

Time is of the essence: exploring a measles outbreak response vaccination in Niamey, Niger

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The current World Health Organization recommendations for response during measles epidemics focus on case management rather than outbreak response vaccination (ORV) campaigns, which may occur too late to impact morbidity and mortality and have a high cost per case prevented. Here, we explore the potential impact of an ORV campaign conducted during the 2003–2004 measles epidemic in Niamey, Niger. We measured the impact of this intervention and also the potential impact of alternate strategies. Using a unique geographical, epidemiologic and demographic dataset collected during the epidemic, we developed an individual-based simulation model. We estimate that a median of 7.6% [4.9–8.9] of cases were potentially averted as a result of the outbreak response, which vaccinated approximately 57% (84 563 of an estimated 148 600) of children in the target age range (6–59 months), 23 weeks after the epidemic started. We found that intervening early (up to 60 days after the start of the epidemic) and expanding the age range to all children aged 6 months to 15 years may lead to a much larger (up to 90%) reduction in the number of cases in a West African urban setting like Niamey. Our results suggest that intervening earlier even with lower target coverage (approx. 60%), but a wider age range, may be more effective than intervening later with high coverage (more than 90%) in similar settings. This has important implications for the implementation of reactive vaccination interventions as they can be highly effective if the response is fast with respect to the spread of the epidemic.

Keywords: epidemiology; vaccination; measles

1. INTRODUCTION

Measles epidemics represent a continuing public health problem in countries that have not effectively implemented routine immunization programmes, as recommended in the WHO/UNICEF measles mortality reduction strategy (WHO 2001). In the event of an epidemic, the key issue is whether a reactive vaccination campaign is worth mounting. The current World Health Organization (WHO) recommendations for responding to measles epidemics in urban areas focus on case management rather than outbreak response vaccination (ORV). This is because the latter is generally thought to occur too late to have an impact on morbidity and mortality; instead, the associated cost of mortality prevention may be more effective if spent on post-

infection health care (WHO 1999). If implemented, the WHO recommendations suggest that vaccination interventions should be concentrated only in areas, where measles virus transmission has not yet occurred, or in closed high-risk populations, such as refugee camps, military camps or schools. Limited resources may be more effectively used to strengthen routine measles coverage. Some previous studies suggest that reactive vaccination will not stop epidemics because measles transmission is so rapid (Aylward *et al.* 1997; Grenfell *et al.* 2001; Strebel & Cochi 2001). Other analyses, however, point to the potential benefits of vaccination interventions in high-burden settings (Broutin *et al.* 2005; Grais *et al.* 2006*a,b*).

During a recent outbreak in Niamey, Niger (2003–2004), the Ministry of Health (MoH) and WHO organized an ORV campaign in the city, with the support of the medical non-governmental organization, Médecins Sans Frontières (MSF). The campaign began

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127 161 days (23 weeks) after the beginning of the epidemic
 128 (defined by a sharp increase in reported cases over a
 129 period of three weeks). The goal of this activity was to
 130 vaccinate 50% of all children aged 6–59 months (the age
 131 group at highest risk) living in Niamey. Considering the
 132 extent of the epidemic and limited resources available
 133 at that time, this objective was reached over 10 days,
 134 during which approximately 57% of children aged 6–59
 135 months received measles vaccine regardless of previous
 136 vaccination status or disease history; 84 563 vaccines
 137 were dispersed across the risk group, estimated to
 138 comprise 148 595 individuals.

139 Three key questions arose from this ORV cam-
 140 paign: (i) What was the impact of the intervention in
 141 terms of the number of cases averted? (ii) How many
 142 cases could have been averted had the intervention
 143 occurred earlier? (iii) What difference would it make if
 144 the target age range was expanded to all children aged
 145 6 months to 15 years? Mathematical models are useful
 146 to address these questions and provide important
 147 insights into the impact of reactive vaccination
 148 campaigns (Tildesley *et al.* 2006). Although a large
 149 body of research has been devoted to modelling
 150 measles transmission dynamics and routine vac-
 151 cination strategies (Remme *et al.* 1984; McLean &
 152 Anderson 1988*a,b*; Nokes *et al.* 1990; Bolker & Grenfell
 153 1996; Bjørnstad *et al.* 2002; Scott *et al.* 2004;
 154 Cummings *et al.* 2006), little research has focused on
 155 control of measles outbreaks in high-burden settings
 156 once epidemics have taken off.

