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Spatial dynamics of pertussis in a small region of Senegal

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Extended time-series analysis of infectious diseases raises two issues: the spread of disease, and its persistence in space and time. Most studies are based on both data and models, corresponding to conditions encountered in developed countries. The present work sought to determine the impact of local heterogeneity on these two issues, regarding pertussis in tropical conditions. First, we tested the 'cities and villages' model in a small community of 30 villages in rural Senegal. Second, we focused on the impact of population size and density, as well as geographic distance, on population dynamics of pertussis. Results showed that pertussis initially arrived in urban centres, and then spread to surrounding areas. Both population size and density are implicated in the persistence of pertussis within the study area, whereas geographical distance between villages is not. This is the first study on pertussis in a developing country carried out on a very fine spatial scale. Furthermore, it confirms previous results for measles in England and Wales.

Keywords: pertussis; Senegal; population dynamics; 'cities and villages' model; persistence; cross-correlations

1. INTRODUCTION

Extended time-series analysis of infectious diseases, mainly in developed countries, and in association with the concomitant development of mathematical models, may be important for increasing our understanding of the dynamics of infection and its persistence in space and time (Bolker & Grenfell 1996; Grenfell & Harwood 1997; Keeling & Grenfell 1997, 1998; Grenfell *et al.* 2001). Such analyses may provide new tools for studying the impact of vaccination over a long time period (Rhodes & Anderson 1997; Rohani *et al.* 2000), thus enabling the development of appropriate vaccination strategies. Ecologically, many investigations have clearly demonstrated that the persistence of most free-living organisms is impossible in homogeneous habitats, but is maintained in complex structures forming distinct patches linked by dispersal (Hanski & Gilpin 1997; Tilman & Kareiva 1997).

In epidemiology, the effect of population size on both persistence and spread of infectious diseases is particularly important (Anderson & May 1991; Grenfell & Harwood 1997; Rohani *et al.* 2000; Grenfell *et al.* 2001). A good example of the effect of population size on disease persistence is the critical community size (CCS) concept, largely developed by both model and data analysis (Bartlett 1960; Black 1966; Grenfell & Harwood 1997; Anderson & May 1991). This concept defines the population size threshold below which disease cannot persist without external inputs.

Another important achievement in the metapopulation dynamics of infectious diseases is the 'cities and villages' model, developed by Anderson & May (1991). It was later confirmed by empirical studies of measles in the British Isles (Grenfell & Bolker 1998; Grenfell *et al.* 2001) and the United States (Cliff *et al.* 1992, 1993), which showed that infection diffuses progressively from urban centres to the surrounding rural areas. Unfortunately, very few studies have addressed the spatial dynamics of disease, mainly because of lack of reliable space and time data, especially for developing countries. The 'cities and villages' model has been proven to be correct on a large (Grenfell & Bolker 1998) and a regional (Cliff *et al.* 1993) scale, but more detailed, spatially explicit analyses of local diffusion of epidemics are clearly needed.

The purpose of the present work was: (i) to extend empirical studies by providing a new example of urban–rural hierarchy in a different childhood disease metapopulation based on a uniquely detailed spatio-temporal data set for whooping cough in rural Senegal; (ii) to introduce and develop the idea that the 'cities and villages' model may also be relevant on a finer spatial scale, i.e. in a county of 220 km^2, comprising 30 villages; and (iii) to show how analysis of empirical patterns could be extended to a wide range of local conditions to better explore the stochastic properties of the metapopulation dynamics of disease.

2. METHODS

(a) *Data and population*

The data used were taken from weekly pertussis notifications and demographic information in Niakhar, a rural area of western Senegal. The area, located 150 km to the east of Dakar, is a dry Sahelo-Sudanian savannah. The population, principally belonging to the Serer tribe, consists of *ca.* 30 000 inhabitants grouped into 30 distinct villages. Cases of whooping cough have been registered since 1983. Definitions of cases and survey methods have been described previously by Préziosi *et al.* (2002). Vaccination campaigns started at the end of 1986, but pertussis

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remains endemic, with epidemic outbreaks occurring every 3–4 years (Broutin *et al.* submitted).

