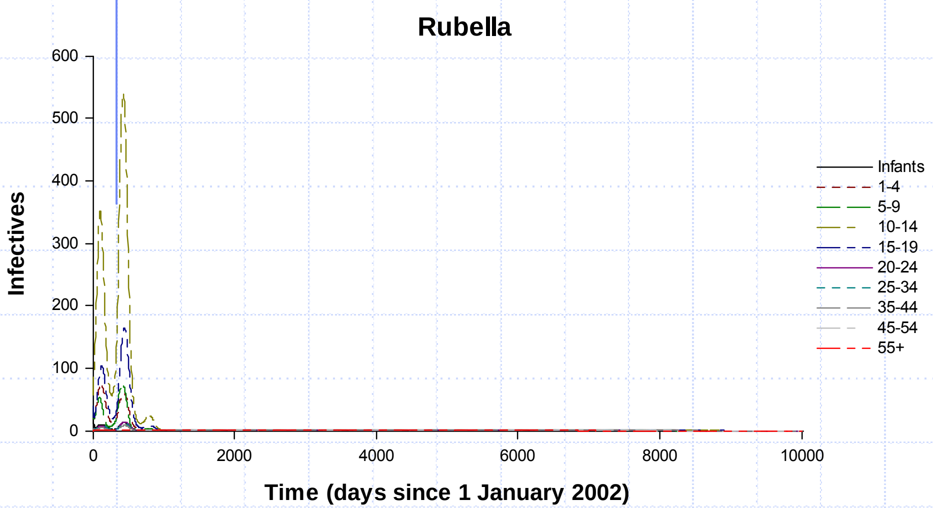


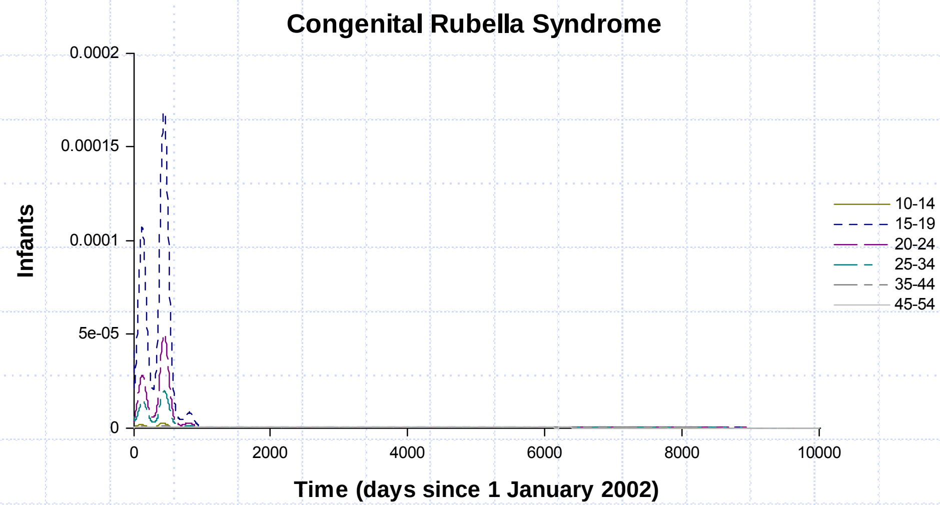


Age Distribution, Catch-up Campaign



With Catch-up Campaign among 2-14 yr old Children 1 yr Later

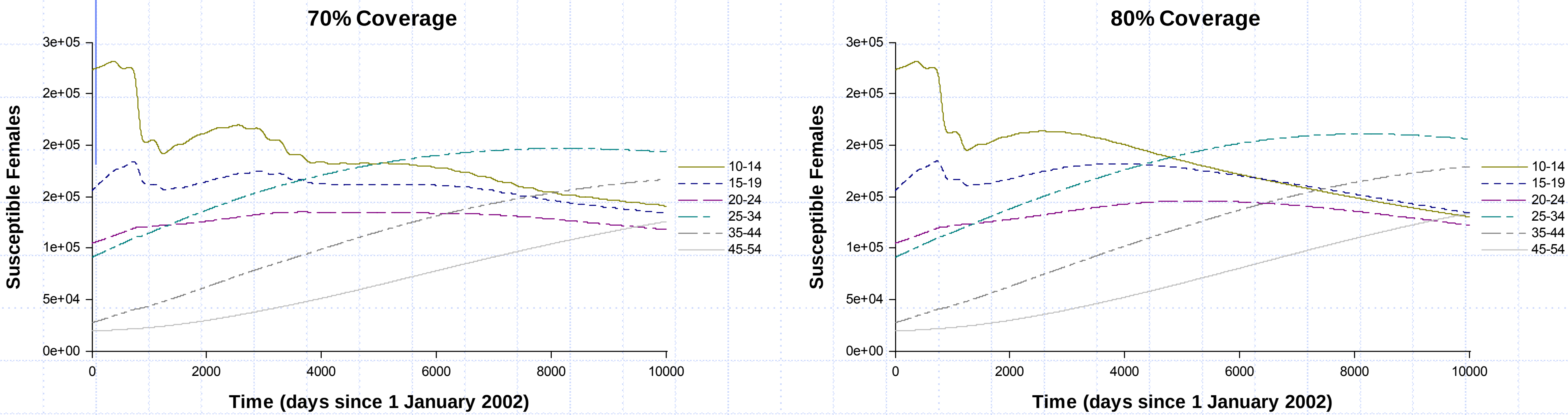




Conclusions about the Policymaking Tool and Childhood Vaccination

- Model predicts two quarters of surveillance and reproduces 5-year cycle typically observed
- Multi-annual periodicity obliterated as model population approaches stable age distribution
