Optimal Vaccination Policy: Theory and Application to Measles and Rubella in China

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Outline

- I'll begin by explaining that, while the population-immunity threshold has captured the popular imagination, it is applicable only to homogeneous host populations
- In heterogeneous ones, it does not answer the quintessential policy question, "How should resources be allocated to prevent or control infectious diseases?"
- Then I'll explain why we use the gradient of the effective reproduction number with respect to modeled interventions for this purpose
- Finally, I'll describe our use of the gradient to identify optimal strategies for accelerating elimination of two vaccine-preventable diseases in China

Theory

Optimal Vaccination Policy

This approach is general

- The gradient is the multivariate partial derivative of an expression for the effective reproduction number derived from an appropriate meta-population model with respect to interventions of interest
- It is not new mathematics, but this application is new public health
- And it exemplifies why we make models that can be analyzed (i.e., systems of equations vs computer programs)
- Because of my responsibilities at the CDC, we have only devised optimal vaccination strategies, but the approach would work for any modeled intervention

Mixing

- I'll start with a simple model of a meta-population composed of two sub-populations (e.g., children and adults or an urban area and its rural environs)
- Anette Nold[†] devised an elegant function in which a fraction ϵ of the average daily *per capita* contacts, a are reserved for members of one's own sub-population and the complements are distributed randomly:

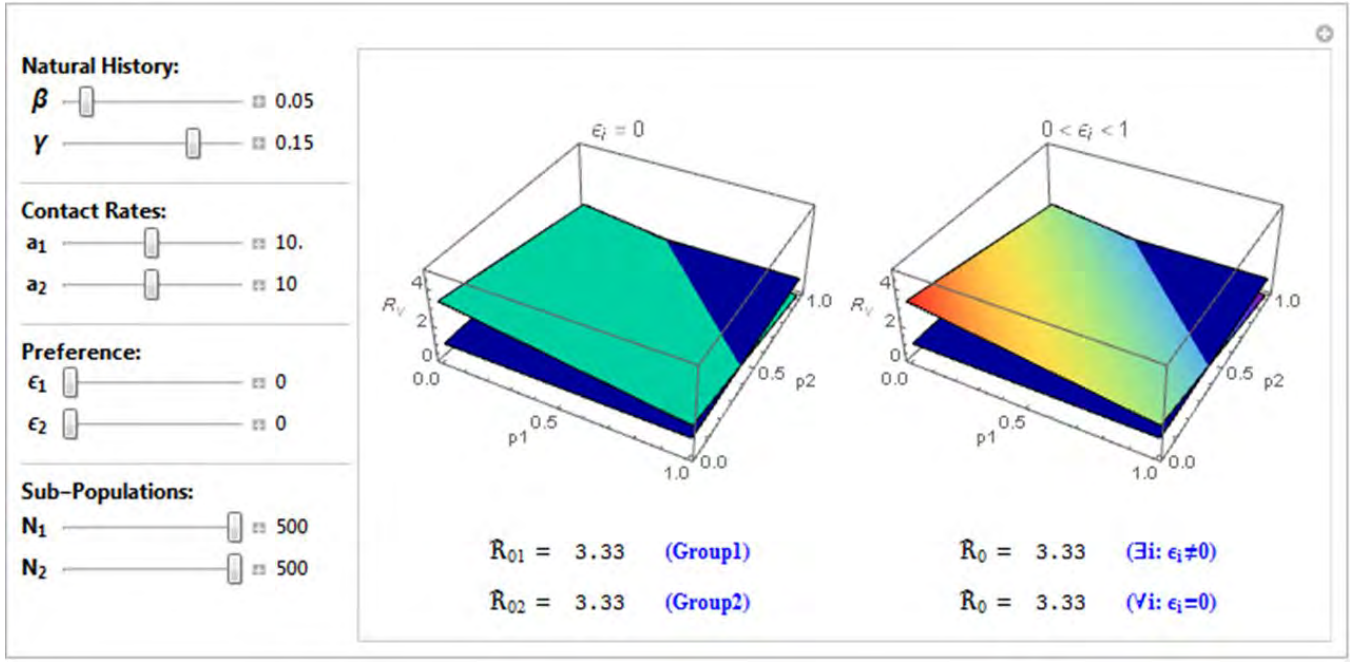
$$c_{i,j} = \epsilon_i \delta_{i,j} + (1-\epsilon_i)\frac{(1-\epsilon_j)a_j N_j}{\sum_k (1-\epsilon_k)a_k N_k},$$

- where $\delta_{i,j}$ is the Kronecker delta (i.e., one when $i = j$ and zero otherwise) and N is sub-population size. The words 'preference', 'activity', and 'proportional' refer to the parameters and fraction, respectively

[†]Nold A. Heterogeneity in disease transmission modeling. Math Biosci 1980; 52:227-40

In heterogeneous host populations (i.e., real world), the population-immunity threshold is not unique

- This is a screen shot of a ‘manipulate’ in Mathematica. The parameters on the left, figures to their right, and tabulated values below are from an SIR model with two sub-populations
- Here they are identical: The probability of infection on contact is 0.05, the recovery rate is 0.15, their *per capita* contact rates are 10 per day, mixing is random, and both have 500 people



Summary of a different story†

- When mixing is non-random, the rainbow colored plane becomes a surface, so its intersection with the blue plane becomes a curve
- When sub-populations differ in reproduction number, the isoclines are asymmetric and meta-population number increases, especially when mixing is non-random
- But this slide illustrates the relevant point: These planes intersect along a line that describes an infinite number of pairs of sub-population 1 and 2 immunities
- If there were three sub-populations, an infinite number of triples would satisfy the condition that the effective reproduction number equal one, and so on
- There is no longer a single population-immunity threshold. So, the policy question becomes “Which is optimal?”

†See extra slides at the end

When the goal is to prevent or control outbreaks, we have an answer to the question, “Which is optimal?”