(b) *Spatial spread of pertussis in the Niakhar region*

Our work is based on the case study of Grenfell & Bolker (1998), who used measles data from 845 cities and towns, and 457 rural districts, in the pre-vaccine era, and then selected the 60 largest cities and towns for the urban aggregate. Population sizes within the Niakhar region ranged from 50 to 3000 inhabitants, which makes the urban–rural division very vague. We defined the urban aggregate by the two largest villages, in terms of population size: Toukar (2815 inhabitants) and Diohine (2697 inhabitants), which are located in the centre of the Niakhar region. The rural aggregate comprised the remaining 28 villages. The two largest villages actually correspond to the most 'urbanised' villages, since they have markets, health care centres and bus stations, which are absent in the 28 other villages.

As an initial step, we determined the dates of the first cases of the year for each locality (in week rank, i.e. in number of weeks since the beginning of the year), and for each year. Means were then calculated for the urban aggregate (i.e. Toukar and Diohine), and for the rural aggregate (i.e. the remaining 28 villages), for both endemic and epidemic years between 1986 and 2000. An epidemic year is defined as a year with at least 500 cases. We repeated this count for dates of the maximum number of cases. Means were compared by the non-parametric Kruskall–Wallis test (Zar 1996).

Next, we calculated Pearson correlation coefficients between the total rural time series and the proportion of cases in each of the 30 villages (i.e. number of cases in a village i / total number of cases). This correlation was then plotted against population sizes, for the period between 1987 and 1997. We corrected for multiple tests (30 tests) using Bonferroni correction (critical $\alpha = 0.0017$), as described in Grenfell & Bolker (1998). They indicated that a strong negative urban–rural correlation might suggest that disease cases arise in towns before the spread of rural epidemics. Our investigation analysed time-series data for both rural and urban aggregates. Periodicity and synchrony between the urban and rural series were investigated through auto- and cross-correlations (Box *et al.* 1994).

Finally, we computed auto- and cross-correlations between urban and two rural rings around both Toukar and Diohine after vaccination (1987–1997). The first ring represented villages that share limits with at least one of the two largest villages; the second ring grouped the remaining villages. We also suggest differences between the spatial dynamics in the pre-vaccine era (1983–1986) and that observed during post-vaccination. During the post-vaccination period, the data collection process changed in 1998, 1999 and 2000. Consequently, most cases were recorded up to the month, so the data could not be used in the weekly analyses.

(c) *Regional metapopulation dynamics and spatial disease persistence*

The existence of an urban–rural infection hierarchy in whooping cough epidemics in the Niakhar region clearly raises the question of a higher likelihood of disease persistence in large communities and, conversely, its extinction in small rural villages. We previously explored this question by calculating the relationships between the number of fadeouts and the total time of fadeouts (in weeks), and the population size across the 30 villages (Broutin *et al.* 2004). A fadeout (extinction) corresponds to a period of at least 3 weeks without a case in a locality. Detailed calculations and results are described in Broutin *et al.* (2004). To relate the mean total fadeout duration in weeks to both human patch size and density, and their two-way interaction term, Broutin *et al.* (2004) employed a generalized linear model, the GLIM (Venables & Ripley 1999) from the *S-Plus* statistical package. It also incorporated a Poisson error structure and a log link function (Wilson & Grenfell 1997; Wilson *et al.* 1996), which was the most appropriate statistical tool for analysing the data.

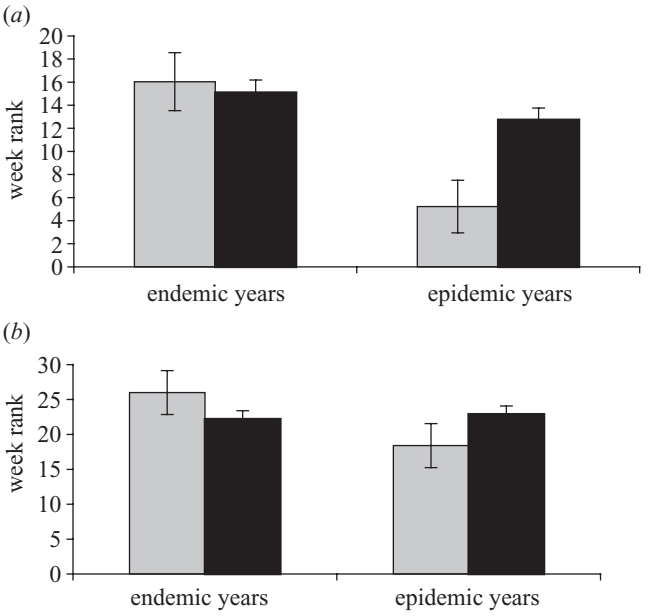

Figure 1. (*a*) Week rank means of first cases of pertussis during the year in urban (grey) and rural (black) aggregates. (*b*) Week rank means of maximum cases during the year for urban (grey) and rural (black) aggregates. Years are aggregated according to their epidemic versus endemic status: endemic for 1987–1989, 1991, 1992, 1994–1996, 1998, 1999; epidemic for 1986, 1990, 1993, 1997, 2000.

