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Estimating transmission intensity for a measles epidemic in Niamey, Niger: lessons for intervention

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Summary The objective of this study is to estimate the effective reproductive ratio for the 2003—2004 measles epidemic in Niamey, Niger. Using the results of a retrospective and prospective study of reported cases within Niamey during the 2003—2004 epidemic, we estimate the basic reproductive ratio, effective reproductive ratio (RE) and minimal vaccination coverage necessary to avert future epidemics using a recent method allowing for estimation based on the epidemic case series. We provide these estimates for geographic areas within Niamey, thereby identifying neighbourhoods at high risk. The estimated citywide RE was 2.8, considerably lower than previous estimates, which may help explain the long duration of the epidemic. Transmission intensity varied during the course of the epidemic and within different neighbourhoods (RE range: 1.4—4.7). Our results indicate that vaccination coverage in currently susceptible children should be increased by at least 67% (vaccine efficacy 90%) to produce a citywide vaccine coverage of 90%. This research highlights the importance of local differences in vaccination coverage on the potential impact of epidemic control measures. The spatial—temporal spread of the epidemic from district to district in Niamey over 30 weeks suggests that targeted interventions within the city could have an impact.

1. Introduction

Although global incidence has been significantly reduced through vaccination, measles remains an important public health problem. Measles, the leading vaccine-preventable killer of children worldwide, is estimated to have caused 614 000 global deaths annually in 2002, with 50% of all

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global measles deaths occurring in sub-Saharan Africa (WHO, 2004a). The persistence of measles in many African countries points to the need to further investigate the dynamics of measles epidemics in endemic areas.

The reproductive ratio is the number of secondary cases that result from a single infectious individual in an entirely susceptible population. It is a key epidemiological quantity, because it determines the size and duration of epidemics and is an important factor in determining targets for vaccination coverage. Although a significant body of research modelling the epidemic dynamics and on estimating the reproductive ratio of measles has been conducted in industrialized countries (see for example: Anderson and May, 1991; Bjornstad et al., 2002; Bolker and Grenfell, 1995, 1996; Duncan et al., 1997; Fine and Clarkson, 1982; Grenfell, 1992; Mossong and Mullers, 2000; Wallinga et al., 2001; Xia et al., 2004), little research has focused on measles in countries with the greatest morbidity and mortality (McLean and Anderson, 1988a, 1988b; Broutin et al., 2005). Policy documents, many based on the results of these mathematical models, have provided important guidance for vaccination policies in industrialized nations, but may not adequately reflect epidemiological conditions in the developing world. Research focused on assessing the reproductive ratio in developing countries is essential to elucidate key shortcomings and subsequent areas for improvement to reduce measles morbidity and mortality.

The objective of this study was to estimate the reproductive ratio during the 2003—2004 measles epidemic in the urban area of Niamey, Niger. This will allow an assessment of the minimal vaccination coverage necessary to decrease the chances of a major epidemic in the future. That is, how many susceptible (unvaccinated or unsuccessfully vaccinated) children would have needed to be vaccinated, given the current population, to pre-empt a major epidemic? Using the results of a retrospective and prospective study of reported cases within Niamey, we are able to provide these estimates on a finer spatial scale than have been reported previously. We calculate the effective reproductive ratio using a recent method that allows estimation based on the epidemic case series (Ferrari et al., 2005).

Our estimates of the reproductive ratio within neighbourhoods of Niamey provide guidance for local policy-makers to identify areas of the city at greater risk. In addition, these estimates describe how the measles epidemic spread within the city. We demonstrate that the strength of transmission may have changed during the course of the epidemic with significant variations in intensity within the city.

1.1. Background

Niger, located in the Sahel region, had a total population of 11 972 000 people in 2004, with approximately 750 000 of these living in the urban community of Niamey (WHO, 2004b). The child mortality risk, defined as risk of death before age 5, is one of the highest in the world: 249 per 1000 (males) and 256 per 1000 (females) (WHO, 2004b). Measles is endemic—epidemic in Niger, with annual epidemics reporting 40 000 cases nationally almost every year (WHO, 2004b). Measles incidence exhibits annual seasonal cycling, with increased incidence coinciding with the dry season. Over a longer time frame, these epidemics show yearly cycling, often with 1—3 years of lower incidence, a 'honeymoon', followed by an epidemic (Figure 1). The previous epidemic in 2001 had 61 208 cases reported nationally (52.4/10 000). with 9184 cases (127.2/10 000) in the urban community of Niamey (WHO, 2004b).

