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Impact of vaccination on the spatial correlation and persistence of measles dynamics

(spatial heterogeneity/disease eradication/critical community size/simulation models)

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ABSTRACT **The onset of measles vaccination in England and Wales in 1968 coincided with a marked drop in the temporal correlation of epidemic patterns between major cities. We analyze a variety of hypotheses for the mechanisms driving this change. Straightforward stochastic models suggest that the interaction between a lowered susceptible population (and hence increased demographic noise) and nonlinear dynamics is sufficient to cause the observed drop in correlation. The decorrelation of epidemics could potentially lessen the chance of global extinction and so inhibit attempts at measles eradication.**

The combination of practical importance and theoretical interest has made measles in urban populations one of the most studied epidemiological systems, but spatial and stochastic effects remain less well explored (1). Practically, the continuing failure of mass vaccination campaigns to eradicate measles in developed countries and the importance of measles mortality among children in developing countries has led to continuing interest. Theoretically, recent work showing that nonlinear dynamics can reduce the extinction rate of spatially subdivided populations (2, 3) may be testable with the body of theory and data gathered to evaluate the persistence of measles and other childhood infections under mass vaccination (4–7).

The basic dynamics of measles epidemics have been extensively studied (8–13). Large measles epidemics exhaust a pool of susceptible children, who gain lifelong immunity after having the disease; the interepidemic period is determined by the severity of the epidemic and the length of time taken to build up the pool of susceptibles again from new births. The seasonal pattern of aggregation of children in schools is also important in determining the size and pattern of epidemics (14–16). Furthermore, seasonality strongly influences the recurrent epidemic behavior of measles, where there is strong evidence for nonlinear (and possibly chaotic) effects (17–23).

In small isolated communities, large epidemics are often followed by extinction of disease as the chain of transmission breaks down (8, 24, 25). The critical community size (8, 24, 26), the threshold population size above which measles can persist through interepidemic troughs, may depend on the spatial structure and connectedness of the regional population. The persistence behavior of measles is of particular interest in connection within the eradication of a disease by mass vaccination. Most theoretical estimates focus on the invasibility threshold, the level of control at which a disease will not only go extinct but also be unable to reinvade the population (13). One can also locally eradicate infection simply by driving it below its persistence threshold, the point at which the disease is likely to go extinct during the troughs between epidemics (27). The persistence threshold is greater than the invasibility threshold and hence easier to reach, but eradication through local extinction is fragile; reintroduction of the disease sparks a new epidemic, which cannot occur below the invasibility threshold.

Persistence is more difficult to analyze than invasibility because invasibility requires only a linear calculation (around the disease-free equilibrium), while persistence demands consideration of the full stochastic system. In addition, local extinctions ("fade-outs") interact with nonlinear dynamics and seasonality to change the dynamical behavior of measles epidemics qualitatively.

The detailed interaction of spatial structure with persistence, nonlinear dynamics, and seasonality is just beginning to receive attention (28–30). Vaccination, and in particular the mass vaccination programs begun in developed countries in the late 1960s, serve as a natural experiment for exploring these topics. At the simplest level, vaccination of young children reduces the recruitment rate of new susceptibles and therefore the reproductive rate of the infection (13). A number of theoretical studies have shown that vaccination should significantly reduce the amplitude of epidemics (and hence disease incidence) as well as changing their phase (4, 13). Various authors have explored the effects of spatial heterogeneity on the necessary effort and optimum strategy for vaccination (31) and the nonlinear interactions of seasonality and vaccination (32). What has not been done, however, is to consider simultaneously the important factors of spatial heterogeneity, nonlinear dynamics, and vaccination along with data from the onset of mass vaccination.

In this paper, we explore the impact of mass measles vaccination on the spatial dynamics of measles. Specifically, we show that the onset of measles vaccination in England and Wales corresponded to a marked reduction in the temporal correlation of epidemics between cities. Explicitly spatial models indicate that this reduction is probably a nonlinear dynamic effect: vaccination eliminated large epidemics, which had acted to correlate measles dynamics in different cities before vaccination. Finally, we demonstrate that this decorrelation of epidemics could inhibit attempts at measles control by lessening the chance of simultaneous extinction of disease in all subpopulations.