Demographic data were extracted from the Institute of Research for Development census in Senegal (see http://www.ird.sn/activites/niakhar/tabl2bord/index.htm). We used average values of population size and density for the 30 villages, with the means calculated for yearly data from 1983 to 2002. To test the potential effect of geographical distance on the duration of fadeouts across the different villages, we then employed the procedure of Poulin & Morand (1999). We also used the method of Legendre *et al.* (1994), based on the permutation of distance matrices, to perform multivariate analysis of the determinants of mean total fadeout duration, with a basic expectation that two neighbouring villages would show similarities in patterns of fadeout duration. These computations were performed using the program PERMUTE 3.4 (designed by P. Casgrain, and available on the internet at http://alize.ere.umontreal.ca/~casgrain/).

3. RESULTS

(a) *Urban–rural pattern of pertussis transmission*

Results of week rank means of first case and maximum number of cases in the year are illustrated in figure 1. Dates of first cases in the rural aggregate during endemic years, epidemic years, and for the urban aggregate during both endemic and epidemic years were 15.9 (standard error of the mean, s.e. = 1.10), 12.7 (s.e. = 1.02), 16.0 (s.e. = 2.51) and 5.2 (s.e. = 2.28), respectively (figure 1*a*). The rural aggregate showed similar dates of first cases during endemic and epidemic years ($H = 2.8123$, d.f. = 1, $p = 0.094$), whereas first cases arrived sooner in the two

urban centres during epidemic years than during endemic years ($H = 6.6478$, d.f. $= 1$, $p = 0.010$). Moreover, dates of first cases were not significantly different between rural and urban aggregates during endemic years ($H = 0.0313$, d.f. $= 1$, $p = 0.859$). By contrast, during epidemic years, urban and rural aggregates showed significantly different means ($H = 6.4888$, d.f. $= 1$, $p = 0.011$), revealing that cases arrived first in the two urban centres. Week rank means of a maximum number of cases in the rural aggregate during endemic years and during epidemic years, and for the urban aggregate during both endemic and epidemic years, were 22.3 (s.e. = 1.19), 22.9 (s.e. = 1.18), 26 (s.e. = 3.15) and 18.4 (s.e. = 3), respectively (figure 1*b*). In contrast to results of first cases, all rank means were homogenous, i.e. for rural aggregate between endemic and epidemic years ($H = 0.2309$, d.f. $= 1$, $p = 0.631$), for urban centres between endemic and epidemic years ($H = 1.6896$, d.f. $= 1$, $p = 0.194$), during endemic years between urban and rural aggregates ($H = 1.1142$, d.f. $= 1$, $p = 0.291$), and during epidemic years between urban and rural aggregates ($H = 0.8098$, d.f. $= 1$, $p = 0.368$).

Figure 2 illustrates the results of correlations between the total rural time series and the proportion of cases in each of the 30 villages (i.e. number of cases in village *i* / total number of cases) against population size (square root transformed) for the post-vaccination period. Briefly, the largest town, Toukar, had a strong negative urban–rural correlation, indicative of a rise in pertussis cases in this particular 'city' before the start of the rural epidemic. The proportion of pertussis cases in small villages exhibited a correlation near zero, with the rural epidemic indicative of irregular disease dynamics, possibly owing to the small population. For a medium population community, the urban–rural correlations reached a maximum positive correlation. This pattern was also confirmed by cross-correlation between rural and urban cases (figure 3). In Niakhar, auto-correlations (top left and bottom right) clearly showed the familiar 3–3.5-year cycle of pertussis after vaccination (Broutin *et al.* submitted) for both time series; cross-correlations (top right and bottom left) revealed a *ca.* 10-week lag between rural and urban cases. All these analyses suggested spatial diffusion of disease from the two largest towns to the rural surrounding aggregates. We then decided to divide rural aggregate into two rings. The first ring, i.e. a group of villages sharing limits with at least one of the two 'cities', constituted 12 villages; the last 16 villages formed the second ring (figure 4*a*). Cross- correlations between the two rings, and urban aggregate, both showed lags, in that urban cases arrived about 5–9 weeks before cases in the first rural zone (figure 4*b*), whereas in the second rural zone they appeared 4–16 weeks after the first cases in the two urban centres (figure 4*c*).

