Modeling the Potential Impact of Heterogeneity in Vaccine Coverage due to Religious and Philosophical Exemptions

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3 August 2010

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

Exemptions to Vaccination†

- Vaccination is mandatory because communicable diseases interrupt social activities such as the schooling of children
- But exemptions are allowed, and religious and philosophical ones are increasing, especially in states where the criteria are easily met
- Unvaccinated children may reside in the same neighborhoods, or attend the same schools
- Does the resulting spatial heterogeneity in coverage affect the risk of outbreaks?
- Surveys indicate that coverage is above the population-immunity threshold for most vaccine-preventable diseases
- But is their spatial scale appropriate?
- Can models, the source of this threshold and related concepts, allay or affirm our concerns?

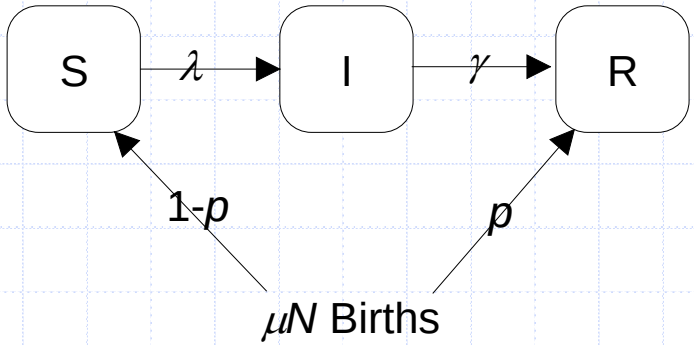
†Omer SB, Salmon DA, Orenstein WA, deHart MP, Halsey N. Vaccine refusal, mandatory immunization, and the risks of vaccine-preventable diseases. N Engl J Med 2009; 360: 1981-88

Spatial Heterogeneity

- Dietz (1980), Anderson et al. (1986), May and Anderson (1987), and Diekmann et al. (1990) have shown that, when mixing among strata is proportional to activity, $\Re_0$ is proportional to mean activity plus the variance to mean ratio. Nold (1980) and Jacquez et al. (1988) developed a more general mixing framework that allows fraction(s) of one's contacts to be reserved for others in one's own group and complement(s) to be distributed proportionately among groups. Barbour (1978), Dye and Hasibeder (1986), Hasibeder and Dye (1988), and Adler (1992) showed that $\Re_0$ attains its maximum value when individuals with the greatest activity mix solely within their own groups
- Using the simplest meta-population model capable of informing vaccination policy, we derive the basic and control reproduction numbers and explore the impact of sub-population sizes, activities and mixing regimes. We then determine the conditions under which heterogeneity in population immunity affects $\Re_v$, the control reproduction number, and hence p_c, the population-immunity threshold, as descriptive (Wallinga et al. 2005) and simulation modeling studies (Glass et al. 2004) suggest

Formulating these questions as simply as possible, but not more so

- Omit demographic phenomena
- By setting birth and death rates equal and vaccinating at birth
- If necessary, these details can be restored and others added later



$$\frac{dS}{dt} = \mu N(1-p) - (\lambda + \mu)S$$

$$\frac{dI}{dt} = \lambda S - (\gamma + \mu)I$$

$$\frac{dR}{dt} = \mu Np + \gamma I - \mu R$$

$$N = S + I + R$$

NB: uN deaths omitted from the flow diagram

Assess impact of heterogeneity via $\mathfrak{R}_v$, which is related to $\mathfrak{R}_0$, the …

- Average number of effective contacts while infectious, where *effective* contacts are sufficiently intimate for transmission if the contacted person is susceptible
- Derive from our SIR model, use to facilitate our understanding of control via vaccination, generalize to a meta-population, and explore the impact of heterogeneity

See slide A1 for derivation of:

$$\Re_v = \frac{(1-p)\beta a}{\gamma + \mu} = \Re_0 (1-p)$$

$$\Re_v = 1 \Rightarrow p_c = 1 - \frac{1}{\Re_0}$$

Table 4.1 from Anderson and May (reference later) includes estimated values of $\Re_0$ for various diseases, locations, epochs

Disease	Location	Period	$\Re_0$
Measles	Cirencester, England	1947-50	13-14
	England and Whales	1950-69	16-18
	Kansas, USA	1918-21	5-6
	Ontario, Canada	1912-13	11-12
	Willesden, England	1912-13	11-12
	Ghana	1960-68	14-15
	Eastern Nigeria	1960-68	16-17

Of what use is this threshold?

- For measles, $\Re_0$ = 5-18, so p_c = 0.8-0.94
- Ignoring naturally-acquired immunity, the coverage required to attain p = 0.94 is ≈ 1 (because p = coverage × efficacy, and MMR is ≈ 0.95 effective against measles)
- As this is essentially impossible, we have a second dose

So far, …

- We have reviewed reproduction numbers and the population-immunity threshold
- Familiar concepts among vaccine-preventable disease epidemiologists
- Now we will introduce heterogeneity by spatially stratifying our model
- Will the corresponding meta-population results be equally useful?

In our meta-population model, …

- People are Susceptible, Infected or Removed (by immunization or recovery from infection), μ is the birth and death rate, p_i are proportions immunized at birth, λ_i are risks of infection per susceptible, and γ is the recovery rate
- The risk of infection, $\lambda_i = a_i\beta\Sigma_j c_{ij}[I_j/N_j]$, where a_i is the number of contacts per person in sub-population i, β is the probability of transmission on contact with an infectious person, and $[I_j/N_j]$ is the probability that a contacted member of sub-population j is infectious
- We write the proportion of contacts a member of sub-population i has with j as $c_{ij} = \varepsilon_i\delta_{ij} + (1-\varepsilon_i)f_j$, where $f_j = (1-\varepsilon_j)a_jN_j/\Sigma_k(1-\varepsilon_k)a_kN_k$, ε_i is the fraction of contacts with others in the same sub-population, and δ_{ij} is the Kronecker delta (i.e., 1 when $i=j$ and 0 otherwise)[†]

[†]Jacquez JA, et al. Modeling and analysis of HIV transmission: The effect of contact patterns. Math BioSci 1988; 92:119-99

See slide A2 for derivation of the limits of $\Re_v$ when $\forall i: \varepsilon_i = 0 \vee \varepsilon_i = 1$