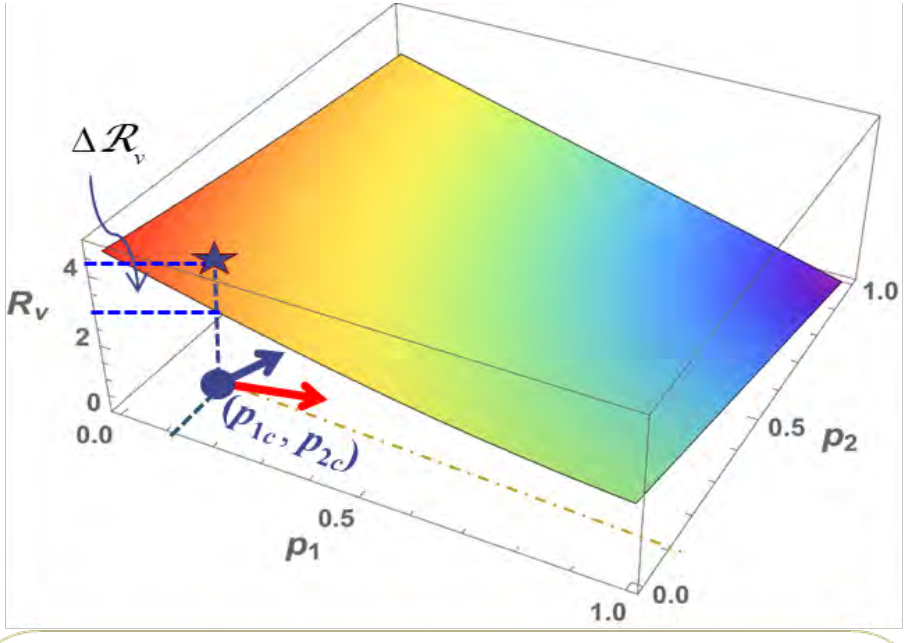
If $n = 2$,

$$\Delta\mathcal{R}_v = \mathcal{R}_v(p_{1c} + a, p_{2c} + b) - \mathcal{R}_v(p_{1c}, p_{2c}) \approx \nabla\mathcal{R}_v\Big|_{(p_{1c}, p_{2c})} \cdot (a, b)$$

$$= a\frac{\partial\mathcal{R}_v}{\partial p_1}\Big|_{(p_{1c}, p_{2c})} + b\frac{\partial\mathcal{R}_v}{\partial p_2}\Big|_{(p_{1c}, p_{2c})}$$, where $\mathcal{R}_v$ is the effective reproduction number, the p_{ic} are sub-population immunities, a and b are amounts by which they change, and

$\nabla\mathcal{R}_v\Big|_{(p_{1c}, p_{2c})} = \left(\frac{\partial\mathcal{R}_v}{\partial p_1}, \frac{\partial\mathcal{R}_v}{\partial p_2}\right)\Big|_{(p_{1c}, p_{2c})}$ is the gradient evaluated at (p_{1c}, p_{2c})

Methods

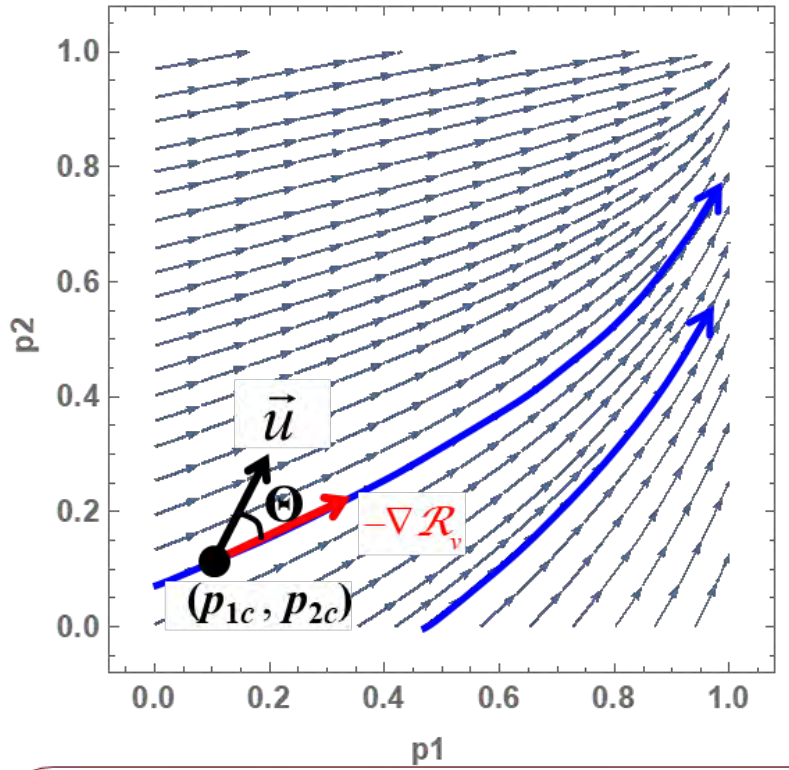


Let $P_c = (p_{1c}, p_{2c})$. Changes in p_i and $\mathcal{R}_v$:

$$(\Delta p_1, \Delta p_2) = r\vec{u} \quad (|\vec{u}| = 1)$$

$$\Delta\mathcal{R}_v = \mathcal{R}_v(P_c) - \mathcal{R}_v(p_{1c} + \Delta p_1, p_{2c} + \Delta p_2)$$

Gradient at P_c: $\nabla\mathcal{R}_v(P_c) = \left(\frac{\partial\mathcal{R}_v}{\partial p_1}, \frac{\partial\mathcal{R}_v}{\partial p_2}\right)\Big|_{P_c}$

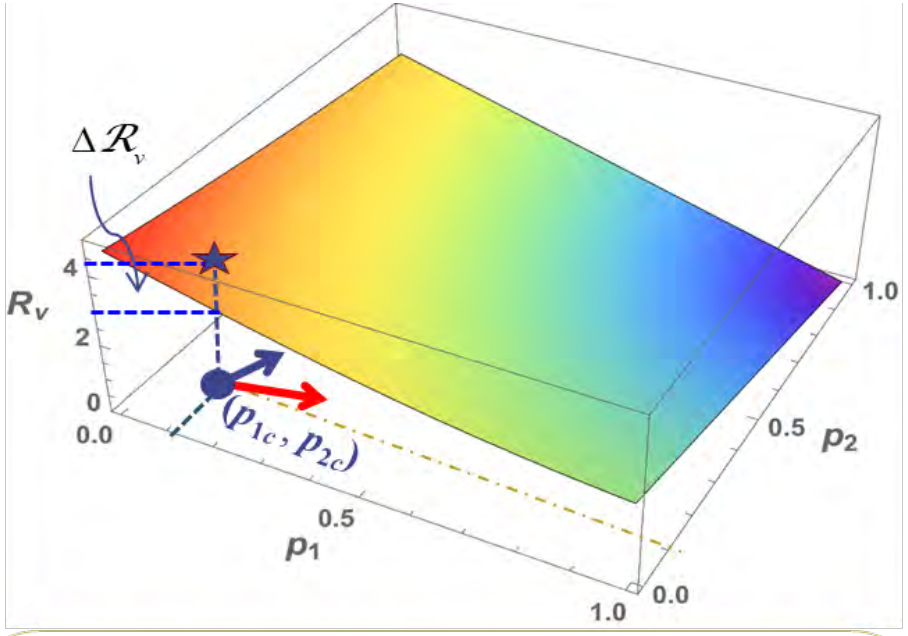


$$\Delta\mathcal{R}_v \approx \nabla\mathcal{R}_v(P_c) \bullet (\Delta p_1, \Delta p_2) = r\nabla\mathcal{R}_v(P_c) \bullet \vec{u}$$

$$|\Delta\mathcal{R}_v| \approx r|\nabla\mathcal{R}_v(P_c)| \times |\cos\Theta|$$

