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An assessment of the impact of heterogeneity in vaccine uptake due to religious and philosophical exemptions on the potential for outbreaks

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Abstract

Background—The goal of vaccination programs designed to prevent outbreaks following the introduction of infectious persons is maintaining the average number of secondary infections per infectious person < 1 . Our aim was to assess heterogeneity in vaccine uptake and other characteristics that, together with non-random mixing, may increase this number and to evaluate strategies to mitigate its impact.

Methods—Because most US children attend elementary school in their own neighborhoods, surveys of children entering kindergarten (attaining 5 years of age before 1 September) permit assessment of spatial heterogeneity in the proportion immune. We obtained results for 39,132 children who began school in 2008 in San Diego County, where a measles outbreak began in a school 12 of whose 40 students (30%) had personal-belief exemptions to vaccination. Using a mixing model suitable for spatially-stratified populations, we calculated the average numbers of secondary infections per infectious person for the diseases against which MMR vaccine protects. We also mapped contributions to this number for measles in San Diego County's 638 schools and its largest District, comprising 200 schools (31%), and determined the impact of plausible interventions to reduce heterogeneity in vaccine uptake.

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Findings—Impacts ranged from negligible to nearly complete reduction in outbreak potential. Vaccinating the 972 children with personal-belief exemptions was comparable to the most effective intervention considered, vaccinating 638 children attending the 114 schools < 90% of whose students were immune, which increased MMR uptake by 50%.

Interpretation—Insofar as children with personal-belief exemptions to vaccination not only live in the same households or neighborhoods or attend the same schools, but associate preferentially with other children with like-minded parents, they increase the risk of outbreaks more than may have been appreciated heretofore.

Keywords

measles, mumps and rubella; heterogeneity in vaccine uptake; non-medical exemptions; meta-population reproduction numbers

Introduction

In the United States, most states allow religious exemptions to vaccination and some allow philosophical exemptions.¹ Communities with higher personal-belief exemption rates have more outbreaks of vaccine-preventable diseases than communities with lower rates.² Nonetheless, parents are increasingly electing not to vaccinate their children.³ While vaccine uptake (proportion vaccinated as recommended) remains high overall, sub-populations are heterogeneous. In 2012, the most recent year for which National Immunization Survey (NIS) estimates are available (<http://www.cdc.gov/vaccines/imz-managers/uptake/nis/index.html>), 90.8% of children aged 19 to 35 months had received one dose of MMR vaccine, but uptake ranged from 64-95% among states and large cities. Similarly, while 91.4% of adolescents aged 13 to 17 years had received two or more doses, uptake ranged from 83-98%. Some counties are large enough for reliable NIS estimates, but only school-entry surveys achieve higher spatial resolution.

Travelers infected abroad who become or remain infectious upon returning home regularly introduce novel genotypes or reintroduce pathogens that have been eliminated.⁴ Whether or not outbreaks (locally increased infections within particular periods) occur after infectious people enter communities depends partly on the intimacy and rate of their inter-personal contacts and partly on the proportion of residents that is immune. The rate or intimacy of contacts may vary with individual (e.g., age, gender, gregariousness) or population characteristics (e.g., density). Such heterogeneity increases the potential number of secondary infections per infectious person, the basic or intrinsic reproduction number of the pathogen in the host population (cf. average number of daughters per woman in demography⁵), and heterogeneity in immunity also increases the realized number. Outbreaks may occur if realized reproduction numbers exceed 1.

Elsewhere we reviewed, refined and extended theoretical results about populations composed of groups differing in salient characteristics, to which Levins⁶ referred as meta-populations. Then we explored the interplay between differences among sub-populations in characteristics affecting their average numbers of secondary infections per infectious person (heterogeneity) and non-random mixing via the simplest meta-population model capable of

informing vaccination policy.⁷ Here we estimate the reproduction numbers for measles, mumps and rubella in San Diego County, California, where a 2008 measles outbreak began in a school 30% of whose students had personal-belief exemptions.^{8,9} We also map contributions to measles' meta-population reproduction numbers and estimate the impact of plausible interventions to reduce heterogeneity in MMR vaccine uptake. These include targeting schools whose students contribute disproportionately to the outbreak potentials of these childhood diseases and vaccinating children with personal-belief exemptions.

Methods

In the US, most children attend elementary (primary) school in their own neighborhoods. To enroll children in California schools, parents must document their receipt of or exemption from required vaccinations. In some jurisdictions, children may be enrolled conditional on vaccination in the near future. Rodewald and his colleagues¹⁰ describe the methods employed in school-entry vaccination surveys, which provide the observations needed to assess the impact of spatial heterogeneity in the proportions of children who are immune on the potential for outbreaks of vaccine-preventable diseases. The salient feature of these surveys is that they summarize, by elementary school, receipt of required vaccines, even if students have multiple healthcare providers.