When $n = 2$, the matrix

$$K = \begin{bmatrix} \Re_{v1} c_{11} & \Re_{v1} c_{12} \\ \Re_{v2} c_{21} & \Re_{v2} c_{22} \end{bmatrix} \text{and}$$

$$\Re_v = \frac{1}{2}\left[A + D + \sqrt{(A-D)^2 + 4BC} \right], \text{ where}$$

$$A = \Re_{v1} c_{11},\ B = \Re_{v1} c_{12},\ C = \Re_{v2} c_{21},\ D = \Re_{v2} c_{22}$$

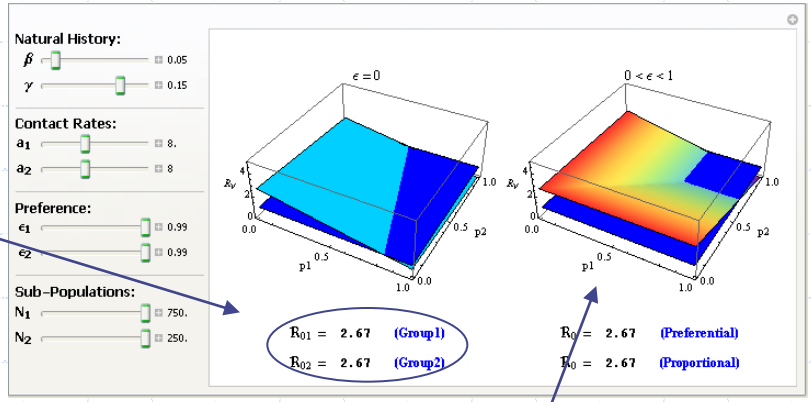
Possible Approaches

- Biologically interesting questions concern the joint effect of p_i on $\Re_v$ and modification by a_i, ε_i and N_i (e.g., is low coverage a problem only if sub-populations are large, their members are active, and they mix with others?)
- We could evaluate such questions via the multi-variable analogue of the partial derivative of $\Re_v$ with respect to p_i (a vector[†]) and its magnitude and direction
- Alternatively, we could ***manipulate*** the reproduction numbers in Mathematica™, with these potentially modifying variables as controls. This approach is not only more heuristic, but demonstrates this software

$$^{\dagger}\nabla\Re_v\Big|_{(p_{1c},p_{2c})} = \left(\frac{\partial\Re_v}{\partial p_1}, \frac{\partial\Re_v}{\partial p_2}\right)\Big|_{(p_{1c},p_{2c})}$$

“Manipulate” in Mathematica™

- Note that $\mu = 1/(70 \times 365.25)$
- The $\Re_{0i}$ vary directly with a_i and β and inversely with γ
- Neither ε_i nor N_i affect the $\Re_{0i}$, but they do affect the composites, $\Re_0$ and $\Re_v$
- Mixing is proportional in the figure on the left ($\varepsilon = 0$) and preferential in that on the right ($0 < \varepsilon \leq 1$)
- The dark blue planes are joint values of p_i at which $\Re_v = 1$. Note that preferential mixing increases $\Re_v$ (cf. the multicolored and light blue surfaces)
- Moreover, whereas the light blue surface is flat, the multicolored surface is curved
- Does heterogeneity in p_i affect $\Re_v$?



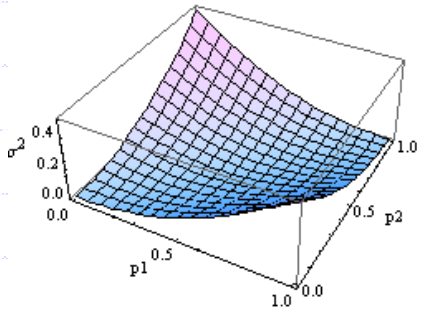
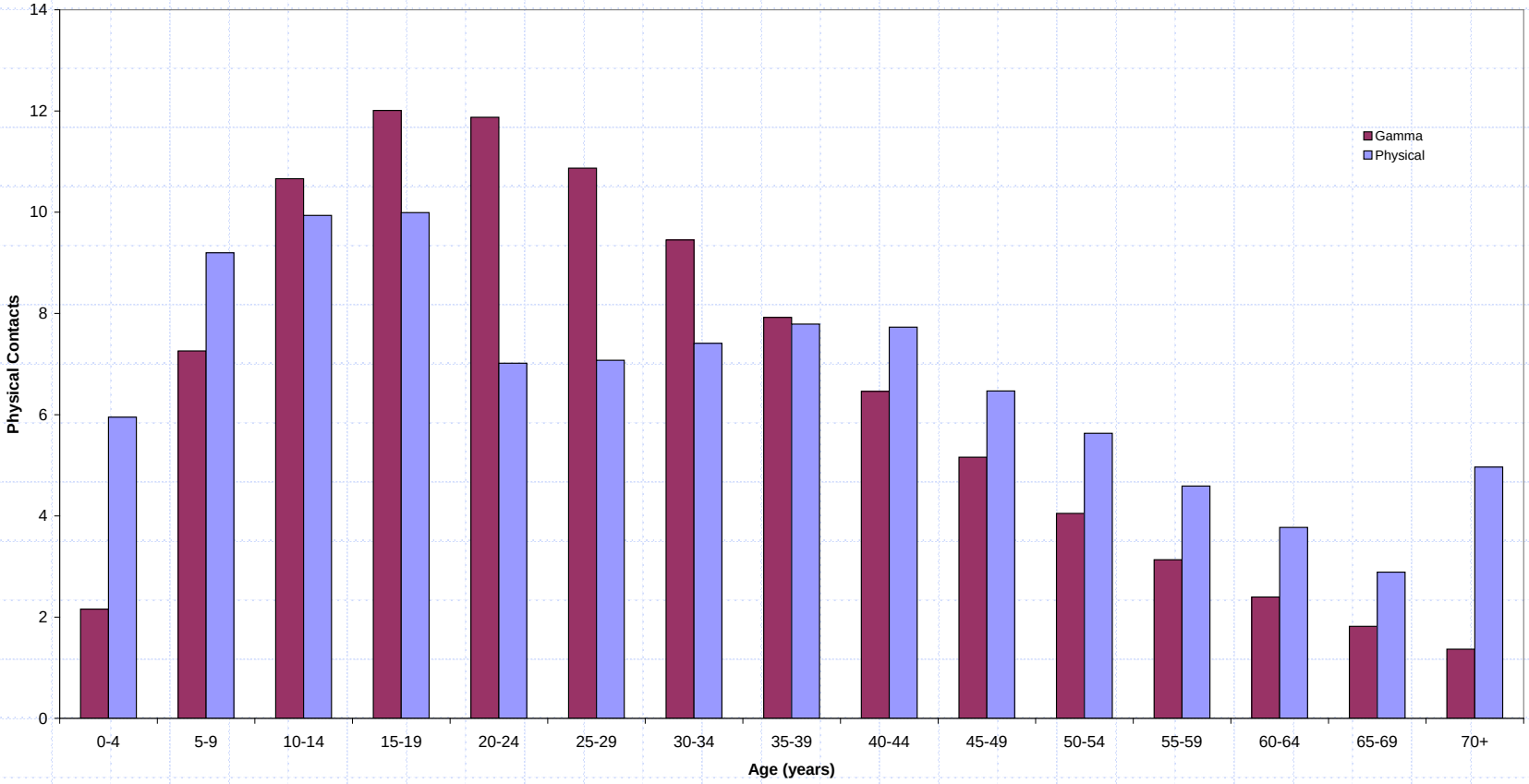