Optimal at P_c: $\Theta = -\pi$ or $|\cos\Theta| = 1$

Methods (cont'd)



Let $P_c = (p_{1c}, p_{2c})$. Changes in p_i and $\mathcal{R}_v$:

$$(\Delta p_1, \Delta p_2) = r\vec{u} \quad (|\vec{u}| = 1)$$

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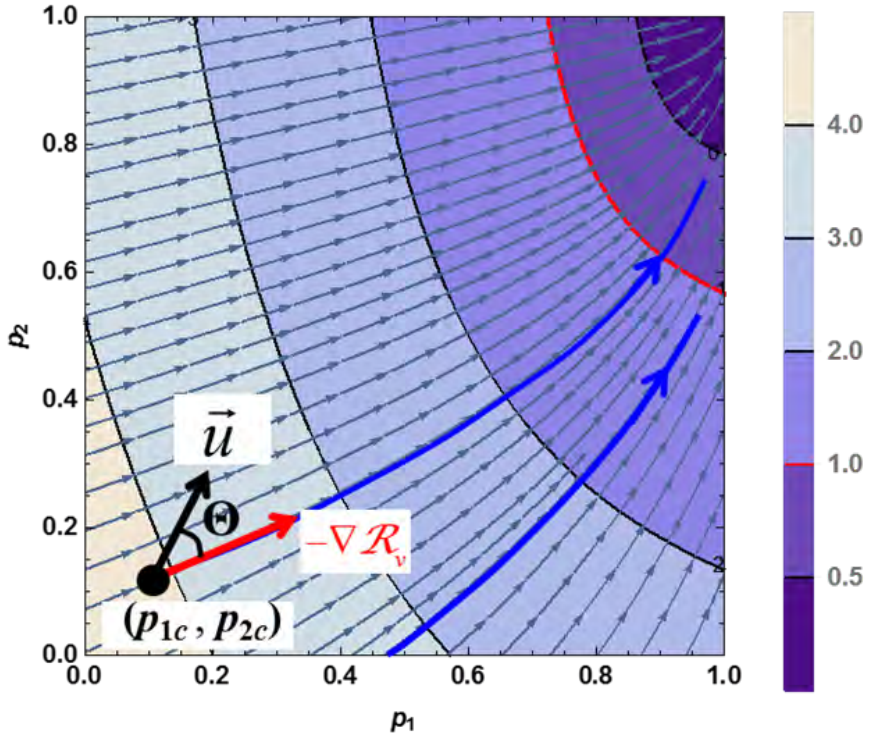

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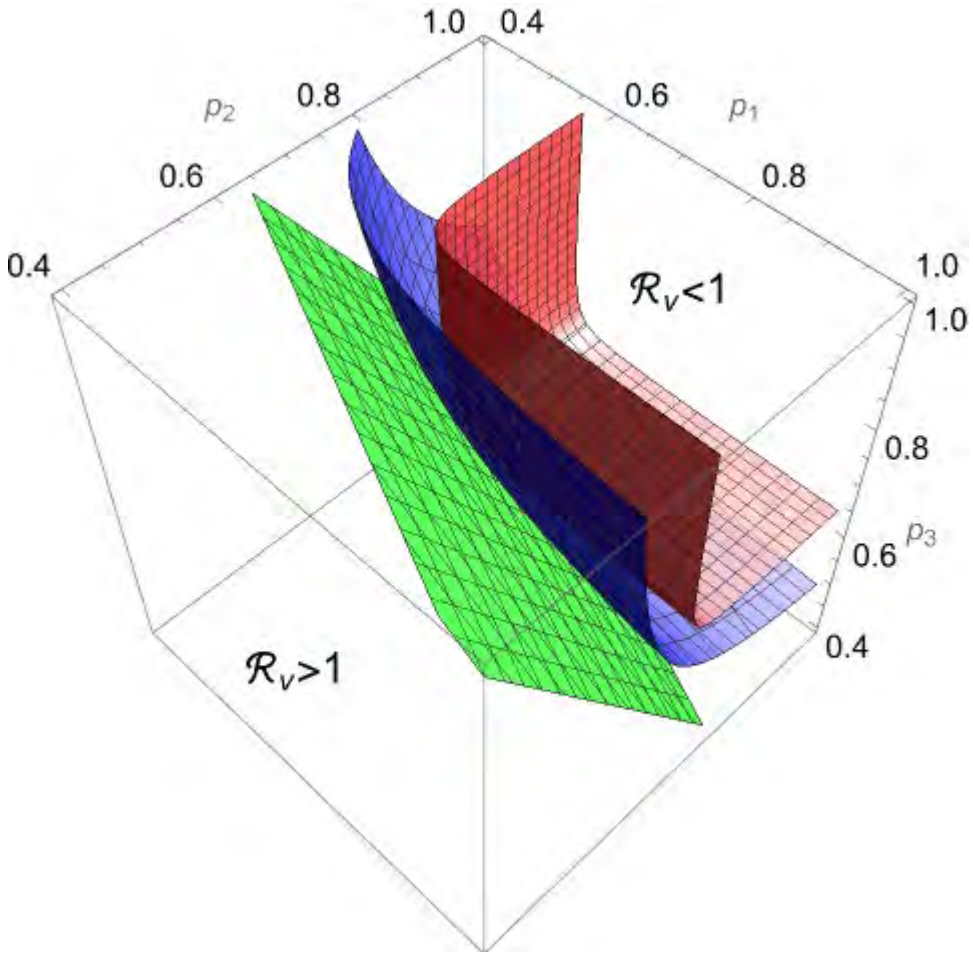
Optimal at P_c: $\Theta = -\pi$ or $|\cos\Theta| = 1$

