Practice of Epidemiology

Reaching Hard-to-Reach Individuals: Nonselective Versus Targeted Outbreak Response Vaccination for Measles

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Current mass vaccination campaigns in measles outbreak response are nonselective with respect to the immune status of individuals. However, the heterogeneity in immunity, due to previous vaccination coverage or infection, may lead to potential bias of such campaigns toward those with previous high access to vaccination and may result in a lower-than-expected effective impact. During the 2010 measles outbreak in Malawi, only 3 of the 8 districts where vaccination occurred achieved a measureable effective campaign impact (i.e., a reduction in measles cases in the targeted age groups greater than that observed in nonvaccinated districts). Simulation models suggest that selective campaigns targeting hard-to-reach individuals are of greater benefit, particularly in highly vaccinated populations, even for low target coverage and with late implementation. However, the choice between targeted and nonselective campaigns should be context specific, achieving a reasonable balance of feasibility, cost, and expected impact. In addition, it is critical to develop operational strategies to identify and target hard-to-reach individuals.

hard-to-reach individuals; Malawi; measles; outbreak response; vaccination

Abbreviation: MSF, Médecins sans Frontiers.

The World Health Organization (Geneva, Switzerland) guidelines for response to measles outbreaks in countries with mortality reduction goals recommend vaccination campaigns as an effective control measure. If there are sufficient resources and a high risk of a large outbreak, campaigns should be nonselective with respect to the immune status of individuals (1). The underlying arguments for nonselective campaigns are both logistical and medical. The speed of response is a critical determinant of the success of an outbreak response (2), and the vaccination status of children is seldom known because of weak or absent vital registration systems and public health infrastructure. Nonselective campaigns, which do not require verification of vaccination status, facilitate swift implementation of the intervention. In addition, nonselective campaigns provide a second-dose opportunity for those who failed to seroconvert after the first dose.

A necessary consequence of nonselective vaccination is that a portion of vaccine doses will be delivered to individuals who are already immune because of a previous vaccination or infection (L. Grout, Epicentre, unpublished data, 2011). Under the assumption that immune and nonimmune individuals are vaccinated in proportion to their representations in a population, the coverage of nonimmune individuals should equal the population coverage for a nonselective campaign. However, even nonselective campaigns may preferentially favor those with high access to vaccination or willingness to be vaccinated (3). In that event, the effective coverage of a nonselective campaign (i.e., the coverage of nonimmune individuals) will be less than or equal to the population coverage of the campaign. Understanding the potential impact of this interaction between heterogeneity in immunity and the potential bias in vaccination during campaigns is critical to predicting the impact of campaigns.

Heterogeneity of access to vaccination and the likelihood of vaccination during nonselective campaigns confound efforts to quantify the remaining susceptible population and subsequent outbreak risk. The distribution of hard-to-reach

individuals and groups with low immunity within a population is difficult to assess a priori. Some low-immunity communities may be easily identifiable (e.g., groups with low physical access to health care or those who refuse vaccination for religious or cultural reasons (4, 5)). However, heterogeneity may also arise because of suboptimal measles control programs, allowing the progressive building-up of unprotected individuals. This may be particularly likely in low-transmission settings, where natural infection contributes little to the distribution of immunity.

Although Malawi has had low measles incidence since the early 1990s, a large measles outbreak occurred there in 2010. Outbreak response was conducted by the Ministry of Health with the support of Médecins Sans Frontières (MSF) and included reinforced surveillance, case management, and nonselective mass vaccination campaigns for children aged 6 months to 15 years in 8 of the 28 districts of the country (during weeks 18–26 in 2010) (6). Further, the Ministry of Health implemented a nationwide nonselective mass vaccination campaign for children aged 9 months to 15 years (during weeks 33–34 in 2010). Previously, model-based methods have been used to estimate the number of measles cases averted through targeted outbreak response vaccination in a setting with low measles vaccine coverage (2). Here, we evaluate the effective impact of the Ministry of Health/MSF campaign in Malawi in terms of the estimated coverage of the nonimmunized population. We then use simulation models to explore the efficiency of a nonselective campaign versus targeted vaccination in populations with heterogeneous access to mass vaccination campaigns.