We obtained results of the 2008 school-entry surveys performed by the Immunization Division of the California Department of Public Health in San Diego County ($n = 638$ elementary schools). Data include school addresses; enrollments; proportions of students with 1 and 2 doses of measles, mumps and rubella (MMR) and 1 dose of diphtheria, tetanus and pertussis (DTaP), poliovirus, hepatitis B, and varicella vaccines; and proportions with medical or personal-belief exemptions (appendix 1). We calculated inter-school distances from the addresses, geocoded for figure 3 of the article by Sugerman and his colleagues.⁹

Outbreak Potentials

The reproduction numbers that describe outbreak potential depend on host as well as pathogen characteristics. In models of pathogen transmission in homogeneous or randomly-mixing host populations without demographic dynamics, they are products of average *per capita* contact rates, probabilities of infection on contact with infectious persons and durations of infectiousness. In otherwise similar meta-population models, reproduction numbers are characteristics of matrices (appendix 2) whose elements are products of sub-population reproduction numbers (identical to those for homogeneous, randomly-mixing populations) and a function describing mixing among sub-populations. In appendix 3, we derive a function suitable for spatially-stratified populations.

The reproduction numbers of pathogens causing measles, mumps and rubella in San Diego County are unknown. Given durations of infectiousness from table 3-1 of Anderson and May,¹² we chose probabilities of infection on contact with infectious persons ($\frac{1}{3}$ for measles, 0.25 for mumps and 0.1 for rubella) and the rate of change in contact rates ($b = 10^{-3}$ per unit distance) to obtain average *per capita* effective contact rates that yield basic reproduction numbers within the ranges reported in their table 4-1. We refer to these numbers as naïve because they ignore the heterogeneity and non-random mixing

characterizing all human populations. To validate our approach (appendix 4), we estimated measles' basic reproduction number in the school where the 2008 outbreak began using methods that, by making limiting assumptions about the distribution of generation times (periods between symptom onsets in successive generations), bound its true value.

Then we calculated the meta-population reproduction numbers for measles, mumps and rubella in San Diego County. In contrast to the naïve numbers mentioned above, for which we used weighted average *per capita* effective contact rates and proportions immune (which is tantamount to assuming homogeneous, randomly-mixing populations), these use school-specific ones. (When possible without confusion, we omit the term meta-population when referring to reproduction numbers henceforth.) Next we mapped school or neighborhood contributions to measles' reproduction numbers.

Plausible Interventions

We deduce the impact on measles' outbreak potential, the number of secondary measles infections per infectious person or realized reproduction number, of 1) vaccinating children with personal-belief exemptions; 2) increasing uptake by 10, 30 or 50% in all or only influential (appendix 3) low-immunity schools; or 3) increasing private school uptake to the public school average.

To model vaccinating children with personal-belief exemptions, we increment proportions immune to each disease by products of proportions with non-medical exemptions and dose-specific vaccine efficacies (92 and 95%, respectively),¹⁵ weighted by proportions of children who had received 1 and 2 doses. In a hypothetical school 90 and 85% of whose students had received 1 and 2 doses of MMR, respectively, and 5% had personal-belief exemptions, for example, this intervention would increase the proportion immune to measles from $0.05 \times 0.92 + 0.85 \times 0.95 \approx 0.85$ to $[0.05 + (0.05 \times 0.05)] \times 0.92 + [0.85 + (0.85 \times 0.05)] \times 0.95 \approx 0.9$.

To model increasing uptake in low-immunity (here defined as < 90%) or influential schools (here defined as having average *per capita* contact rates ≥ 3 , proportions of contacts with children in other schools or neighborhoods ≥ 0.3 , or both), we multiply the proportions of their children who are immune by 1.1, 1.3, or 1.5. In a hypothetical school where 50% of students were immune, for example, this intervention would increase immunity to 0.55, 0.65 or 0.75. In a school 89% of whose students were immune, however, post-intervention proportions immune would be 0.98, 1, and 1.

To model increasing private school uptake, which averaged 0.89 in 2007, to that in public schools, which averaged 0.93, we multiply the proportions of children immune in each private school by the ratio of the public and private school averages. In a private school 85% of whose students were immune, for example, immunity would increase to $0.85 \times (0.93/0.89) \approx 0.89$ post-intervention.

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publication. All data were accessible to the corresponding author, who had final responsibility for the decision to submit the manuscript for publication.

Results

We estimate the average numbers of secondary infections per infectious person for measles, mumps and rubella in San Diego County and School District and impact of plausible interventions to reduce this number for measles. Our figures describe San Diego School District, whose smaller area allows higher resolution than the larger county. This district also is the most populous of 36 in San Diego County and location of the 2008 measles outbreak. Our tables in the main text and figures in the on-line supplement describe the entire county.

The spatial distribution of children's *per capita* contact rates and distribution of their contacts by school for the $n = 200$ schools in San Diego School District are illustrated in figures 1 and 2, respectively. The peaks in figure 1 indicate clusters of nearby schools. In figure 2, schools are not in any particular order. But ones with relatively large diagonal elements have relatively small enrollments or are isolated while ones with smaller diagonal elements are larger or more highly interconnected. The school (neighborhood) contributions to measles' basic and realized reproduction numbers are mapped in figures 3a and b, respectively. A red point locates the school where the 2008 outbreak began.

