

Whooping cough metapopulation dynamics in tropical conditions: disease persistence and impact of vaccination

Hélène Broutin^{1,2*}, François Simondon¹ and Jean-François Guégan²

¹Unité de Recherche 024, *Epidémiologie and Prévention*, and ²GEMI (ex-CEPM)-UMR 2724 IRD/CNRS, *Equipe 'Evolution des Systèmes Symbiotiques'*, Institut de Recherche pour le Développement, 911 Avenue Agropolis, BP 64501, 34394 Montpellier cedex 5, France
* Author for correspondence (broutin@mpl.ird.fr).

Recd 08.12.03; Acctpd 21.01.04; Published online

Recent insights in compiling metapopulation models and infectious disease dynamics have enabled a better understanding of spatial and temporal persistence of diseases. The concept of the critical community size (CCS) has been developed with major consideration on analyses of whooping cough and measles dynamics from temperate countries for which large datasets are available. However, few studies have questioned the generality of CCS curves for other regions, i.e. tropical areas, mainly because data are very sparse. This work constitutes, to our knowledge, the first study of whooping cough persistence in a tropical area, in a rural part of Senegal (Western Africa) where the population has been followed for 20 years. In this small community, the CCS is not reached even if we observe CCS-like curves showing persistence increasing with population size. In addition, our analysis supports the idea that vaccination has impacted the spatio-temporal dynamics and persistence of the disease. These findings suggest the need for more comparative analyses of spatio-temporal data series from a wide range of contrasted countries, for example developed and developing nations, so as to have a better understanding of vaccination effects on disease dynamics and persistence.

Keywords: critical community size; whooping cough; metapopulation; persistence; Senegal; vaccination

1. INTRODUCTION

Many recent advances in metapopulation dynamics theory of infectious diseases (Ferguson *et al.* 1996; Grenfell & Bolker 1998; Rohani *et al.* 1999; Keeling & Gilligan 2000; Grenfell *et al.* 2001; Fulford *et al.* 2002; Keeling & Grenfell 2002) have led to the finding that many infectious diseases are facing local fade-outs but global persistence at the between-city level (Grenfell & Harwood 1997; Keeling & Grenfell 1997). Analyses of extensive time-series datasets for measles and whooping cough in both England and Wales have greatly contributed to a better understanding of disease population dynamics in space and time with an important result: the concept of the

critical community size (CCS). CCS is the minimal population size below which a disease is unable to maintain itself without external input. Some studies have shown that large cities in Britain (Bartlett 1957; Grenfell & Harwood 1997; Keeling & Grenfell 1997) and America (Bartlett 1960) harbour enough individuals (*ca.* 250 000–400 000 people) to allow the persistence of the disease. In addition, the CCS concept has also been applied for isolated populations on islands (Black 1966; Cooper & Fitch 1983), and this similarity could be easily attributed to the simple fact that small isolated insular communities that are spatially connected to a continent correspond to a mainland–island metapopulation model (Hanski & Gilpin 1997). However, Holmes (1997) questioned the veracity of the threshold community size in a spatial context of local transmission, and she demonstrated, using analyses of cellular automata models, that there exists a threshold neighbourhood size below which the disease dies out. This finding indicated that it was more difficult for a given disease to maintain itself when considering the local nature of contact neighbourhoods instead of assuming that the pattern of spread was long-distance transmission. Indeed, for many host–parasite systems (Anderson & May 1991; Grenfell & Dobson 1995), disease spread is a combination of local transmission and of larger scale colonization.

Most studies analysing the patterns of regional persistence of disease do so by looking at high frequencies of local extinction at a between-city level within an entire country, or focus on a group of large regions such as Wales and England, for instance. No study, to our knowledge, has attempted to examine the existence of this pattern at a smaller spatial scale, e.g. a county within a network of villages connected to each other and to a main city. One important question is whether disease dynamics at the local population level do necessarily correspond to dynamics at a larger scale. For instance, erratic local epidemics have been used to explain irregular epidemics of measles in small communities (Bartlett 1957). In addition, to our knowledge, no study of the spatio-temporal dynamics of disease in tropical areas has been done in a way that would favour the comparison of patterns, permitting a better comprehension of disease dynamics across different conditions. As recently pointed out by Bjørnstad *et al.* (2002), one important challenge today is to obtain reliable data not only for large or dense populations but also on small or sparse populations. These kind of data are dramatically lacking in the epidemiological literature. We model disease spatial behaviour in the human communities of developed countries as being representative of many other parts of the world but lack data on disease in tropical areas, in which a very large proportion of the human population lives today. Thus, a key question in our attempt to understand disease dynamics is to what extent we are quantitatively in error in our understanding of disease dynamics as a result of this discrepancy?