MATERIALS AND METHODS

Estimating effective campaign impact

The coverage of vaccination campaigns is conventionally assessed through administrative coverage (i.e., the number of doses administered divided by the target population). However, in populations that are partially immune because of either prior vaccination or prior natural exposure, the more relevant measure of the impact of vaccination campaigns is the proportion of the remaining susceptible population that was immunized by the campaign. We define this proportion as the "effective impact" of the campaign.

In contexts with large-scale outbreak response interventions for measles, the effective impact is difficult to measure directly because the immune status of vaccinees is rarely known, nor is the size of the susceptible population known. However, for age-targeted campaigns, we would expect a greater reduction in incidence in the target age classes than in the nontargeted age classes. If the effective impact were 100%, then we would expect to see few cases in the targeted age classes after the campaign. Following this logic, we can use the relative magnitude of the change in targeted and nontargeted incidence to derive a measurement of the effective impact of campaigns. This derivation is analogous to prior estimators of vaccine effectiveness in vaccinated and unvaccinated populations (7–9), though here, the unvaccinated and vaccinated populations are separated in time (before and after the campaign).

Consider a population with A individuals in the targeted age class and B individuals in the nontargeted age class. Though these numbers may be known, the numbers of susceptible individuals in these age groups, A' and B', respectively, are likely to be unknown. Consider further that the attack rate (cases per 100) in age class A is p, and the attack rate in age class B is q. Then, at any point in the epidemic before vaccination, the observed ratio of cases, CR, in age classes A and B is

$$CR_{before} = \frac{pA}{qB}. \qquad (1)$$

Consider a vaccination campaign targeting only individuals in age class A, that immunizes a fraction, θ, of the susceptible individuals. Note that θ is the fraction immunized, not the fraction vaccinated, and thus incorporates the product of coverage and the probability of generating a protective immune response. If we assume that the attack rates in the remaining susceptible individuals in groups A and B do not change, then the observed ratio of cases in age classes A and B after the campaign should be

$$CR_{after} = \frac{(1 - \theta)pA'}{qB'}. \qquad (2)$$

We can then solve for the effective proportion of the susceptible individuals in A' who were immunized in terms of the observed ratios of cases before and after the campaign as

$$\frac{CR_{after}}{CR_{before}} = \frac{(1 - \theta)(pA'/qB')}{pA'/qB'}. \qquad (3)$$

If we make the simplifying assumption that the attack rates in classes A and B are the same before and after the vaccination campaign, then we can estimate θ on the basis of the observed ratios of cases before and after the campaign as follows:

$$\theta = 1 - \frac{CR_{after}}{CR_{before}}. \qquad (4)$$

By using equation 4, we estimated the effective impact of vaccination campaigns conducted in 8 districts of Malawi during the 2010 outbreak. Between weeks 18 and 26 of 2010, more than 3.3 million individuals aged 6 months to 15 years were vaccinated, achieving overall vaccine coverage of 95.5%. Measles vaccine coverage, as estimated by post-campaign surveys, ranged from 92.3% in Mzimba to 98.0% in Chiradzulu. Between weeks 1 and 52 of 2010, a total of 134,039 measles cases and 304 deaths were reported, with 42% of all cases in children younger than 5 years, 30% in those aged 5–14 years, and 28% in adults aged 15 years or older. The overall cumulative attack rate was 0.96%, and the case fatality rate was 0.23% (6).

The calculations in equation 4 assume that the age-specific attack rates are the same before and after the campaign. As observed by Haber et al. (8), violation of this assumption can lead to biased estimates. Here, there are 2 ways in which this

assumption may be violated. The first is if, in the absence of the campaign, the epidemic would have exhausted susceptibles in 1 group faster than in the other. This is challenging to assess in the absence of observed data from a noncampaign setting. During the 2010 Malawi outbreak, the nationwide surveillance system allowed for evaluation of the age-specific attack rates. In districts in which MSF did not intervene (20 of 28 districts), we can assess the ratio, CR_{after} / CR_{before}, for any reference week in the epidemic (Figure 1A). Though the ratio of cases before and after the reference week is highly variable early and late in the epidemic because of low numbers of cases, the ratio during the central portion of the outbreak was very near 1 for noncampaign districts. This suggests that, for the 2010 outbreak in Malawi, the relative age-specific attack rates late in the epidemic were similar to those early in the outbreak in the absence of vaccination campaigns. The second way the assumption may be violated is if the campaign itself reduced the attack rate in the remaining susceptible individuals in the targeted age class through herd immunity. Although this cannot be explicitly discounted, this herd immunity effect would result in positive bias in the estimate of the campaign impact.

