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Original article

Epidemiological impact of vaccination on the dynamics of two childhood diseases in rural Senegal

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Abstract

Measles and pertussis are ubiquitous vaccine-preventable diseases, which remain an important public health problem in developing countries. Hence, developing a deep understanding of their transmission dynamics remains imperative. To achieve this, we compared the impact of vaccination at both individual and population levels in a Senegalese rural community. This study represents the first such comparative study in tropical conditions and constitutes a point of comparison with other studies of disease dynamics in developed countries. Changes in the transmission rates of infections are reflected in their mean ages at infection and basic reproductive ratio calculated before and after vaccination. We explored persistence of both infections in relation to population size in each village and found the inter-epidemic period for the whole area using wavelets analysis. As predicted by epidemiological theory, we observed an increase in the mean age at infection and a decrease in the reproductive ratio of both diseases. We showed for both the pre- vaccination and vaccine eras that persistence depends on population size. After vaccination, persistence decreased and the inter-epidemic period increased. The observed changes suggest that vaccination against measles and pertussis induced a drop in their transmission. Similarities in disease dynamics to those of temperate regions such as England and Wales were also observed.

Keywords: Vaccination; Transmission; Persistence; Measles; Pertussis; Senegal; Population dynamics

1. Introduction

Measles and whooping cough are two vaccine-preventable diseases frequently encountered in childhood. Measles, due to a paramyxovirus, is transmitted by aerosol particles and is highly infectious; its latent period lasts about 8 days, after which individuals are infectious for some 5 days. Whooping cough (pertussis) is a respiratory disease caused by the bacterium *Bordetella pertussis*. It is also highly infectious and has a similar latent period of 8 days; its infectious period lasts from 14 to 21 days. Waning of immunity has been reported for measles and whooping cough after both natural infection and vaccination [1–4]. In developed countries, large vaccination programmes against both diseases started between 40 and 60 years ago. Systematic vaccination in developing countries was initiated in 1974 via the Expanded Programme on Immunisation, which has been implemented in Africa since the mid-1980s. Even nowadays, vaccination levels are rather patchy. Global incidence of both infections has been dramatically reduced with vaccination, but measles and pertussis remain an important public health problem in developing countries [5,6]. Furthermore, in several developed countries, a resurgence in whooping cough has been detected in the last decades [7,8], despite high vaccine coverage [9,10]. The persistence

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of both diseases in spite of substantial mass vaccination all around the world raises questions about the actual impact of vaccination on reducing disease transmission in the population.

Newly employed approaches based on ecological theory have explored changes in epidemic dynamics coinciding with the onset of vaccination. The combination of epidemiology and ecology has improved our understanding of disease dynamics, persistence and transmission. Previous studies that integrate models and data have analysed the effect of immunisation in disease transmission both for measles and for whooping cough. These have shown the comparative effect of immunisation on transmission dynamics [11] and stochastic persistence, as measured by the Critical Community Size (the minimum population size above which the infection remains endemic) [12–18]. As expected from models [17], vaccination increases the inter-epidemic period and the mean age at infection. These predictions have been confirmed in data from England and Wales [11,15,17].

All these studies are based on data or parameters characteristic of developed countries and no study has, to our knowledge, explored equivalent aspects of these infections' incidence and dynamics in the developing world, principally due to a lack of data. This void is particularly worrying because it is in these regions that morbidity and mortality from these infections are highest. Furthermore, our comparison of their main features in developed and developing countries questions the need to adapt vaccination strategies to particular environments.

In this paper, we present a first analysis of the impact of immunisation against both whooping cough and measles in a small rural community of Senegal. For this, we examine the changes observed at three different spatial scales. First, we focus on the changes in transmission at the individual level by looking at the mean ages at infection and the estimated basic reproductive ratio (R_0). Second, we show how vaccination modified the relationship between disease persistence and population size by calculating disease fadeout frequency for the different villages. Third and last, we present the impact of vaccination on the inter-epidemic period of these infections, using case records for the entire area. We demonstrate that vaccination against measles and pertussis results in a substantial reduction in the transmission of these pathogens.

2. Methods

2.1. Study setting

The surveyed area, Niakhar, (a territory of some 220 km^2) is located about 150 km east of Dakar, the main city of Senegal (Fig. 1). This county is a dry sahelo-sudanian area made of a typical savannah landscape. It contains 30 villages of sizes ranging from 50 to 3000 inhabitants. Each village is divided into hamlets composed of a variable number 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.