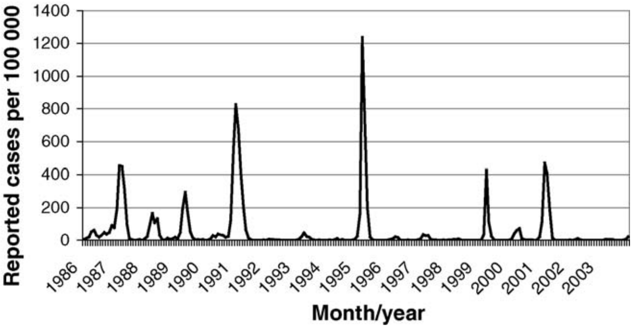

Figure 1 Reported cases of measles in Niger (1996—2003), Ministry of Health, Niger.

The national measles routine vaccination program [part of the Expanded Program on Immunization (EPI)], introduced in 1987, consists of one dose of vaccine, ideally administered in infants between 9 and 11 months, but with all children under age 5 eligible (Kaninda et al., 1998; Malfait et al., 1994; WHO, 2004a). There is no formal second opportunity for measles vaccination (two-dose schedule) currently in place (WHO, 2004a). Estimations of measles vaccination coverage (VC) over the past 15 years suggest that it has remained consistently inadequate (Kaninda et al., 1998; Malfait et al., 1994). In addition to the national vaccination programme, several mass vaccination campaigns have been organized with the aim of increasing the VC (national immunization days). In response to the continued epidemics, the medical non-governmental organization Médecins Sans Frontières (MSF), under the coordination of the Ministry of Health of Niger, also organized a vaccination campaign for measles, in conjunction with vaccination against meningococcal meningitis, in 2001 in the urban community of Niamey.

2. Materials and methods

2.1. Data

The data from the 2003—2004 epidemic in Niamey consists of reported measles cases to health centres, 'Centres de Santé Intégrés' (CSIs), and hospitals from a retrospective study (from 1 November 2003 to 20 April 2004) and prospective study (from 21 April to 6 July 2004) conducted during the epidemic by Epicentre in conjunction with the Ministry of Health, Niger, WHO and MSF. The WHO measles clinical case definition was used. At the beginning of the outbreak, 10 cases were laboratory confirmed through detection of measles-specific IgM antibodies by the Ministry of Health, Niger. Data on patients' quartier (neighbourhood) of origin, age, sex, date of symptom onset and vaccination status were collected.

The urban community of Niamey is divided into three districts (called communes) (Figure 2) with 34 CSIs and five

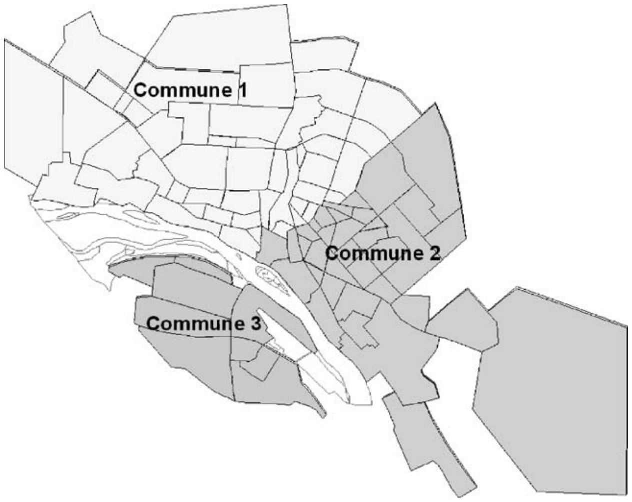

Figure 2 Administrative Districts (Communes) of Niamey, Niger.

hospitals. To estimate the population served by each CSI, the population of the quartiers served by each CSI were summed. The catchment area of each hospital was assessed in a similar manner. The quartier populations were extrapolated from the most recent census of residents (2001) using a 4.8% annual growth rate.

Estimates of the vaccine efficacy (VE) of measles vaccine, the proportion of vaccinees who gain protective immunity from the vaccination, vary by age at vaccination and epidemiological setting. Malfait et al. (1994) assessed age-specific measles vaccine efficacy using three different methods for the urban community of Niamey. The VE for children under 60 months ranged from 86 to 94% (WHO, 2004b), in agreement with previous estimates (Garly and Aaby, 2003). We assumed a VE of 90% and considered a percentage change of 5% during sensitivity analyses.