DATA SETS AND MODELS

Data Sets. Spatially disaggregated weekly case reports are available in published form for England and Wales for the period 1948–1988, giving 20 years of data before and after the onset of mass vaccination. The analysis is based on data from seven large cities (London, Birmingham, Liverpool, Manchester, Sheffield, Bristol, and Newcastle), with a population size range of ≈300,000 to 10 million (out of a total population of

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Abbreviations: SEIR, susceptible/exposed/infective/recovered; RAS, realistic age-structured.

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50 million), to obtain a preliminary idea of the geographic coherence of measles epidemics in England; since we are interested in patterns of relative incidence through time, incompleteness of case reports is not a significant difficulty. These cities are generally widely separated in space, although Manchester and London are within 50 miles of each other. For comparative purposes, we also analyze the change in correlation on a smaller spatial scale, among the boroughs of London.

Data Analysis. We apply a variety of standard classical and time-series statistics to the data to estimate the geographic coherence of epidemics.

Measuring overall coherence. The primary estimate of coherence is the mean of the correlation [Pearson's r of $\log(1 + n)$; n = number of cases] for all pairwise combinations of cities in the data set. Short-term correlations (4-year blocks) identify rapid changes in the correlation structure but may magnify the effects of transient differences in epidemic cycles, while long-term correlations (20-year blocks) give an accurate measurement of correlation but blur rapid changes in correlation. A good summary statistic for changes in correlation is the size of the drop in mean pairwise correlation between the periods immediately before and after the start of mass vaccination; correlations for 4-, 10-, and 20-year blocks indicate the short-, medium-, and long-term effects on correlation, respectively.

Estimating significance. Correlation between epidemics in different cities could be induced by epidemiological coupling (essentially cross-infection between sites); this is the mechanism we are most interested in. However, there are a number of external influences (notably the common seasonal forcing associated with school terms) that could also tend to synchronize epidemics, independent of epidemiological coupling. We distinguish between these two effects using prewhitening (33, 34), removing all detectable autocorrelation from a multivariate time-series, so that all that remains is a set of series that are individually indistinguishable from white noise (33). If the noise that remains after prewhitening (which corresponds to fluctuations around the baseline epidemic trajectory) is correlated between centers, there is indirect evidence for an epidemic coupling between them; otherwise, the correlation is more likely to be caused by common driving factors. We used a combination of a spline fit (to remove low-frequency and irregular patterns) and an autoregressive model (removing short-term autocorrelation) to whiten the data, testing the residuals to check that they were statistically indistinguishable from white noise (33).

Models. Stochastic simulation models can demonstrate some of the interactions of noise with the nonlinear dynamics of epidemics. These formulations, which we have previously used to explore the dynamics of measles epidemics in England and Wales in the prevaccination period (12, 29, 35), incorporate age structure, simple metapopulation structure, and environmental or demographic stochasticity. The models are extended versions of the standard susceptible/exposed/infective/recovered (SEIR) model, which has been exhaustively analyzed in the mathematical epidemiology literature (10, 11, 13, 36–42). We use a more realistic age-structured (RAS) measles model (12, 16, 35), which takes the basic epidemiological structure of the SEIR model and adds age structure and a more detailed seasonal pattern to it. The RAS model divides the population by its school status (preschool, primary school, adolescent, and adult), with different contact rates between and within groups and during holiday and school periods. Contact is highest in primary school children during school, next highest among primary school children during holidays and preschool children at all times, and progressively lower among adolescents and adults, matching observed patterns of exposure to disease (43). Contact rate among school children follows a binary high/low pattern based on the English school calendar. To incorporate the movement of children through school in annual cohorts, age is recorded in annual blocks rather than continuously. [For more details, see Schenzle (16) or Bolker and Grenfell (29, 35).]

The spatial models we use mimic a population of 1 million individuals, subdivided into 10 identical subpopulations ("cities"). Contact between susceptibles and infectives in different cities occurs at a rate equal to 1% of the within-city contact rate, adding to the infections from within-city contacts. Individuals do not move explicitly, but Sattenspiel and Dietz (44) have shown that individual movement can be expressed in terms of between-city contact rates. We use a between-city contact rate of 1% of within-city contact rate, which is in the center of the range of previous estimates (45) [estimating the actual contact rate from data is a difficult and largely unexplored problem (44), which we will not tackle here]. [Trial simulations with different between-city contact rates gave average correlations before vaccination that were unrealistically low (with a relative cross-contact rate of 0.01%) or high (with a cross-contact of 10%); otherwise, the simulations gave results qualitatively similar to those reported below for a cross-contact rate of 1%.] All age classes mix equally between cities, which is unrealistic, but in the absence of data, we aim for parsimony. As in most stochastic measles models (10, 11), we also allow for a low level of infective immigration from outside the population, at a rate of 20 per million per year; this assumption is again difficult to test against data, but is a "feature" of all stochastic measles models to date (10–12). For very small populations or very high vaccination rates, this assumption could fail badly.