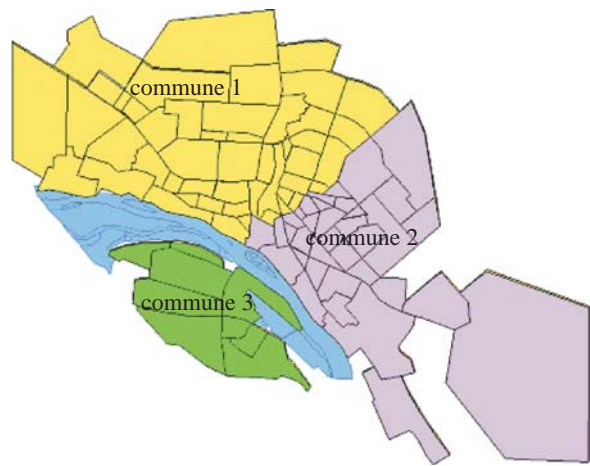
157 The slow stochastic spatial spread of measles in
 158 Niger revealed by previous studies suggests that a
 159 prompt reactive intervention may reduce morbidity
 160 (Grais *et al.* 2006*a,b*). Here, we explore the impact of
 161 ORV on the 2003–2004 epidemic in Niamey, Niger. We
 162 examine the impact of the intervention and the
 163 probable impact of other campaigns, using an individ-
 164 ual-based simulation model, firmly rooted in epidemio-
 165 logical data.

166 2. METHODS

167 2.1. Study setting

172 Measles exhibits seasonal outbreaks in Niamey with
 173 increased incidence during the dry season (November
 174 to May). Over a longer timeframe, major epidemics
 175 have occurred in Niamey every 2–4 years, with 1–3
 176 years of reduced incidence following major epidemics.
 177 The epidemic in 2001 reported 9184 measles cases
 178 (WHO 2004*a*).

179 The national measles routine vaccination strategy
 180 consists of one dose of vaccine, administered to infants
 181 between 9 and 11 months, but with all children under
 182 age 5, being eligible to receive vaccine (WHO 2004*b*).
 183 There is no routine second opportunity for measles
 184 immunization (i.e. a two-dose schedule) currently in
 185 place (WHO 2004*b*). Supplementary mass vaccination
 186 campaigns, called SIAs, have been organized previously
 187 with one occurring in 2001, 2 years before the 2003–
 188 2004 epidemic. The WHO/UNICEF coverage estimate
 189 for the country in 2003 was 64% (WHO 2004*b*).



Q3 Figure 1. Map of Niamey, Niger showing the three communes and quarters.

202 2.2. Data sources

203 2.2.1. Population, surveillance and vaccine coverage.

211 The city of Niamey is divided into three communes
 212 (districts; figure 1). Within these are 33 Centre de Santé
 213 Intégré (CSI) or health centres, serving 104 quartiers
 214 (neighbourhoods). Estimates of the size and age
 215 structure of the population were obtained from the
 216 2001 Niger National Population Census. Assuming a
 217 4.8% annual growth rate, the city population at the
 218 time of the epidemic was estimated to be 769 454. Only
 219 total quartier population sizes were available. The
 220 population served by CSIs was assumed to be the sum
 221 of each of the quartiers in the catchment area. The
 222 population of each commune was estimated as the sum
 223 of all quartiers in the commune. As both the at-risk
 224 population for measles and the target population for
 225 intervention were children under 15 years, we restricted
 226 our analysis to this age group. Given the age pyramid
 227 for Niger in 2005 (Brown *et al.* 1999; US Census Bureau
 228 2005), 45% of the population was estimated to be under
 229 15 years, of which 46% are estimated to fall in 6–59
 230 months age range and 54% in the 5–14 years range.

231 Surveillance data consisted of reported measles cases
 232 to each CSI between 1 November 2003 and 6 July 2004.
 233 Measles was diagnosed clinically using the WHO case
 234 definition and laboratory confirmation was not routi-
 235 nely performed (Guris 2001). At the beginning of the
 236 outbreak, 10 cases were laboratory confirmed by the
 237 MoH through detection of measles-specific IgM
 238 antibodies in sera collected after rash onset. The start
 239 of the epidemic was identified retrospectively as
 240 occurring during the last week of October 2003, when
 241 four cases were reported in commune 1. The peak in
 242 case reports were in March 2004 with the epidemic
 243 beginning to subside in April 2004. In total, the
 244 epidemic lasted 30 weeks (1 November 2003 to 6 July
 245 2004) with 10 880 cases reported citywide. At the
 246 commune level, 5789 cases were reported in commune
 247 1, 3598 cases in commune 2 and 587 cases in commune 3
 248 (Dubray 2004; Dubray *et al.* 2006). Cases were first
 249 reported in commune 1, spreading several weeks later
 250 to commune 2 and were not reported in commune 3
 251 until later in the epidemic (see figure 2 for epidemic
 252 curves by commune and figure 3 for the citywide