(b) *Pre-vaccination era*

Before vaccination (figure 5*a*), no correlation between the total rural aggregate and the proportion of cases in each village (number of cases in locality *i* / total number of cases) was significant after the Bonferroni correction (figure 5*b*). This contrasts strongly with the post-vaccine period, when several localities revealed significant correlations with the rural aggregate (figure 2). All correlations in the pre-vaccination era were close to zero. Auto-correlations (figure 5*c*, top left and bottom right) showed the familiar annual periodicity of pertussis cases (Broutin *et al.*

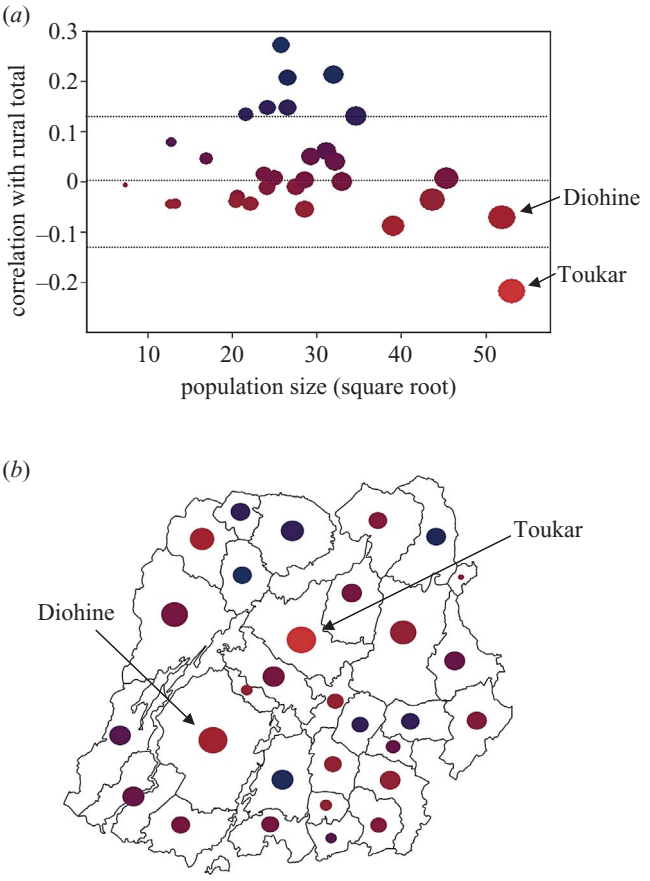

Figure 2. Illustration of the spatial patterns of urban and rural pertussis cases, using calculations of Grenfell & Bolker (1998). (*a*) Correlations between total rural and proportional cases for each urban location (cases in location *i* / total urban and rural cases) are plotted against population size (square root transformed). The population size is coded by symbols of proportional size, and the correlation in disease spatial synchronization is colour coded (red, minimum; blue, maximum). Black dashed lines indicate 95% confidence interval for no zero correlation after Bonferroni correction. (*b*)Same results plotted on a map of the Niakhar region.

submitted) for both rural and urban time series, with a peak correlation at weeks 50–52. Cross-correlations (figure 5*b*, right top) showed a peak correlation at zero lag, which expressed the global synchrony between rural and urban time series before vaccination, in contrast with the post-vaccine period, when a lag of 10–15 weeks was observed between rural and urban cases. Results obtained from pre-vaccine period data (figure 5*b*,*c*) showed a different spread pattern for pertussis in the zone compared with the vaccine era (figures 2 and 3), where an overall pattern of diffusion from a source to the surroundings was clearly sustained. We cannot, however, ignore the effect of short-term series (4 years only) on statistics for the pre-vaccine study.

