



Improved measles surveillance in Cameroon reveals two major dynamic patterns of incidence

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Summary

Objective: To characterize the province-specific incidence patterns of measles in Cameroon and determine if an increase in measles incidence during the period January 2000–June 2001 is consistent with coincident epidemics in several regions with different inter-epidemic periods.

Method: Periodic behavior of the monthly measles incidence time-series from each province of Cameroon was analyzed using time-series analysis and cluster techniques. Cumulative incidence in each province of Cameroon over a five-year period was associated with birth rates, and vaccination coverage.

Results: Distinct patterns of measles incidence were found in two different areas of Cameroon. The three northern-most provinces experience major epidemics every year. Seven southern provinces show evidence of experiencing major epidemics every

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third year. In January 2000, Cameroon experienced coincident peaks in these two cycles and thus an increase in measles incidence countrywide over the previous year. Higher cumulative province-specific incidence rates were associated with higher birth rates and lower routine vaccination coverage rates.

Conclusion: Within one country, two dramatically different dynamic patterns of measles incidence were observed. Long-term surveillance data is crucial to the evaluation of measles immunization campaigns. The availability of a five-year record of measles incidence in Cameroon reveals an interesting dynamic pattern of measles incidence that accounts for the increase in countrywide incidence in 2000–2001.

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Introduction

In the last months of 2000 and the first few months of 2001, Cameroon experienced a large increase in measles incidence over previous years (EPI unpublished data). All provinces of the country (Figure 1) experienced increases in incidence over the previous year, even provinces that had observed low incidences of measles for several years. This dramatic increase heightened concern among health professionals, prompting a search for potential precipitating factors.

An increase in the inter-epidemic period, the time between major outbreaks of disease, has been observed following the introduction of immunization campaigns in several settings^{1–3} and is predicted by mathematical models of measles virus transmission.^{4,5} The length of this period has been

found to be dependent upon vaccination coverage, population density and birth rates.⁵ Differences in these factors across Cameroon could create different patterns of incidence. The present analysis seeks to determine if there are differences in the patterns of measles incidence observed in the regions of Cameroon, and if simultaneous peaks in these varied patterns could explain the observed increase in the incidence of measles between January 2000 and June 2001.

Measles modeling

An extensive body of work explores the dynamics of measles virus transmission.^{4–9} Its public health significance, the existence of large spatiotemporal data sets, the relatively simple natural history of the disease and the observation of non-linear dynamics has attracted epidemiologists, population dynamicists and physicists to its study. Mathematical models of measles virus transmission have successfully replicated historical observations and back-predicted the effect of interventions, such as vaccination.^{5,6} At the essence of the dynamics of measles epidemics is a predator–prey relationship between the virus and susceptible individuals. After large epidemics, the population of susceptible children is greatly depleted, limiting incidence in subsequent years until the susceptible population has been replenished by births to a critical threshold.⁴ In the USA and UK before vaccination, large epidemics occurred every two years reflecting a two-year period of replenishment. The time between large epidemics has been shown to be dependent upon birth rates,^{6,9} population density⁷ and vaccination rates.^{4,6}

Mathematical models have been used to approach several problems surrounding measles virus transmission in developing countries, including determining the optimal age of vaccination^{10,11} and estimating the average age of infection after immunization campaigns.^{4,12} One predicted outcome of this work, as mentioned earlier, is a lengthening of

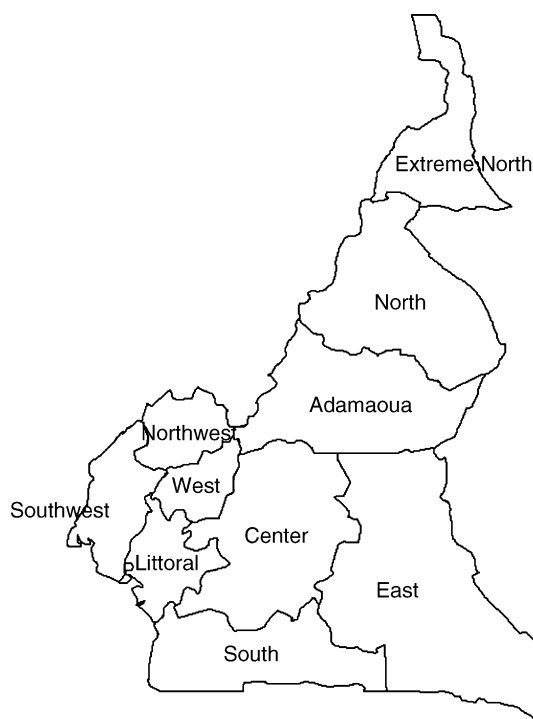


Figure 1 Map of the provinces of Cameroon.