In addition to the heterogeneity in contact structure built into the models, we account for two types of dynamical noise affecting the system. Environmental noise (unpredictable changes in the parameters of the system over time) is simulated by multiplying the contact rate by a normal deviate with a mean of 1 and standard deviation equal to the noise amplitude (usually ≈5–15%; ref. 39). (High-frequency variation in vaccine uptake levels can be incorporated in a similar way.) Demographic noise describes stochastic fluctuations caused by the essentially random and discrete nature of individual infection, recovery, etc.; this stochasticity is generated in our models by a standard Monte Carlo algorithm, picking exponential deviates for the length of time elapsed between epidemiologic or demographic events.

RESULTS

Effects of Vaccination. Before vaccination began in 1968, measles epidemics in cities in England and Wales showed a regular, geographically coherent, biennial pattern (9). The overall pattern of incidence indicates a well-documented and much-analyzed transition from large, regular biennial epidemics before vaccination to much smaller epidemics with a slightly longer and less regular period in the vaccine era. The annually aggregated spatial data (Fig. 1*a*) indicate an equally dramatic differentiation between the pre- and postvaccination series in seven major English cities (London, Birmingham, Liverpool, Manchester, Sheffield, Bristol, and Newcastle). The prevaccination epidemic series are highly correlated between major cities, but the correlation drops markedly after vaccination (Fig. 1*b*). The drop in correlation is visually striking and statistically significant: the mean correlations for all 1-year periods before 1968 are significantly larger than those for all years after 1968 ($P < 0.01$, Mann–Whitney rank-sum test). An equivalent drop in correlation after vaccination is also apparent in the measles data for the United States (46, 47).

Vaccination, Correlation, and Spatial Scale. Fig. 2*c* shows the mean raw correlation for London boroughs for the prevaccine and vaccination eras. In marked contrast to the between-city results, there is no evidence of a drop in correlation. The raw correlation between boroughs (at least within London) stays high after the start of vaccination, whereas the

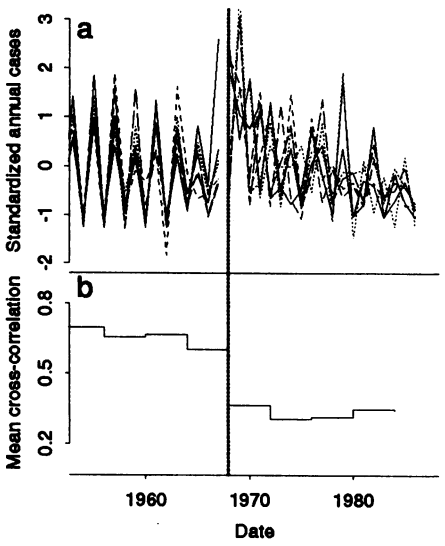

FIG. 1. (*a*) Standardized cases per "epidemiologic year" (September–August) for English cities pre- and postvaccination. Cases are aggregated by epidemiologic year, then standardized by annual mean and standard deviation by city within period (pre- or post-1968). (*b*) Mean pairwise cross-correlation of cities by 4-year blocks.

between-city correlation falls. [Note that this is a preliminary analysis, with no attempt to correct for boundary changes between 1959 and 1970; a more detailed analysis may reach different conclusions (N. Ferguson, personal communication).] As discussed below, contiguous boroughs in a city are likely to be much more epidemiologically coupled than cities separated by countryside (25). This implies that the decorrelating effects of vaccination (seen between cities) may be reduced by strong (within-city) coupling [in simulations run with proportional cross-contact at 10%, there was little difference in the (unrealistically high) average pairwise cross-correlations before and after vaccination].