2.2. Estimation of the reproductive ratio

From a practical point of view, it is important to distinguish between two quantities: the basic reproductive ratio, R0, and the effective reproductive ratio, RE. R0 is defined by epidemiologists as the average number of secondary cases resulting from a single infectious individual in a completely susceptible population (Anderson and May, 1991). When R0 is greater than 1, the disease will spread, and when the reproductive ratio is less than 1, the infection will fail to spread. RE is the parallel quantity for partially immunized populations, such as those of Niamey. The minimal proportion of the susceptible population that needs to be removed (P), in this case vaccinated, from the susceptible population to pre-empt an epidemic, is given by 1−1/RE (Anderson and May, 1991; Mossong and Mullers, 2000). In practice, this translates into an increase in vaccination coverage of (1−VC)*P. This calculation assumes 100% VE. We modified the calculation to account for less than 100% efficacy by calculating the necessary removal proportion (P) as (1−1/RE)/VE, as has been used in past research on estimation of measles vaccine efficacy (Anderson and May, 1991; Mossong and Mullers, 2000). RE is further a determinant of the total number of susceptible individuals that will be infected, the overall duration of the epidemic, and the time to the epidemic peak. Therefore, RE provides information on the potential impact of an intervention at a given time during the course of an epidemic (Anderson and May, 1991).

Standard estimations of reproductive ratios are derived from continuous time epidemic birth and death processes. The data necessary to apply this model, collected in discrete units (days, weeks), leads to clear difficulties in model fitting of the continuous time birth-and-death process assumed by the standard ordinary differential equation SEIR epidemic models (Anderson and May, 1991). These models also make simplistic assumptions about the stochastic nature of epidemics, especially at the city level, and often assume perfect reporting. We developed an estimator for R0 based on a discrete time epidemic model, which better matches the timescale at which data are reported (Ferrari et al., 2005).

We model the time course of an epidemic as a chain of binomial infection events from the pool of susceptible (S) individuals (Bailey, 1975), such that the probability of I infected individuals at time t is given by:

$$P(I_{t+1} = I) = \binom{S_t}{I} (1 - e^{\beta S_t I_t})^I (e^{\beta S_t I_t})^{S_t - I}.$$

Noting that $S_t = S_0 - \sum_{j=1}^{t} I_j$, where S_0 is the initial number of susceptible individuals, we can write a likelihood for the time series of case counts, I_t, in terms of the transmission rate, β, and the initial number of susceptibles, S_0. We can then solve for these parameters using standard maximum likelihood methods. The use of discrete time steps to model a continuous time infection process introduces a small bias, which can be corrected using the method detailed in Ferrari et al. (2005). This method also allows for key epidemiological inputs into the model to vary, yielding a time- and place-specific estimate not possible in more conventional approaches. We calculated the CSI-specific reproductive ratios (R0 and RE) and removal proportions for the epidemic for susceptible children under 5.

3. Results

3.1. Description of the epidemic

The measles epidemic in Niamey started in November 2003 (defined by a sharp increase in reported cases over a period of 3 weeks), with peak cases reported in March 2004 (Figure 3). The epidemic began to subside at the end of April 2004. In total, the epidemic lasted 30 weeks. Between 1 November 2003 and 6 July 2004, a total of 10 880 cases was reported to the CSIs and regional hospitals. The overall attack rate reached 1.4% (10 880/769 454), 3.5% for children under age 5 (5774/163 894), 3.7% for children under age 1 (1334/36 164) and 7.1% for children between 6 and 9 months (640/9003). At the district level, 5789 cases were reported in District 1, 3598 in District 2 and 587 in District 3.

A reinforcement of EPI activities was organized between 9 and 16 April (the 24th week of the epidemic). Over that week, 56.9% of children between the ages of 6 and 59 months

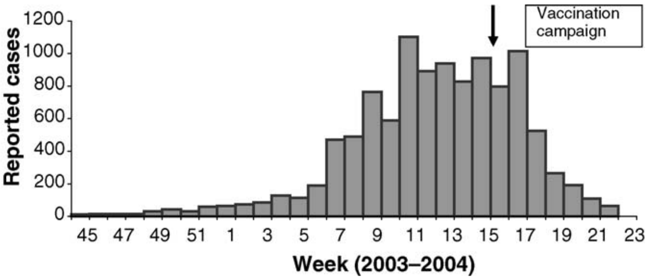

Figure 3 Number of reported cases of measles in the urban community of Niamey, 1 November 2003 to 6 June 2004.