2.2. Study population, surveillance and immunisation

People living in the Niakhar area, mostly belonging to the Sereer ethnic group, are generally farmers or shepherds. Since 1983, its population was followed for demographic and epidemiological information. Total population was 23,413 in 1984 and 30,452 in 2000 with about 47% below 15 years of age [19]. From 1983 to 2001, the mean annual population growth was 1.6% [19]. From 1984 to 2000, mean life expectancy at birth was 51 years and mean per capita birth rate 4.7‰ [19]. Details of the demographic data collection have already been provided by Delaunay [19]. Préziosi et al. [20] and Aaby et al. [21] have detailed the survey's methodology for whooping cough and measles, respectively.

Campaigns of mass vaccination against both infections started at the end of 1986. Whooping cough vaccine coverage was not homogeneous among age classes and has changed through time [20]. In particular, it shows a trough in 1997. Taking into account these factors, we estimate that 40% of the whole population has been protected over the vaccination era. In spite of this, pertussis remains endemic with epidemic outbreaks every 3–4 years. Measles vaccine coverage has also been irregular in time; it increased among 1- to 2-year-old

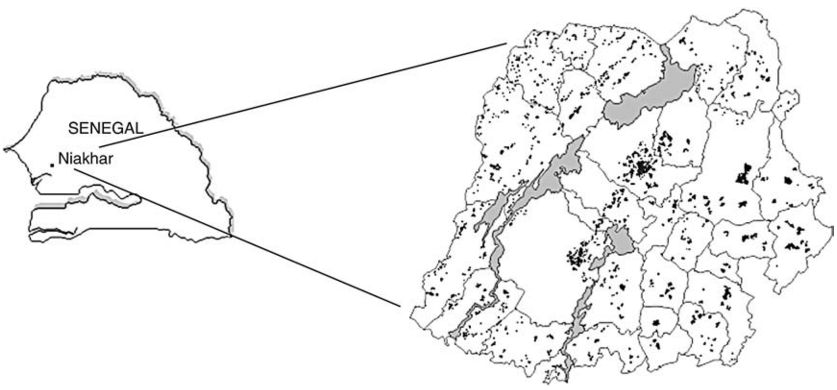

Fig. 1. Map of Niakhar county, a small rural region located around 150 km east of Dakar, the main city of Senegal. The studied area (about 220 km^2), a rural zone, comprises 30 distinct villages (the blacks points represent compounds). The blue areas correspond to backwaters during the rainy season.

children from 36% in 1987 to 81% in 1992 [21], but declined again in 1997. Accounting for these changes, vaccine coverage in the whole population was around 38%. Measles also remains endemic in Niakhar.

2.3. Analyses

2.3.1. Mean age at infection

The mean age at first infection (A) was calculated for each disease before vaccination (1983–1986). Then we estimated their basic reproductive ratio according to the theoretically derived relationship $R_0 = G/A$ (where G is the reciprocal of the per capita birth rate), in preference to the classic relationship $R_0 = L/A$ (where L is the life expectancy at birth) because the population is growing [17]. The quantity R_0 is defined as the mean number of secondary cases that result when one case enters a fully susceptible population. We estimated the expected effective reproductive ratio after vaccination, $R = S \times R_0$ where S corresponds to the proportion susceptible in the population, given by (1-vaccine coverage) [17,22]. Finally, we calculated the R_0 after vaccination (1987–2000) directly from demographic data using the first equation. We compared the expected and the empirical R_0 after vaccination to estimate the effective impact of vaccination on transmission. We assessed the significance of the change in the mean ages at infection using the Kruskall–Wallis test.

2.3.2. Disease persistence

For each village, we calculated (i) the mean number of fade-outs, and (ii) the mean duration in weeks of these fade-outs both before (1983–1986) and after the start of mass vaccination (1987–2000). A fade-out was defined as a period of at least three consecutive weeks without cases [12,15]. The number of consecutive weeks without cases defines fadeout duration. Finally, we plotted the mean number of fade-outs per year and their mean duration against village size. Differences in disease persistence before and after vaccination were tested using non-parametric pair-wise comparisons [23]. This work had already been performed for whooping cough and was described in Broutin et al. [24]. In the present paper, we complement it with measles fadeout analysis. We worked with weekly notifications of cases for each village.