The outbreak potentials of measles, mumps and rubella in San Diego County and impact of vaccination are illustrated in table 1. With the disease-specific probabilities of infection on contact with infectious people and durations of infectiousness chosen, and weighted average contact rates (assuming that contacts diminish with distance at a constant rate), the naïve basic reproduction numbers for measles, mumps and rubella are 10.7, 8.5, and 4.1, respectively. The corresponding population-immunity thresholds (proportions immune at which an average infectious person would infect exactly 1 susceptible person) are 91, 88, and 76%. Given the dose-specific vaccine efficacies shown, together with uptake – sums of the proportions of children with 1 and 2 doses in each school weighted by school enrollments – the respective population immunities are 92, 87, and 92% for measles, mumps and rubella, near or above those naïve (randomly-mixing homogeneous) population-immunity thresholds. The meta-population basic reproduction numbers however are about 70% greater, 18.1, 14.3, and 6.9, respectively. While vaccination reduces them substantially (table 1), all remain > 1 .

The impact of plausible interventions to remedy the residual outbreak potential of measles in San Diego County are illustrated in table 2, whose first row includes the observed 2008 uptake and calculated number of secondary infections per infectious person, and subsequent rows indicate changes in uptake and this reproduction number. The first row also indicates the numbers of students and schools in the entire county and other rows the numbers affected by each intervention. Where ranges are indicated (by hyphens), they correspond to 10 and 50% increases in uptake in selected schools described above. Results for mumps and rubella (not shown) are similar.

Because some schools or neighborhoods are more influential than others, by virtue of enrollments (neighborhood sizes) or proximities to others, vaccine uptake affects realized reproduction numbers disproportionately. Targeting schools whose students have high average *per capita* contact rates and low proportions immune ($n = 65$) affects overall uptake less, but decreases the realized reproduction number as much as targeting all high-activity schools ($n = 385$). Similarly, targeting low-immunity, highly connected schools ($n = 52$) has almost as much impact as targeting all highly connected schools ($n = 231$). Notably, vaccinating children with personal-belief exemptions reduces the realized reproduction number as much as increasing uptake by 50% in schools where $< 90\%$ of students are immune. In contrast, increasing private school ($n = 208$) uptake to the public school average has little effect.

Discussion

As most US children attend neighborhood elementary schools, information from school-entry surveys in San Diego County, California, informs us about the neighborhoods comprising that county. We evaluated the a) effects of heterogeneity in children's *per capita* contact rates and proportions of their contacts that are with children in other schools or neighborhoods on the basic reproduction numbers of measles, mumps and rubella by virtue of elementary school locations and enrollments and on measles' realized reproduction number by virtue of MMR vaccination. We also evaluated the b) impact of plausible interventions to reduce heterogeneity in vaccine uptake.

Personal-belief exemptions are not solely responsible for spatial heterogeneity in vaccine uptake. But children with exemptions tend to live in the same neighborhoods and to associate preferentially with other children with like-minded parents.¹⁶ In San Diego County, moreover, the proportion of children with personal-belief exemptions is inversely correlated with 2-dose MMR uptake.⁹ Thus, vaccinating children with personal-belief exemptions was among the plausible interventions that we investigated. We found that this intervention was comparable to increasing uptake in schools where $< 90\%$ of children were immune by 50%, which would decrease the average number of secondary infections per infectious person to 1.11. Such small residual outbreak potential could be easily reduced by parents keeping or teachers sending sick children home.

As some children with personal-belief exemptions may attend private schools, another sort of heterogeneity, we also evaluated increasing private school uptake to the public school average. This had relatively little effect, presumably because private school enrollments or inter-school connections are small compared with those of public schools.

Because other environmental characteristics (e.g., access to providers who advocate vaccination) might be heterogeneous, we also compared targeted and untargeted increases in uptake. We defined high activity as average *per capita* contact rates of 3 or more per day and high connectedness as 30% or more contacts with children in other schools (neighborhoods), different measures of influence that include some of the same roughly 60% of schools. If health authorities wished or needed to focus their efforts, concentrating on influential schools would be efficient (figure 3). But, in San Diego County, vaccinating children with

personal-belief exemptions would be more effective. The generality of this result remains to be demonstrated, but that intervention targeted the heterogeneity affecting measles' reproduction number almost as much as increasing uptake by 50% in schools < 90% of whose students were immune.

Sugerman and his colleagues⁹ concluded that the 2008 measles outbreak was largely confined to a school with an unusually high personal-belief exemption rate partly because of a robust response, but also because it was embedded in a district with a lower exemption rate. While their assessment is correct, this school's location is perilously close to the epicenter of larger contributions to the reproduction numbers of measles in San Diego School District (figure 3), which in turn contributes substantially to those of the entire county (on-line supplement). Such maps could guide pre-emptive public health efforts inasmuch as travelers infected abroad will continue to reintroduce pathogens responsible for diseases that have been eliminated from the United States.