If Resources are Limited

Determining the optimal with constraint is a matter of solving

$$\nabla \mathcal{R}_E(\chi_i) + \lambda[S_i] = 0 \text{ and } \sum_i \chi_i S_i = D$$

simultaneously, where the χ are possible vaccination rates, λ is the Lagrange multiplier, S are numbers susceptible, and D is the number of vaccine doses available



Application

Optimal Vaccination Policy

Measles and Rubella in China

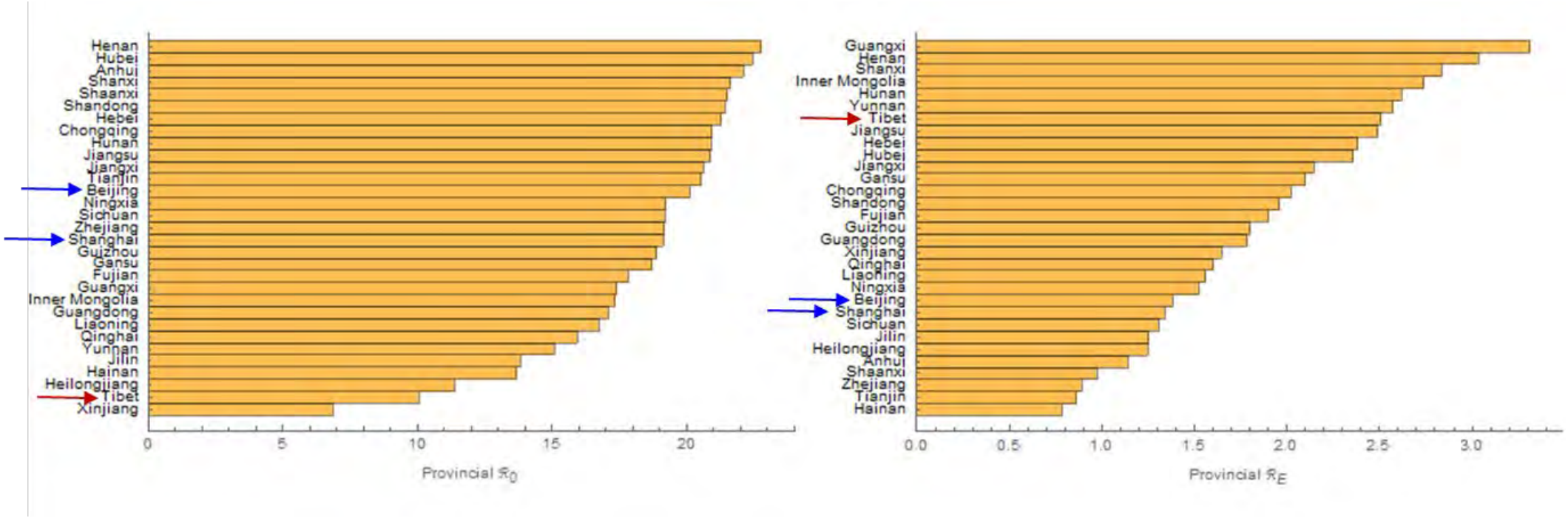
- In China, our objective pre-pandemic was to devise a program using MMR to accelerate the elimination of measles and rubella that colleagues at China's CDC could convince the MOH to implement
- Authorities began vaccinating against measles in 1960, but did not include rubella in the Expanded Program on Immunization until 2007. And there was not enough vaccine for a catch-up campaign or routine vaccination until 2011. MMR coverage was as high among Chinese children as ours pre-pandemic, but wasn't always
- Consequently, adults are susceptible to measles while rubella susceptibility is concentrated among adolescents, both of whom were protected by the vaccination of others when they were younger

Metapopulation Reproduction Numbers

- When there are more than a few sub-populations, we cannot write explicit expressions for meta-population reproduction numbers, but can calculate them
- This involves solving for the disease-free equilibrium, forming the Jacobian matrix†, rewriting as $F - V$, where F are the infection and V the transition terms, and forming the next-generation matrix FV^{-1}
- The reproduction number is the dominant eigenvalue of the next-generation matrix and the associated eigenvectors are sub-population contributions and prevalence
- To calculate the gradient, we assume that mixing is proportional, whereupon the dominant eigenvalue is the trace of the next-generation matrix, an analytical expression whose partial derivatives can be calculated

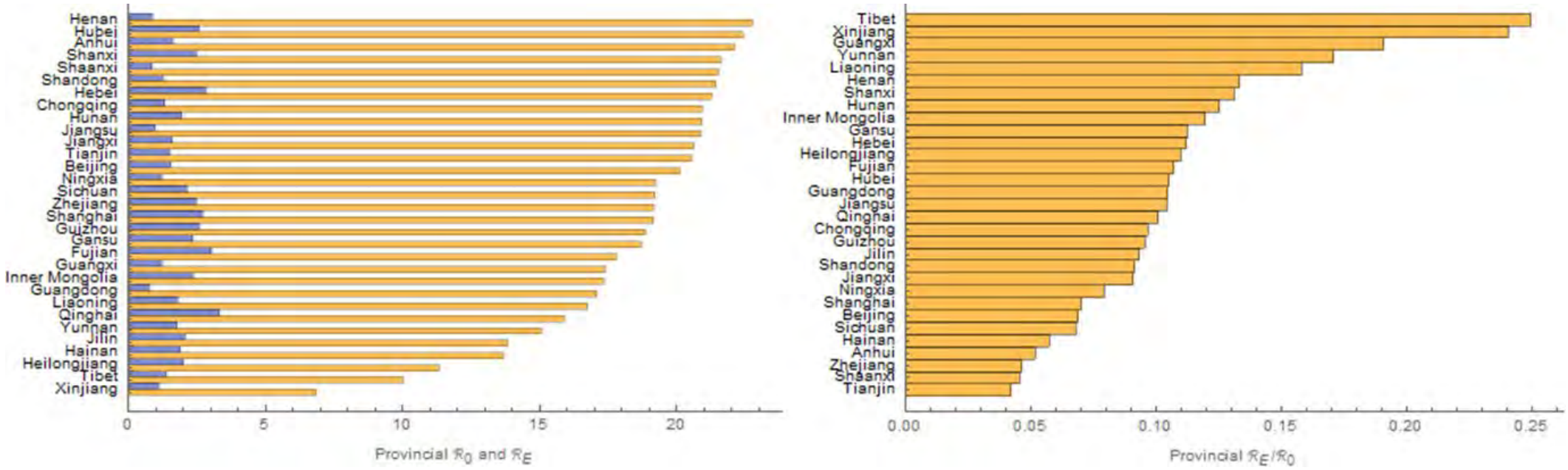
†partial derivatives of the linearized system of the infected equations at equilibrium with respect to the remaining variables