2.3.3. Temporal analysis

We determined the inter-epidemic period for the whole area of Niakhar by means of wavelet analysis [25,26]. For each week, we considered the total number of cases in the Niakhar region I_t. Wavelet analysis detects the frequencies where the largest part of the variation occurs at each point in time. Additionally, we calculated the Fourier spectra of the 4 years before the start of vaccination era and of a similar extent after immunisation began (1987–1990). Their comparison allows us to discard edge effects as the cause behind the period detected before vaccination. Statistical significance was determined by bootstrapping the data. Time series were normalised using the maximum value in the data and were padded with zeros before calculating their wavelet power, to reduce edge effects and speed up the calculations. We calculated the contribution to the power of the observed oscillations at various scales s, using the Morlet wavelet

$$\psi_0(\eta) = \pi^{-1/4}\exp(i\omega_0\eta)\exp(-\eta^2/2)$$

where $\omega_0 = 6$ is the frequency and $\eta = t/s$ the time. Scales relate to conventional Fourier periods [25]. In this case, the lowest scale corresponds closely to the Nyquist frequency. The power of the series at each time and frequency (middle panel in Fig. 4A, B) is then summarised in the last panels. These exhibit the frequencies with the largest and second largest contributions to the power for each time step focusing in the longer term variations (half a year and longer). Fourier analyses confirm wavelet results but fail to reveal when period changes occur, they are therefore omitted from this paper.

3. Results

3.1. Mean age at infection and reproductive ratio R_0

The mean age at infection for measles before vaccination (1983–1986) was A = 4.6 years (95% confidence interval: 4.4,4.8), which suggests $R_0(\sim G/A) = 21.3/4.6 \sim 4.6$ ($G = 1/0.047 = 21.3$). Based on this value, we can predict the effective reproductive ratio after 38% vaccine coverage $R = 4.6 \times 0.62 = 2.9$. The reported ages of infected children provide us with a field estimate of the mean age at infection of 7.2 years (7.0,7.4) after vaccination. This gives an effective R_0 of $G/A = (21.3/7.2) \sim 3$ after vaccination, well within the expected range. Furthermore, measles mean age at infection is significantly different before and after vaccination ($P < 0.001$).

Pertussis mean age at infection before vaccination (1983–1986) was A = 4.7 years (4.6,4.8). Consequently, $R_0(\sim G/A) = 21.3/4.7 \sim 4.5$ before vaccination. The expected reproductive ratio in the vaccination era (with 40% vaccine coverage), R, is $(4.5 \times 0.60) = 2.7$. The corresponding field values after the start of vaccination are A = 6.3 years (6.2,6.4) and $R \sim G/A = (21.3/6.3) \sim 3.4$. In this case, the observed reproductive ratio is somewhat higher than expected but there is a significant increase in the mean age at infection of pertussis after vaccination ($P < 0.001$).

For both infections, vaccination reduced the R_0, although this reduction was smaller than expected for pertussis considering the reported vaccine coverage levels. After vaccination, the mean age at infection of measles is significantly different from that of whooping cough ($P < 0.001$).

3.2. Disease persistence

Whooping cough fadeout frequency and duration have previously been described in Broutin et al. [24]. Fig. 2 shows the mean number of fadeouts per year before and after vaccination for measles (top) and whooping cough (bottom). Fig. 3