Limitations

The naïve reproduction numbers of measles, mumps and rubella in San Diego County are unknown. Given durations of infectiousness from the literature, we chose 2 parameters to yield numbers in the range reported: disease-specific probabilities of infection on contact and the rate at which inter-school (or neighborhood) contacts diminish with distance. Our independent calculations using information from the school where the 2008 outbreak began (appendix 4) indicate that the basic reproduction number thus estimated for measles is conservative. While results for mumps and rubella are in the range of reported values, absent outbreaks of those diseases, we cannot evaluate the chosen parameters for the pathogens causing them in this host population.

Our study population is composed of kindergartners attending San Diego County's 638 elementary schools, 92% of whom we estimate are immune to measles. This exceeds estimates for California from the 2008 National Immunization Survey among either 12-39 month- or 13-17 year-old children. But a) some of their siblings were too young for vaccination and others would be vaccinated before beginning school and b) enforcement of school-entry requirements, which contributed substantially to the elimination of these childhood diseases in the US, has increased since those adolescents were kindergartners.

We assume that contacts in this spatially-stratified population vary inversely with distance at a constant rate (appendix 3). As most children attend elementary school in their own neighborhoods, this is a reasonable first approximation. But our understanding of spatial mixing will improve by virtue of analyses of information from the geo-location devices that are embedded in mobile phones, possibly together with proximity detectors. When results become available, our mixing model can be evaluated and improved or replaced with a better model or, potentially, the observations themselves.

Were children with personal-belief exemptions vaccinated during the school year, we overestimated the impact of vaccinating them. As MMR is the vaccine that has been falsely associated with autism,¹⁷ however, it seems unlikely that many children with personal-belief

exemptions when school began received it subsequently. Be that as it may, evaluating this possibility requires accurate child- versus school-based records.

Assessing Population Immunity

Despite elimination from the United States in 2000, importations continue to cause measles outbreaks,¹⁸ so evidently its realized reproduction number > 1 in some communities.

Outbreak prevention requires the average number of secondary infections per infectious person to be < 1 , which is equivalent to immunity being above naïve population-immunity thresholds only in randomly-mixing homogeneous populations.

In heterogeneous or non-randomly-mixing populations, sets of sub-population immunities (i.e., pairs if there are only 2 sub-populations, triplets if there are 3, and so on) satisfy the condition that only one susceptible person be infected per infectious person. These sets cannot simply be averaged for comparison with overall or weighted average sub-population immunities,⁷ as is current public health practice. Requiring properly calculated realized reproduction numbers to be < 1 for outbreak prevention is suitable irrespective of heterogeneity or mixing regime. Consequently, we advocate using them or the gradient, their partial derivatives with respect to sub-population immunities, to guide vaccination efforts instead of the naïve population-immunity threshold.⁷

Future Research

There are several policy options for reducing personal-belief exemption rates. These include targeted communications, favoring vaccination by making the process of obtaining exemptions more onerous, and eliminating all non-medical exemptions. The California legislature recently adopted the third option (appendix 5), but the impact of this policy is as yet unclear. Parents who refuse to vaccinate their children may opt for home schooling or pressure healthcare providers to issue medical exemptions. Therefore, we will monitor the impact of eliminating personal-belief exemptions in California and continue to explore other interventions (e.g., community engagement).

Personal-belief exemptions are easier to obtain in some states than others.³ The National Immunization Survey indicates that unimmunized adolescents are accumulating in some states.²⁰ Because inter-personal contacts are most intense among older children and adolescents, who mix almost exclusively with each other,²¹ we are developing multi-level (e.g., age and space) mixing models. Together with survey results, those models will enable us to evaluate the accumulation of susceptible schoolchildren – by virtue of personal-belief exemptions, conditional admissions that haven't been followed-up to ensure that children are vaccinated, and vaccine failures – into the ages at which mixing is most intense.

Research in Context

Evidence before this study

The population-immunity threshold – which health authorities world-wide use to establish vaccination uptake targets to prevent outbreaks upon the introduction of people who are or become infectious – is not based on empirical observations, but rather, on models of

pathogen transmission in homogeneous host populations whose members mix randomly. Recently, the authors reviewed and extended the theory underlying this concept and suggested an alternative that is also appropriate in heterogeneous or non-randomly-mixing host populations. They also searched PubMed using the terms “vaccine hesitancy”, “vaccine refusal”, “personal-belief exemptions”, and “population immunity” for reports in any language since their 2009 review of this literature.

Added value of this study

Here the authors apply their theory to a vexing public health problem, outbreaks of diseases that have been eliminated locally when infectious persons (generally travelers infected abroad) enter populations whose immunity is above this threshold. They use information from school-entry surveys in San Diego County, California – conducted annually at the behest of the federal government – to show that heterogeneity or non-random mixing could account for this inconsistency. Then they identify neighborhoods (in the US, children typically attend elementary school in their own neighborhoods) where the risks of measles, mumps or rubella outbreaks upon the introduction of infectious persons are greater than average. (The MMR vaccine, required for matriculation in all states, protects against these childhood diseases.) Next they explore plausible interventions to reduce heterogeneity in measles immunity, given a mixing model in which proximity and school enrollments (a proxy for neighborhood sizes) affect inter-school (or neighborhood) contacts. And finally, they identify and demonstrate the impact of eliminating the arguably most important single source of heterogeneity in San Diego County, personal-belief exemptions. The impact of vaccinating children with non-medical exemptions would be commensurate with that of increasing immunity by 50% in all schools where < 90% of students were immune.