the inter-epidemic period after the implementation of vaccination programs.¹² Following the introduction of vaccination, a period of low incidence is predicted, followed by an increase in incidence as the pattern of incidence settles to a longer inter-epidemic period.⁵ Immunization reduces the rate at which susceptible individuals enter the population and increases the amount of time required for a critical level of susceptible individuals to accumulate in order for large outbreaks to occur.

Review of measles in Cameroon and West Africa

Measles immunization programs began in Cameroon in 1965.¹³ Guyer and McBean reviewed the epidemiology and control of measles in Yaounde from 1968 to 1975.¹⁴ The authors found that 40% of cases during this period occurred among children less than 12 months of age.¹⁴ With the exception of 1969 and 1970, when intensive vaccination under the Smallpox Eradication and Measles Control Program was undertaken, measles epidemics occurred every year during this period.¹⁴ In 1974, the Ministry of Health of Cameroon adopted the WHO recommendation of a minimum age at vaccination of nine months.¹⁵ A report by Heymann et al. in 1983 found that following this change a reduction in incidence among all age groups was observed.¹⁵

Time-series of measles cases from 1965 to 1982 in Benin, Burkina Faso, Gambia, Ghana, Guinea-Bissau, Mali, Nigeria, and Senegal have been reported and analyzed by Cliff.¹⁶ For the most part, annual epidemics are observed in these countries, like those observed in Cameroon over a similar time period.^{14,16}

Descriptions of the measles viral strains circulating in West and Central Africa appear in work by Kouomou et al.¹⁷ and Hanses et al.¹⁸ Kouomou et al. described the strains circulating in 1983 and in 2001 in Yaounde, Cameroon. The authors found that viruses isolated in 1983 differed in genotype from viruses isolated in 2001.¹⁷

Approach

In order to assess the impact of measles immunization in Cameroon, cumulative incidence within each province for all five years for which data are available was associated with vaccination rates and birth rates in each province to determine if vaccination coverage is associated with a reduction in measles incidence. Two analytical techniques, autocorrelation functions and hierarchical clustering, were used to characterize the patterns of incidence observed in each province.

Methods

Data sources

Monthly numbers of measles cases and measles deaths occurring in the period 1997 through 2001 for each of the ten provinces of Cameroon were obtained from the Cameroon Ministry of Health (EPI unpublished data). These data are presented in Appendix B (Table 1 (cases) and Table 2 (deaths)). Months for which no cases and no deaths were reported were assumed to have zero cases and deaths. A conservative algorithm was developed to identify out-of-range values. Individual values were labeled out of range if they were either five times greater or less than the expected value calculated by linear interpolation of the month following and the month preceding each value, and if it also differed by 200 cases from that expected value. Of the 600 data points, four data points were identified as out-of-range and replaced by the estimate calculated by linear interpolation (Extreme North, May 1997; Northwest, October 1997; Extreme North, May 1999; Extreme North, December 1999). Figures 2 and 3 present the incident cases and deaths summed over all ten provinces. Figure 4 presents monthly incidence time-series for each province in order from most northern to most southern.

Province-specific birth rates and vaccination rates were obtained from a demographic and health

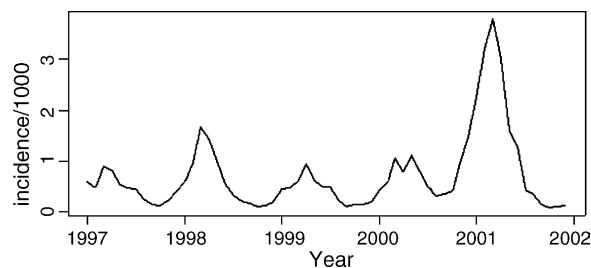


Figure 2 Monthly measles incidence in Cameroon (sum of all provinces), 1997–2001.