(c) *Effects of regional metapopulation dynamics and local population density on disease persistence*

Results of fadeout structure paralleled the decline in the number of fadeouts, with community size indicating that small villages experienced rare but durable extinctions, and larger villages experienced numerous short extinctions (Broutin *et al.* 2004). Using GLIM, our results implied an

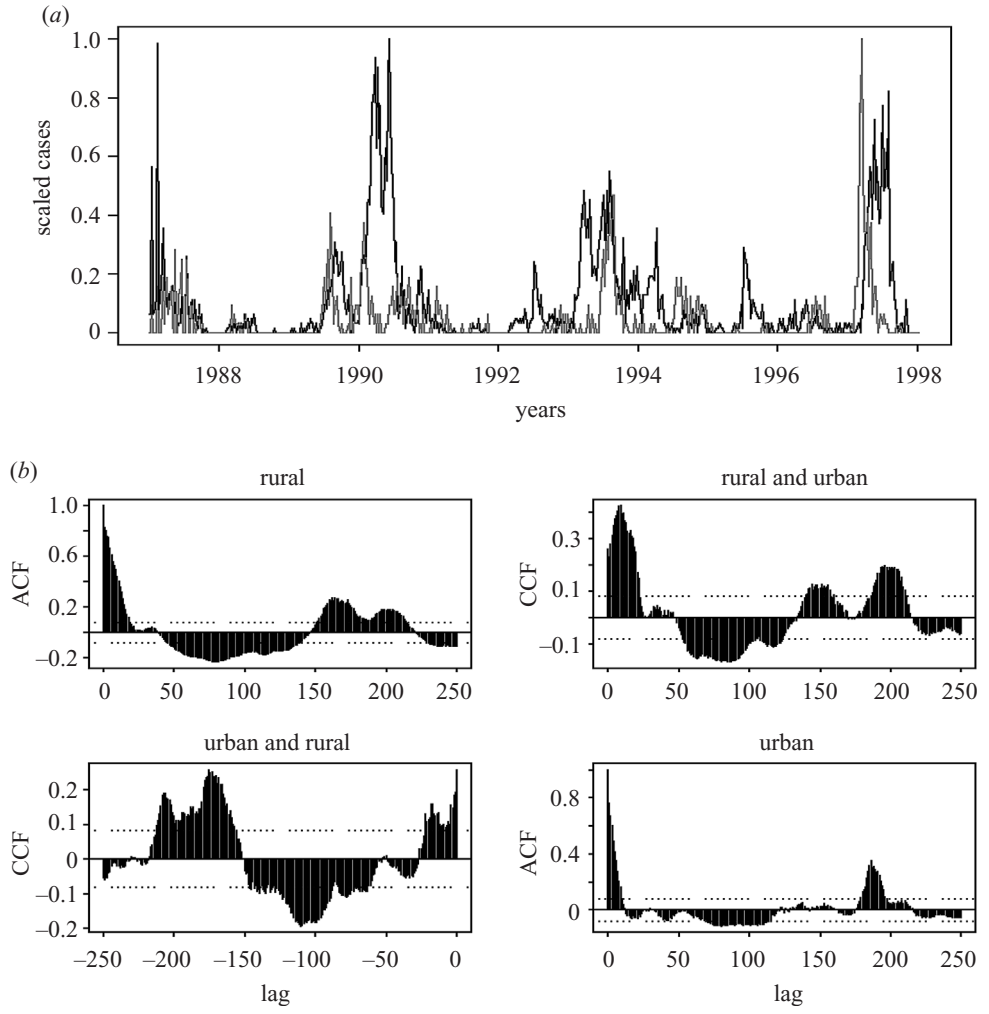

Figure 3. (*a*) Rural (black) and urban (grey) weekly time series between 1987 and 1997 (post-vaccine era only) in the Niakhar region. (*b*) Auto- and cross-correlations factor (ACF and CCF, respectively) for the same time series. The top left and bottom right graphs illustrate auto-correlation patterns at a weekly lag for rural and urban cases, respectively. The off-diagonal graphs show cross-correlation between the two specified time series. The top right shows positive weekly lags (leads) for urban cases; the bottom left, negative weekly lags. Dashed lines indicate 95% approximate confidence intervals for no correlation.

independent, but complementary, effect of population density on the persistence of pertussis across patches; when controlling for the effect of population size, the total period of disease extinction clearly declined with population density (table 1*a*). This result suggests that the spatial pattern of the pertussis infection rate depended on both regional metapopulation dynamics, i.e. source of infection and diffusion, and on the local population density across the different villages. Also, when the importance of geographical distance between villages, as a potential predictor of disease dynamics behaviour, i.e. similarity in mean duration of fadeouts between two neighbouring villages, is taken into account, our analysis showed that geographical distance between villages in the Niakhar region was not retained as a predictor of mean duration of fadeouts (table 1*b*). Again, this result suggests that no statistical pattern can be detected when comparing time series in small patches experiencing stochastic events.