(84 563/148 595) were vaccinated at health centres. There was considerable range in the number of children reached in different CSIs. The total vaccination coverage reached after the campaign was estimated to be 71.2% (confirmed by vaccination card) by a Lot Quality Assurance Sampling survey (Epicentre unpublished data, 2004).

3.2. Estimation of the reproductive ratio and the percentage of susceptibles requiring vaccination (P)

Age in months was not available for 30% of reported cases. Of cases with age reported, 79.9% occurred in children less than 60 months (6148/7691). For Niamey as a whole, we estimated the RE to be 2.5. At the scale of individual CSIs, estimates of RE ranged from 1.4 to 4.7 (median = 2.8). Table 1 shows the estimated RE and 95% CI for each CSI. Assuming 70% total immunity in the population (Ministry of Health vaccination coverage estimate) at risk (children under 60 months) due to vaccination or previous exposure, this translates to estimates of R0 for individual CSIs ranging from 4.7 to 15.7 (Figure 4).

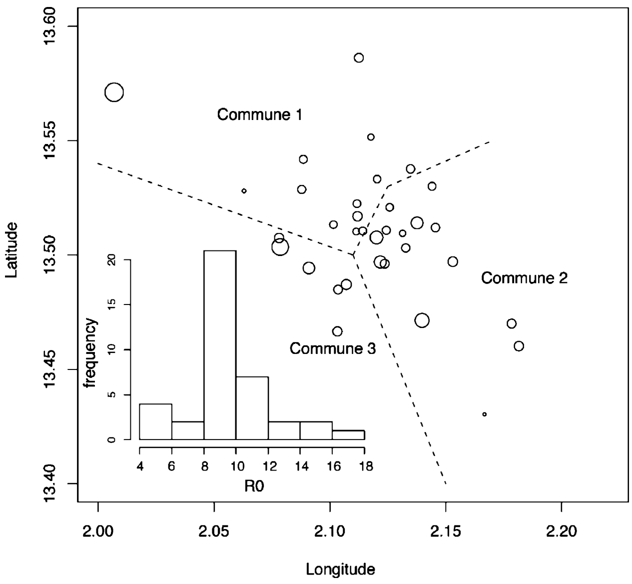

Figure 4 Distribution of estimates of R0 for Niamey epidemic. Areas of circles give magnitude of R0 for each CSI. Inset gives histogram of R0 estimates in CSIs.

Table 1 Estimated RE and 95% CI by CSI

Commune	CSI	RE	95% CI[a]	
Commune 1	Foulan Kouara	2.8	2.2	2.9
	Banifandou	2.8	1.9	3.0
	Garde Républicaine	2.7	1.5	3.4
	Gendarmerie	2.6	1.1	3.5
	Recasement	2.7	1.9	2.8
	Deyzeibon	2.6	1.7	2.9
	Maourey	3.0	2.1	3.2
	Yantala	2.7	1.9	2.8
	Tondibia	4.7	3.2	5.6
	Boukoki	2.6	NA	NA
	Goudel	1.6	NA	NA
	Lazaret	2.0	1.8	2.0
Commune 2	Abidjan	2.5	1.9	2.5
	Aéroport I	2.9	2.0	3.2
	Aéroport II	3.0	1.9	3.5
	Banigoungou	1.4	0.8	1.4
	Kalley	2.7	1.8	3.0
	Madina	2.6	2.2	2.6
	Nouveau Marché	2.3	1.6	2.4
	Saga	3.9	3.0	4.2
	République	1.6	NA	NA
	Talladjé	3.1	2.2	3.2
	Gamkallé	2.9	1.8	3.5
	Camp Bano	3.5	2.2	4.3
	Cité Fayçal	2.8	1.2	3.4
	FAN	3.0	2.3	3.7
	Wadata	2.8	2.1	2.7
Commune 3	Karadjé	3.5	2.2	3.9
	Saguia	3.0	1.1	4.5
	Lamordé I	3.0	1.5	5.3
	Lamordé II	4.4	2.8	5.4
	Gawey	2.9	2.0	3.2

NA: not applicable.