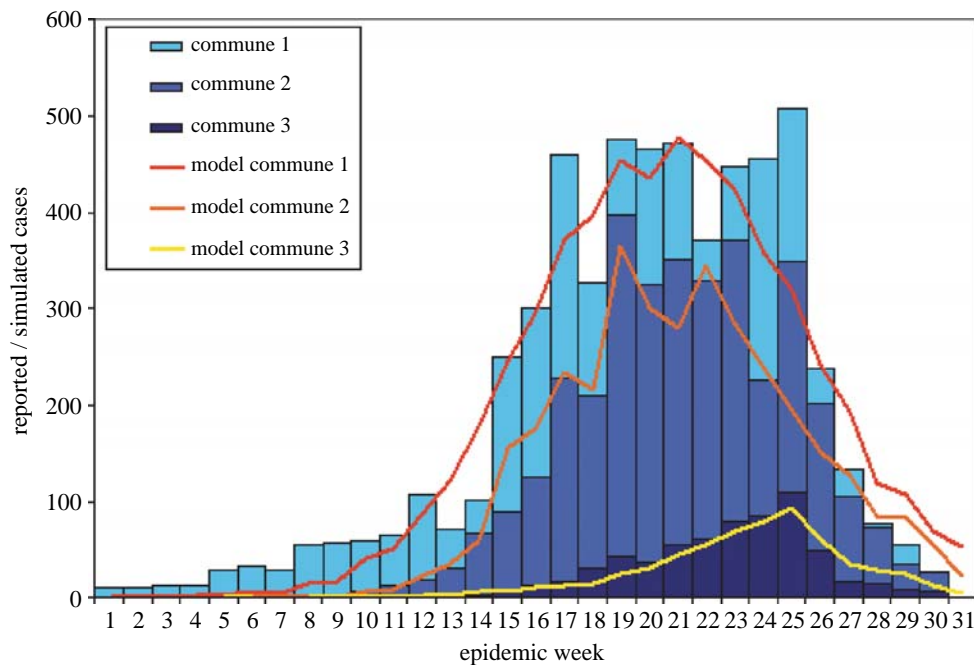


Figure 2. Reported measles cases in Niamey, Niger (November 2003 to July 2004) by commune and the performance of the model by commune. The solid lines depict the median forecast epidemic curve over 1000 simulations including the vaccination intervention targeting 50% of children aged 6–59 months for each commune.

epidemic curve). Further epidemiological details of this epidemic have been described previously (Dubray 2004; Dubray et al. 2006).

In 2003, measles vaccination coverage (VC) in children aged 9–11 months was estimated to be 62.0% in commune 1, 68.0% in commune 2 and 75.4% in commune 3 by the MoH (Dubray 2004). The citywide VC estimated by a Lot Quality Assurance Survey was 60.1% (95% CI: 57.9–61.9) before the vaccination intervention and 70.9% (95% CI: 68.8–72.6) after the intervention, based on both parental recall and vaccination card confirmation (Dubray et al. 2006).

2.3. Model structure

We developed an individual-based computational model for the 2003–2004 measles epidemic in Niamey. The infection process was modelled stochastically using a discrete-time model formulation with a 1-day time-step.

Our previous study of this epidemic (Grais et al. 2006b) revealed a slow spatial spread between communes, with more rapid local transmission within quarters. Children were therefore assumed to belong to one of the 104 quarters of the city. We assumed the probability of a susceptible child becoming infected to be a function of the numbers of infectious children at the quarter, CSI catchment, commune and citywide scale with a reduced rate of interaction at each greater scale. On day $t+1$, the probability $P_{q,t+1}$ that a susceptible child in quarter q is infected is assumed to be governed by

$$P_{q,t+1} = 1 - \exp \left\{ - \left(\frac{\beta_{\text{quarter}} I_{q,t}}{N_q} + \frac{\beta_{\text{CSI}} I_{\text{CSI},t}}{N_{\text{CSI},q}} + \frac{\beta_{\text{commune}} I_{\text{commune},t}}{N_{\text{commune},q}} + \frac{\beta_{\text{city}} I_{\text{city},t}}{N_{\text{city}}} \right) \right\}, \quad (2.1)$$