- Simulations confirm $R_0 \approx 3.8$ calculated from cross-sectional serosurvey …
- … as coverage of about 80% is required to control rubella in Romania (i.e., $0.78*0.95 \approx 1-[1/3.8]$)
- At this coverage, catch-up campaign among 2-14 year olds shortens time to elimination, …
- But, in answer to one policy question, it is not necessary despite the fact that …

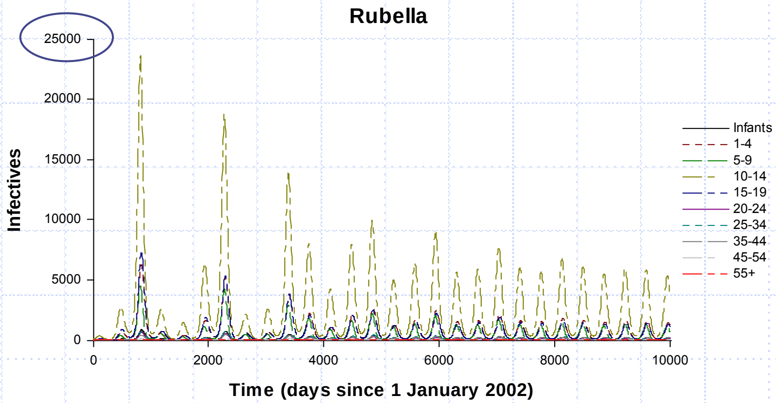
Childhood Vaccination Increases Susceptibility among Older People