Table 3.1 from Anderson and May 1991. *Infectious Diseases of Humans: Dynamics and Control*. Oxford, 757 pp.

Disease	Incubation	Latent	Infectious
Measles	8-13	6-9	6-7
Mumps	12-26	12-18	4-8
Pertussis	6-10	21-23	7-10
Rubella	14-21	7-14	11-12
Diphtheria	2-5	14-21	2-5
Varicella	13-17	8-12	10-11
Hepatitis B	30-80	13-17	19-22
Poliomyelitis	7-12	1-3	14-20
Influenza	1-3	1-3	2-3
Smallpox	10-15	8-11	2-3
Scarlet Fever	2-3	1-2	14-21

Face-to-Face Conversations†



†Mossong J, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. PLoS Medicine 2008; 5:381-91

Mathematica™

Expressing concern about the impact of heterogeneity in vaccine coverage …

… leads to answerable questions

Q: Does the variance of p_i affect $\Re_v$?

A: When $\varepsilon_i > 0$

Q: Is it modified by other heterogeneities (e.g., in a_i, N_i)?

A: Yes, and they interact

Q: Does this model describe the recent outbreaks of measles well enough or …?

A:

It also may lead to refinements and as-yet-unanswerable new questions

- What causes preferential mixing in a spatial context? Airplanes, automobiles, … notwithstanding, proximity
- While this may seem perfectly obvious, it defines relevant spatial scales. Sub-populations are groups of people within which mixing is proportional and between which preferential
- Are counties sub-populations? What about classrooms, schools, households, neighborhoods, …? How do we tell? If necessary, by comparing empirical c_{ij} matrices element-by-element to model ones
- Other mixing models may be more appropriate in a spatial context and this transmission model may be too simple (we may need an exposed class, age structure, seasonal forcing, …), but those possible needs describe a research agenda

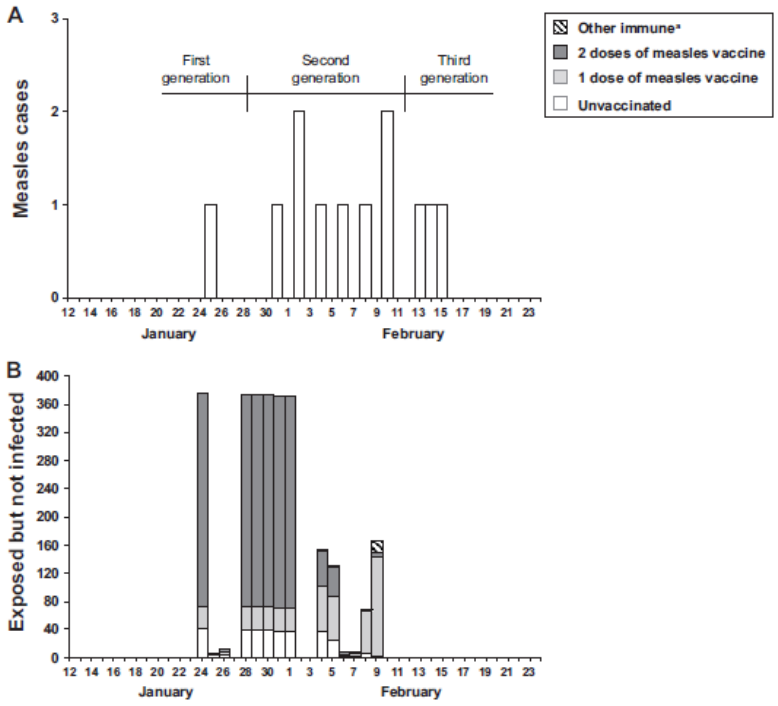
Summary

- If $\Re_0$ is calculated correctly, $1 - 1/\Re_0$ is the meta-population immunity threshold
- But, because the $\Re$'s are functions of c_{ij}, the p_i required to ensure that $\Re_v < 1$ depend on mixing
- Mixing is proportional within spatial strata of interest and preferential between them
- Less intuitive results (slides A3-5) may nonetheless be capable of guiding interventions