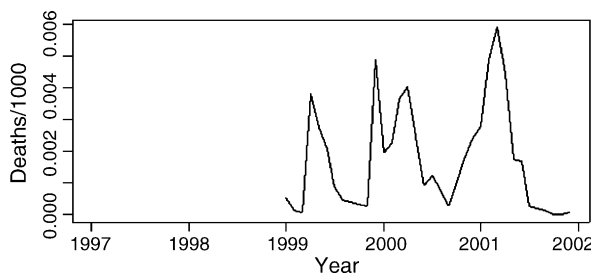


Figure 3 Monthly measles death incidence in Cameroon (sum of all provinces), 1999–2001.

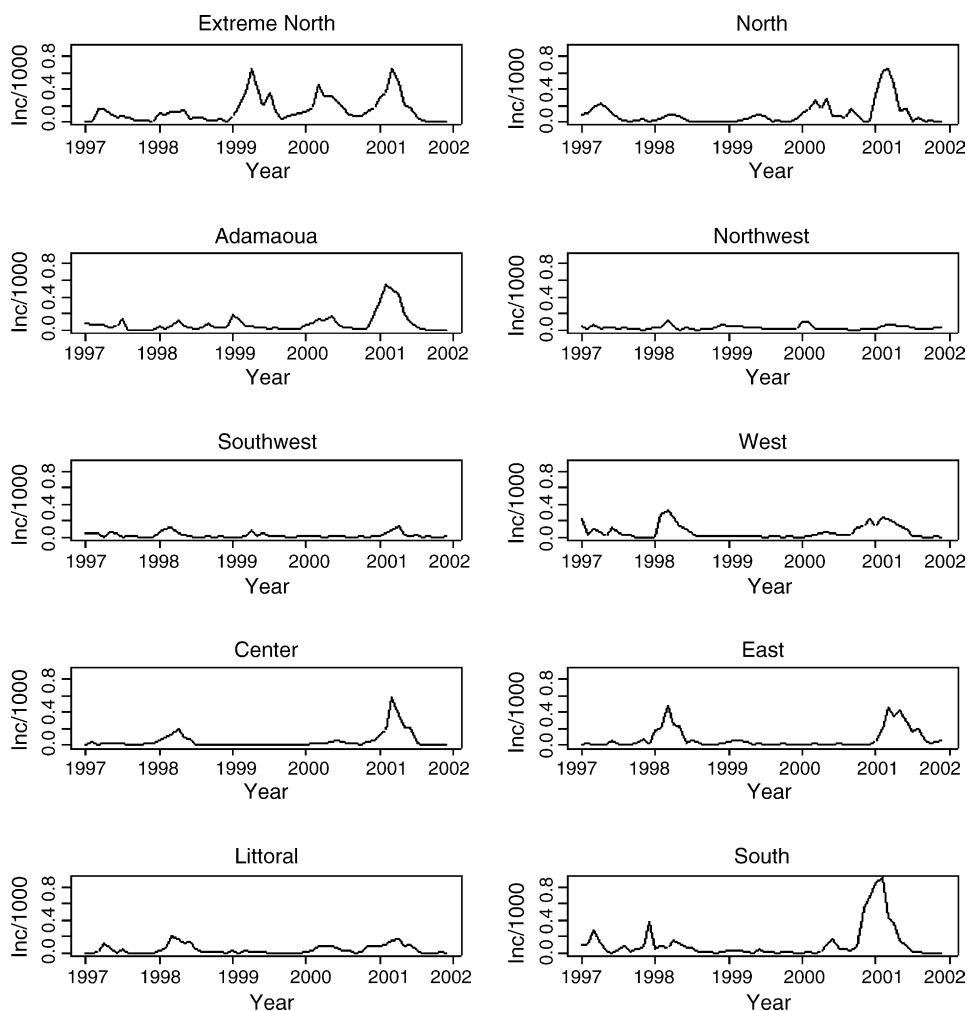


Figure 4 Monthly measles incidence (per 1000) for each province in Cameroon (provinces are ordered from most northern to most southern).