Implications of all the available evidence

The population-immunity threshold is uninformative in populations that are heterogeneous or whose members mix non-randomly. Here the authors demonstrate the utility of an alternative, the average number of infections per infectious person in a meta-population, whose sub-population contributions can not only identify locales where the risks of outbreaks are elevated (main text), but evaluate the impact of interventions to mitigate such risks (on-line supplement). While the generality of their conclusion about personal-belief exemptions in San Diego County remains to be demonstrated, their approach can identify problematic locales whatever their etiology and evaluate the impact of appropriate interventions. Moreover, as more is learned about mixing in heterogeneous populations, it can be improved. Meanwhile, the authors will demonstrate the utility of the gradient, a vector-valued function of the realized reproduction number, in identifying optimal strategies for reducing the risk of vaccine-preventable disease outbreaks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendices

1. We use the subscripts i , j , and k to denote the elements of arrays. Thus, x_j is the j^{th} element in an $n \times 1$ array, a conventional list or vector in mathematics. Similarly, x_{ij} is the ij^{th} element, with i denoting the column and j the row, in an $n \times n$ array, a conventional table or matrix in mathematics. In such an array, we denote the diagonal elements, whose column and row indices are the same, by x_{ii} . Our n are schools (or neighborhoods), of which there are 638 in San Diego County and 200 in San Diego School District. Our $n \times 1$ arrays are the observations and these calculated quantities: children's average *per capita* contact rates, a_i , to which many authors refer as activity, and sub-population reproduction numbers, \mathcal{R}_{0i} and \mathcal{R}_{vi} . Our $n \times n$ arrays are distances between schools i and j , d_{ij} , proportions of their contacts that children in school (or neighborhood) i have with children in all schools (or neighborhoods), c_{ij} (including their own, c_{ii}), and elements of the next-generation matrices defined in appendix 2.
2. The arrays mentioned in this section are called next-generation matrices because they transform, by multiplication, vectors composed of the numbers infectious in each sub-population in one generation into the corresponding vectors in subsequent generations. The largest eigenvalue is the average factor by which successive vectors differ in magnitude, or average number of secondary infections per infectious person. It has two associated nonzero vectors whose dot products with this matrix or its transpose equal their products with the eigenvalues. These eigenvectors also have biological interpretations: one is the prevalence of infection by sub-population and other is their contributions to the reproduction number.¹¹ Figures 3, S3, and S4 illustrate spatial distributions of the second of these, denoted $E_{\mathcal{R}_0}$ or $E_{\mathcal{R}_v}$.
3. In spatially-stratified populations, proximity must affect contact rates. We define the average *per capita* contact rate or activity of children enrolled in school (or residing in neighborhood) i as a negative exponential function of inter-school (or neighborhood) distances, $a_i := \sum_j \exp(-b \times d_{ij})$, where b is a scaling constant and the d_{ij} are distances between school (or neighborhood) i and all others. Note that, because $\exp(0) = 1$, $a_i - 1$ of these contacts are inter-school (or neighborhood). To obtain contacts, we multiply these rates by school enrollments, N , and to obtain proportions, we divide by the sum of this quantity over all schools, $c_{ij} := N_j \exp(-b \times d_{ij}) / \sum_k N_k \exp(-b \times d_{ik})$. Insofar as classroom sizes are similar,

neighborhood sizes are proportional to school enrollments, whereupon these c_{ij} are proportions of their contacts that children in school (or neighborhood) i have with children in all schools (or neighborhoods) including their own (i.e., $\sum_j c_{ij} = 1$). Consequently, complements of the proportions of contacts that are intra-school (or neighborhood), $1 - c_{ii}$, are interpretable as connectedness (sensu strength of connections with other schools or neighborhoods).