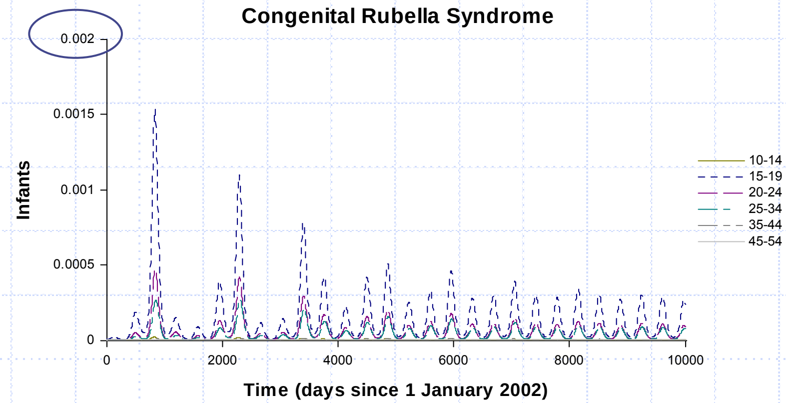


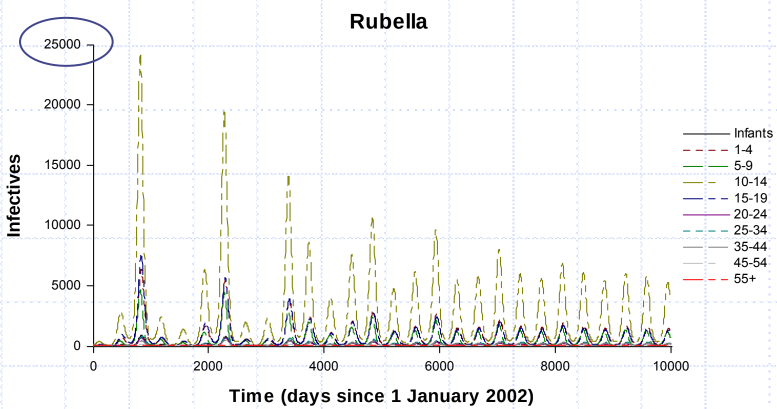
NB: Susceptibility increases among women 25-54 years old because 20-30% of girls are not vaccinated and (1-VE) of the remainder not immunized. On the left, this increase is slowed by disease among adolescent and young adult females.

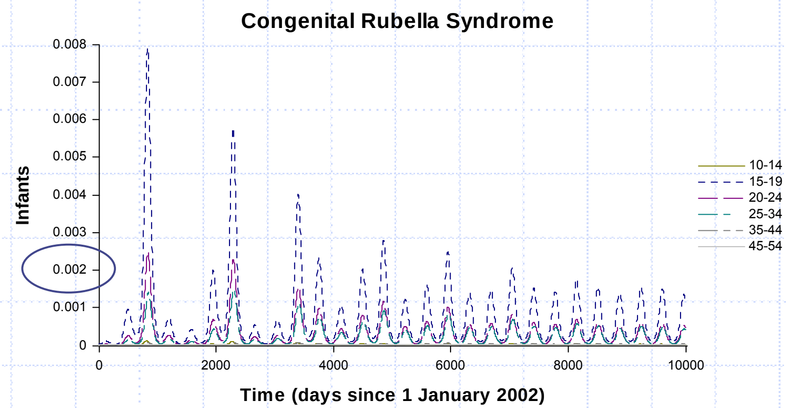
Age Distribution, Targeted Vaccination

Vaccination of Adolescent Girls and Young Women (cf. no vaccination, bottom panels)