A Case Study

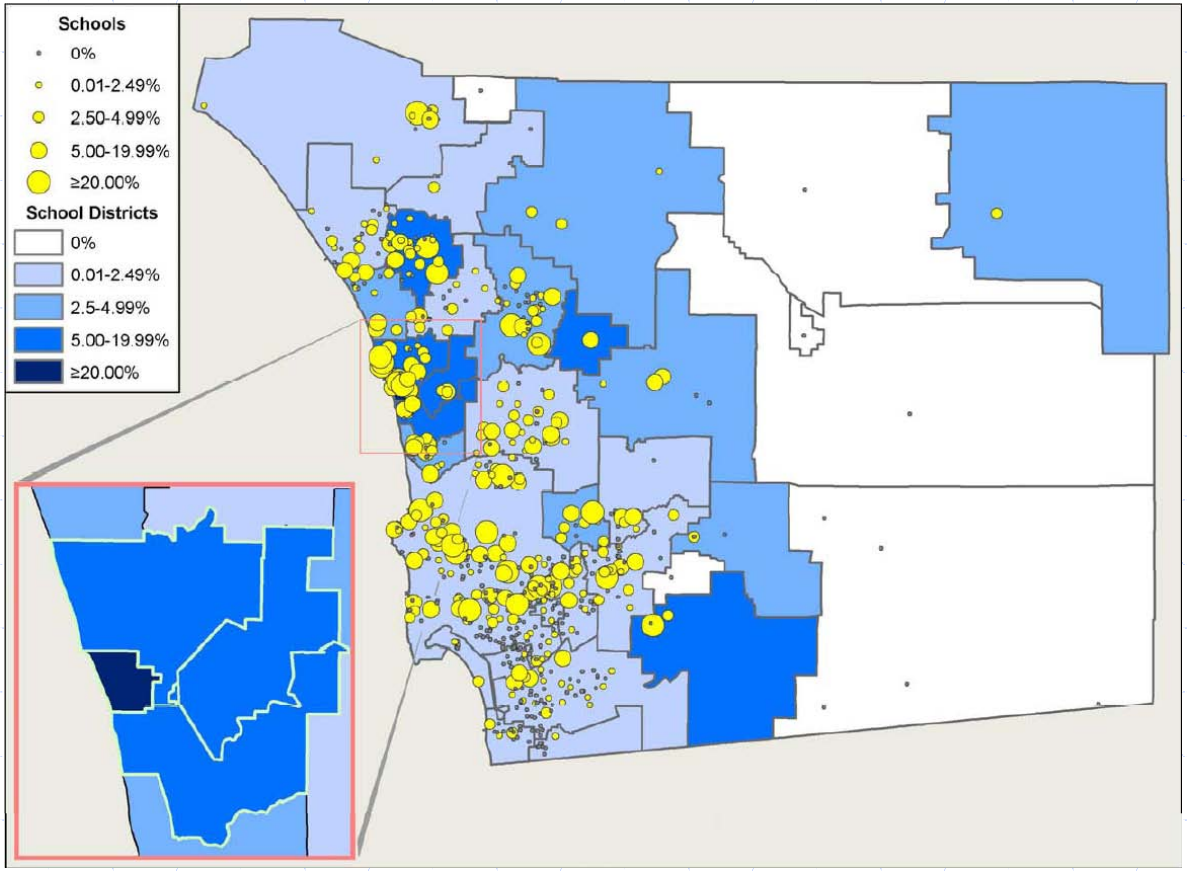
In 2000, authorities declared measles eliminated from the United States. In January 2008, an intentionally unvaccinated 7-year-old boy unknowingly infected with measles returned from Switzerland, resulting in the largest outbreak in San Diego, California, since 1991

Measles in San Diego, 2008 (from Sugerman et al. Pediatrics 2010; 125:747-55)

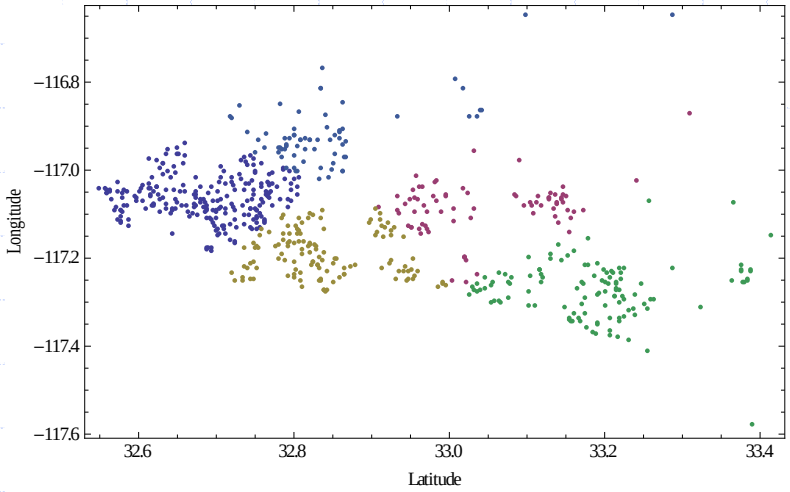


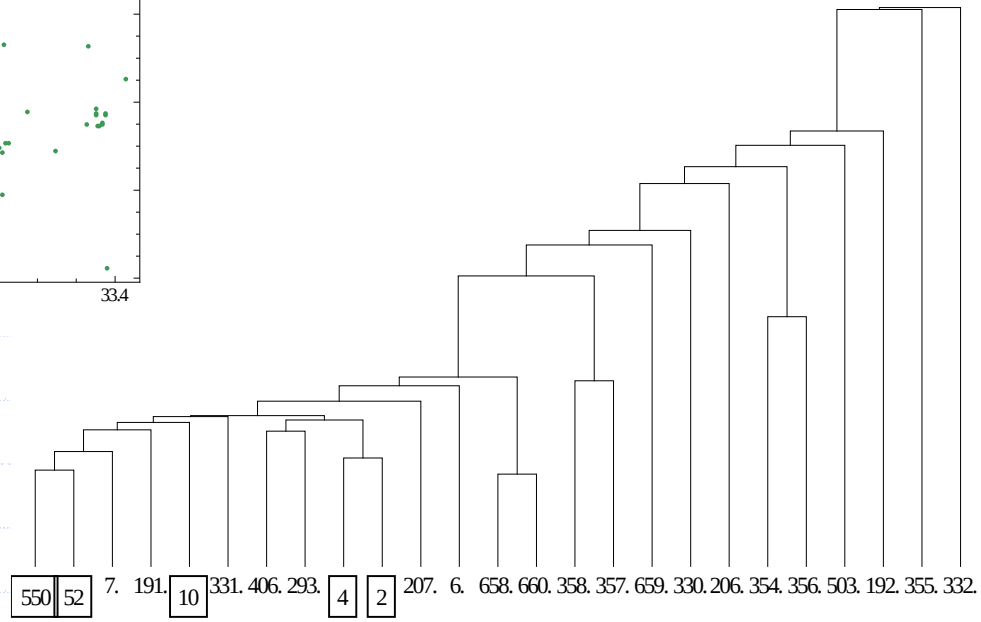
Patient age ranged from 10 months to 9 years. Of the 12 case-patients, 11 were white and 6 were female. All were unvaccinated: 9 had parents who had signed PBEs, and 3 were below the minimum age for vaccination. All had parents who were college-educated and lived in middle- to upper-income neighborhoods (zip code median household income: $44 521–$72 806). Five patients required urgent outpatient care, and an infant aged 10 months (too young to be vaccinated) was hospitalized for 72 hours and received intravenous hydration for diarrhea. No deaths or long-term complications occurred.