Outbreak response in populations with heterogeneous immunity

We developed a simple simulation model to illustrate the role of heterogeneous immunity, such as might arise because of differences in access to vaccination services or because of groups that refuse routine vaccination, in the context of an outbreak response. Consider a population of size N divided into the following 2 groups: those with high access to vaccination (i.e., high immunity), N_{high}, and those with low access to vaccination (i.e., low immunity), N_{low}. Note that, although we motivate this model in terms of groups that differ in their access to vaccination, this framework would apply broadly to any setting in which the population can be dichotomized into groups with high and low levels of immunity.

For an outbreak response vaccination campaign with a goal of θ coverage, we consider 3 scenarios for the correlation between vaccination in the campaign and the following access categories: 1) nonselective "random" vaccination, 2) nonselective "current" vaccination, and 3) targeted vaccination. The first scenario reflects the presumption that the outbreak response vaccination is nonselective with respect to access. In this case, individuals in the 2 groups will be vaccinated at random, and the final coverage rates in both groups (θ_{high} and θ_{low}, respectively) will be the same, $\theta = \theta_{high} = \theta_{low}$.

In the second scenario, which better reflects current vaccination strategies, individuals in the high-access group are more likely to be vaccinated first. In this case, we would expect only individuals in the low-access group to be vaccinated if the target coverage is greater than the proportion of the population in the high-access group (i.e., $\theta_{high} \geq \theta_{low}$); then, coverage in the low-access group would reflect only those doses remaining after full vaccination of the high-access group. If individuals in the high-access group were preferentially vaccinated before the low-access group, then
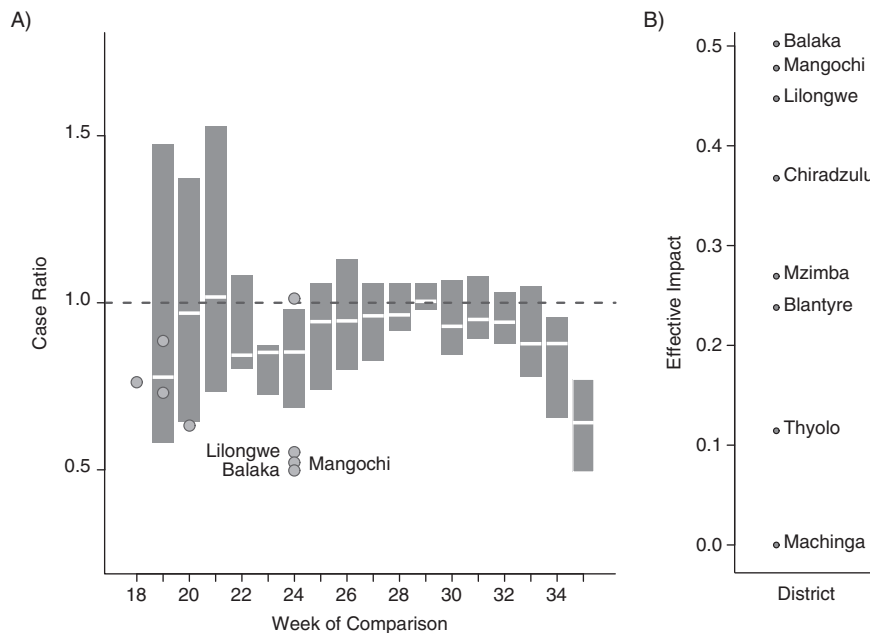

Figure 1. A) The ratio of cases in the targeted and nontargeted age classes after a reference date to before a reference date. Box plots indicate the interquartile range of the case ratios in 20 noncampaign districts in Malawi as a function of the epidemic week used as the reference time point; white lines indicate the median. Grey circles indicate the case ratios for the 8 districts with outbreak response vaccination campaigns with the start week of the campaign as the reference date. B) Estimated effective campaign coverage for outbreak response vaccination campaigns conducted by Médecins sans Frontières (Geneva, Switzerland) in 8 districts in Malawi in 2010.

the final coverage in each group would be as follows:

$$
\text{if } \theta \leq \tfrac{N_{\text{high}}}{N} \begin{cases} \theta_{\text{high}} = \theta/(N_{\text{high}}/N) \\ \theta_{\text{low}} = 0 \end{cases}
$$

$$
\text{if } \theta > \tfrac{N_{\text{high}}}{N} \begin{cases} \theta_{\text{high}} = 1 \\ \theta_{\text{low}} = (\theta - (N_{\text{low}}/N))/(N_{\text{high}}/N). \end{cases}
$$