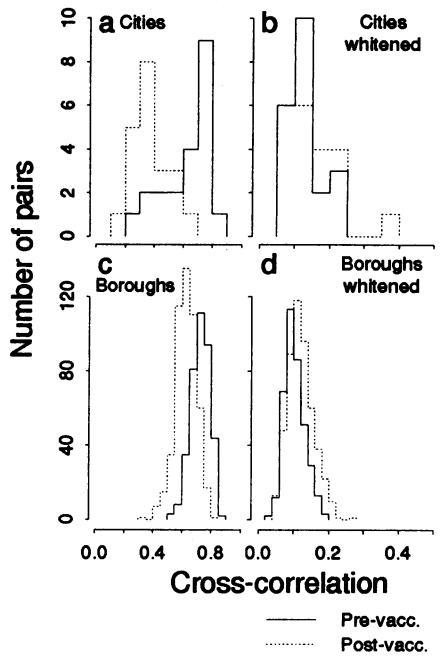

FIG. 2. Distributions of pairwise cross-correlations among the seven English cities and among London boroughs, before and after the start of vaccination (cities, 1948–1968, 1968–1988; boroughs, 1950–1959 and 1970–1979), with (*b* and *d*) and without (*a* and *c*) prewhitening.

Exploring the Drop in Correlation. There are three categories of explanation for the drop in correlation, which we deal with in turn using a combination of time series analysis and epidemiological modeling.

Contingent changes due to intermittency. Both observed and simulated dynamics of measles in developed countries are capable of a variety of cyclical behaviors (48, 49); in particular, dynamics can shift to annual or triennial cycles from the predominant biennial patterns. In terms of models, this intermittency can arise simply out of the intrinsic strong nonlinearity of the system. In patch models, these shifts in dynamics are also associated with changes in the average level of between-city correlation (50); during high-correlation periods, the aggregate population behaves more coherently and has more violent epidemics, deeper troughs, and hence more fade-outs (see Fig. 4). In principle, therefore, the observed drop in correlation could be a result of the intrinsic dynamics and unrelated to the impact of vaccination.

However, there are several strong objections to this purely contingent explanation. First, Cliff *et al.* (46, 47) have observed a similar a drop in correlation between measles epidemics in U.S. cities following mass vaccination. Second, simple probability argues against a coincidental dynamical change unrelated to vaccination. The largest drop in 2-year and 4-year mean cross-correlations coincided exactly with the start of vaccination, which in a time series consisting of 20 2-year blocks, would occur by chance only 5% of the time. Finally, as discussed below, the maintenance of a high correlation between London boroughs during the vaccination era suggests a vaccination-induced decorrelation of the more weakly coupled cities rather than the effect of chance. We therefore do not explore this possibility further.

Extrinsic factors. The observed decorrelation could be caused by coincident changes in population parameters, unrelated to vaccination. The signature of long-term population changes are certainly apparent in the measles record—for example, secular changes in birth rates can produce dynamical effects (3). The most likely parameter to affect correlation would be the coupling, the amount of epidemiological contact between individuals in different cities.

We test for differences in coupling by analyzing the prewhitened data. The prewhitened cross-correlations (see above) among cities in England (and between London boroughs) are smaller than the unwhitened correlations, but still significant (Fig. 2); more importantly, the prewhitened cross-correlations do not drop after vaccination, suggesting that the drop in correlation was not caused by a lessening of contact between cities.

Extrinsic factors seem to be an unlikely explanation on other grounds. Infrastructural improvements in the 1960s would be more likely to increase than to decrease correlation between cities. Also, the increasing average age of infected individuals after the onset of vaccination (13) would tend to increase the mobility of infectives, causing (if anything) greater coupling between cities. Finally, the strong coincidence between the timing of vaccination and the timing of decorrelation, both on the local scale and comparing England and the United States, speak for some role of vaccination.

Decorrelating effects of vaccination. There are two possible dynamical mechanisms for decorrelation: dynamical changes caused by variation in the timing of onset of vaccination or the proportion vaccinated (vaccine uptake) and an interaction between vaccination, demographic stochasticity, and epidemic dynamics.

(*i*) Spatial variations in vaccination. The implications of differences in timing of onset of vaccination have already been explored, in a nonspatial context, in important papers by Aron (32) and Schenzle (16). Aron in particular found that differences of a few months in the timing of onset of vaccination can push the deterministic SEIR model into different dynamical

regimes. Regional differences in the timing of the start of the vaccination program could push initially correlated regions into different dynamical regimes, decorrelating them. However, simulations show that even at extremely low levels of epidemiological coupling the deterministic dynamics in different model regions very quickly become synchronized. For zero coupling, the cross-correlation between two regions with different vaccination timing can decline from ≈1.0 to 0.5 after 70 years of vaccination; for a cross-coupling as small as 0.005, the correlation dips briefly but rapidly returns to nearly 1.0. Adding environmental or demographic noise to the model does not alter this qualitative conclusion; essentially, enough noise to decorrelate the cities after vaccination will also decorrelate them before. These results echo, in the context of vaccination, recent work by Lloyd and May (30), which illustrates the strong synchronizing effects of epidemiological coupling in these models.