4. We can estimate \mathcal{R}_{0j} for measles in the school where 2008 outbreak began from the cumulative incidence, generation time,¹³ and proportion immune. Absent interventions (e.g., sending or keeping sick children home), epidemics will grow exponentially until susceptible people begin being depleted; thus, $\mathcal{R}_0 = \exp(rT)$, where T is the generation time. From the slope of a line fitted to natural logarithms of cumulative incidence from days 5 to 9, 0.4159, and mean (SD) generation time for measles, 11.1 (1.79) days,¹⁴ \mathcal{R}_{vj} is between $0.4159 \times 11.1 = 4.6$ and $0.4159 \times 11.1 - 0.5 \times 0.4159^2 \times 1.79^2 = 4.3$. Observing that 28 of this school's 40 students had received one dose of MMR and that 24 had received two doses, which have efficacies of 0.92 and 0.95 respectively,¹⁵ $p_j = (24/40) \times 0.95 + [(28-24)/40] \times 0.92 = 0.66$. Then $\mathcal{R}_{0j} = \mathcal{R}_{vj} / (1 - p_j) = 13.7$ or 12.8. Evidently, the biological parameters (probability of infection on contact and duration of infectiousness) that we chose for measles, together with $a_j = 4.87$ from our mixing model, yield a conservative estimate of its \mathcal{R}_0 in San Diego County during 2008.
5. California health authorities also survey vaccine uptake among children exiting kindergarten and entering middle school. The proportions of children enrolled conditional on vaccination in the near future (conditional admissions in the main text) are comparable,¹⁹ possibly indicating the need for additional follow-up. On 30 June 2015, Governor Jerry Brown signed Senate Bill 277, which eliminated personal-belief exemptions to vaccination in California. Resources to help parents elsewhere make wise choices about vaccination are available at <http://www.cdc.gov/vaccines/parents> and <http://www.cdc.gov/vaccines/parents/infants-toddlers.html>. Resources to help health-care providers counsel parents effectively are available at <http://www.cdc.gov/vaccines/hcp.htm>.

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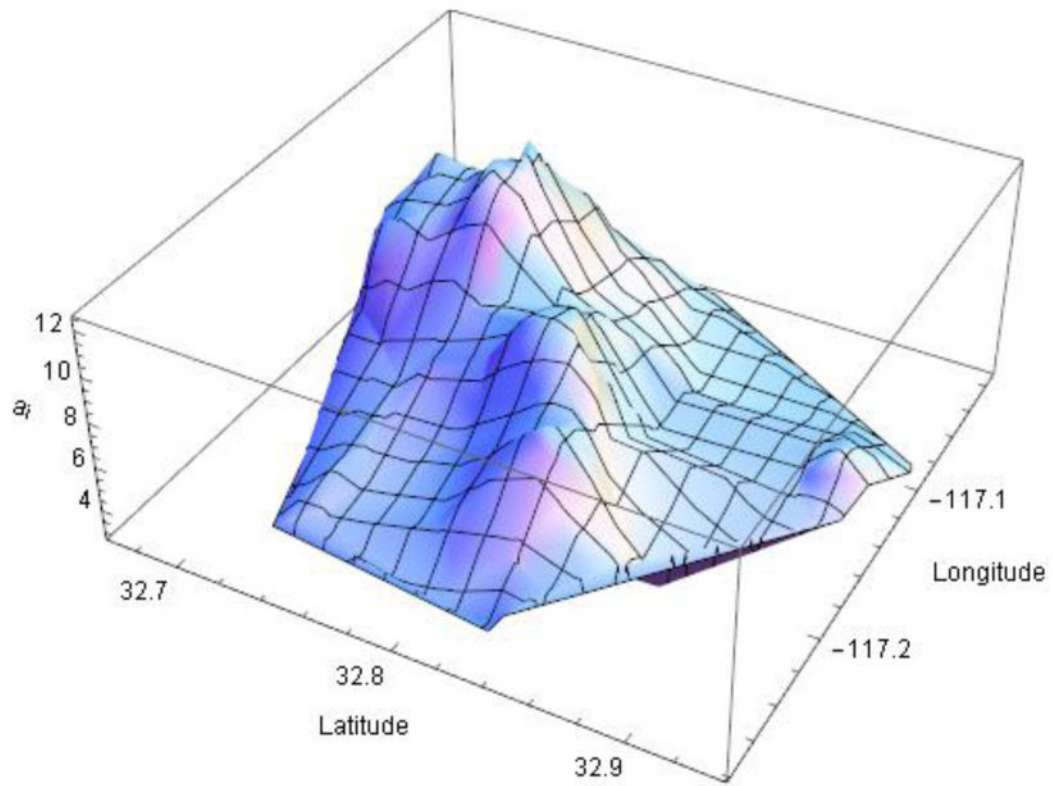


Figure 1.

Spatial distribution of average *per capita* contact rates, a_i (appendix 3) of elementary schoolchildren in San Diego School District ($n = 200$).

The peaks and valleys of this surface are indicative, respectively, of the nearby or isolated schools or neighborhoods characterizing more and less densely-populated areas. Those whose students have larger average *per capita* contact rates contribute more to the reproduction numbers (figure 3) than others.

