SUPPLEMENT ARTICLE

# Should Outbreak Response Immunization Be Recommended for Measles Outbreaks in Middle- and Low-Income Countries? An Update

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***Background***. Measles caused mortality in >164,000 children in 2008, with most deaths occurring during outbreaks. Nonetheless, the impact and desirability of conducting measles outbreak response immunization (ORI) in middle- and low-income countries has been controversial. World Health Organization guidelines published in 1999 recommended against ORI in such settings, although recently these guidelines have been reversed for countries with measles mortality reduction goals.

***Methods***. We searched literature published during 1995–2009 for papers reporting on measles outbreaks. Papers identified were reviewed by 2 reviewers to select those that mentioned ORI. World Bank classification of country income was used to identify reports of outbreaks in middle- and low-income countries.

***Results***. We identified a total of 485 articles, of which 461 (95%) were available. Thirty-eight of these papers reported on a total of 38 outbreaks in which ORI was used. ORI had a clear impact in 16 (42%) of these outbreaks. In the remaining outbreaks, we were unable to independently assess the impact of ORI.

***Conclusions***. These findings generally support ORI in middle- and low-income countries. However, the decision to conduct ORI and the nature and extent of the vaccination response need to be made on a case-by-case basis.

Measles was estimated to cause mortality in >164,000 children in 2008 [1], with most cases and deaths occurring during the course of outbreaks. It is a highly infectious, frequently seasonal viral disease characterized in settings of endemicity by epidemics of multiyear periodicity. Respiratory droplets carrying virus spread from infected individuals to susceptible hosts' respiratory tract epithelial cells. A 10–14 day incubation period occurs between infection and symptom onset; during this period, viral replication occurs first in respiratory tract epithelial cells, followed in sequence by replication in local lymphatic tissue, viremia, and viral spread to organs. Viral replication occurs in macrophages, lymphocytes, and monocytes and in epithelial and endothelial cells [2]. To stop virus transmission, population immunity of ~95% is generally considered to be necessary [3]. Measles is associated with case-fatality ratios of 2%–15% in developing countries [4]. In emergency settings, case-fatality ratios as high as 30% have been reported [5]. For >45 years, a cheap, safe, and highly efficacious measles vaccine has existed. Antibodies to measles appear 12–15 days after vaccination, peaking 20–28 days later [6]. Vaccination within 72 h after exposure to measles virus has been shown to result in prevention or decreased severity of disease [7–10].

Despite global progress in measles control since 2000, measles remains endemic in many countries. Even in areas where measles is no longer endemic, outbreaks of varying magnitude have occurred. Although the importance of conducting outbreak response immunization (ORI) in emergency situations has been well recognized and accepted [11, 12], the impact and desirability of conducting measles ORI, particularly mass

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vaccination campaigns, in middle- and low-income countries has been controversial [13]. This controversy was in part a response to Aylward's 1997 manuscript entitled "The Impact of Immunization Control Activities on Measles Outbreaks in Middle and Low Income Countries." This review found 17 papers published during 1977–1993 that reported on 13 outbreaks with ORI. Aylward concluded that "The data that are available…suggest that outbreak immunization activities in developing countries do not have significant impact on the course of measles epidemics…Immunization activities did not begin until well after the onset of the outbreaks, by which time the measles virus had probably spread widely…" [14]. In 1999, the World Health Organization (WHO) stated that "the immunization response in most outbreaks occurs too late to affect the impact of the outbreak…Supplementary vaccination activities (SVAs) in the course of an outbreak are not recommended unless there is substantial political or community pressure…If implemented, SVAs should focus on unaffected areas where the epidemic is…likely to spread" [15, pp. 6, 7]. However, in 2009, these guidelines were revised to provide guidance to countries with a measles mortality reduction goal and recommended ORI in certain situations. The reasons for this revision are clearly and succinctly stated as follows:

- The expanded use of a second opportunity for measles immunization through nationwide mass-vaccination campaigns in high burden countries has resulted in marked reductions in measles incidence associated with reduced community acceptance of large outbreaks.
- Endorsement of the International Health Regulations (2005) highlighted the importance of timely detection and response to events that are of potential international public-health concern.
- Recent literature on the impact of outbreak response immunization found measles epidemics in endemic, pre catch-up supplementary immunization activity (SIA) settings can last 3-9 months providing adequate time to mount a focused, high quality campaign [16, p. 2].