(*ii*) Interaction of noise and dynamics. The second possibility is that vaccination reduces correlation by reducing the susceptible population size. Lloyd and May (30) show that in the deterministic, spatially explicit SEIR system, vaccination does not have a strongly decorrelating effect. However (as they observe), vaccination also has strong implications for the stochastic dynamics. Reducing the susceptible population size by vaccination amplifies the effects of demographic noise (4). We therefore explore the interaction of vaccination and demographic noise using spatially explicit age-structured models; in particular, we use a RAS model with a population size of 1 million, divided into 10 cross-coupled patches, as described in *Models*.

The basic result is presented in Fig. 3. Fig. 3*a* shows histograms of the drop in correlation for 4-, 10-, and 20-year blocks for 50 simulations of the age-structured model with vaccination. Vaccination is imposed at realistic levels (but homogeneously in space), based on reconstructions by Schenzle (16) of the actual vaccination coverage in different age classes in the early years of mass vaccination; the average levels start at ≈60% and rise over time. The figure superimposes a point to show the observed drop in correlation in England and Wales. The simulations indicate a significant drop in correlation (Table 1). We tested the changes in simulated mean correlation (ΔC) of 50 model runs between the periods immediately before and after vaccination (Fig. 3*a*) against a null distribution of the changes in correlation in contiguous periods in 2000 years of simulation without vaccination (*cf.* Fig. 4). The distribution of ΔC from the vaccination simulations for 4-, 10-, and 20-year periods before and after vaccination had a significantly smaller median than the null distribution for equivalent periods (Mann–Whitney $P < 0.03$, 0.005, and 0.02, respectively). However, the observed drop in correlation falls within the lower tail of the null distribution (Fig. 3*a* and Table 1); most simulations produce less of a drop in correlation than that observed among English cities.

Table 1. Changes in correlation immediately following vaccination: Observed (English cities), maximum decrease, and median change for 50 simulation runs (no vaccination heterogeneity)

Correlation length, years	Observed	Maximum decrease	Median
4	−0.24	−0.33	−0.05
10	−0.29	−0.34	−0.11
20	−0.22	−0.35	−0.07

Heterogeneity in vaccine uptake. One explanation for this discrepancy between observed and simulated decorrelations is that the level of vaccination is spatially variable. The timing of onset of vaccination (as described above) and/or spatial differences in vaccine uptake could combine with the intrinsic effects of vaccination to decrease correlation further. Heterogeneity in vaccine uptake between cities could take two forms. At one extreme (pure spatial heterogeneity), different cities could have intrinsically different levels of vaccine uptake that are constant through time. At the other extreme (spatiotemporal heterogeneity), independent temporal variation in vaccination uptake could swamp spatial differences. Fig. 3 *b* and *c* show the results of simulations incorporating these two extreme assumptions. We also explored simulations where vaccination was started out of phase in different cities. None of the various extra heterogeneities in vaccination caused qualitative differences in the results.

Analysis of the observed levels of vaccine uptake for England and Wales indicates significant heterogeneities among regions, superimposed on a general (approximately linear) increasing trend in uptake from the early 1970s onwards. Incorporating these extra complexities, as well as variations in the starting time of vaccination, does not alter the conclusions of Fig. 3. We return to discuss the relatively large drop in correlation for the English cities associated with vaccination after exploring the implications of decorrelation for the success of vaccination programs.