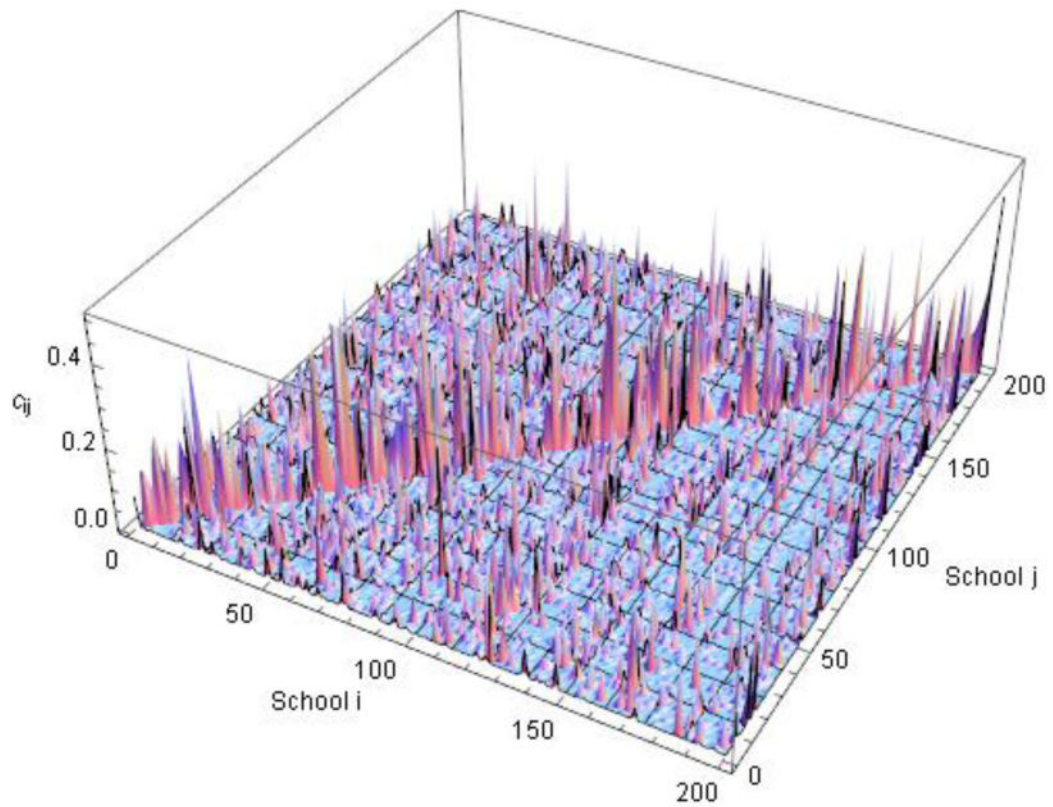


Figure 2.

Proportions of their contacts that children in San Diego School District have with other children, c_{ij} , $i, j = 1, \dots, n$ (appendix 3).

Because rows sum to one, children in schools or neighborhoods with larger diagonal elements (i.e., more of their contacts within schools) have smaller enrollments or are more isolated while ones with smaller diagonal elements (i.e., greater proportions of their contacts between schools) are larger or more highly interconnected.