Personal belief exemption rates by school and district, San Diego County



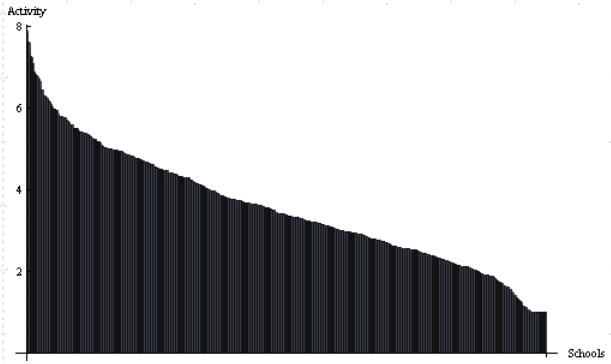
Spatial distribution of schools (n=638) in San Diego County (rotate 90° for North at the top)

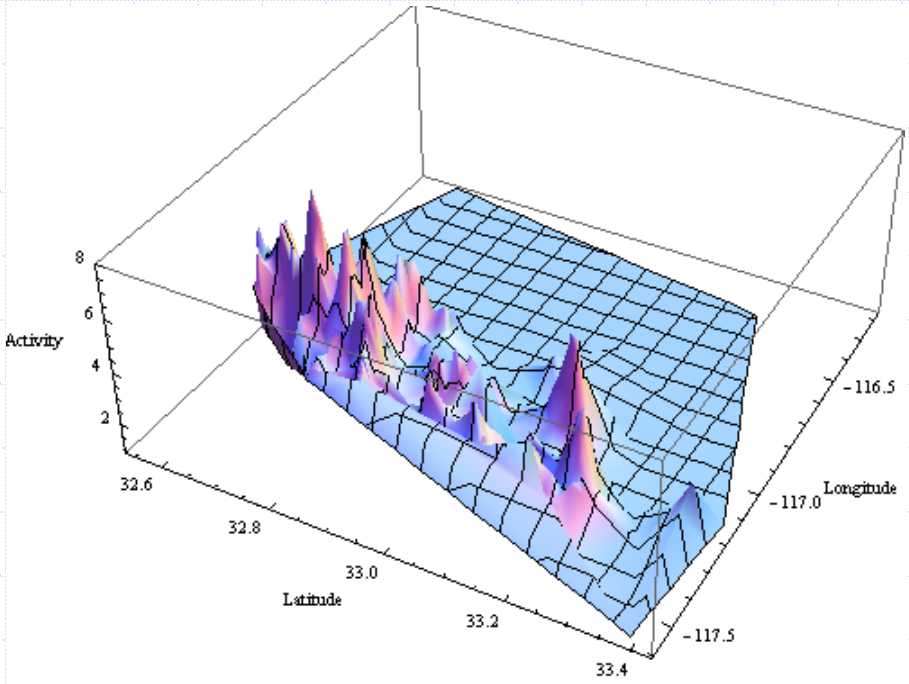




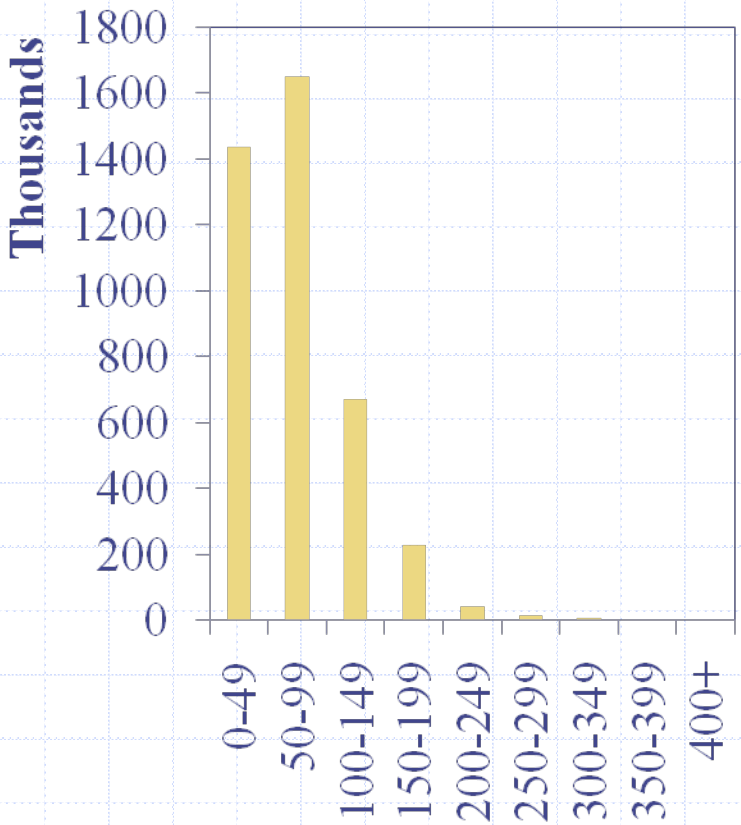
Spatial Mixing (n=638 schools)

- $M_{ij} = \exp(-b \times d_{ij})$, where the d_{ij} are inter-school distances, we can divide each element by the marginal total, $\sum_j M_{ij}$