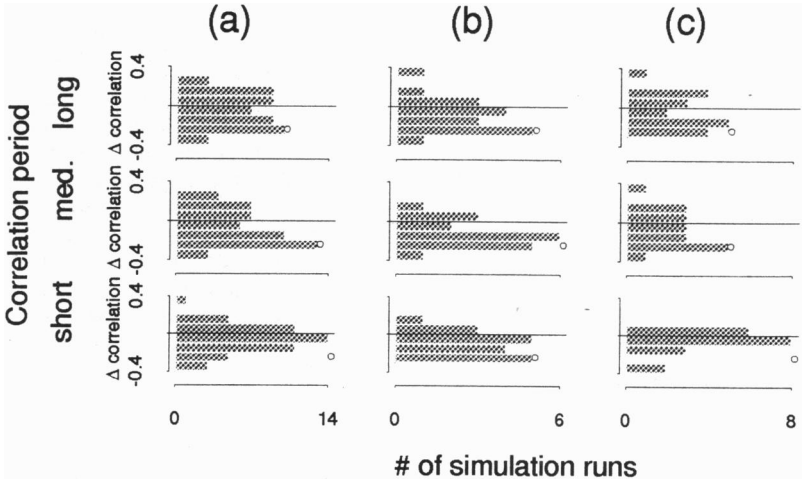

FIG. 3. Histograms of changes in mean pairwise cross-correlation in stochastic simulations of 10 identical cities (total population, 1 million), before and after vaccination for short (4-year), medium (10-year), and long (20-year) correlation blocks. Circles indicate observed drops in correlation among English cities. (*a*) Vaccination applied homogeneously in space and time; (*b*) random spatial heterogeneity in vaccination at the level of different cities; and (*c*) random spatiotemporal heterogeneity in vaccination at the level of one week.

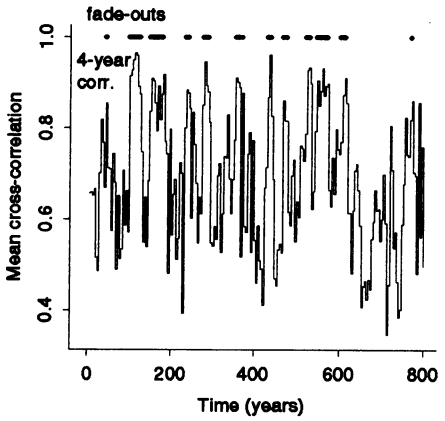

FIG. 4. Correlations and occurrence of fade-out in a metapopulation model. Solid line shows the 4-year mean pairwise cross-correlation for an 800-year simulation run ($n = 10 \times 10^5$, coupling = 0.01). Dots show global fade-outs.

Consequences for the Success of Vaccination. A vaccination-induced drop in correlation may have significant consequences for the spatial dynamics of disease eradication. Decorrelation of population dynamics in different subpopulations favors the survival of a metapopulation (2), and measles metapopulations work the same way (50). Fig. 4 shows that fade-out of disease is associated with periods of high correlation in a stochastic simulation without vaccination.

To illustrate how decorrelation could enhance persistence, we performed a manipulative experiment on the simulation model, artificially shifting the phase of one city in a two-city model and showing that it can prevent fade-out of disease in one particular case (Fig. 5). This is essentially a "rescue effect" (51)—for example, city 2 in Fig. 5 does not fade out at time 4.0

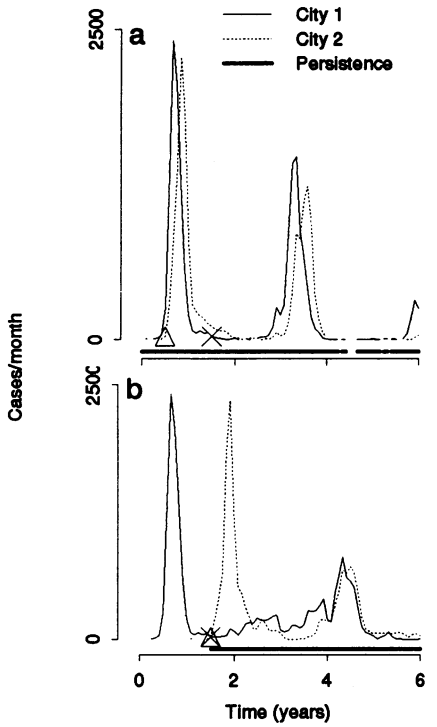

FIG. 5. Simulation of a two-population ($n = 2 \times 400{,}000$) model, baseline (*a*) and with subpopulation 2 phase-shifted by a year (*b*). (*b*) The same simulation, but with initial conditions changed so that the dynamics of population 1 are initially phase-shifted by 1 year. Heavy lines show periods of global persistence.

because of cross-coupling with a relatively large, uncorrelated epidemic in city 1.