In this paper, we focus on a microparasitic bacteria infection, i.e. whooping cough, in a rural county of Senegal called Niakhar, for which the long-term database (1983–2000) in a small human community enables us to explore microparasite dynamics. Here, we test the hypothesis of a regional persistence of whooping cough in-between villages of the Niakhar area in a way similar to that proposed by Grenfell & Harwood (1997) and Rohani *et al.* (1999, 2000).

2. MATERIAL AND METHODS

(a) *The disease*

Whooping cough is a respiratory disease caused by a Gram negative bacteria, *Bordetella pertussis*, which exclusively infects its human host, principally children. Other *Bordetella* species that usually infect animals, e.g. *B. bronchiseptica* and *B. parapertussis*, are also associated with some human infections inducing whooping cough-like syndromes (Yih *et al.* 1999; Mazengia *et al.* 2000). *Bordetella pertussis* is a classical microparasite multiplying within human individuals with highly infectious aerosol transmission. The latent period of the disease is *ca.* 8 days, followed by an infectious period that can last between 14 and 21 days. When infected, recovery is within one to two months, and since the beginning of mass vaccination programmes more than 50 years ago in developed countries, death rarely results. However, in many parts of the world whooping cough remains an endemic disease with epidemic outbreaks every 3 to 5 years (Crowcroft & Britto 2002).

(b) *The area and data*

The rural area of Niakhar (*ca.* 220 km²) is located *ca.* 150 km east of Dakar, Senegal. The study area is dry sahelo-sudanian, savannah landscape. The area consists of 30 villages with a population size ranging from 50 to 3000 inhabitants. Each village is divided into hamlets, themselves composed of 'compounds'. The compound, representing the smallest structure of the zone, corresponds to a group of houses where extended families live in one or several households. Vaccination campaigns started at the end of 1986. Despite vaccination, whooping cough remains endemic with epidemic outbreaks occurring every 3 to 4 years. Cases of whooping cough have been registered since 1983 in the 30 villages forming the surveyed area. Definitions of cases and methods used to collect information were previously described by Préziosi *et al.* (2002).

(c) *Statistical and mathematical methods*

For each village, we first calculated the total number of inhabitants per month within the period of study. Second, we determined the mean number of inhabitants per village for two periods: the pre-vaccine era (from 1983 to 1986, inclusive) and the post-vaccine era (from 1987 to 2000). Third, the weekly records of whooping cough for each village were compiled, and we calculated for both periods (i) the mean number of fade-outs per village; and (ii) the mean duration, in weeks, of these fade-outs. A fade-out was defined as a period of at least three weeks without any cases (Bartlett 1957; Grenfell & Harwood 1997). The number of consecutive weeks without cases corresponded to the length of a fade-out period. Then we plotted the mean number of fade-outs per year and their mean duration against the community sizes for the 30 different villages. We repeated this procedure for both periods. Differences between disease spatial series behaviours before and after the vaccination period were tested using non-parametric pairwise comparisons (Zar 1996). Then, to summarize the spatio-temporal persistence and fade-outs of whooping cough, we plotted the spatial distribution of whooping cough records over the past 17 years as a function of village population sizes according to the procedure of Grenfell & Harwood (1997) and Rohani *et al.* (1999).

3. RESULTS

Fade-out counts for whooping cough across the 30 different villages within the Niakhar area are illustrated in figure 1. Results show that large villages exhibit a higher number of fade-outs whereas small villages have a lower number of fade-outs. The mean number of fade-outs (figure 1*a*) rises logarithmically with population size per village, with a significant difference ($t = 6.8365$, d.f. = 29, $p < 0.001$) observed between the pre-vaccination era ($y = 0.763\ln(x) - 2.9623$, $r^2 = 0.42$, $p < 0.01$) and the post-vaccination era ($y = 0.6534\ln(x) - 3.0876$, $r^2 = 0.76$, $p < 0.01$). When considering the mean duration of fade-outs, we observed the opposite pattern (figure 1*b*), with the smallest villages exhibiting longer fade-outs. The duration of fade-outs declined as a power function for both the pre-vaccination era ($y = 2372.7x^{-0.7181}$, $r^2 = 0.57$, $p < 0.01$) and the post-vaccination era ($y = 3515.7x^{-0.6684}$, $r^2 = 0.87$, $p < 0.01$), with a significant