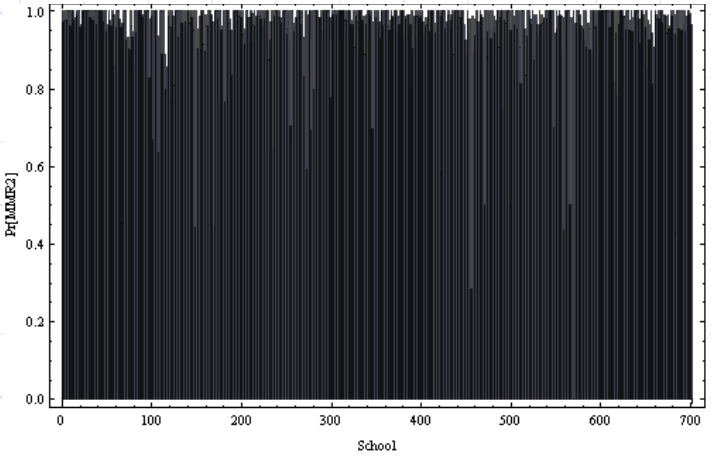


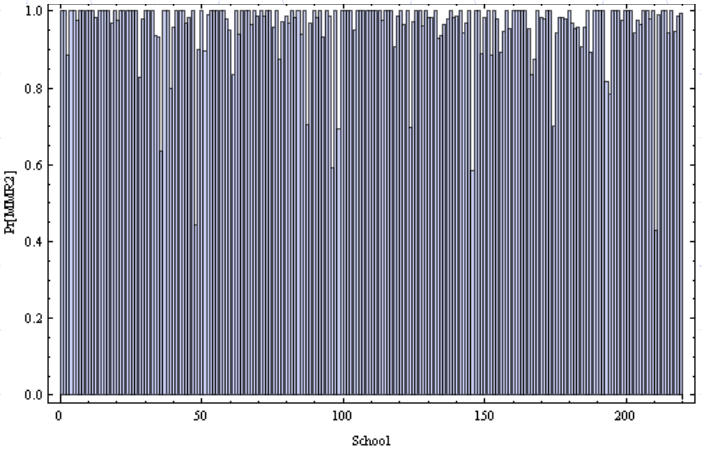
Total Contact Duration (in hours) as a Function of Distance from Home (in kilometers) from EpiSimS (Del Valle et al. Social Networks 2007; 29:539-54)

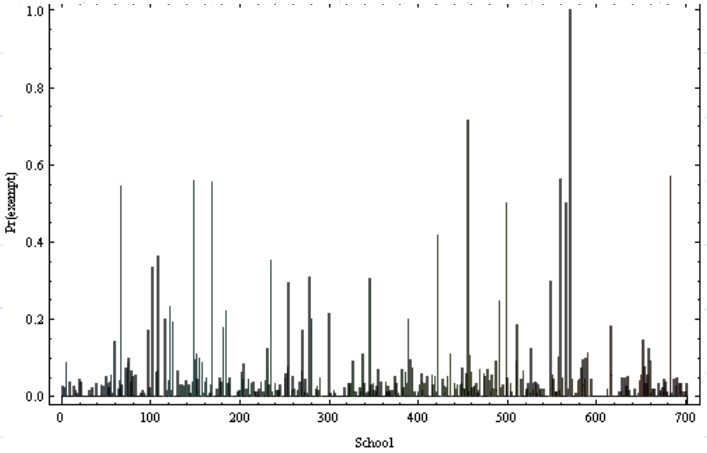


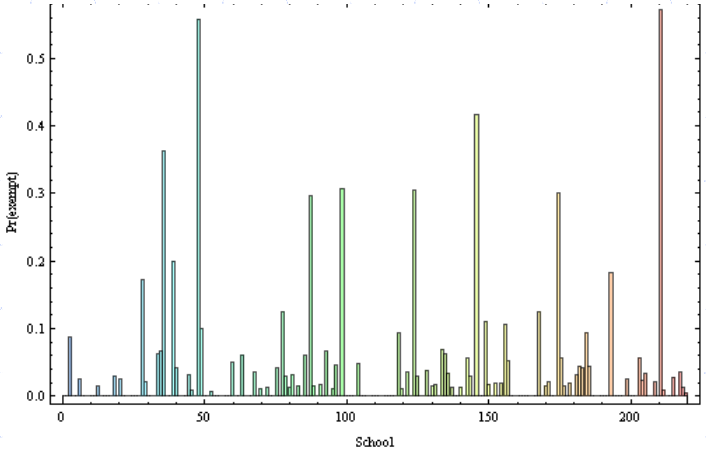
- In EpiSimS, assumed the number of occurrences in period δt were Poisson with parameter σ
- Thus, the probability of no occurrences in time interval δt is $\exp(-\sigma\delta t)$ and that of at least one occurrence is $1 - \exp(-\sigma\delta t)$
- Using the mean duration T_{ij} of contacts between a person in group i with people in group j, the probability of transmission is $P_{ij} = 1 - \exp(-\sigma T_{ij})$

Proportions of children with two doses of MMR (top) and exempt from vaccination (bottom) by school in San Diego County (left, n=638) and School District (right, n=200)