The marginal benefit of vaccination in the high-access group is necessarily lower than in the low-access group. Thus, an idealized scenario would be a targeted campaign that first vaccinated the low-access group and then the high-access group (i.e., $\theta_{\text{low}} \geq \theta_{\text{high}}$). If individuals in the low-access group were preferentially vaccinated before those in the high-access group, then the final coverage in each group would be as follows:

$$
\text{if } \theta \leq \tfrac{N_{\text{low}}}{N} \begin{cases} \theta_{\text{low}} = \theta/(N_{\text{low}}/N) \\ \theta_{\text{high}} = 0 \end{cases}
$$

$$
\text{if } \theta > \tfrac{N_{\text{low}}}{N} \begin{cases} \theta_{\text{low}} = 1 \\ \theta_{\text{high}} = (\theta - (N_{\text{high}}/N))/(N_{\text{low}}/N). \end{cases}
$$

These 3 vaccination scenarios represent idealized versions of the presumed, worst-case, and best-case vaccination scenarios.

We simulated susceptible-infected-recovered–type outbreaks in a partially vaccinated population divided into high-access and low-access groups. We assumed that 60% of individuals in the high-access group had received 1 dose of measles vaccine with an efficacy of 0.85, and that 40% of individuals in the high-access group had received both a first and second dose of measles vaccine with an efficacy of 0.99. We assumed that 50% of individuals in the low-access group had received 1 dose of measles vaccine with an efficacy of 0.85 and no second dose. Thus, simulations with a high proportion of hard-to-reach individuals have more susceptible individuals initially and a higher effective R, where R is the expected number of secondary infections due to each infectious individual in a partially immune population. We note that these proportions are not intended to reflect any particular population; rather, this is a heuristic example intended to illustrate the impact of variations in access to vaccination on campaign outcomes. In the analysis below, we present results for simulated populations that vary in the proportion of individuals in the high-access groups. We provide an analysis of the sensitivity to the proportion of individuals in the low-access groups receiving a first dose of vaccine (Web Figure 1, available at http://aje.oxfordjournals.org/), the proportion of individuals in the high-access groups receiving a second dose of vaccine (Web Figure 2), and the basic reproductive ratio (R_0) (Web Figure 3).

The epidemiologic characteristics were assumed to be measles-like, with a basic reproductive ratio, R_0, of approximately 20, a 6-day exposed class following infection in which individuals were not infectious, and an 8-day infectious period [10]. The transmission rate was assumed to be mildly seasonal, with a sinusoidal seasonal pattern. Outbreaks were simulated by using a discrete time, stochastic

susceptible-exposed-infectious-removed model; equation 5 gives the expected value of each compartment in the model, conditional on the value of all states at the previous time. Stochastic realizations of the epidemic through time were generated by using the τ-leaping algorithm [11]. Following exposure, individuals are modeled as progressing through three 2-day-long stages in the exposed class and four 2-day-long stages in the infected class; this formulation yields a distribution of exposed and infectious periods that is gamma distributed rather than exponentially distributed with mean durations of 6 and 8 days, respectively [10]. In each access class, S_t and E_t are the numbers of susceptible and exposed individuals, respectively, at time t. For the high-access or low-access class, $I_{j,\text{in},t}$ and $I_{j,\text{out},t}$ are the numbers of infected individuals (in each of the infectious stages indexed by j) within that class and in the other class, respectively. We assumed homogenous mixing within the 2 access groups, but that the rate of mixing between the high-access and low-access groups was half that of the within-group rate. We assessed the sensitivity of the results to this assumed mixing pattern by running simulations with a well-mixed population (no difference between within-group and between-group mixing) and a population with highly assortative mixing (between-group mixing rate that was 25% of the within-group mixing rate) (Web Figures 4 and 5).