[a] 95% CI for RE estimates are presented where possible for CSI.

Across all CSIs, the median increase in vaccination coverage of susceptible children, i.e. to pre-empt an epidemic in 50% of the CSIs, is 67%, assuming 90% VE. This translates into a citywide increase in vaccination coverage from 70 to 90%. There was significant variation when looking at individual CSIs. The minimum additional vaccination coverage increase necessary to avert epidemics at the local scale ranges from 32% in Banigoungou (District 2) to 93% in Tondibia (District 1), assuming 90% VE. Overall, the removal proportion increased non-linearly with decreasing vaccine efficacy at different levels of RE. For a decrease VE of 5%, the removal proportion increased from 2 to 6% at increasing values of RE. Table 2 shows estimated RE value and the corresponding increase in vaccination coverage required for the susceptible population at three different assumptions of vaccine efficacy.

When the CSI-specific REs are explored in a spatial—temporal context, a general trend emerges. As the epidemic progressed, the strength of transmission also increased slightly. It was also apparent that the outbreak originated in District 1, then progressed to District 2, with District 3 the last to report cases. Figure 5 shows the progress of the

Table 2 Estimated RE and the proportion of susceptible children requiring vaccination to prevent a future epidemic at three different assumptions of vaccine efficacy

RE	Vaccine efficacy (%)		
	85	90	95
1.3	0.34	0.32	0.3
1.6	0.44	0.42	0.39
2.3	0.66	0.63	0.59
2.6	0.72	0.68	0.65
2.7	0.74	0.7	0.66
2.8	0.76	0.71	0.68
2.9	0.77	0.73	0.69
3.0	0.78	0.74	0.7
3.1	0.8	0.75	0.71
3.5	0.84	0.79	0.75
3.9	0.87	0.83	0.78
4.4	0.91	0.86	0.81
4.7	0.93	0.87	0.83

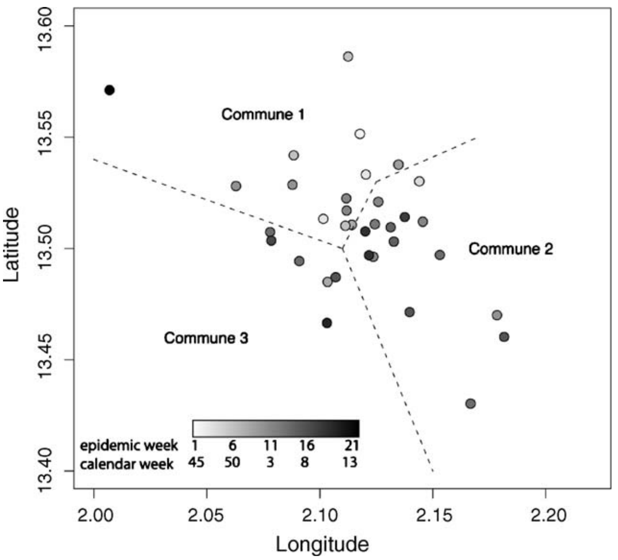

Figure 5 Spatial and temporal spread of the epidemic by CSI. The shading of the circles reflects the date of the first reported case (white = early; black = late).

epidemic in the urban community of Niamey by calendar week and epidemic week in 4-week intervals.

4. Discussion

The results of this research suggest that measles dynamics in urban African settings may have some similarities to those in industrialized settings, but also present many key differences that should be considered when designing and evaluating epidemic response plans. Standard estimates for the reproductive ratio of measles are between 12 and 20 for an entirely susceptible population (Anderson and May, 1991). Our estimates of both R0 and RE are lower than this. The low REs estimated here may also help explain the prolonged duration of epidemics. These results suggest that the dynamics of measles in African urban environments requires further reflection.

The differences in R0 in our analysis may reflect differences in mixing patterns among children in different areas of the city. Higher values of R0 were not clustered in any particular commune of the city. In District 3, R0 values were slightly higher, although not statistically different from the other two districts (Wilcoxon rank-sum test). Relatively large and small values of R0 were found in each of the three communes, suggesting that mixing patterns vary at a small spatial scale. Our lower estimates of R0 also point to the importance of collecting information on population mixing within African cities and performing additional research on the spread of infectious disease within these settings. Assumptions of population mixing from industrialized settings may not apply to resource-poor contexts such as Niamey. Limited internal mobility within the city (limited public transportation and mobility in certain areas due to non-navigable roads) may contribute to different epidemic dynamics from those in industrialized cities. Values of RE also varied within neighbourhoods. These differences highlight neighbourhood differences in susceptibility of the population at risk, due either to lower routine vaccination coverage or natural exposure.