4. DISCUSSION

During epidemic years, the first cases of pertussis arrived in urban centres sooner than in the rural aggregate (in week 5.2 in urban centres, against week 12.7 in rural aggregate). Moreover, first cases arrived in urban centres earlier during epidemic years than during endemic years. By contrast, first cases were reasonably synchronous in rural and urban aggregates during endemic years. This pattern is of interest, since epidemic years could be 'recognized' by the fact that the first cases emerge in urban centres earlier than expected (i.e. sooner than during endemic years). We observed a strong negative correlation for the largest village, Toukar; the second largest village, Diohine, showed an urban–rural correlation near zero. There are two non-exclusive explanations for this situation. First, Diohine has a lower population density than Toukar, and, thus, the likelihood of disease transmission may be lower, producing many more local fadeouts than expected on the basis of its community size. Second, the use of the Bonferroni multiple test correction (which is considered a

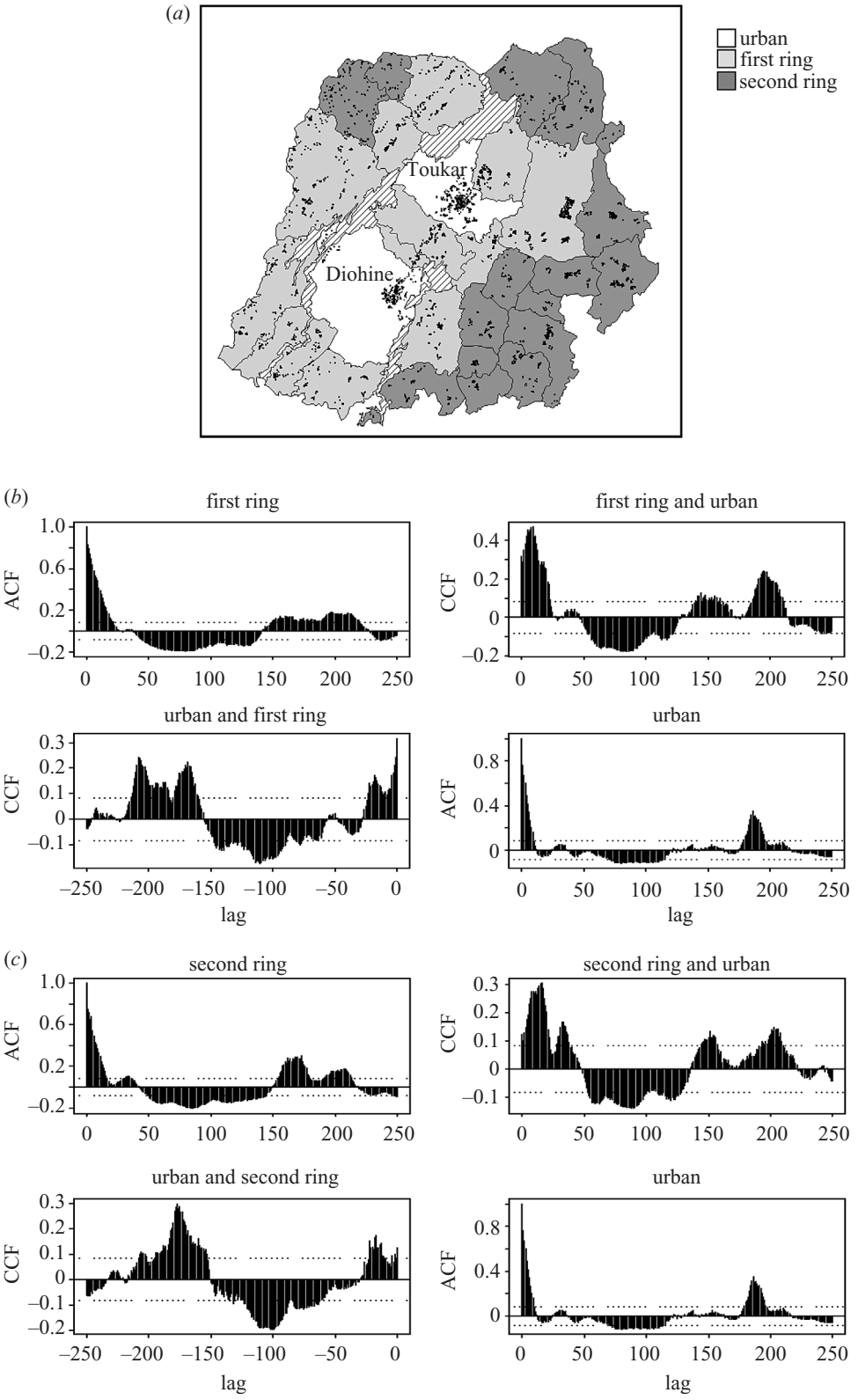

Figure 4. (*a*) Spatial distribution for urban centres, and first and second rural rings. The first ring (light grey) groups 12 villages; the second ring (dark grey) groups 16 villages. Urban centres are represented in white. Hatching shows marsh areas during the rainy season. (*b*) Auto- and cross-correlations between urban and the first ring. (*c*) Auto- and cross-correlations between urban centres and the second ring, as described in figure 3*b*.

very conservative procedure) in the urban–rural hierarchy study may lead to the conclusion of an absence of correlation when false. Unfortunately, our study involved a small number of villages (30), compared with the study of Grenfell & Bolker (1998) (1302 cities, towns and rural districts), thus rendering any statistical test highly sensitive to a low power.

Classical time-series analysis of whooping cough cases in Niakhar clearly illustrated a lag between rural and urban cases. We also showed diffusion from the two largest cities,