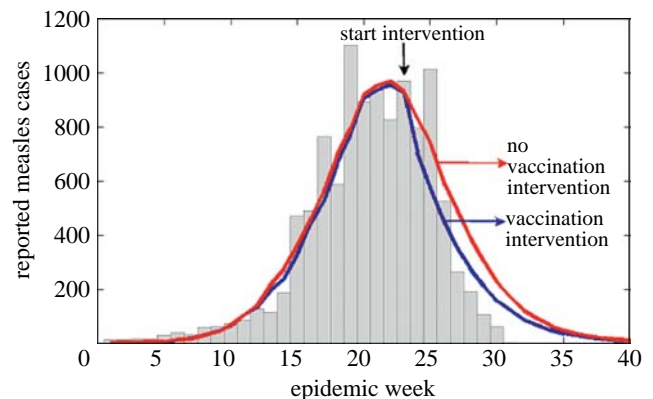


Figure 3. Simulation of epidemic with and without vaccination intervention. The number of reported measles cases per week is shown in the grey histogram. The blue line depicts the median forecast epidemic curve over 1000 simulations including the vaccination intervention targeting 50% of children aged 6–59 months. The red line shows the median of 1000 simulations of the forecast epidemic curve without any intervention.

where β_{quarter} is the transmission rate between children within the same quarter, β_{CSI} within the same health centre catchment area, β_{commune} within commune and β_{city} as the citywide scale. The variables $I_{q,t}$, $I_{\text{CSI},t}$, $I_{\text{commune},t}$ and $I_{\text{city},t}$ are the quarter-specific number of infectious individuals on day t , i.e. $I_{\text{CSI},t}$ is the number of infectious individuals in the particular CSI that contains quarter q , etc. The parameters N represent the appropriate scale-specific total population sizes for each quarter, CSI catchment area, commune and the citywide total.

At each time-step, susceptible children are assumed to be infected with a binomial probability $p_{q,t+1}$, i.e. $I_{q,t+1} \sim \text{Binom}(S_{q,t+1}, P_{q,t+1})$. Once infected, the

infectious process is assumed to be deterministic; children are infected but not infectious (latent) for 10 days and infectious for 6 days (Heymann 2004). Upon recovery, children progress into the removed class and are assumed immune for the remainder of the epidemic (and the remainder of their life).

We evaluated the result of the ORV in terms of response time and the target coverage percentage. For enhanced realism, we assumed a 15-day delay between the decision to intervene and the implementation of the ORV, based on MSF experience (Medecins Sans Frontiers 1999). Once vaccinated, children were assumed to progress through a period of 3 days during which they have partial protection (50%) before full immunity (Heymann 2004). We quantified the effect of the ORV as the ratio of the predicted final size of the epidemic with intervention to that without.

Given the estimated citywide VC (see above) and natural immunity, we assumed that 30% of children under 15 years of age were susceptible (not vaccinated, unsuccessfully vaccinated or have no naturally acquired immunity). Of these, we assumed that 75% would be children between 6 and 59 months based on the age pyramid (see above) and an assumption that prior immunity (natural or vaccine provided) was higher in the 5–15-year group than in the younger age group. Vaccines were assumed distributed at random across the risk group. Vaccine efficacy during the ORV was assumed to be 85% (with allowance for the partial immunity during the 3 days just after vaccination; WHO 2004b).

We simulated 1000 stochastic epidemics over a period of 365 days beginning from an index case located in the same quartier where the first case was reported in commune 1. A paired Wilcoxon rank sum test was used to evaluate the performance of the model fit: if the p -value obtained is greater than 0.05, then the null hypothesis that simulated and observed epidemic curves are from the same distribution cannot be rejected. For this assessment, only simulated epidemics that ‘took off’—for which at least 10 cases were predicted—were included. We performed the statistical test for each simulation run and for the median epidemic.

2.4. Model calibration

As the surveillance data available to calibrate the model included the ORV campaign targeting 50% of children aged between 6 and 59 months living in Niamey over a 10-day period at week 23 (day 161), we calibrated the model including the campaign. We assumed that only a fraction of cases would be detected by the surveillance system, estimated at 50% based on previous analyses (Médécins sans Frontières 1996; Arudo *et al.* 2003; Grais 2006b).