Although some previous evidence suggests that epidemics may not be averted once cases have been reported in urban areas (Strebel and Cochi, 2001), our analyses point to the importance revisiting our assumptions about how measles epidemics spread in developing countries. The relatively low overall RE and long duration of this epidemic points to the importance of tailoring epidemic control strategies and routine vaccination policies to specific population dynamics. The geography of African cities, population densities, migration and local differences in vaccination coverage within cities play an important role in the forecast impact of control measures once an epidemic has begun. The apparent spatial—temporal spread of the epidemic from district to district in Niamey suggests that targeted interventions within the city may have had some impact, although the feasibility of such interventions is another question.

Our results also provide further evidence that present vaccination levels are insufficient to prevent further outbreaks in Niamey. The WHO and UNICEF developed a joint strategic plan for measles mortality reduction, including a goal of improving routine vaccination coverage to above 80% in all districts (WHO, 2004a). Although the vaccination coverage in Niamey has apparently been increasing from 61% in all age groups in 1990 (Malfait et al., 1994), through 69% in 1995 (Kaninda et al., 1998) to 71.2% in 2003—2004 (Epicentre unpublished data, 2004), higher vaccination coverage levels must be achieved to break the endemic—epidemic cycle of measles transmission.

Although increasing vaccination coverage is a clear goal, how to achieve this is the subject of debate. Lowering the recommended age of first vaccination from 9 to 6 months could potentially reduce mortality in the youngest age groups. Despite the fact that measles seroconversion does not reach high levels until vaccination at 9 months (80—85%) and better still at 12 months (98%), due to the interference of maternal antibodies, targeting this vulnerable age group should be re-evaluated (WHO, 2004a). Large-scale mass vaccination campaigns in anticipation of future epidemics are an effective way to rapidly bring measles transmission under control and help to provide a second vaccination opportunity for many children. However, the impact of these campaigns is likely to be limited unless there is a strong routine immunization programme preventing the build-up of numbers of susceptible children (Strebel et al., 2003; WHO, 2004a). A combination of improving routine coverage, catch-up campaigns and strengthening surveillance systems are necessary to achieve long-term reductions in morbidity and mortality.

The results of this research, identifying areas with low vaccination coverage within Niamey, could be used for targeted vaccination reinforcement activities before the next epidemic. The methodology applied in this research could also be used in other endemic—epidemic settings to identify areas at higher risk within urban communities. Even applications of this methodology at the city level provide an additional indicator of the level of vaccination coverage without requiring additional data collection.

There are several important limitations to this analysis that require discussion. We estimate the reproductive ratio based on CSI of residence. Cases may consult in a clinic other than their neighbourhood clinic, but we feel that this would not lead to a significant difference in the estimation of the reproductive ratio for CSIs in Niamey. Even if significant differences in CSI consult compared to case residence occurred, interventions would be put into place at the CSI level. Therefore, identification of higher-risk CSIs would remain the same. Further, our analysis is based only on cases of measles that consulted. Consulted cases are likely to be an underestimate of the actual number of cases and therefore of the realized RE and removal proportion necessary to avert an epidemic. We also excluded cases where we could not verify the age of the individual. This would not be likely to bias our results, as with many measles epidemics, the greatest number of cases occurred in children below 60 months (83.1%). We also did not calculate age-specific reproductive ratio for each CSI. It may be the case that R0 and/or RE estimates vary considerably within this age range. Calculating the age-specific RE is a clear direction for future research to explore further groups with the highest risk and transmission intensity.

5. Conclusions

Mathematical models of epidemic dynamics like the one employed here serve to highlight areas where additional discussion and research is needed. Our results indicate the importance of attaining high vaccination coverage to prevent epidemics. In addition, improving early warning and disease surveillance systems, and early institution of control measures during outbreaks are of clear importance. As has been suggested previously, implementation of a formal two-dose schedule once high vaccination coverage is achieved (WHO, 2004b) should also be evaluated.

Conflicts of interest statement

The authors have no conflicts of interest concerning the work reported in this paper.

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