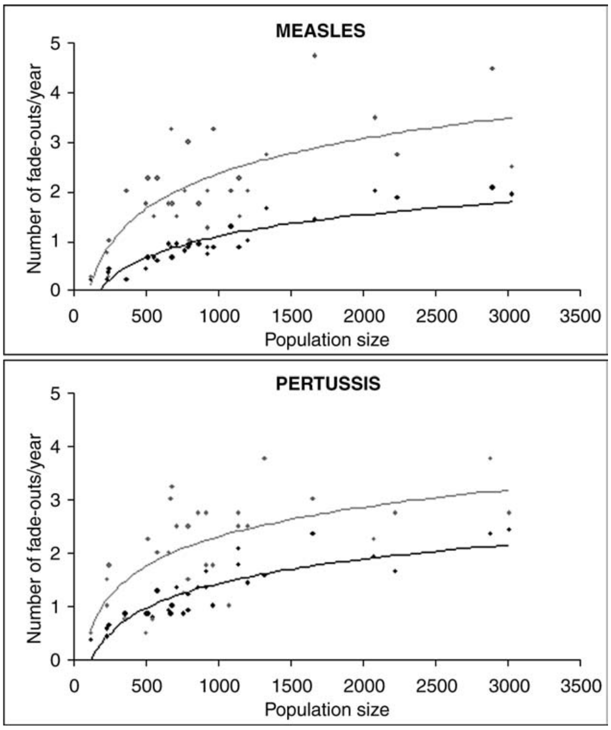

Fig. 2. Mean number of fade-outs per year against the population size for measles (top) and for whooping cough (bottom) in the Niakhar area, during the pre-vaccine period, i.e. from 1983 to 1986 (in grey) and during the post-vaccine period, i.e. from 1987 to 2000 (in black). The curves are simple logarithmic functions: measles in pre-vaccination period—$y = 1.0204\ln(x)4.6819$, $r^2 = 0.5339$); measles in post-vaccine period—$y = 0.6222\ln(x) - 3.2045$, $r^2 = 0.8079$; pertussis in pre-vaccine period—$y = 0.7914\ln(x) - 3.16$, $r^2 = 0.434$; pertussis in post-vaccine period—$y = 0.6541\ln(x) - 3.0902$, $r^2 = 0.7612$.

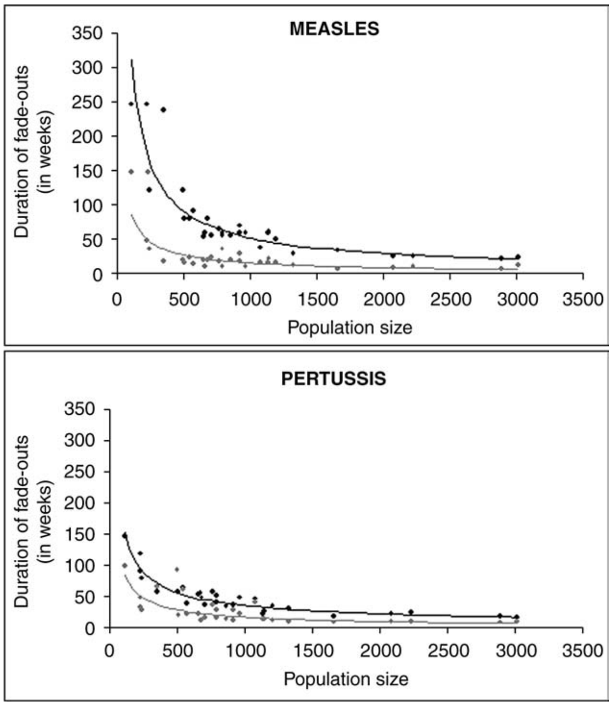

Fig. 3. Mean duration of fade-outs against the population size for measles (top) and for whooping cough (bottom) in the Niakhar area during the pre-vaccine period, i.e. from 1983 to 1986 (in grey) and during the post-vaccine period, i.e. from 1987 to 2000 (in black). The curves correspond to power functions: measles in pre-vaccination period—$y = 3150.1x^{-0.7686}$, $r^2 = 0.6537$; measles in post-vaccine period—$y = 14374x^{-0.8157}$, $r^2 = 0.8792$; pertussis in pre-vaccine period—$y = 2705.2x^{-0.7368}$, $r^2 = 0.588$; pertussis in post-vaccine period—$y = 3521.6x^{-0.6689}$, $r^2 = 0.8681$.

shows the mean duration of a fadeout (in weeks) for each period. Fade-out structure for pertussis before and after vaccination is significantly different, both for the mean number of fade-outs ($P < 0.001$) and for their mean duration ($P < 0.001$). The same holds true for measles, both for the mean fadeout number ($P < 0.001$) and mean fadeout duration ($P < 0.0001$). Note that after vaccination both infections are less persistent (show an increase in fadeout length). Similar changes have been described for pertussis in England and Wales at an inter-city level [11]. All our findings are consistent with a drop in transmission in the Niakhar area.