$$
\begin{aligned}
S_{t+1} &= S_t - \beta S_t \sum_{j=1}^{4} \left(I_{j,\text{in},t} + .5 I_{j,\text{out},t} \right) \\
E_{t+1}^1 &= E_t^1 + \beta S_t \sum_{j=1}^{4} \left(I_{j,\text{in},t} + .5 I_{j,\text{out},t} \right) - \phi E_t^1 \\
E_{t+1}^2 &= E_t^2 + \phi E_t^1 - \phi E_t^2 \\
E_{t+1}^3 &= E_t^3 + \phi E_t^2 - \phi E_t^3 \\
I_{t+1}^1 &= I_t^1 + \phi E_t^3 - \gamma I_t^1 \\
I_{t+1}^2 &= I_t^2 + \gamma I_t^1 - \gamma I_t^2 \\
I_{t+1}^3 &= I_t^3 + \gamma I_t^2 - \gamma I_t^3 \\
I_{t+1}^4 &= I_t^4 + \gamma I_t^3 - \gamma I_t^4 \\
R_{t+1} &= R_t + \gamma I_t^4.
\end{aligned} \tag{5}
$$

We simulated epidemics according to the model above with a 14-day vaccination campaign (outbreak response vaccination) starting between days 20 and 100 of the outbreak (note the seasonal peak of transmission was on day 88). We simulated 3 levels of target vaccination coverage (80%, 90%, and 99%) and calculated the impact of the campaign as the number of cases averted as a percentage of the case burden from a simulation with no intervention.

RESULTS

Estimating effective campaign impact

Despite a target coverage of 95% of the population aged 6 months to 15 years, the effective coverage (the proportion of the susceptible population immunized by the campaign) of the 2010 nonselective vaccination campaigns was estimated

to range from −1% in Machinga, where there was a greater proportion of cases in the targeted age group after the campaign, to 50% in Balaka (Figures 1A and 1B).

Only the ratios for Lilongwe, Mangochi, and Balaka fell outside the interquartile range for all noncampaign districts across all weeks (excluding early and late weeks in which low case numbers contributed to high variability). This suggests that the reduction in cases in the age groups targeted by vaccination in these districts is unlikely to be due to random variation, but rather to successful targeting of susceptible individuals. The observations in the other districts were within the range of variation for noncampaign districts at the time; thus, there is no evidence that the observed reduction of cases in the targeted age class was due to the campaign itself.

Outbreak response in populations with heterogeneous access to vaccination

In the random scenario, in which both the high-access group and the low-access group are vaccinated at equal rates,

the impact of the campaign, measured as the proportion of cases averted relative to a no-campaign simulation, increases for campaigns that are conducted early in the outbreak and for settings where the hard-to-reach population is small (Figures 2A, 2D, and 2G). Though not surprising, this result serves as a baseline against which to evaluate the other scenarios.

Campaigns that are biased toward those with previous high access to vaccination always achieve lower impacts than campaigns that are random with respect to prior access (Figures 2B, 2E, and 2H). In particular, when the campaign target coverage is smaller than the proportion of the population that is in the low-access class, the expectation is that the current scenario (i.e., biased toward those with prior access) would achieve very low effective coverage in this group and would, thus, have only limited impact (Figures 2B and 2E). If, however, the campaign target is high enough, the limitation of the current scenario is mitigated (Figure 2H).