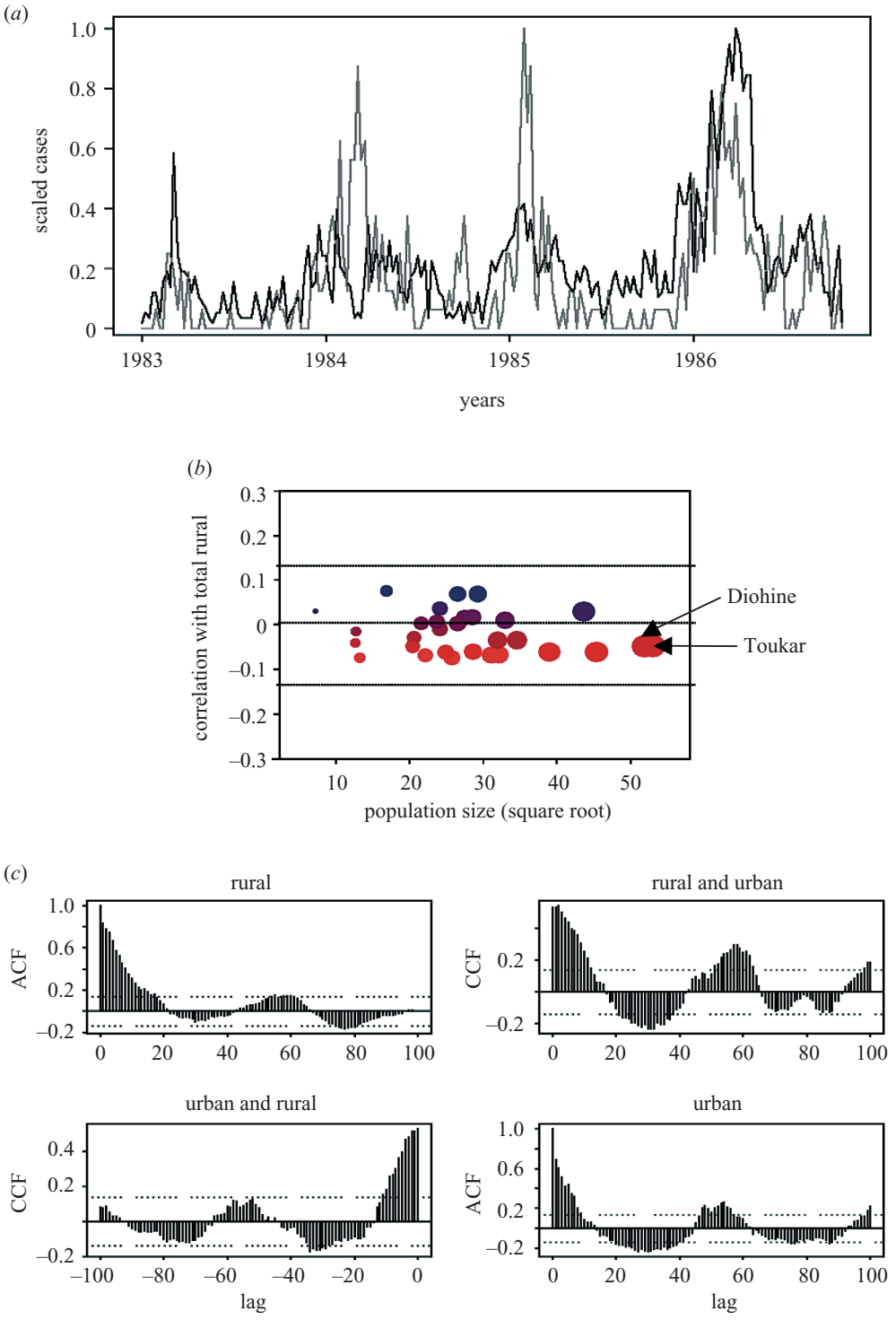

Figure 5. (*a*) Time series of urban (grey) and rural (black) cases of pertussis in the Niakhar region during pre-vaccination period (1983–1986). (*b*) Correlations between rural aggregate and case proportions in each location, as described in figure 2, during the same pre-vaccine period 1983–1986. (*c*) Auto- and cross-correlations of time series in (*a*), as described in figure 3*b*, from 1983 to 1986.

Toukar and Diohine, to rural villages, with a spread across two 'rings'. Urban centres report pertussis cases earlier in the year than other villages. All the data seem to show the existence of an urban–rural hierarchy in Niakhar pertussis epidemics, with a lag of *ca.* 10–15 weeks between urban and rural epidemics after vaccination, conforming with the 'cities and villages' model. Moreover, we have shown in previous work (Broutin *et al.* 2004) that whooping cough cannot persist in the area without external input of new cases. To this mechanism, we can now add the new fact that, in all probability, cases from outside the zone arrive principally in the two largest villages, Toukar and Diohine, before spreading to surrounding areas. This pattern of urban–rural hierarchy represents a global mechanism explaining disease spread in the studied area, but, clearly, does not exclude the possibility of external pertussis arriving in small villages surrounding the zone. The latter scenario, however, represents an 'invasion' without consequences for the global pattern illustrated in this work. The conclusions of our study on whooping cough spatial

Table 1. Summary of generalized linear models for the mean duration of fadeouts in human patches across 30 villages in the Niakhar region of Senegal. (*a*) Effect of density, population size and their two-way interaction term. (*b*) Effect of density, population size and geographical distance between villages, as described in Legendre *et al.* (1994).
(Population size is square-root transformed. d.f. is the residual degree of freedom in analysis. For model (*a*), the dispersion parameter is $\phi = 2.18$.)

(*a*)	d.f.	residual deviance	$Pr(\chi^2)$
null	29	459.60	—
density	28	265.58	< 0.0001
population size	27	67.25	< 0.0001
density × population size	26	56.62	0.0011

(*b*)	slope coefficient	d.f.	$Pr(F)$
population size	0.301 996 11	1999	0.001
density	0.095 497 65	1898	0.025