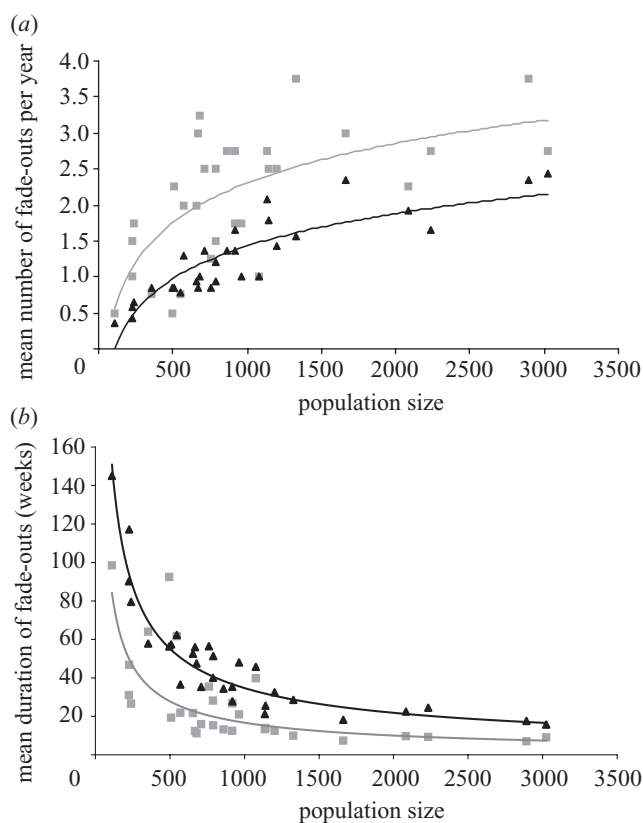


Figure 1. Relationship between (a) the mean number of fade-outs for whooping cough; and (b) the mean duration of fade-out (in weeks), and human community sizes across the 30 villages for the pre-vaccination era (1983–1986; grey squares) and for the post-vaccination era (1987–2000; black triangles). (a) The curves are simple logarithmic functions. (b) Data are fitted to power functions.

difference between both of them ($t = -5.4601$, d.f. = 29, $p < 0.001$). Thus, the transition in whooping cough dynamics was reflected in the mean number of fade-outs and the duration of fade-outs in the weekly time-series. The CCS for which no fade-out was observed was thus never achieved in the Niakhar area. Figure 2 illustrates the spatio-temporal behaviour of whooping cough in Niakhar from 1984 to 2000 in relation to population size evolution per village. Results show that long-lasting local extinctions of whooping cough happened in the smallest villages and, on the contrary, the largest villages were more prone to maintain the disease, or were subject to shorter fade-outs. The high frequency of small to very small villages in comparison with the largest ones within the Niakhar county does not permit conclusions on a minimal population size below which fade-outs are more frequent, but visual examination of figure 2 indicates that, below 1200–1500 inhabitants, the disease extinctions were more likely to last. Also of interest is that endemic persistence of whooping cough was never observed in the largest villages, and many fade-outs occurred over two epidemics.

4. DISCUSSION

We have shown the existence of a decelerating curvilinear trend between the fade-out duration of whooping cough and human population sizes within a tropical area of Senegal. This pattern was previously described for