survey published in 1998.¹⁹ Birth rates were available only by region, with one value for the Extreme North, Adamaoua and North provinces, one for the Center, East and South provinces, one for the West and Littoral provinces and one for the Northwest and Southwest provinces.¹⁹ Birth rates were reported as births per 1000 individuals. Vaccination rates were available for each province.¹⁹

Population estimates were calculated by assuming that each province had maintained a constant proportion of the overall population of Cameroon since 1987, the year of the last census. These proportions were applied to estimates of the total population of Cameroon for 2001.¹⁹ Areas of provinces, used to calculate the estimates of population density found in Table 1 were obtained from the World Gazetteer website.²⁰

The cumulative incidence for all 60 months for which data are available along with crude birth rates

(births/1000 individuals), percent of children under age two years vaccinated, percent of children under age five years vaccinated, the annual rate of new susceptibles entering the population (defined as the percent of under two-year-olds not vaccinated multiplied by the birth rate), estimates of population density, and the number of cities with population greater than 100 000 are reported for each province in Table 1.

Correlates of cumulative incidence

Associations between cumulative measles incidence and province-specific birth rates, vaccination rates (for both children under two years of age and children under five years) and annual rates of new susceptibles entering the population (birth rate multiplied by percent of two-year-olds not vaccinated) were measured using a linear model.

Table 1 Vaccination rates for children under age two years and children under age five years, birth rates, annual rates of new susceptibles entering the population (percent of under two-year-olds not vaccinated multiplied by the birth rate), population density and the number of cities with population greater than 100 000 for each of the provinces of Cameroon.

Province	Percent vaccinated under age two years	Percent vaccinated under age five years	Crude birth rate (births/1000 individuals)	Annual rate of new susceptibles (ind./1000)	Cumulative five-year incidence (per 1000)	Population density (ind./km ²)	Number of cities with population greater than 100 000	Cities with population greater than 100 000 (population in 1000s listed)
Extreme North	18	23	42.8	35	8.43	82.21	4	Kaale (109), Kourserri (313), Maroua (284), Mokolo (201) Garoua (387)
North	16	20	42.8	36	5.61	19.33	1	
Adamaoua	25	29	42.8	32	4.55	11.80	1	Ngaoundere (180)
Northwest	51	61	31.1	15	1.56	105.41	1	Bamenda (290)
Southwest	35	45	31.1	20	1.59	23.13	1	Kumba (130)
West	40	51	32.2	19	4.02	146.50	1	Bafoussam (250)
Center	35	45	34.6	23	3.08	36.35	1	Yaounde (1154)
East	24	31	34.6	27	4.32	7.20	1	Bertoua (148)
Littoral	41	49	32.2	19	2.51	101.54	4	Doula (1274), Loum (133), Nkongsamba (120), Edea (107)
South	20	31	34.6	28	6.65	27.00	0	—

Inter-epidemic periods

The inter-epidemic period, or the periodicity of major outbreaks can be measured by several techniques.²¹ The present approach uses autocorrelation functions to determine the periodicities present in the incidence time-series. Sample autocorrelation coefficients measure the correlation between observations at different lags within the time-series.²² The plot of the sample autocorrelation coefficients versus lag is called the autocorrelation function of a time-series.²² Oscillations in time-series data generate oscillations at the same period or frequency in the calculated autocorrelation function. Observed correlations can be compared to confidence limits based upon randomly distributed, uncorrelated data.²¹ In order to obtain smoother autocorrelation functions, the log transform of each incidence time-series was analyzed.²¹

The availability of only five years of monthly data limits our ability to resolve the period of multi-year oscillations. However, rather than yielding exact estimates of longer-term periodicities, the autocorrelation functions can be used to gain a sense of the importance of annual periodicity in relation to super-annual periodicity for each of the time-series.

Cluster analysis

Clustering of the ten time-series of province-specific measles incidence was performed to determine which provinces had similar patterns of incidence. Differences between time-series were measured as the Euclidean difference between two time-series. Hierarchical clustering using complete linkage was used to aggregate the time-series into clusters of similar patterns.²³ Time-series were log transformed and normalized by mean and standard deviation before using the clustering algorithm.