Conversely, targeted campaigns that are biased toward those with low access to vaccination always achieve higher impacts than either of the other scenarios (provided the campaigns are not too late to be effective). Targeted campaigns,
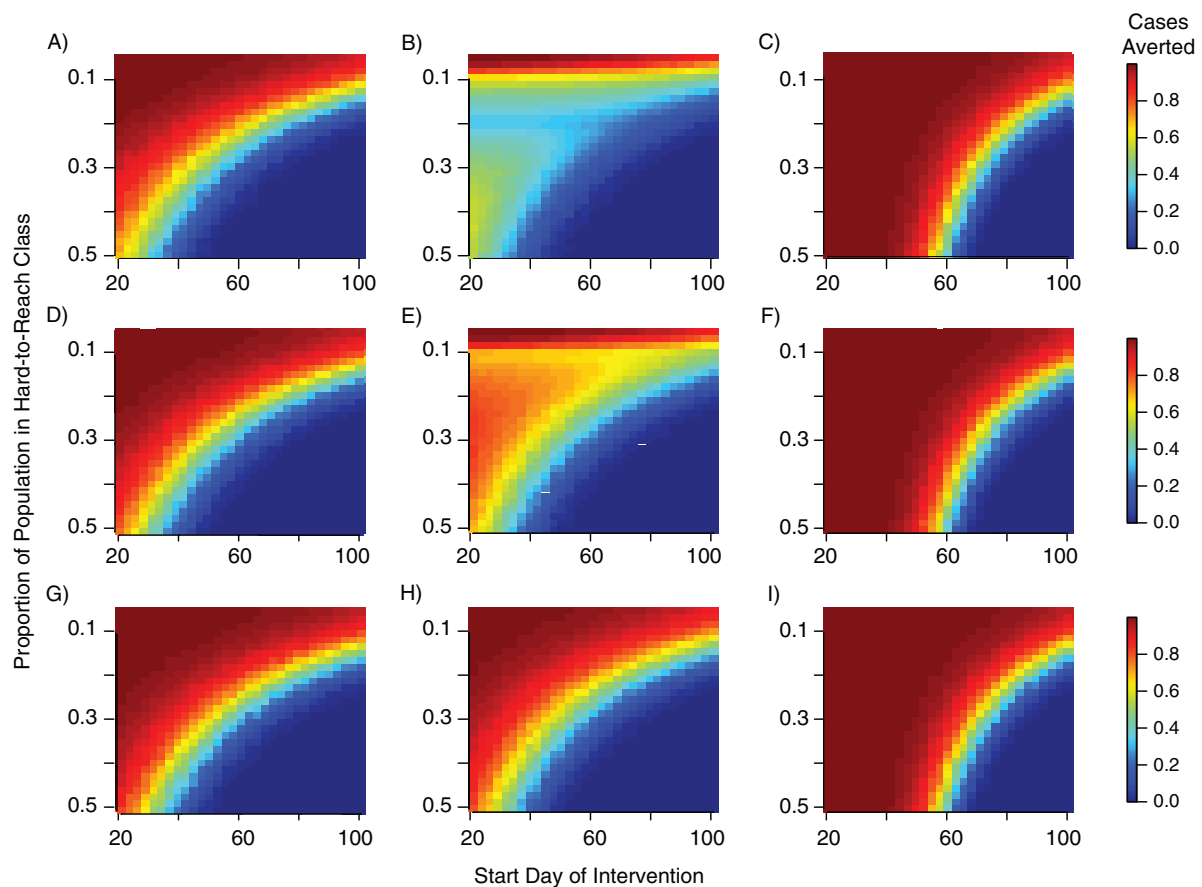

Figure 2. The impact of simulated vaccination campaigns (colors indicate cases averted as a proportion of cases in a noncampaign simulation; scale bar at right) as a function of the timing of the start of the campaign (*x*-axis) and the proportion of the population in the hard-to-reach class (*y*-axis). Rows indicate the target coverage of the campaign (top row is 80%, middle row is 90%, and bottom row is 99% of target population), and columns indicate campaigns that are nonselective with respect to access class (left column, A, D, G), campaigns that are biased toward those with prior access to vaccination (i.e., the current strategy) (middle column, B, E, H), and campaigns that are targeted toward those with low prior access to vaccination (right column, C, F, I).

although logistically difficult, are highly effective, even for relatively low target coverage (Figure 2C), and they allow high impact with relatively late implementation (e.g., 90% cases averted for campaigns implemented 30 days later than the random vaccination scenario) (Figure 2).

We note that the qualitative simulation results are not changed when we assume alternative mixing patterns (well-mixed or assortative) (Web Figure 4). We further ran simulations in which the time required to conduct a campaign was positively correlated with the target coverage; we assumed 7 days to achieve 50% coverage increasing linearly to 14 days to achieve 99% coverage. These simulations did not affect the qualitative results of the comparison among campaign types (Web Figure 5).

DISCUSSION

In Malawi, the effective impact of the reactive vaccination campaigns implemented by the Ministry of Health/MSF was much lower than expected considering the high vaccine coverage achieved. Only 3 districts (Lilongwe, Mangochi, and Balaka) of the 8 where campaigns were conducted had a reduction in measles cases in the targeted age groups compared with nontargeted age groups greater than those observed in nonvaccinated districts.