Previous research on the data for this epidemic provided the estimates of the overall transmission rate within the city (Grais 2006a,b), following the removal method developed by Ferrari *et al.* (2005). The assumptions of this method are that on the time-scale of the epidemic generation time (Δt =latent + infectious period) of around two weeks, the epidemic progressed according to a chain-binomial model (e.g. Bailey 1957;

Ferrari *et al.* 2005), in which the binomial denominator is the pool of susceptible individuals, S_t , and the associated probability distribution for the expected number of new cases, $I_{t+\Delta t}$, is

$$P(I_{t+\Delta t} = I) = \binom{S_t}{I} (1 - e^{-\beta S_t I_t})^I (e^{-\beta S_t I_t})^{S_t - I}. \quad (2.2)$$

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 full likelihood for the time-series of case counts, I_t , in terms of the overall (i.e. ignoring within-city spatial heterogeneities) transmission rate, β , and the initial number of susceptibles, S_0 , according to standard likelihood theory (Ferrari *et al.* 2005).

To carry out this estimation, the time-series of day-specific case reports were aggregated in two-week time-intervals as detailed by Grais *et al.* (2006a). Based on this prior analysis and our assumption that transmission was more rapid at smaller spatial scales, the scale-specific transmission rates were chosen and fixed as 10 for local transmission within a quartier, 5 for transmission across quartiers within any given CSI catchment area, 2.5 between catchment areas within any given commune and 1.25 for citywide transmission.

2.4.1. Scenario analysis. Our principal aim was to study the impact of the intervention and explore the consequences of any earlier implementation. Although the survey conducted just after the epidemic provided an estimate of baseline pre-intervention VC (approx. 60%), we also used the model to examine higher (90%) and lower (50%) level of coverage and their associated predicted outcomes, given the ORV intervention strategies. We further explored several other candidate interventions by comparing proportions of cases potentially prevented by interventions at different times in the epidemic, the proportion of children targeted during the outbreak response intervention and different intervention lengths. We examined decisions to intervene at 60, 90 and 120 days from the start of the epidemic, with proportions of children (except those children who were classified as infectious) vaccinated between 30 and 100% at 10% increments. We explored vaccination interventions lasting 6, 10 and 14 days, and the difference between targeting only children aged between 6 and 59 months and targeting all children aged 6 months to 15 years. Results are presented as the median percentage of cases potentially averted compared to final epidemic size in the absence of intervention.

3. RESULTS

Overall, the median forecast epidemic curve from 1000 simulations is in good agreement with the observed dynamics of the 2003–2004 epidemic (paired Wilcoxon rank sum test, $p=0.25$; figure 3). No cases were predicted in 6% of 1000 simulations; in those runs for which cases were reported, 92.3% were in good agreement with the observed dynamics (paired Wilcoxon rank sum test, α -level=0.05).

505 In commune 1, where the epidemic began, cumu-
 506 lative cases were overestimated by a median of 0.5%
 507 (paired Wilcoxon rank sum test, $p=0.63$). The model
 508 performed less well in commune 2 (paired Wilcoxon
 509 rank sum test, $p=0.81$) and commune 3 (paired
 510 Wilcoxon rank sum test, $p=0.57$), where cumulative
 511 cases were overestimated by a median of 11.3 and
 512 13.4%, respectively, over 1000 epidemics (figure 2). The
 513 reasonable fit shown here—despite the simplicity of the
 514 model—gives us some confidence in our predictions
 515 regarding different scenarios of intervention.

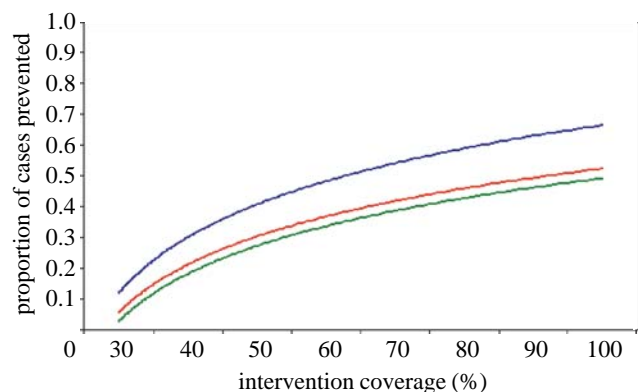
516 Comparing the simulated epidemic with and without
 517 the implemented vaccination intervention with an
 518 objective of vaccinating 50% of children between 6
 519 and 59 months at week 23 (day 161) from epidemic
 520 onset, we estimated a median of 7.6% [4.9, 8.9] cases
 521 averted (figure 3).