3.3. Inter-epidemic period

As a last point, we examine the overall temporal patterns of epidemics in this region (Fig. 4). In the brief period before vaccination (1983–1986), both infections have annual outbreaks with peaks around springtime. This pattern is evident from the case records plotted in the first panels of Fig. 4A, B and comes up in their Fourier and wavelet analyses as the frequency with the largest long-term detectable power (last panels, black line). This maximum switches to multi-annual frequencies after the start of vaccination, both for measles and for whooping cough. Measles oscillations have a considerable variation in period in these years, but measles incidence is in clear decline throughout the era. Whooping cough cases have a dramatic drop coincident with the start of vaccination and take the form of large epidemics only every 3–4 years up to 1998. The periodicity analysis on the last part of the whooping cough data shows a multi-annual cycle of decreasing power. This change coincides with the lower vaccination coverage observed between 1997 and 2000. Pertussis is evidently still very present in Niakhar. Measles incidence has an underlying annual fluctuation throughout the vaccination era (red, dashed lines in the last panels of Fig. 4A, B), which becomes stronger with the 1997 decrease in vaccination. The increase in the inter-epidemic period brought about by vaccination is expected from classical epidemiological models [17]. Work on these infections for records from England and Wales has corroborated similar changes for a number of populations [11,26].

4. Discussion

Incidence of both measles and pertussis decreased after introduction of vaccination in the Niakhar area. Nevertheless, both infections remain endemic with regular epidemic outbreaks. This study showed the impact of vaccination at three spatial scales. At the individual level, immunisation significantly increased the mean ages at infection, as already