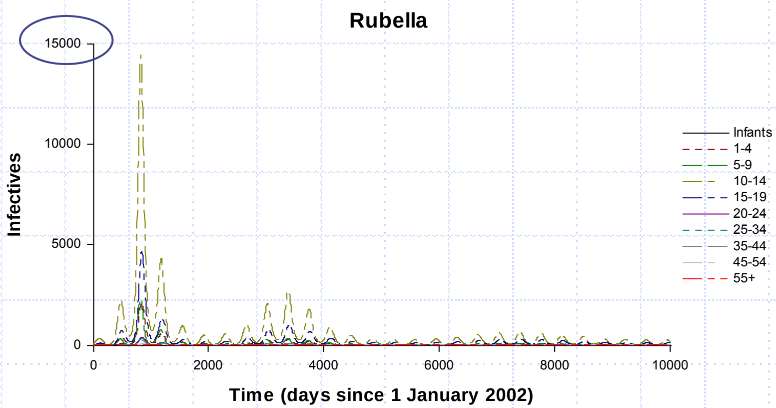


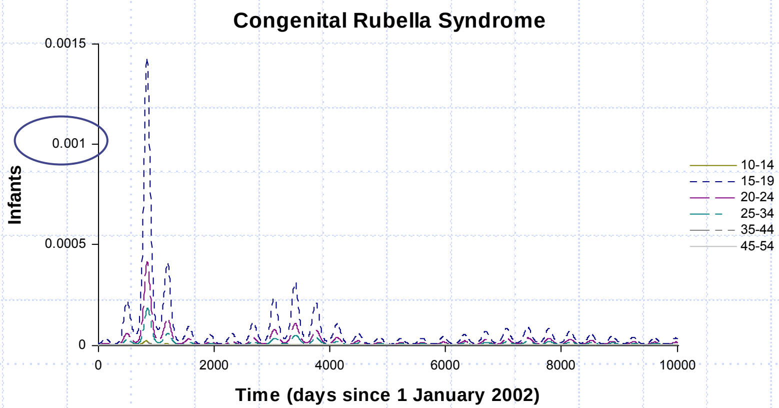


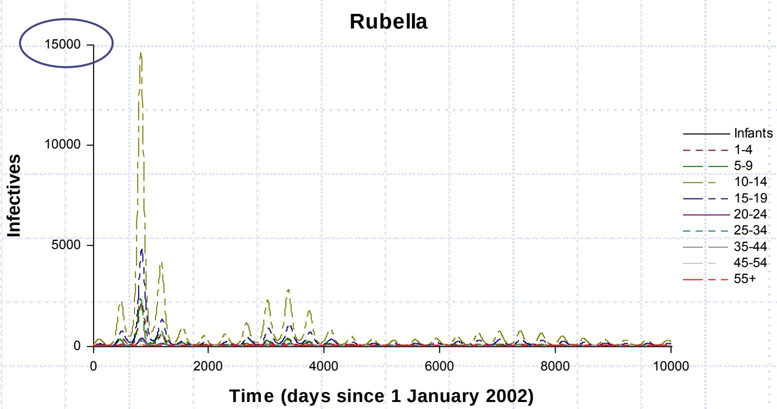
Considerations

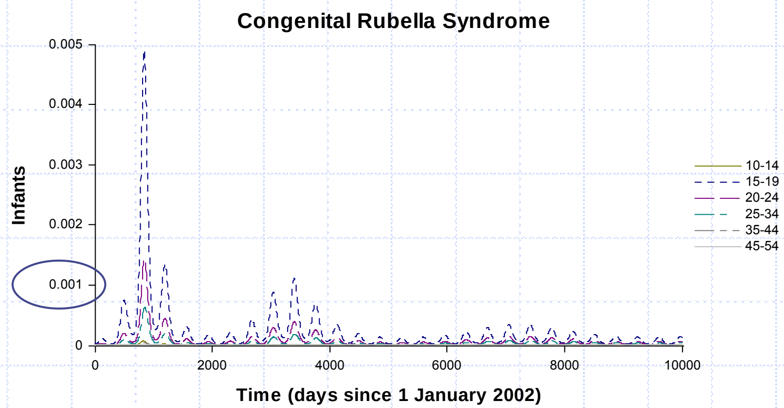
1. Because targeting of adolescent girls and young women reduces CRS by 3/4, supplementing childhood vaccination would insure against insufficient coverage. This essentially is the rationale for childhood plus post-partum vaccination in the developed world
2. But need one-time catch-up campaigns among women of childbearing age accompany the introduction of childhood vaccination? If so, all childbearing ages?
   - As risk of exposure declines with age, individual benefits decrease, except for women who might become pregnant
   - As older people are less likely to infect others than younger ones, the benefit to society also decreases with age
   - Accessibility declines too, increasing the cost per person vaccinated
   - Cost-effectiveness consequently decreases with age, limiting optimal campaigns to young women
   - How young depends on demographic and social phenomena that vary among countries