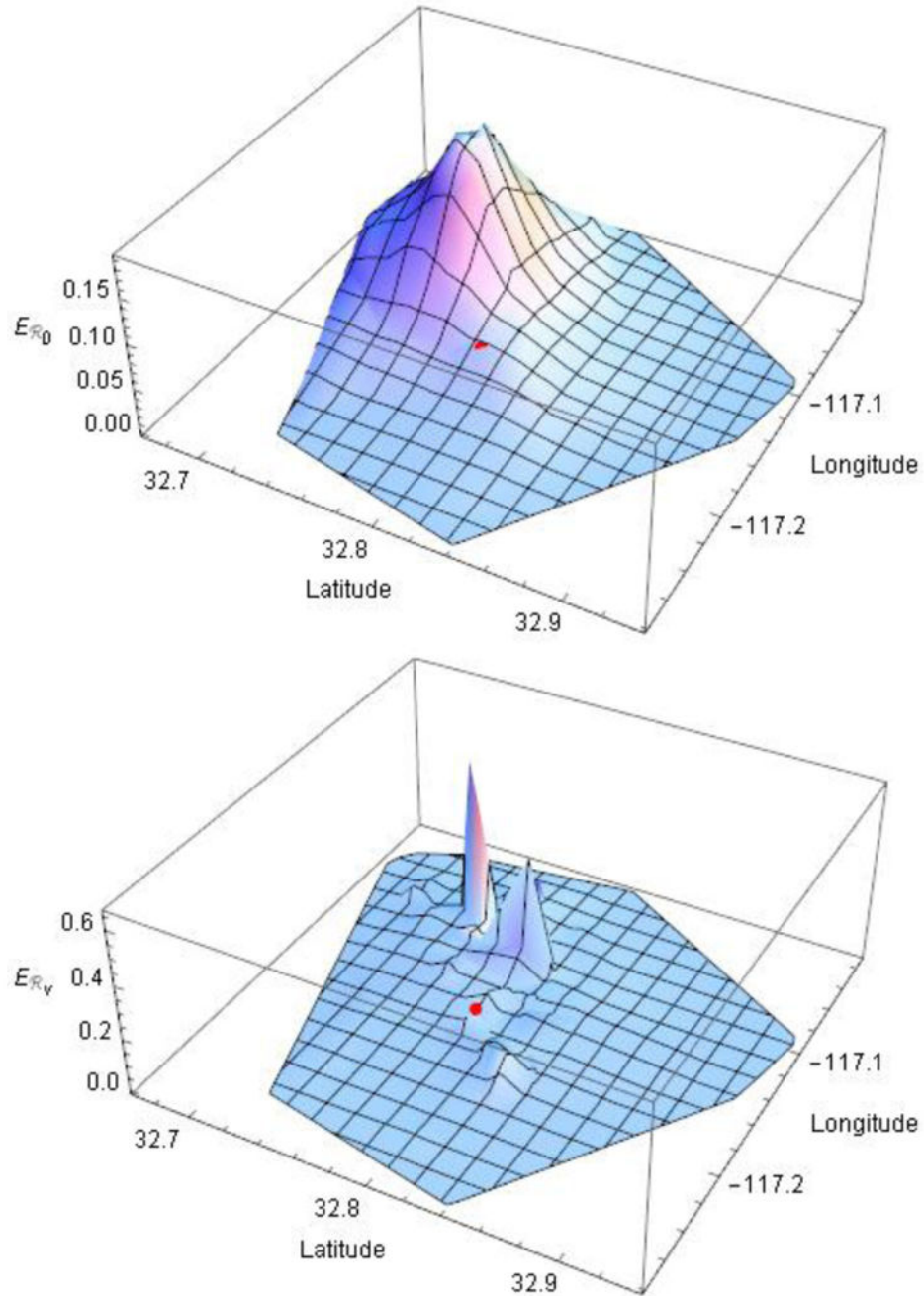


Figure 3.

Spatial distributions of contributions to the basic (above) and realized (below) reproduction numbers, E_{R_0} and E_{R_v} (appendix 2) in San Diego School District.

The red dots locate the school where the 2008 measles outbreak began. The small peak of residual outbreak potential (figure 3b) is attributable to 30% of its children having personal-belief exemptions to vaccination. Comparison of figures S3 and S4 illustrates the impact of vaccinating all such children in San Diego County.

Table 1

Outbreak potentials of measles, mumps and rubella in San Diego County, California, ignoring and accounting for heterogeneity and non-random mixing.

The first four rows show that, ignoring heterogeneity, the San Diego County, California, population immunities – efficacies of 1 and 2 doses of MMR vaccine against measles, mumps, and rubella¹⁵ weighted by the proportions of children with 1 and 2 doses – compare favorably with the naïve population-immunity thresholds (immunities at which average infectious persons would infect exactly one susceptible person) of these three childhood diseases. The last two rows show that, accounting for heterogeneity and non-random mixing, the basic reproduction numbers increase by approximately 70%. As an infinite number of sets of n sub-population immunities would yield any realized number of secondary infections per infectious person,⁷ moreover, we advocate using realized reproduction numbers instead of population-immunity thresholds. Our estimates of the average such numbers for these diseases in this population exceed one, meaning that introduced infectious persons may cause outbreaks.

Characteristic	Measles	Mumps	Rubella
\mathcal{R}_0 ignoring heterogeneity and non-random mixing	10.71	8.49	4.08
Population-immunity threshold	0.91	0.88	0.76
Vaccine efficacy – dose 1	0.92	0.8	0.9
Vaccine efficacy – dose 2	0.95	0.9	0.95
Average population immunity	0.92	0.87	0.92
\mathcal{R}_0 considering heterogeneity in factors affecting \mathcal{R}_{0i} and non-random mixing	18.06	14.33	6.88
\mathcal{R}_v (includes heterogeneity in p_i as well as factors affecting \mathcal{R}_0)	3.39	2.88	1.29

Table 2

Estimated impacts of interventions to reduce the outbreak potential of measles in San Diego County, California, by immunization with the MMR vaccine.

The first row shows the situation when school began in 2008 and subsequent rows show results of plausible interventions, some targeted to schools or neighborhoods whose children affect the reproduction numbers more than others. The first column describes the interventions considered and successive columns indicate a) impact on uptake and the outbreak potential, denoted \mathcal{R}_v , and b) numbers of schools and students affected. To evaluate the impact of vaccinating children with personal-belief exemptions, we assigned each of the 972 such children 1 or 2 doses of MMR in proportion to others in their respective schools. Similarly, we increased uptake in all or only highly active ($a_j = 3$) or connected ($c_{ij} = 0.3$) low immunity ($p_j < 90\%$) schools by 10-50%. In the results columns, hyphens illustrate this range. And finally, we increased private school uptake to the public school average. The impact of vaccinating children with personal-belief exemptions was comparable to increasing immunity in all low-uptake schools by 50%, virtually eliminating measles' outbreak potential.

Intervention	MMR Uptake	\mathcal{R}_v	Schools	Children
Estimated at school entry	97.1	3.39	638	39,132
Eliminate personal-belief exemptions	+2.48	-2.28	292	972
Increase immunity in all low-uptake schools	+0.9-1.6	-0.24-2.37	114	361-638
Only in low-uptake, high-activity schools	+0.4-0.9	-0.24-1.37	65	164-342
In all high-activity schools	+0.9-1.4	-0.26-1.37	385	369-547
Only in low-uptake, highly-connected schools	+0.15-0.31	-7.9E-05	52	60-121
In all highly-connected schools	+0.24-0.4	-0.0006	221	93-155
Increase private school uptake to public school average	+0.4	-0.02	208	145