The $\mathcal{R}_0$ and $\mathcal{R}_E$ of Measles in China are 18 and 2.3, respectively, but Provincial Numbers Vary†



†Similar slides for rubella are at the end

Reproduction Numbers and their Ratios, which Approximate Provincial Immunity†



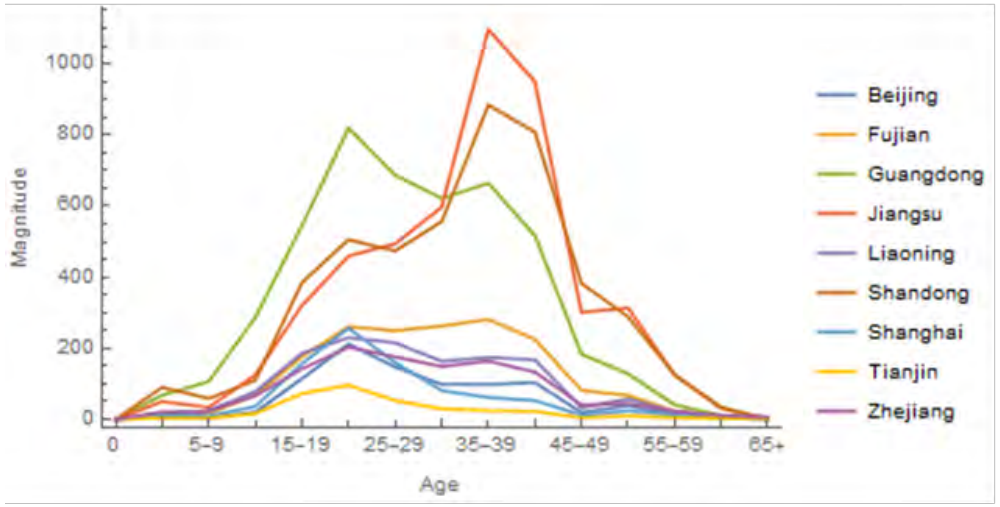
†Similar slides for rubella are at the end

Spatial Distribution†

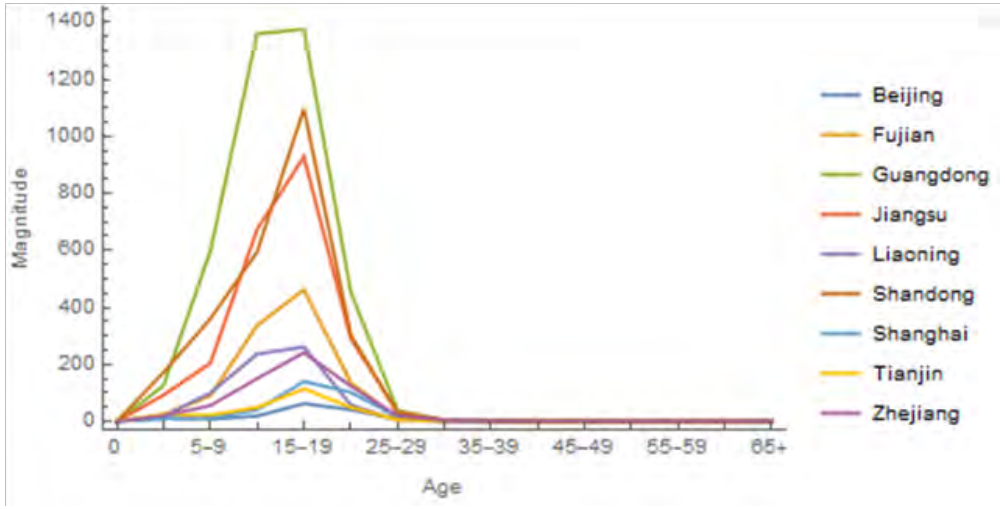
†Similar slides for rubella are at the end