522 3.1. Scenario analysis

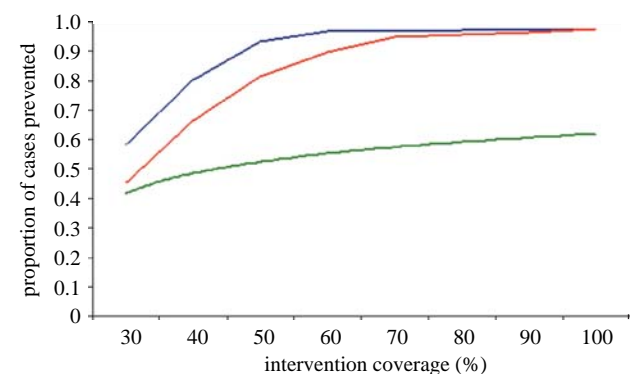
523 First, we examined the impact of the implemented
 524 intervention under two extreme scenarios of population
 525 susceptibility. Assuming only 10% of the eligible
 526 population susceptible, vaccinating children between
 527 6 and 59 months yielded a median estimated reduction
 528 of 55.9% [41.1, 59.3] cases. Expanding the age range to
 529 include children aged 6 months to 15 years yielded a
 530 median reduction of 70.8% [58.6, 88.6] cases compared
 531 with no intervention. Less benefit was seen when we
 532 assumed a VC of 50% in the eligible population
 533 susceptible. In this case, i.e. vaccination of children
 534 between 6 and 59 months, we estimated that a median
 535 18.1% [12.4, 20.2] of cases could be averted.

536 Second, we explored the proportion of cases poten-
 537 tially averted for interventions targeting from 30 to
 538 100% of non-infectious children aged 6–59 months with
 539 a decision to intervene at 60, 90 and 120 days from the
 540 start of the epidemic (figure 4). A target proportion of
 541 50% of children (except ill children) resulted in up to 38,
 542 27 and 20% of cases averted for campaigns at 60, 90 and
 543 120 days from the start of the epidemic, respectively.
 544 For campaigns at day 60, increasing the target
 545 proportion vaccinated from 30 to 40% led to up to an
 546 additional 18% of cases averted. Increasing the
 547 proportion vaccinated between 40 and 90% led to 5–
 548 9% additional cases averted for each 10% increase in
 549 coverage. There was little benefit in increasing the
 550 proportion vaccinated from 90 to 100%. Campaigns at
 551 90 and 120 days followed a similar pattern, with the
 552 greatest proportion of cases averted when the pro-
 553 portion vaccinated was increased from 30 to 40%, and
 554 no benefit was observed in increasing coverage from 90
 555 to 100%.

556 Third, we examined the proportion of cases averted
 557 if the intervention targeted all children aged 6 months
 558 to 15 years. For a campaign with an objective of
 559 vaccinating 50% of non-infectious children aged 6
 560 months to 15 years, up to 93% of cases were potentially
 561 averted at day 60, 81% at day 90 and 52% at day 120.
 562 Expanding the target population resulted in substan-
 563 tially more cases averted, but little additional gain was
 564 seen when increasing the proportion vaccinated during
 565 the intervention above 70% (figure 5).



568 Figure 4. Estimated proportion of cases averted with a
 569 vaccination intervention targeting children aged between 6
 570 and 59 months for a vaccination intervention lasting 10 days.
 571 The blue line shows an intervention at 60 days, the red line an
 572 intervention at 90 days and the green line an intervention at
 573 120 days.



581 Figure 5. Estimated proportion of cases averted with a
 582 vaccination intervention targeting children aged 6 months to
 583 15 years for a vaccination intervention lasting 10 days. The
 584 blue line shows an intervention at 60 days, the red line an
 585 intervention at 90 days and the green line an intervention at
 586 120 days.

587 Increasing the length of the intervention from 10 to
 588 14 days, holding all else constant, did not markedly
 589 change the forecast number of cases prevented (data not
 590 shown). There was no difference in the forecasted
 591 proportion of cases prevented when all age groups were
 592 targeted at vaccination target levels above 60%. For
 593 intervention vaccination objectives under 60%, there was
 594 a median 1% increase in the number of cases averted.
 595 Similarly, reducing the intervention length to 6 days,
 596 holding all else constant, with target intervention cover-
 597 age levels above 60% gained a median of an additional 1%
 598 of cases averted. In contrast, the 6-day intervention at
 599 lower coverage levels led to an additional median 2%
 600 increase in averted cases with an intervention proportion
 601 to be vaccinated of 50%, 3% of averted cases at 40%
 602 vaccinated and 4% of averted cases at 30% vaccinated.