This experiment is a preliminary illustration, and much more work is needed to explore the significance of the rescue effect. Nevertheless, it could have significant implications for vaccination strategies. The phenomenon is likely to be most important at intermediate levels of vaccinations since for very high levels of vaccination eradication will be achieved regardless of local epidemic dynamics (13). However, if some or all cities are below the persistence threshold but above the invasibility threshold, we might expect the combination of coupling and decorrelation to have a significant effect; the emergent spatial dynamics mean that the performance of intermediate levels of vaccination could be worse than we would predict from simple theory.

CONCLUSIONS

We have shown that the start of mass vaccination in England and Wales in 1968 coincided with a significant drop in intercity epidemic correlations. This result parallels previous work on vaccination in the United States; however, we also use epidemiological models to seek dynamical explanations for the effect and its implications. Time series analysis and stochastic simulations suggest that this drop is a straightforward dynamical effect of lowered incidence. We further propose that a decrease in correlation may correspond to a decrease in fade-out of disease, making it more difficult to eradicate the disease. However, given the complex nonlinear spatial dynamics of measles, this analysis has also raised a number of issues.

First, why is the observed drop in correlation in England and Wales larger than most of our model predictions? The essential statistical point here is that we currently have only one observed data point, based on our records from seven English cities. Of the 50 replicate simulations of vaccination in a spatially structured population (Fig. 3), 6 (or 13%) showed more decorrelation than the English data; statistically, therefore, we cannot say that the observed point was drawn from a different distribution of drops in correlation. However, this is a weak argument and we are currently amassing other data sets (from the United Kingdom and other countries) to test this effect more carefully.

Another explanation for the discrepancy between observation and models is that the latter omit significant epidemiological detail. In particular, though the RAS model does give an accurate description of pre- and postvaccination measles dynamics for England and Wales as a whole, it omits much spatial and demographic detail. For example, we could include more spatial structure, and in particular hierarchical structure using individual-based models and allowing for the explicit diffusion of infection between cities (25, 52). This more intricate web of spatial relationships might then produce the observed drop in correlation—however, preliminary work along these lines suggests not. We nevertheless hope to pursue this topic further, although the already large parameter space of current models will become even more huge (and difficult to relate to data) as we include more hierarchical spatial structure, family dynamics, etc.

Second, what is the proximate dynamical explanation for the decorrelation observed in models and data? At least part of the explanation for England and Wales as a whole appears to be the elimination by vaccination of large epidemics, which acted to synchronize the depletion of susceptibles and therefore subsequent peaks in infection. The direction of causality is not clear, however, since correlation also produces larger epidemics. Though again we could make more detailed models to understand this process, the key to understanding it probably lies in the analysis of more detailed data sets. Specifically, we need to solve the difficult problem of quantifying levels of

epidemiological coupling between different centers at different spatial scales.

The maintenance of a high correlation between epidemics in the London boroughs after vaccination illustrates the importance of examining the system at several levels (53). Examining correlations at a range of spatial scales, before and after vaccination, could provide a powerful tool for analyzing levels of epidemiological coupling.

The degree of coupling is also central to understanding the possible applied implications of decorrelation. We have shown here for the first time that decorrelation of epidemics probably caused by vaccination could inhibit disease control at intermediate levels of vaccine uptake. Most previous theoretical studies have concentrated—very successfully—on questions of eradication (13, 31); however, the present analysis indicates that we may also need to think about the emergent spatial dynamics consequent upon intervention.

Again, the priority is to examine what the data tell us about the importance of these effects. For example, Fine and Clarkson (5) made the important observation that vaccination in England and Wales did not significantly alter the critical community size of ≈250,000 below which infection disappears in the troughs between epidemics (8, 24). This observation confounds simple theoretical predictions (4) that the critical community size should increase significantly with vaccination. However, the stability of the critical community size after vaccination is consistent with a rescue effect caused by the decorrelation of city epidemics after vaccination. Further work (B.T.G., unpublished data) indicates that the critical community size did not increase even in the late 1980s, when measles incidence was very low, possibly a consequence of decorrelation. Quantifying this effect will (again) require hierarchical spatial data from within cities above and below the critical threshold, to establish on what spatial scale it occurs.

Overall, these results indicate considerable scope for further work on the mass of hierarchical spatial incidence data available for childhood infections (54). Apart from its specific epidemiological application, this work should shed light on the persistence of metapopulations in general.

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