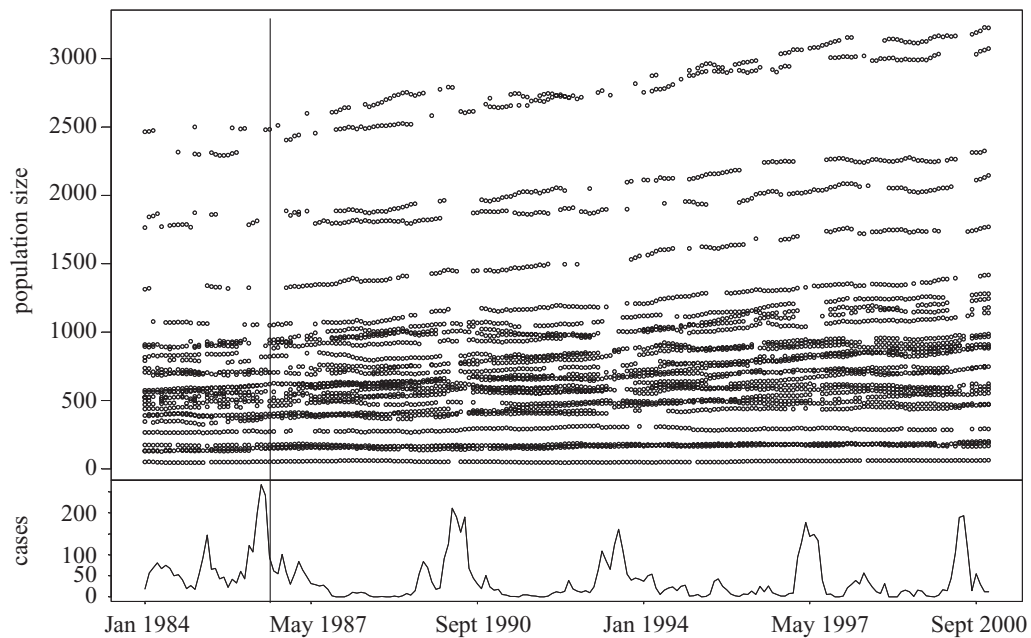


Figure 2. Monthly cases of whooping cough in the Niakhar population in the period 1984–2000 (bottom box). Illustration of persistence of whooping cough with time and population sizes across the 30 villages (top box). Dots indicate months without disease notifications. This schematic illustration takes into account the evolution of host demography across the 30 villages that is simply visualized by a general increase in the number of inhabitants, especially in largest villages, over time. The vertical solid line indicates the beginning of mass vaccination in the area.

pertussis in England and Wales at a larger scale (Rohani *et al.* 2000). It should be noted here that the smallest villages in the Niakhar area exhibit a significantly longer fade-out fraction than the largest villages of the same population. This situation is indicative that the two largest villages, i.e. Diohine and Toukar, experience stronger epidemiological coupling to neighbouring areas than more isolated small populations (Broutin *et al.* 2004). At the very fine spatial scale at which Senegalese data were collected, we did not reach the CCS threshold above which the disease may persist with time. One simple interpretation is that within the Niakhar area there was no village large enough to maintain the disease. These findings tend to confirm the idea that the network of villages within the Senegalese area does not strictly conform to a mainland–island metapopulation model in which the disease never goes extinct, but that it works as a non-equilibrium metapopulation, or source–sink model, where the long-term recolonization rate may exceed the extinction rate.

The investigation of vaccine efficacy by studying the patterns of fade-outs showed a similar pattern to that obtained for pertussis in England and Wales (Rohani *et al.* 2000), both finding that fade-out structure was strongly affected by vaccination. Indeed, we also observed in the Senegalese data a longer duration of fade-out periods in the post-vaccine era when compared with the pre-vaccine era, indicating that vaccination did successfully reduce pertussis persistence within this surveyed area.

To our knowledge, this work constitutes the first analysis of infectious disease persistence under vaccine pressure in tropical conditions. Similar approaches for other settings, especially in developing countries, are recommended to allow comparative analyses of the epidemiological implications of local vaccine campaigns for disease transmission and dynamics.

Acknowledgements

We thank the many people who were engaged in the demographic census and the epidemiological survey, and M. Hochberg, B. T. Grenfell, P. Rohani, N. B. Mantilla, E. Elguero and M. Choisy (from the *ARISE* group) for useful conversations and criticisms on the work presented here. H.B. thanks Fondation des Treilles, Aventis Pasteur and CNRS for providing fellowships. J.-F.G. thanks IRD and CNRS.