The Gradient in the Eastern Provinces

Measles

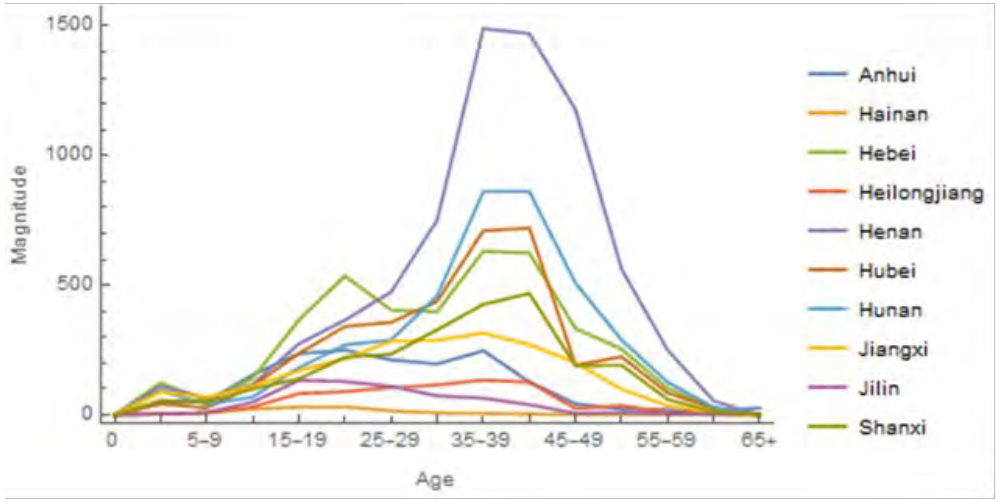


Rubella

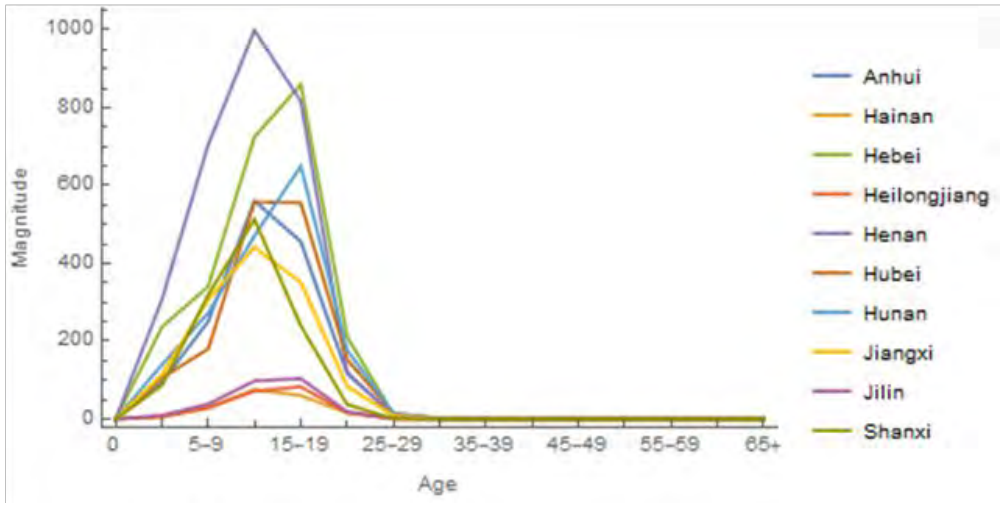


The Gradient in the Central Provinces

Measles

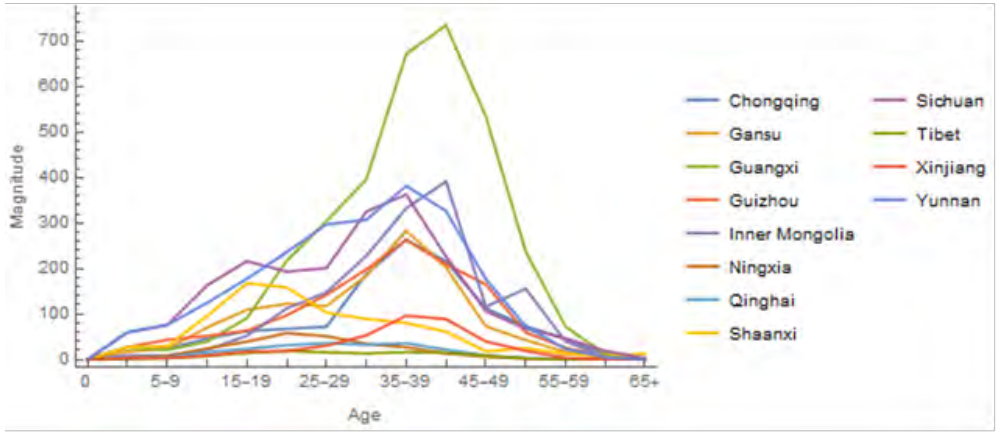


Rubella

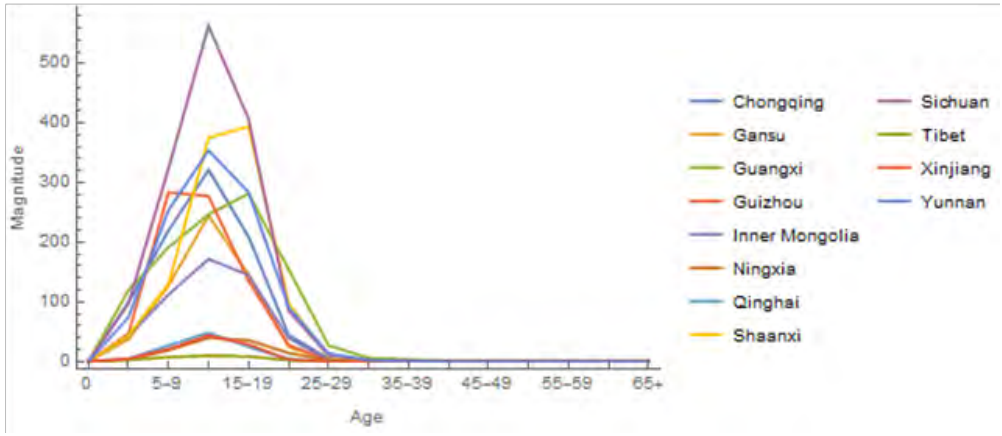


The Gradient in the Western Provinces

Measles

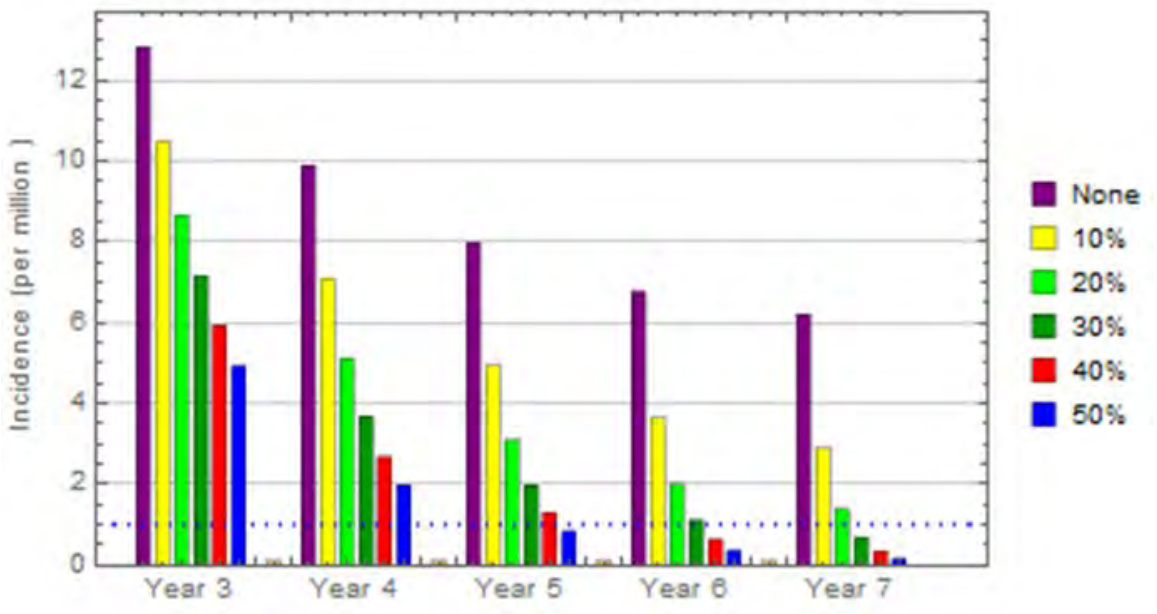


Rubella



Patterns

- Gradient directions generally involve younger people for rubella than measles
- Consequently, vaccinating adolescents without documentation of immunity during the first months of school over several years would be more effective for rubella than measles
- Simulations indicated that, while not optimal for measles, this would accelerate elimination



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- Feng Z, et al. Influence of demographically realistic mortality schedules on vaccination strategies in age-structured models. Theor Popul Biol 2020; 132:24-32
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Optimal Vaccination Policy: Theory and Application to Measles and Rubella in China

We developed the gradient approach together with Andrew Hill, a US CDC colleague, and used it to identify optimal strategies for accelerating the elimination of measles and rubella in China together with Wang Huaqing, Hao Lixin, Ma Chao, Lance Rodewald, our China CDC colleagues, and Su Qiru, formerly at the China CDC, but now at Shenzhen Children's Hospital. The findings and conclusions in this report are those of the authors and do not necessarily represent the official positions of the Centers for Disease Control and Prevention, National Science Foundation, or Purdue University.

