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
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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

![Graph showing the proportion of rubella among Romanians aged 15 years and older from 1960 to 2005. The graph indicates a sharp increase in the proportion around 1995.](image-url)
Childbearing in Romania

![Graph showing the trend of mean age and children per woman in Romania from 1950 to 2000. The graph indicates a decrease in mean age and an increase in children per woman in the early 1960s, followed by a dramatic increase and decrease in the 1970s and 1980s, respectively.]
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
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

Parametric Models of Rubella Immunity in Romania

Risk of Rubella among Susceptible Romanians in 2002

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

![Infection Rates Diagram]

- Age (susceptible)
  - 0.200-0.250
  - 0.150-0.200
  - 0.100-0.150
  - 0.050-0.100
  - 0.000-0.050

- Age (infectious)
  - 0.200-0.250
  - 0.150-0.200
  - 0.100-0.150
  - 0.050-0.100
  - 0.000-0.050

- Beta
  - <1
  - 5-9
  - 15-19
  - 25-34
  - 45-54
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<th>x</th>
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<th>Pr(+)</th>
<th>Population</th>
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<th>DR</th>
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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 $R^2 \approx 0.7$)

Symbols: weekly “observations” from quarterly surveillance reports; Curves: model predictions
Predictions (annual areas under curves) and Surveillance Reports (the next year)

Mid-2004: 160 Suspected, 8 IgM+; 2003: 87 Predicted

2003: 150 Suspected, 7 IgM+; 2002: 8 Predicted
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

![Graph showing age distribution with proportion and cumulative lines.](image-url)
70% Coverage, 1 Dose

Rubella

Congenital Rubella Syndrome

Time (days since 1 January 2002)
80% Coverage, 1 Dose

Rubella

Infectives

Time (days since 1 January 2002)

Congenital Rubella Syndrome

Infants

Time (days since 1 January 2002)
Age Distribution, Catch-up Campaign

Age (years)

Proportion (solid line)

Cumulative (dashed line)
With Catch-up Campaign among 2-14 yr old Children 1 yr Later

[Graphs showing the spread of Rubella and Congenital Rubella Syndrome]
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., $0.78 \times 0.95 \approx 1 - [1/3.8]$)
- 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

![Graph showing age distribution for targeted vaccination. The graph has two lines: a solid line representing proportion and a dashed line representing cumulative proportion. The x-axis represents age in years, ranging from 0 to 50, and the y-axis represents proportion and cumulative proportion, ranging from 0 to 0.8. The peak of the solid line occurs around age 20, while the cumulative line continues to rise past age 50.]
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

Proportion (solid lines)

_cumulative (dashed lines)
## Costs (average annual doses) and Benefits (percent reduction)

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