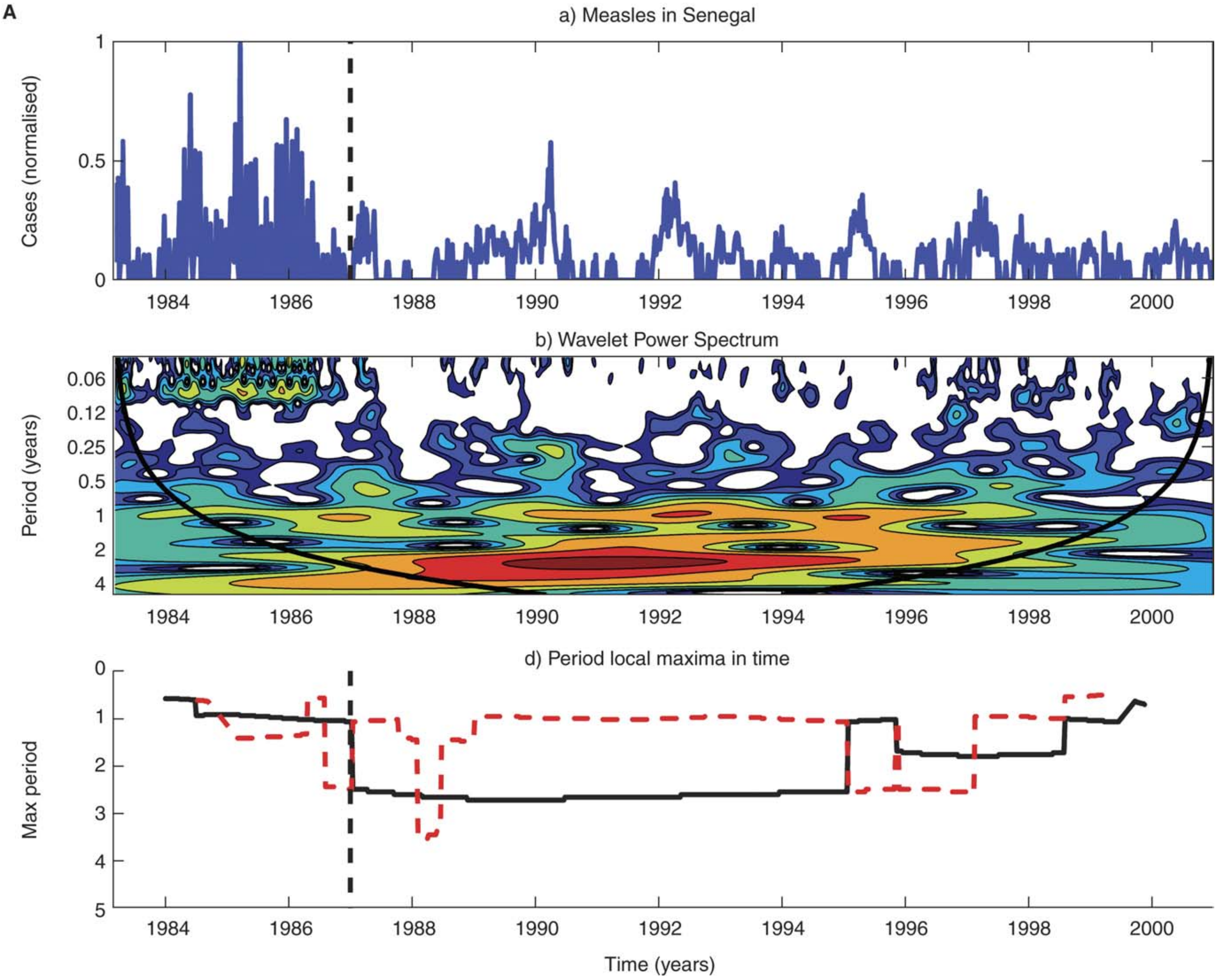

Fig. 4. Temporal analysis. The first panel shows the square root of the weekly cases of measles (A) and whooping cough (B) in the whole Niakhar region from 1983 to 2000. Dotted vertical lines mark the beginning of vaccination (at the end of 1986). For each infection, the wavelet spectrum appears in the middle panel. Time runs along the *x*-axis. The contours limit areas of similar power at the periods indicated in the *y*-axis. High values are coloured in dark red; yellow and green denote intermediate power; cyan and blue, low. Note the cone of influence, a continuous black line that lies underneath the period values that the wavelet can detect at each time. In both A and B, the third panel is an attempt to summarise the main features of the wavelet spectrum. The continuous black line shows the maximum power in the spectrum within the cone of influence for each week. The dashed red line corresponds to the next greatest power. Our summary considers only the part of the spectrum in which periods above half a year can be detected between half a year after the start and before the end of the record. Wavelet software was provided by C. Torrence and G. Compo, and is available at URL: http://www.paos.colorado.edu/research/wavelets/.

described in the zone for a shorter period [20,21], and a drop in their basic reproductive rate. Interestingly, its impact on pertussis transmission is lower than expected considering vaccine coverage levels. This difference could be due to a number of factors: (i) underreporting of cases among adults since surveillance targeted population under 15 years of age, which in turn leads to underestimating the mean age at infection and overestimating R_0; (ii) vaccine failure and (iii) waning immunity after infection and/or vaccination, which could induce an underestimation of the proportion susceptible and of the expected R_0. This last hypothesis is the most likely since loss of immunity against pertussis has been observed in Niakhar [4]. Notwithstanding this, we observed a significant decrease in the R_0 of both infections after the start of vaccination that indicates a substantial reduction in disease transmission.

At the intermediate spatial scale, the fade-out structure for each infection before and after the start of vaccination shows a substantial change. Both fadeout number and duration evidence a clear decrease in persistence as a result of immunisation. Underreporting of cases should not affect this analysis significantly, because it is based on presence/absence of cases and does not take into account their actual number. Moreover, we worked with weekly data, which helps to reduce the risk of bias due to underreporting.

At the largest scale (the whole Niakhar region), temporal analyses exhibited important differences in the inter-epidemic period before and after vaccination. Although pre-vaccination data cover only a few years, both infections have a significant oscillation at the 1-year period from 1983 to 1986 and have no trace of multi-annual cycles. After the start of vaccination,