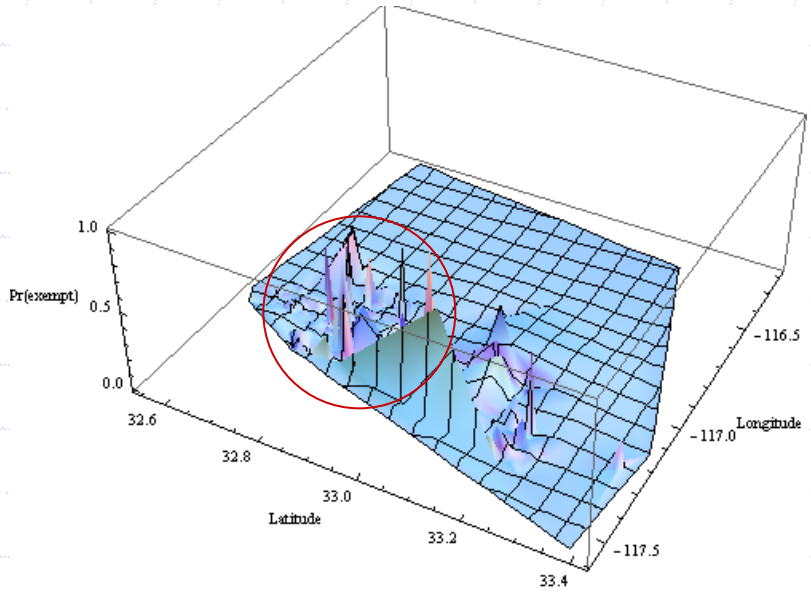


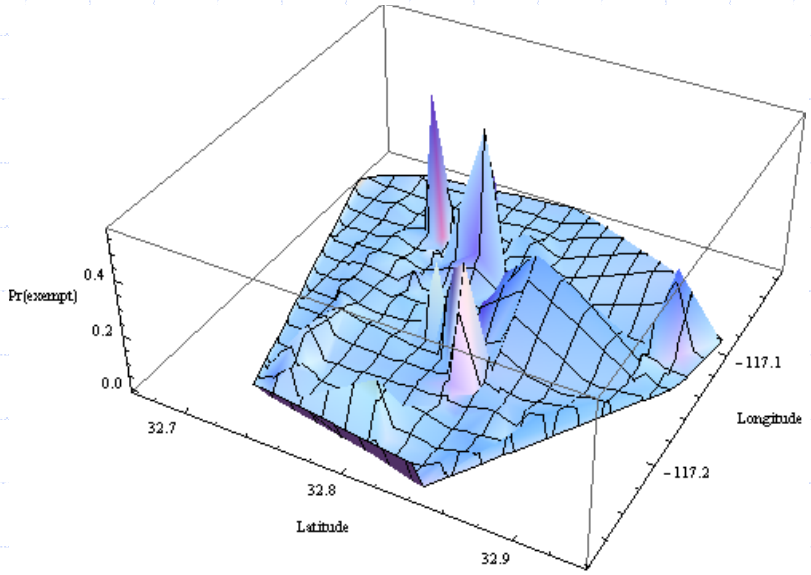






Proportions exempt in San Diego County (n=638 schools, left) and School District (n=200, right)





Objectives

- To adopt if possible and develop if necessary a suitable spatial mixing model
- To assess the impact of a) heterogeneity in vaccine coverage and b) nonrandom mixing on the population immunity threshold
- To explore the utility of the gradient in guiding public health decision-making

A1. The reproduction numbers and population-immunity threshold

$$0 = \mu N(1-p) - (\lambda + \mu) S$$

$$\lambda S + \mu S = \mu N(1-p)$$

$$\lambda \equiv \beta a \left(\frac{I}{N} \right)$$

$$\beta a I S + \mu S N = \mu N^2 (1-p)$$

$$\beta a I S = \mu N^2 (1-p) - \mu S N$$

$$I = \frac{N}{\beta a S} \left[\mu N(1-p) - \mu S \right]$$

$$I > 0 \Leftrightarrow \mu N(1-p) > \mu S \Leftrightarrow \frac{N(1-p)}{S} > 1$$

$$0 = \lambda S - (\gamma + \mu) I$$

$$S = \frac{(\gamma + \mu) I}{\lambda}$$

$$S = \frac{(\gamma + \mu) N}{\beta a}$$

$$\frac{N(1-p)\beta a}{(\gamma + \mu) N} = \frac{(1-p)\beta a}{\gamma + \mu} \equiv \Re = \Re_0 (1-p)$$

$$\Re = 1 \Rightarrow p_c = 1 - \frac{1}{\Re_0}$$

Homework: Do the definitions of the reproduction numbers in terms of states and rates, on the left and right sides of this page, respectively, correspond to the words on the previous page?

A2. The meta-population reproduction numbers include c_{ij} (i.e., mixing matters)

In this model, the basic and control (via vaccination) reproduction numbers, respectively, for sub-population *i* are

$$\Re_{0i} = \frac{\beta a_i}{\mu + \gamma}, \quad \Re_{vi} = \Re_{0i}(1 - p_i).$$

The next generation matrix for the meta-population (with n=2) is

$$K = \begin{bmatrix} \Re_{v1}c_{11} & \Re_{v1}c_{12} \\ \Re_{v2}c_{21} & \Re_{v2}c_{22} \end{bmatrix},$$

and the reproduction number (the larger eigenvalue of *K*) is

$$\Re_v = \frac{1}{2}\left[A + D + \sqrt{(A-D)^2 + 4BC}\right],$$

where $A = \Re_{v1}c_{11},\ B = \Re_{v1}c_{12},\ C = \Re_{v2}c_{21},\ D = \Re_{v2}c_{22}$.

This equation enables us to derive the limiting conditions:

Case 1: When $\varepsilon_1 = \varepsilon_2 = 1$, we have $c_{11} = 1$, $c_{12} = 0$, $c_{21} = 0$, $c_{22} = 1$. Thus, $A = \Re_{v1},\ B = 0,\ C = 0,\ D = \Re_{v2}$, and

$$\Re_v = \frac{1}{2}\left[\Re_{v1} + \Re_{v2} + \sqrt{(\Re_{v1} - \Re_{v2})^2}\right]$$

$$= \begin{cases} \frac{1}{2}\left[\Re_{v1} + \Re_{v2} + \Re_{v1} - \Re_{v2}\right] = \Re_{v1}, & \text{if } \Re_{v1} > \Re_{v2} \\ \frac{1}{2}\left[\Re_{v1} + \Re_{v2} + \Re_{v2} - \Re_{v1}\right] = \Re_{v2}, & \text{if } \Re_{v1} < \Re_{v2.} \end{cases}$$

That is, $\Re_v = \max\{\Re_{v1}, \Re_{v2}\}$.

When $p_1 = p_2 = 0$, we have $R_{vi} = R_{0i}$, whereupon $\Re_0 = \max\{\Re_{01}, \Re_{02}\}$.

Case 2: When $\varepsilon_1 = \varepsilon_2 = 0$, we have $c_{11} = f_1$, $c_{12} = f_2$, $c_{21} = f_1$, $c_{22} = f_2$. Thus, $A = \Re_{v1} f_1,\ B = \Re_{v1} f_2,\ C = \Re_{v2} f_1,\ D = \Re_{v2} f_2$, and