603 4. DISCUSSION

604 Our analysis shows that substantial numbers of measles
 605 cases may be averted through the timely implemen-
 606 tation of measles ORV. Moreover, the proportion of
 607

631 cases averted is associated with the VC obtained and
 632 the number of birth cohorts targeted for vaccination.
 633 The operational implication of this analysis is that,
 634 from a public health perspective, it may be preferable to
 635 intervene earlier, across a wide age range even if a high
 636 intervention VC is not feasible, than waiting until
 637 sufficient resources are mobilized to conduct a mass
 638 campaign capable to reach 90–100% of targeted
 639 children. The key result is that ORV can be highly
 640 effective if the response is fast with respect to the spread
 641 of the epidemic. In Niamey, where epidemic spread is
 642 slow due to the spatial structure and mixing within the
 643 city, outbreak response may be particularly effective.
 644 While the predictions herein are specific to the Niamey
 645 model, we would expect the general utility of ORV to
 646 hold for any situation where the spread is slow relative
 647 to the response. Exploring further the relationship
 648 between spatial spread and reactive vaccination is an
 649 important area for future research.

650 Early interventions may work in two ways: first,
 651 vaccination may immunize a child before they become
 652 infected; and second, the vaccination response can slow
 653 down the epidemic and thereby reduce the total
 654 number of unvaccinated people who would be infected
 655 during the current outbreak. An early but inefficient
 656 response could be working in both ways, mostly
 657 through the first effect, but partly through the second.

658 We estimate that as a result of the intervention in
 659 Niamey, where the target was 50% of children aged
 660 between 6 and 59 months and the intervention took
 661 place about 161 days after the epidemic began,
 662 approximately 7% of cases were averted. Had this
 663 same intervention occurred earlier in the epidemic, we
 664 estimate from our model that up to 38% of cases could
 665 have been averted if the intervention had occurred at
 666 day 60 of the epidemic, up to 27% if it had occurred at
 667 day 90 and up to 20% if it had occurred at day 120.

668 Our results highlight the potential benefits of rapid
 669 intervention, even if a high intervention vaccination
 670 objective is not possible. Targeting children aged 6
 671 months to 15 years was much more effective in
 672 preventing cases than limiting vaccination to children
 673 aged 6–59 months. Experience in many parts of the
 674 world has found measles vaccination campaigns across
 675 wide age ranges to be much more effective in preventing
 676 periodic measles outbreaks (Arudo *et al.* 2003; Kambire
 677 *et al.* 2003; Munyoro *et al.* 2003). This is likely due
 678 to the role older children play in transmission to
 679 younger children and also the importance of limiting
 680 opportunities for virus reintroduction through popu-
 681 lation movement.

682 In any large measles epidemic, ORV averting 7% of
 683 cases can mean many lives saved. A retrospective
 684 mortality survey after the Niamey epidemic estimated
 685 a case fatality ratio in children under age 5 of 3.9%
 686 (Grais *et al.* 2007). In 2005, a mass vaccination
 687 campaign targeting children under age 15 was con-
 688 ducted in Niger. Surveillance data will be an important
 689 indicator of whether wide age range and wide geo-
 690 graphical area campaigns impact measles epidemics in
 691 future years.

692 Our model explicitly took into account the slow
 693 spatial progression of the epidemic (Grais 2006b). As we

694 expected, the analysis showed that the timing of the
 695 intervention plays a more important role than the
 696 proportion of children vaccinated. Intervening very
 697 early in the epidemic (60 days after the start), at
 698 relatively low VC, still led to a substantial proportion of
 699 cases averted. The added benefit of intervening at day
 700 60 decreased for vaccination objectives over 60%. The
 701 same pattern emerged when intervening 90 days after
 702 epidemic onset, where little added gain was seen for
 703 target coverage levels above 70%. Interventions
 704 120 days after epidemic onset still led to more than
 705 half of reported cases averted, when targeting all
 706 children aged 6 months to 15 years. A more intensive
 707 intervention (lasting for 6 days, versus 10 or 14 days)
 708 yielded slightly more averted cases than a longer
 709 intervention. Our results are also in agreement with a
 710 recent theoretical analysis, which found that the
 711 average outbreak size grew exponentially with the
 712 delay from the start of an outbreak to the implemen-
 713 tation of an intervention, highlighting the importance
 714 of early intervention (Drake 2005).