distance	−0.021 827 40	704	0.311

dynamics on a small spatial scale are similar to those of Grenfell & Bolker (1998) for measles dynamics in England and Wales, and conform to the 'cities and villages' model, even on such a small scale. Childhood disease diffuses from the largest, high-density communities to small, low-density rural villages. Our model also shows that two 'cities' of the same population, but with different population densities, have distinct tendencies for local persistence of infection. A comparison of empirical patterns shows significantly lower total duration of local extinction of disease in cities with higher population density. This implies that the spatial pattern of infection rate in whooping cough strongly depends on contact, which occurs more frequently in dense populations.

We computed auto- and cross-correlations between rural and urban aggregates before vaccination, and we also calculated correlations between the rural aggregate and each village. The results show a pattern that differs from that of the vaccination era. Indeed, it seems there is no urban–rural hierarchy for pertussis dynamics, since no time lag between rural and urban time series was observed, and correlations between each village were all near zero, even for the two largest villages. Owing to the very short time series for the pre-vaccination era, however, it is difficult to determine the exact causes of the observed pattern.

In conclusion, this fine-scale analysis of whooping cough, i.e. in an administrative African county of *ca.* 200 km^2, illustrates remarkably well both the regional metapopulation dynamics of transmission and the effect of spatial stochasticity. This is of potential interest since it provides new research perspectives for coupling epidemiology, metapopulation dynamics and population genetics to better understand disease persistence and control. This approach requires further studies, since it could be useful in adapting, or adopting, vaccination strategies. If spread of disease from urban centres to rural areas is generalized, then the mechanism could imply new vaccinations strategies, i.e. less widespread but more precise programmes, which would be more realistic in the field, particularly in developing countries. This new research should lead to better control of disease by vaccination.

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