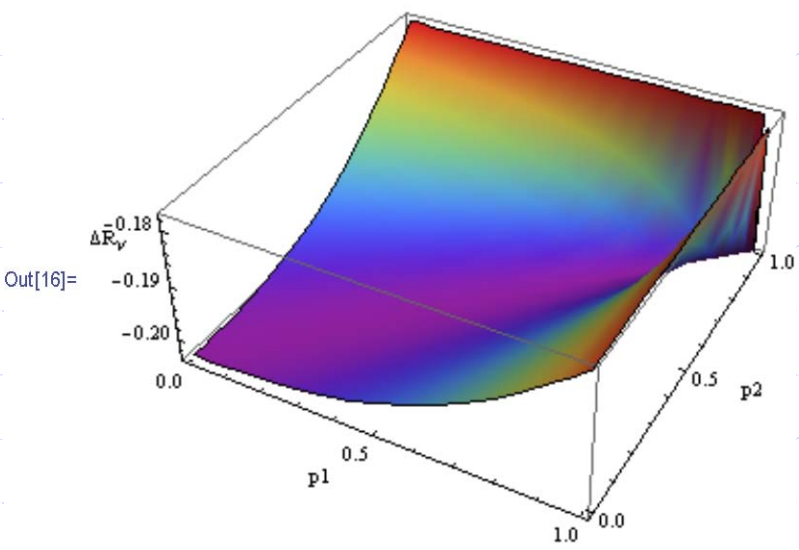
$$\Re_v = \frac{1}{2}\left[\Re_{v1} f_1 + \Re_{v2} f_2 + \sqrt{(\Re_{v1} f_1 - \Re_{v2} f_2)^2 + 4\Re_{v1} f_2 \Re_{v2} f_1}\right]$$

$$= \frac{1}{2}\left[\Re_{v1} f_1 + \Re_{v2} f_2 + \sqrt{(\Re_{v1} f_1 + \Re_{v2} f_2)^2}\right]$$

$$= \Re_{v1} f_1 + \Re_{v2} f_2.$$

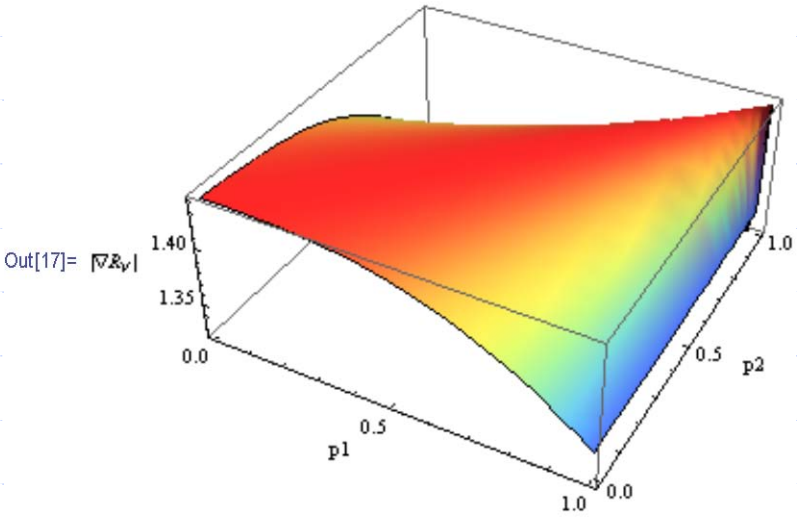
When $p_1 = p_2 = 0$, we have $R_{vi} = R_{0i}$, whereupon $\Re_0 = \Re_{01} f_1 + \Re_{02} f_2$.

A3. $\Delta\Re_v$ at all points (p_1,p_2) corresponding to 10% increases in p_1 and p_2



The more negative $\Re_v$, the greater the reduction associated with Δp_i. At point (0,0), in this example, $\Delta\Re_v$ decreases greatly in response to 10% increases in p_i

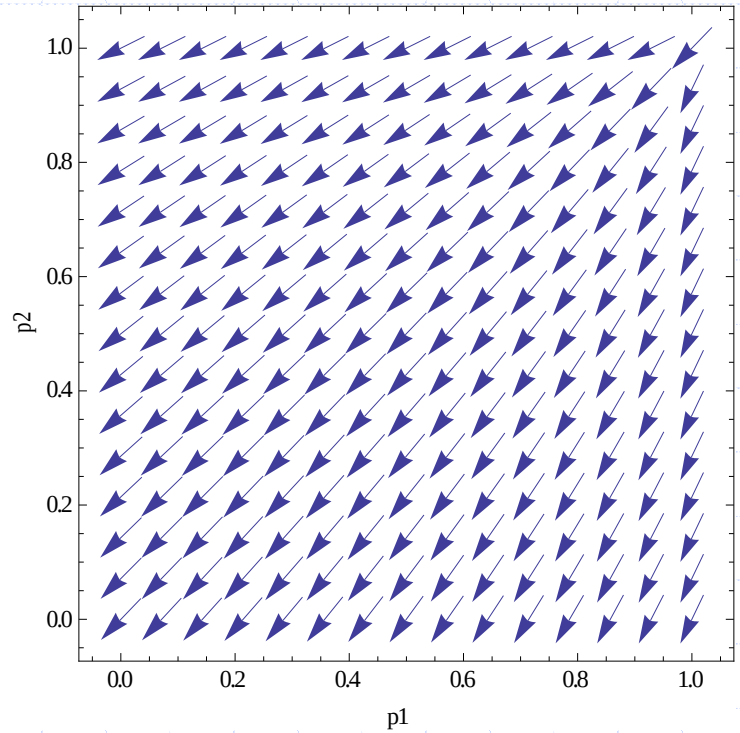
A4. Magnitude of the gradient, $\nabla\Re_v$, at all points (p_1,p_2)



$\nabla\Re_v$ is a vector; its length, $|\nabla\Re v|$, illustrates *magnitudes* of change in $\Re_v$ at points (p_1,p_2). The large gradient at point (0,0) corresponds to a very negative $\Delta\Re_v$ (prior plot)

A5. Directions from evenly spaced points (p_1,p_2) in which $\nabla \Re_v$ is greatest

Out[18]=



Were the vector at a point vertical, the best way to *reduce* $\Re_v$ would be to *increase* p_2 only (as the gradient direction has no p_1 component)

A6. Dallaire et al. J Infect Dis 2009; 200:1602-5

Dallaire F, De Serres G, Tremblay FW, Markowski F, Tipples G. Long-lasting measles outbreak affecting several unrelated networks of unvaccinated persons.

Despite a population immunity level estimated at approximately 95%, an outbreak of measles responsible for 94 cases occurred in Quebec, Canada. Unlike previous outbreaks in which most unvaccinated children belonged to a single community, this outbreak had cases coming from several unrelated networks of unvaccinated persons dispersed in the population. No epidemiological link was found for about one-third of laboratory-confirmed cases. This outbreak demonstrated that minimal changes in the level of aggregation of unvaccinated individuals can lead to sustained transmission in highly vaccinated populations. Mathematical work is needed regarding the level of aggregation of unvaccinated individuals that would jeopardize elimination.