However, because all models are an approximation of reality, the low effective impact reported here may also be due to uncertainties and gaps in the reported time series of cases. Measles surveillance in Malawi is based on individual-based case records, and only the first cases are laboratory confirmed. Only districts where the Ministry of Health/MSF intervened benefitted from reinforced surveillance; therefore, the degree of bias in districts without this support is unknown. Further, because these data were used to inform the model, the effective impact of the reactive campaigns may be more variable within and between districts. Reported vaccination coverage in Malawi prior to the epidemic in 2010 was high countrywide, with variations in coverage by district, although in subsequent coverage surveys conducted after the intervention, coverage was estimated to be insufficient (6). Several reasons could explain this, including the timeliness and the choice of targeted age groups. As previously described, in some districts of Malawi, reactive campaigns were implemented late in the course of the outbreak, and only children aged 6 months to 15 years were targeted, despite the fact that more than one-third of cases were reported in older individuals (6).

Further, a likely explanation of the low effective impact of the vaccination campaigns in Malawi is that susceptible individuals were not vaccinated. Though the campaigns were assumed to reach everybody at the same time (as in the random scenario in the simulations above), the Ministry of Health/ MSF mass vaccination campaign in Malawi was likely to preferentially vaccinate groups with good access to routine immunization before hard-to-reach groups (as in the current scenario in the simulations above).

The impact of a vaccination campaign is multifactorial, depending on the goal of the campaign, timing, population targeted, quality of the implementation, and prior coverage. Nevertheless, successful campaigns have high proportions of individuals who receive their first doses of vaccine, thereby reaching the hard-to-reach populations. Our study shows that a selective campaign preferentially targeting hard-to-reach individuals would be of greater benefit, particularly in settings where vaccine coverage is high, such as Malawi.

Hard-to-reach individuals may remain unvaccinated when neither health services nor conventional communication mechanisms regularly reach their communities. Here, we have presented a simplistic model with only 2 levels of access to vaccination. In practice, access to vaccination is likely to vary on a continuum. Low immunization rates are associated with communities that are located a long distance from health services (12), those with little access or exposure to large-scale or local media (13), those with low doctor-patient and nurse-patient ratios (14), and those with strong philosophical or religious objections to vaccination (15). If such covariates of prior vaccination can be identified, then targeted strategies can be developed on the basis of population metrics rather than the characteristics of individual vaccinees. Such strategies to improve vaccine coverage are likely to be highly context specific, ranging from enhanced outreach activities for segregated communities or nomadic populations to high-quality communication campaigns tailored to meet the informational needs of vulnerable groups (15).

The proportion of the population effectively immunized against measles and the age distribution of cases during outbreaks depend on the performance of national routine control programs and vary from one country to another, ranging from stable countries with high measles vaccine coverage to post-conflict countries with disrupted immunization programs and low vaccine coverage (16). In settings with low levels of immunity, nonselective strategies may remain the most timely, efficient, and cost-effective approach to supplemental vaccination. However, as routine vaccination programs improve, it is possible that disparities between high-access and low-access groups will render nonselective strategies increasingly inefficient. In such contexts, age-specific or regional estimates of measles vaccine coverage (e.g., through community-based surveys) may guide decision-making as to which high-priority groups to target. Ultimately, innovative outreach strategies targeted to reach individuals who are excluded or beyond the reach of routine immunization services will be the key to achieving high levels of population immunity and minimizing the risk of measles resurgence.

In our model, we have taken the proportion of cases averted as the unique measure of the impact of intervention. The proportion of deaths averted would have been a more relevant indicator to evaluate the impact of the intervention on the health of young children. However, in Malawi, measles-related deaths reported by the surveillance system were few, so it was not possible to measure the proportion of deaths averted. Rates of measles-specific mortality are difficult to determine in settings with weak vital registration systems.

The impact of a supplemental mass vaccination campaign is variable and may be lower than expected because of population heterogeneity in immunity and the naïve presumption that the campaign is nonselective with respect to the immune status of individuals. Although logistically challenging, targeted campaigns achieve higher impacts, even when target

coverage is low and implementation is late, and they are the most effective strategy, particularly in highly vaccinated populations. However, the choice between targeted and nonselective campaigns should be context specific, achieving a reasonable balance between feasibility, cost, and expected impact. Indeed, targeted campaigns may introduce additional trade-offs; although a targeted campaign may vaccinate immune individuals, if not well implemented, it may also result in fewer people being immunized. Irrespective of the strategy selected, reinforcement of surveillance and investigation of local epidemiologic data to guide the decision are essential. Finally, comprehensive field evaluations of the specific local factors exacerbating poor access should be encouraged, as well as postintervention evaluations. Developing operational strategies to identify and target individuals and subpopulations with low levels of vaccination is paramount to ensuring the effectiveness of future interventions.

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