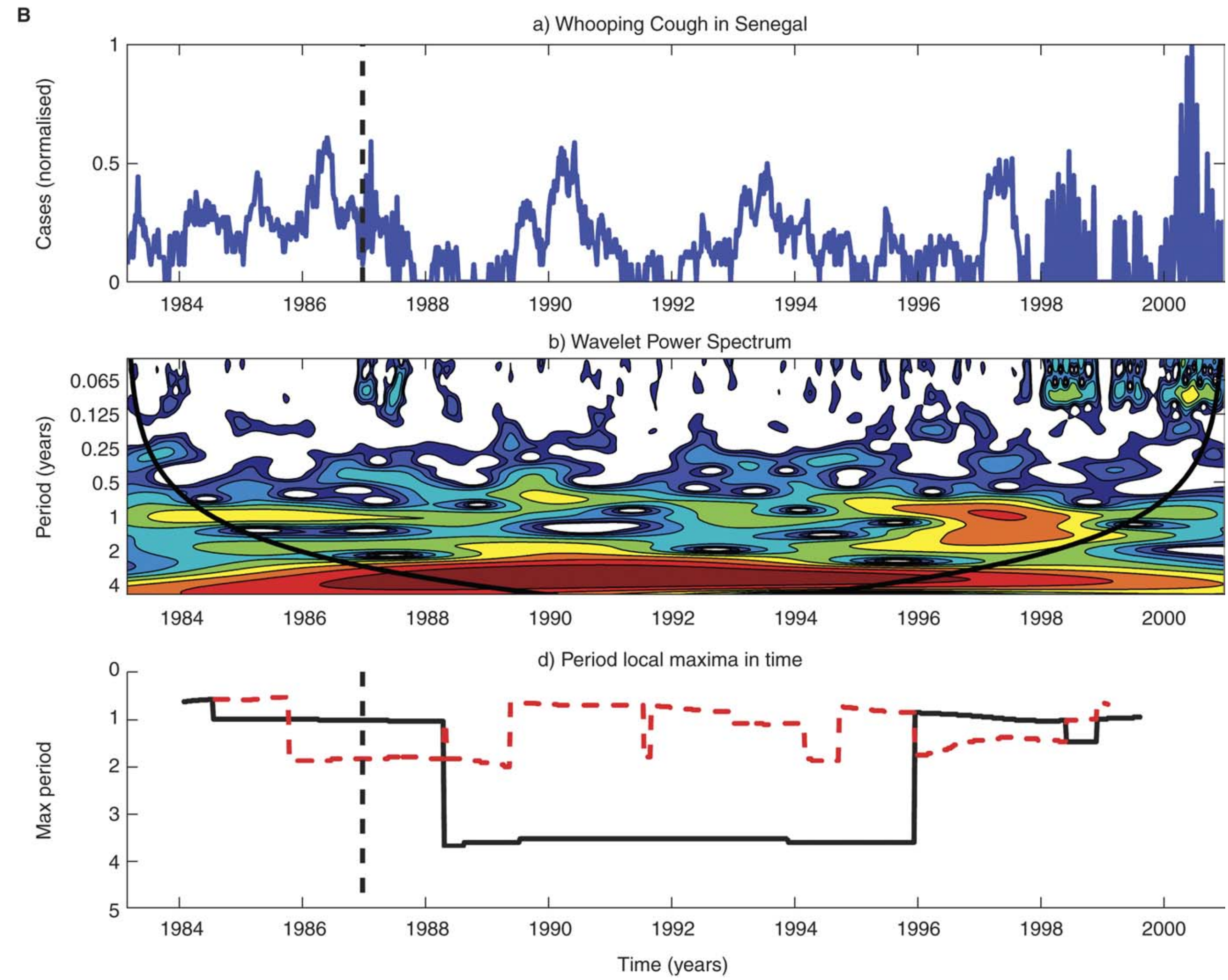

Fig. 4. *(continued)*

case numbers of both infections still have an underlying annual fluctuation (red dashed line in Fig. 4A, B last panel), but this is only secondary to the observed multi-annual cycle (solid, black line), which holds the largest power even when considering a short stretch of data (1987–1990). The size of measles epidemics is also evidently smaller after 1986, and continues its decrease with time. Furthermore, we can see the immediate impact of vaccination in whooping cough transmission in the drop of case numbers in 1987. The first large outbreak of the vaccination era happens only after three more years have gone by. After that, epidemics repeat every 3–4 years, though whooping cough is still very present towards the end of these data and shows some signs of a new increase in epidemic frequency (following a dip in vaccination coverage).

All these findings point towards a dramatic drop in the transmission of both infections in the studied area after vaccination. The changes we note here have been reported for populations in developed countries in the past [11]. This work constitutes a new estimation of important epidemiological parameters, such as R_0, and is the first analysis of the impact of immunisation in developing countries with an ecological approach. Our analysis corroborates the impact of vaccination for a country of markedly different economic, environmental and social conditions. The observed similarities of the impact of vaccination on the short, medium and global spatial scales, for different environments represent a new, important point of view. This suggests that intrinsic factors have a major influence on disease dynamics independently of the surrounding conditions. This new analysis underlines the importance of comparing different environmental and demographic conditions to assess the impact of given vaccination strategies.

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