- Anderson, R. M. & May, R. M. 1991 *Infectious diseases of humans: dynamics and control*. Oxford University Press.
- Bartlett, M. S. 1957 Measles periodicity and community size. *J. R. Statist. Soc. A* **120**, 48–70.
- Bartlett, M. S. 1960 The critical community size for measles in United States. *J. R. Statist. Soc. A* **123**, 37–44.
- Bjørnstad, O. N., Finkenstädt, B. F. & Grenfell, B. T. 2002 Dynamics of measles epidemics: estimating scaling of transmission rates using a time series model. *Ecol. Monogr.* **72**, 169–184.
- Black, F. L. 1966 Measles endemicity in insular populations: critical community size and its evolutionary implication. *J. Theor. Biol.* **11**, 207–211.
- Broutin, H., Elguero, E., Simondon, F. & Guégan, J. F. 2004 Spatial dynamics behaviour of whooping cough in a small area of Senegal. (In preparation.)
- Cooper, E. & Fitch, L. 1983 Pertussis: herd immunity and vaccination coverage in St Lucia. *Lancet* **2**, 1129–1132.
- Crowcroft, N. S. & Britto, J. 2002 Whooping cough: a continuing problem. *BMJ* **324**, 1537–1538.
- Ferguson, N. M., Nokes, D. J. & Anderson, R. M. 1996 Dynamical complexity in age-structured models of the transmission of the measles virus: epidemiological implications at high levels of vaccine uptake. *Math. Biosci.* **138**, 101–130.
- Fulford, G. R., Roberts, M. G. & Heesterbeek, J. A. 2002 The metapopulation dynamics of an infectious disease: tuberculosis in possums. *Theor. Popul. Biol.* **61**, 15–29.
- Grenfell, B. T. & Bolker, B. M. 1998 Cities and villages: infection hierarchies in a measles metapopulation. *Ecol. Lett.* **1**, 63–70.
- Grenfell, B. T. & Dobson, A. P. 1995 *Ecology of infectious diseases in natural populations*. Publications of the Newton Institute, vol. 7. Cambridge University Press.
- Grenfell, B. T. & Harwood, J. 1997 (Meta)population dynamics of infectious diseases. *Trends Ecol. Evol.* **12**, 395–399.
- Grenfell, B. T., Bjørnstad, O. N. & Kappey, J. 2001 Travelling waves and spatial hierarchies in measles epidemics. *Nature* **414**, 716–723.
- Hanski, I. & Gilpin, M. E. 1997 *Metapopulation biology: ecology, genetics, and evolution*. San Diego, CA: Academic.

- Holmes, E. E. 1997 Basic epidemiological concepts in a spatial context. In *Spatial ecology: the role of space in population dynamics and interspecific interactions*. Monographs in population biology, vol. 30 (ed. D. Tilman & P. M. Kareiva), pp. 111–136. Princeton University Press.
- Keeling, M. J. & Gilligan, C. A. 2000 Metapopulation dynamics of bubonic plague. *Nature* **407**, 903–906.
- Keeling, M. J. & Grenfell, B. T. 1997 Disease extinction and community size: modeling the persistence of measles. *Science* **275**, 65–67.
- Keeling, M. J. & Grenfell, B. T. 2002 Understanding the persistence of measles: reconciling theory, simulation and observation. *Proc. R. Soc. Lond. B* **269**, 335–343. (DOI 10.1098/rspb.2001.1898.)
- Mazengia, E., Silva, E. A., Peppe, J. A., Timperi, R. & George, H. 2000 Recovery of *Bordetella holmesii* from patients with pertussis-like symptoms: use of pulsed-field gel electrophoresis to characterize circulating strains. *J. Clin. Microbiol.* **38**, 2330–2333.
- Préziosi, M. P., Yam, A., Wassilak, S. G., Chabirand, L., Simaga, A., Ndiaye, M., Dia, M., Dabis, F. & Simondon, F. 2002 Epidemiology of pertussis in a West African community before and after introduction of a widespread vaccination program. *Am. J. Epidemiol.* **155**, 891–896.
- Rohani, P., Earn, D. J. & Grenfell, B. T. 1999 Opposite patterns of synchrony in sympatric disease metapopulations. *Science* **286**, 968–971.
- Rohani, P., Earn, D. J. & Grenfell, B. T. 2000 Impact of immunisation on pertussis transmission in England and Wales. *Lancet* **355**, 285–286.
- Yih, W. K., Silva, E. A., Ida, J., Harrington, N., Lett, S. M. & George, H. 1999 *Bordetella holmesii*-like organisms isolated from Massachusetts patients with pertussis-like symptoms. *Emerg. Infect. Dis.* **5**, 441–443.
- Zar, J. H. 1996 *Biostatistical analysis*. Upper Saddle River, NJ: Prentice-Hall.