Results

Associations with cumulative incidence

Birth rate, vaccination coverage for both age groups, and the annual rate of new susceptibles were all found to be statistically significantly associated with cumulative incidence for the five-year period in a linear model. As expected, lower vaccination coverage (for both children under two years ($p < 0.003$, $R^2 = 0.68$) and children under five years ($p < 0.005$, $R^2 = 0.60$)), higher birth rates ($p < 0.018$, $R^2 = 0.53$) and higher annual rates of new susceptibles entering

the population ($p < 0.003$, $R^2 = 0.68$) are all statistically significantly associated with higher cumulative case rates of measles.

Inter-epidemic periods

The autocorrelation functions were calculated for each of the incidence time-series. The Extreme North province shows a dominant seasonal periodicity, with statistically significant peaks at 6, 12, 18, 24 and 28 months. The North province shows seasonal periodicity as well, with a statistically significant peak at 11 months. Adamaoua shows annual periodicity but no statistically significant peaks at lags greater than seven months.

The Northwest exhibits seasonal periodicity with positive correlation at lags of 12 and 24 months. The Southwest exhibits seasonality as well, but with its largest autocorrelation (for lags greater than one month) at a lag of 37 months, suggesting the presence of three-year periodicity.

The West, Center, East and Littoral provinces all have large peaks at approximately three years in periodicity. The only statistically significant peaks occurring at lags greater than one in the autocorrelation functions of the West and East provinces are at 34 and at 36–39 months, respectively. The Center province has a large peak at a lag of 36 months, the largest autocorrelation of lags greater than three months. The Littoral province shows seasonal periodicity in its autocorrelation function, but a somewhat larger peak at 36 months than suggested by annual periodicity. The autocorrelation function of the South time-series declines rapidly with increasing lag, showing no statistically significant peaks at lags greater than three months.

Cluster analysis

The cluster dendrogram resulting from hierarchical clustering of the province data is shown in Figure 5. The clusters most similar to one another are connected near the bottom of the dendrogram, while connections made at the top of the dendrogram represent the linkage of provinces that are relatively dissimilar to one another. The cluster consisting of the provinces in the north, the Extreme North, North and Adamaoua and the cluster consisting of the Center, East, Littoral and West provinces are quite self-similar, whereas the South, Northwest and Southwest provinces are less similar to the other provinces. These three provinces report a small proportion of the cases for the country. Figure 6 presents a map of the provinces colored by cluster assignments for an arbitrary cut-off level.

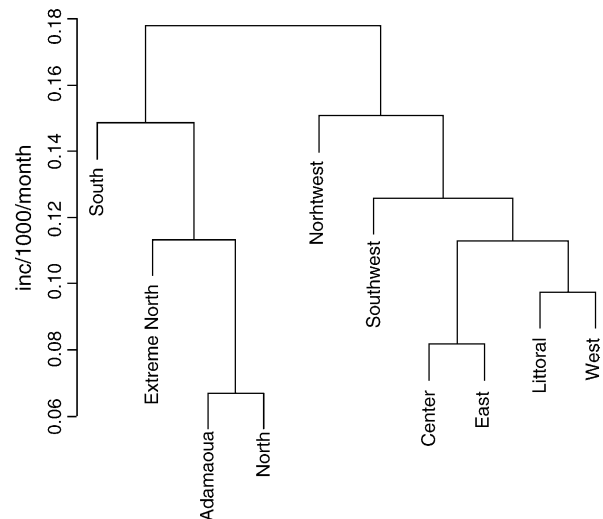


Figure 5 Dendrogram of hierarchical cluster analysis of monthly measles incidence from each province of Cameroon, 1997–2001.



Figure 6 Map of clusters from hierarchical clustering.

Discussion

An interesting pattern of measles incidence is revealed by the surveillance data from Cameroon. Different oscillatory behaviors in measles incidence are observed in different regions of the country. The northern region consisting of the Extreme North, the North and Adamaoua appears to experience large

epidemics every year, while data from the southern region, particularly the Center, East, West, Southwest and Littoral provinces suggest a three-year periodicity in the return of large outbreaks. The assignment of these two sets of provinces to different oscillatory patterns is supported by hierarchical clustering of the incidence series. Figure 7 presents incidence data for these two sets of provinces, with the sum of the incidence in the northern provinces on top and the sum of the incidence in the southern provinces mentioned above shown at the bottom. Differences in birth rate, population density and vaccination rate across provinces could explain the observations, however, differences in virology, and barriers to social contact or migration between regions could contribute to the different behaviors