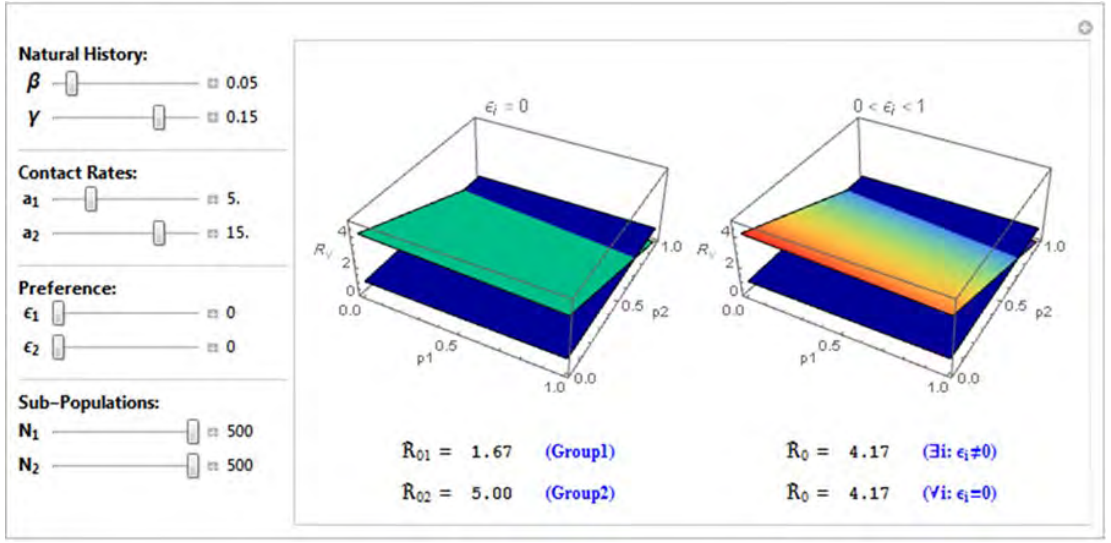
For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

Extra Slides

Optimal Vaccination Policy

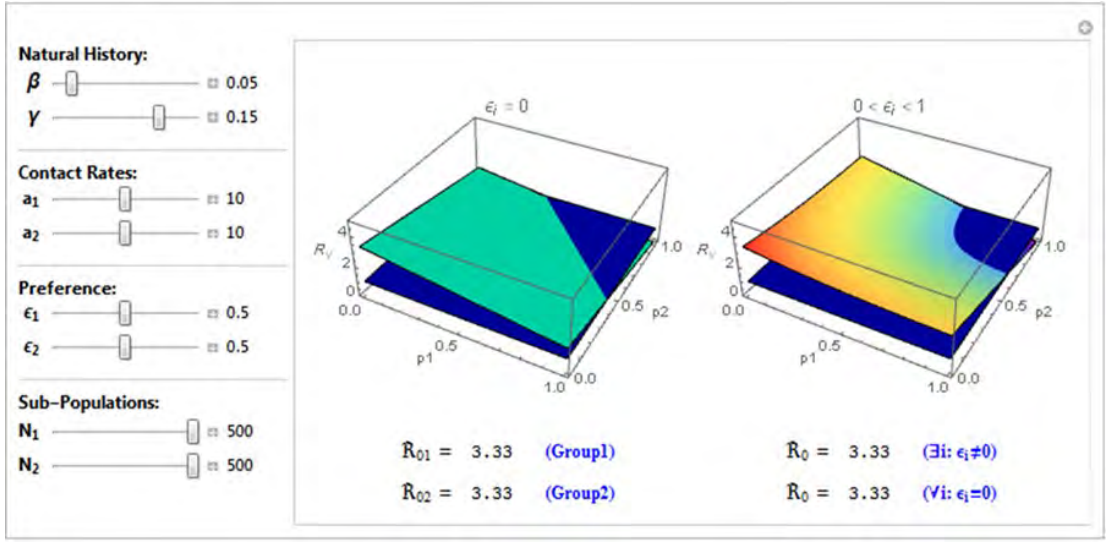
Heterogeneity

- Rather than the *per capita* contact rate in both sub-populations being 10, in one of these it's 5 and other it's 15; their average, however, is the same
- Note that the meta-population reproduction number has increased from 3.3 to 4.17
- Heterogeneity in any parameter affecting sup-population reproduction numbers increases the meta-population reproduction number



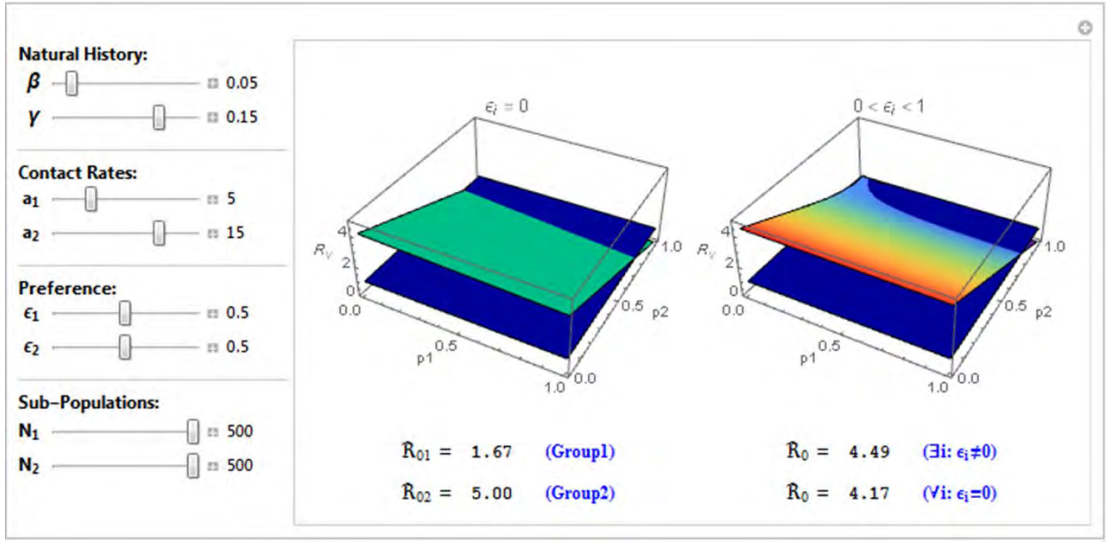
Non-Random Mixing

- Non-random mixing ($0 < \epsilon \leq 1$) bends the rainbow surface such that its intersection with the dark blue plane is curved
- As epsilon is not a parameter in sub-population reproduction numbers, which are $a\beta/\gamma$, however, ...
- Absent heterogeneity, non-random mixing does not affect the meta-population number