70% Coverage with (top) and without Targeting (bottom) Females

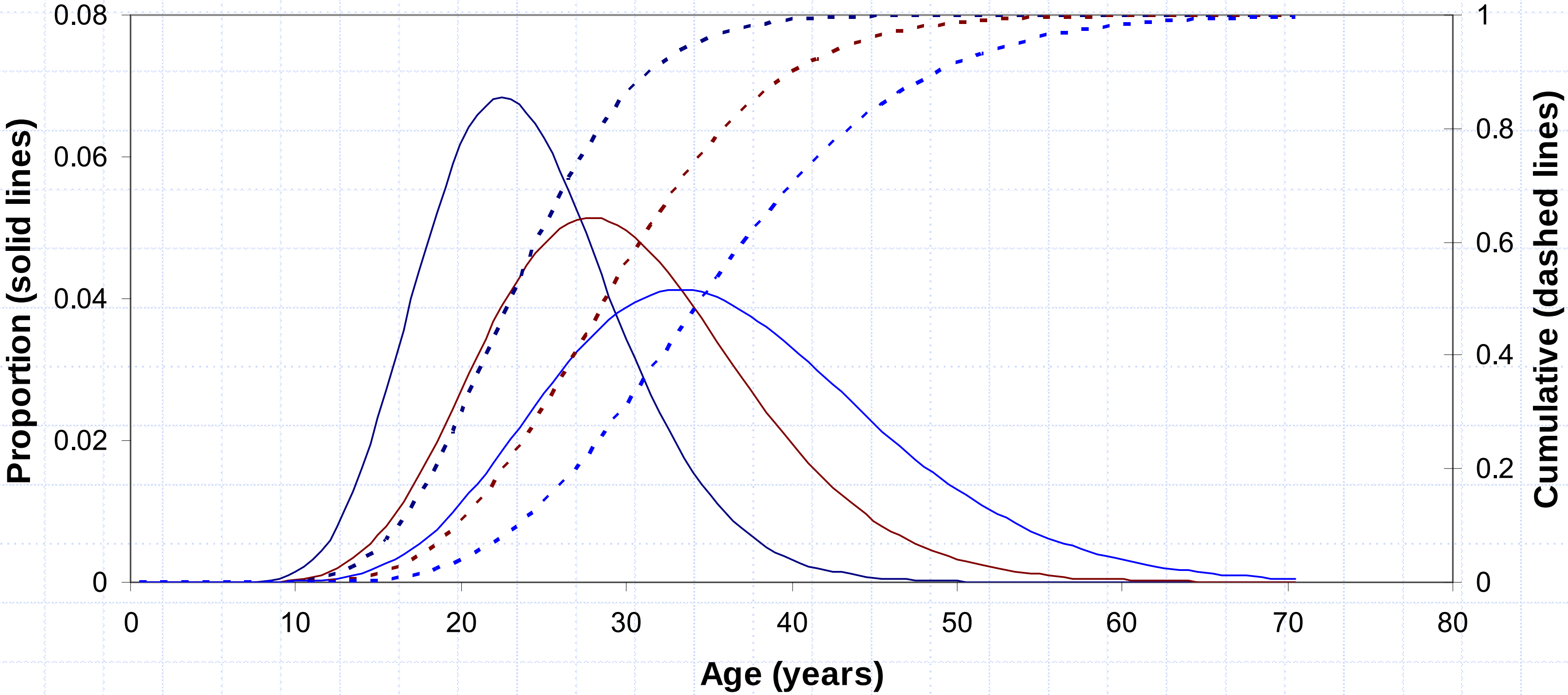








Targeted Female Vaccination



Costs (average annual doses) and Benefits (percent reduction)

Scenario	Doses	Rubella	CRS
80% of children	138,966	89%	86%
Plus catch-up	155,452	99%	99%
Young women	7,818	3%	42%
Older women	7,270	2%	43%
Still older ones	6,685	1%	43%

Conclusions about Vaccinating Adolescent Girls and Young Women

- Targeting adolescent girls and young women reduces CRS, but not rubella
- Childhood vaccination requires much more vaccine, so targeting may be more cost-effective
- But increasing the mean age of targeted female vaccination has no benefit
- Especially where women complete their families at an early age (e.g., contemporary Romania)
- And may have a cost, insofar as older women are less accessible or motivated
- Where childbearing extends to older ages, composite strategies may be indicated

Summary

- Declining birth rates changed dynamics from 5- to 10-year cycles, increasing mean age of infection, and CRS
- Mathematical model reproduces recent rubella surveillance, but predicts more CRS than reported
- 80% coverage with a single dose during the second year of life would control rubella, eliminating CRS eventually
- Catch-up among children 2-14 years old would reduce the time to elimination, but is not necessary
- Vaccination of adolescent girls and young women reduces CRS without affecting rubella
- Could supplement childhood vaccination to insure against insufficient coverage (e.g., post-partum women)
- But including older women of childbearing age has no benefit and may have substantial cost