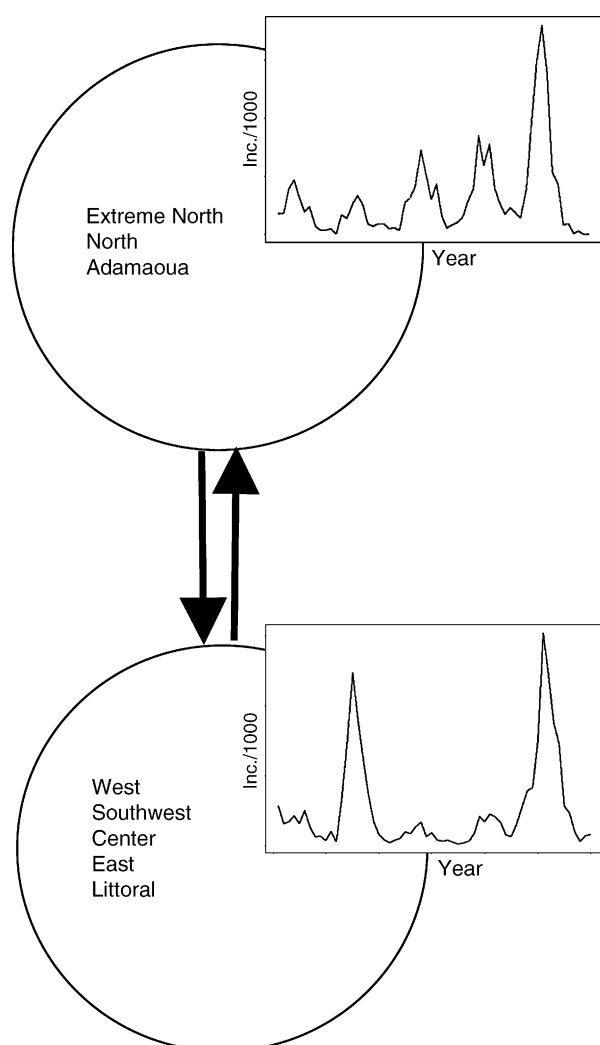


Figure 7 Abstract representation of multiple interacting dynamic patterns. The two circles represent the two parts of the country that have experienced different dynamic patterns of measles incidence. Inset are the sum incidence time-series of the provinces listed in each circle.

observed in these two regions. A subject of further study is how the dynamic oscillations of these two regions may interact. As Africa moves towards the elimination of measles country-by-country, understanding the interactions between populations with very different patterns of measles may become extremely important.

It is difficult to overstate the importance of long-term surveillance data in assessing immunization programs. The patterns of incidence observed in partially immunized populations are very difficult to discern without multiple years of data. The lengthening of the inter-epidemic period, initially encouraging, may present practical problems to countries in the midst of immunization campaigns. During the inter-epidemic period of reduced incidence, social expectations of immunization programs may increase, sparking doubts and concerns once an epidemic finally does take place.¹ Long-term surveillance allows for the assessment of an immunization program over longer time horizons and minimizes the demoralizing effect of 'post-honeymoon' outbreaks. Association of cumulative incidence rates over five years found that the provinces with the lowest incidence are those provinces that have the highest vaccination coverage.

The data shown in Figure 7 are highly suggestive that the recurrence of a major epidemic in the southern provinces after two years of low incidence explains the increase in countrywide incidence during January 2000 through June 2001. Of the 23 934 cases of measles documented in Cameroon in 2001, 47% occurred among the provinces found to have a dominant periodicity of approximately three years.

An extensive supplemental immunization campaign was undertaken in 2001 and 2002. In late 2001, just before the onset of the 2002 measles epidemic season, a supplemental mass immunization campaign was carried out in the three northernmost provinces (Extreme North, North, and Adamaoua), and in late 2002, just prior to the onset of the 2003 measles season, the supplemental mass immunization campaign was carried out nationwide. Preliminary data from 2002 show that these programs have greatly reduced the number of cases of measles reported across Cameroon. Continued long-term surveillance will allow the progress of these campaigns to be followed in years to come.

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Conflict of interest: No conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2004.10.010.

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