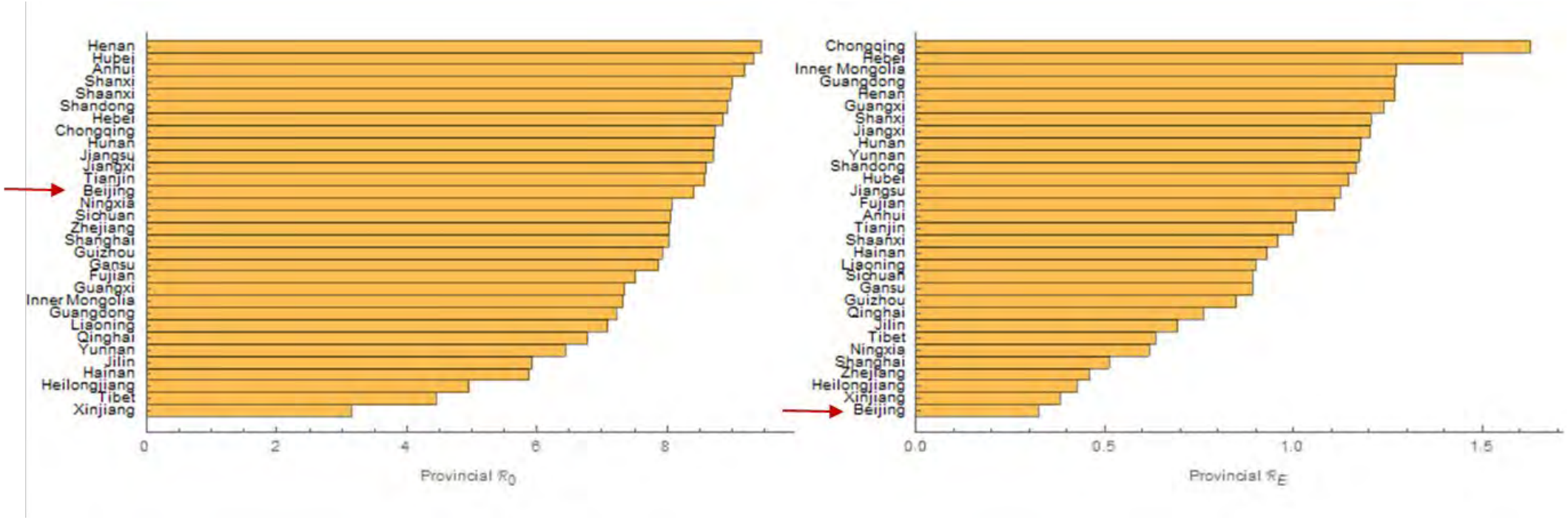


Heterogeneity and Non-Random Mixing

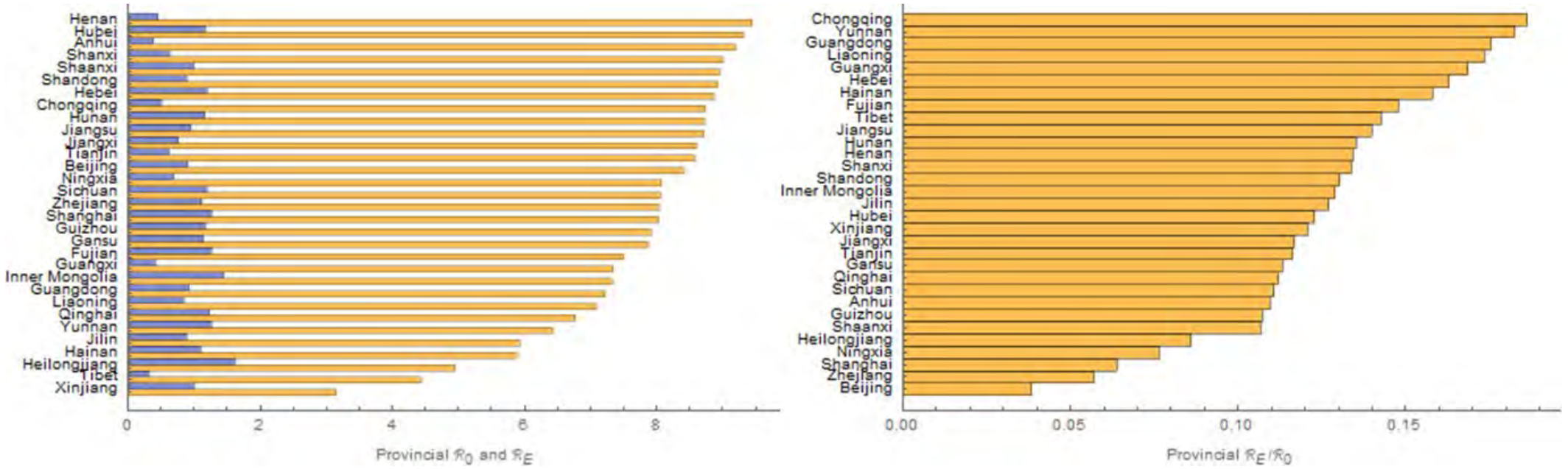
- While non-random mixing alone does not affect the meta-population reproduction number, ...
- Together with heterogeneity in any parameter in sub-population reproduction numbers (one of which here is 1.67 and other is 5), ...
- Non-random mixing increases the meta-population reproduction number, here from 4.17 to 4.49



The $\mathcal{R}_0$ and $\mathcal{R}_E$ of Rubella in China are 7.6 and 1.2, respectively, but Provincial Numbers Vary



Reproduction Numbers and their Ratios, which Approximate Provincial Immunity



Spatial Distribution