715 Our goal was to identify the key factors driving the
 716 number of potentially averted cases, and, as with all
 717 models, ours simplifies reality in a number of respects.
 718 Although model simulations were in agreement with
 719 the observed epidemic dynamics, we did not consider
 720 the details of the spatial dynamics. We are currently
 721 exploring the data using a full meta-population model
 722 with an explicit distance function for transmission. An
 723 additional area for refinement would also be to consider
 724 different assumptions concerning the distributions for
 725 the latent and infectious periods. Our analysis was
 726 constrained by the use of constant contact rates in the
 727 two age groups. Previous research on the force of
 728 infection for measles in pre-vaccination England and
 729 Wales has shown it to be strongly age dependent
 730 (Grenfell *et al.* 2001). In cities like Niamey, or other
 731 dense African cities, there is likely to be much greater
 732 inter-age-group contact, due to differences in household
 733 structure and formal education (Remme *et al.* 1984;
 734 Scott *et al.* 2004), and although we suspect that the
 735 impact of this simplification on our findings may not be
 736 significant, this warrants further investigation. We also
 737 assumed that the proportion of susceptibles was the
 738 same in all quarters, whereas a more refined model
 739 would consider heterogeneities.

740 Although we used surveillance data from a well-
 741 documented epidemic to calibrate the model and began
 742 to estimate the impact of ORV, the results presented
 743 here are only suggestive of potential trends. The
 744 individual-based computational model we used pro-
 745 vided a preliminary analysis to expose questions for
 746 future research and where data collection needs to be
 747 focused. A more detailed model, exploring different
 748 timeframes and modes of intervention, is required. This
 749 can be accomplished via theoretical models of epidemic
 750 diffusion and through a more in-depth analysis of other
 751 well-documented epidemics in similar contexts. We
 752 chose scenarios that were considered operationally
 753 feasible. An in-depth analysis considering different
 754 population immunity profiles and a more complete
 755 range of scenarios is required to investigate how the
 756 lessons learned here may be applied to other contexts.

757 Future collection of epidemiologic, demographic and
758 geographical data in other measles epidemics in similar
759 settings is also a high priority.

760 The model presented here captures only one
761 component of the complex decision whether or not to
762 implement measles ORV activities in an urban area,
763 and we were able to evaluate the impact of this
764 intervention with the aid of retrospective data. Early
765 intervention depends upon a sensitive and functioning
766 surveillance system and rapid response capacity, both
767 of which may be difficult to achieve in resource-poor
768 contexts. Moreover, most large measles outbreaks tend
769 to occur in countries with poorly performing health
770 systems with chronically low routine immunization
771 coverage. Determining whether a measles epidemic is
772 occurring remains difficult, especially in contexts where
773 surveillance systems are neither comprehensive nor
774 sensitive, and data from previous years are unavailable
775 for comparison. ORV in these settings will often occur
776 late in the timeline of an epidemic due to difficulties
777 caused by inadequate surveillance, poor logistics,
778 competing public health priorities, and cost and lack
779 of trained personnel.

780 The decision to implement measles ORV activities in
781 an urban area also depends on the population size,
782 previous routine measles immunization coverage,
783 history of vaccination campaigns and spatial charac-
784 teristics of the city itself. In a city such as Kinshasa,
785 DRC, where approximately one-half of the population
786 is under age 15, this means that an intervention during
787 an epidemic could target potentially millions of
788 children, which is not operationally feasible. An
789 additional constraint during interventions is that an
790 'efficient' campaign, like that modelled here, is selective
791 (targeting only children who were not previously
792 vaccinated). This is not always realistic in settings
793 where children do not always have comprehensive
794 medical records and where the precise age of children
795 may not be available. Further, as providing children
796 with a second-dose of measles vaccine affords increased
797 protection, efficiency must be balanced with issues of
798 logistics, economic and ethical constraints.

799 We demonstrate here that implementing a measles
800 ORV activity early in a measles epidemic in a resource-
801 poor urban setting with chronically low measles VC,
802 like Niamey, may lead to substantial reductions in
803 morbidity and subsequent mortality. However, ulti-
804 mately the decision whether or not to intervene and the
805 means to do so depend upon the political will of public
806 health authorities, and weighing the potential number
807 of cases averted with the economic and political costs of
808 conducting a measles vaccination campaign.

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