A portion of the literature review summarized in this article was presented at a WHO meeting held in consideration of revising the previous guidelines, and 2 of the authors (KLC and RFG) served as expert reviewers for the 2009 guidelines.

More than 15 years have elapsed since the publication of the last article reviewed by Aylward, and more than a decade since the publication of Aylward's article. Over this period, the status of global measles control has changed dramatically; the Americas have seen the elimination of indigenous measles [17, 18], and 4 of the 5 remaining WHO Regions have time-limited measles elimination goals. Worldwide, measles-associated deaths are estimated to have decreased by 78% in 2008, compared with 2000 [1]. This decrease in measles is attributed to an emphasis on increasing routine immunization coverage, offering a second dose of measles vaccine to all children either through routine immunization services or periodically through supplemental immunization activities (SIAs), strengthening measles surveillance, and improving measles case management [1, 19]. Relative to the 1980s and 1990s, many countries now have increased political commitment to measles control, more timely measles surveillance, national experience with high-coverage SIAs, and smaller, less frequent measles outbreaks [20, 21].

In this context, we wished to reassess the potential impact of mass campaigns to control measles outbreaks in middle- and low-income countries as documented in the more recently published literature. This impact could be determined either at the individual level (eg, the decrease in severity of disease among vaccinated cases) or at the population level, at which decreases in incidence and transmission might be measured. ORI was classified as selective (ie, targeting only those without evidence of vaccination) or nonselective (ie, targeting all in a selected age group regardless of vaccination status).

## METHODS

We searched PubMed/MEDLINE, EMBASE, Latin American and Caribbean Center on Health Sciences Information, Index Medicus for the Eastern Mediterranean Region, and African Index Medicus for articles published from 1 January 1995 through 3 July 2009 in English, French, Italian, Portuguese, or Spanish. We searched PubMed/MEDLINE and EMBASE using the key words "measles" and "outbreak" or "outbreaks" or "epidemic" or "epidemics." In the remaining databases, separate searches were done using the keyword "measles." The results of all searches were reviewed to identify and remove articles that did not report on a measles outbreak in humans. (Measles is primarily associated with outbreaks in humans, but has also been reported in outbreaks among nonhuman primates.) Papers were then obtained, reviewed by 2 reviewers, and categorized as relevant or not relevant; the bibliographies of the papers were also reviewed for additional citations. Any article that mentioned the use of ORI was considered to be relevant. ORI was considered to be any immunization with measles-containing vaccine beyond routine services in response to an increase in measles cases. Any discrepancy between reviewers with regard to the relevancy of papers reviewed was resolved through discussion. All articles considered to be relevant were classified according to the World Bank designation [22] of the outbreak country's income level for the year during which the outbreak occurred. For the purposes of this article, we considered only articles reporting on outbreaks in middle- or low-income countries, based on the World Bank designation.

Aylward's article, published in 1997, fell within the period of our search. However, because his article was a review of articles published before 1995 and because our goal was to discover what more recent data showed, we did not include in our analysis any of the historical outbreaks that he described.

## RESULTS

We identified a total of 485 articles through our search strategy. We were able to obtain 461 (95%) of these articles; the 24 that we were unable to obtain were from journals not published or accessible in the United States or were theses or technical reports archived in libraries not located in the United States. Of these 461 articles, 38 reported on 38 outbreaks in which ORI was used and that occurred in middle- or low-income countries. Some articles described >1 outbreak, whereas in other instances multiple papers described the same outbreak. We attempted to determine objectively the impact of ORI on the basis of the data provided (Table 1).

During the period considered, WHO Regions varied substantially in their approaches to, goals for, and extent of measles control. Because we believed that these characteristics might affect the use and impact of ORI, the articles discussed below are grouped by region. Table 1 provides a comprehensive listing of outbreaks in which ORI was used.

### Western Pacific Region

Two papers reported on outbreaks in Papua New Guinea [23, 24]. Mgone et al [23] described 314 cases that were part of a 1999 epidemic occurring in an area with only 8% routine coverage. Control measures included "flying vaccination clinics" (the authors do not describe exactly what is meant by this) to reach remote communities, and a mass vaccination campaign. Of these patients, 126 (40%) had received at least 1 vaccine dose according to the child health record book, although 32 were vaccinated when they were <6 months of age and 44 were vaccinated <14 days before rash onset. Children vaccinated >14 days before rash onset had a decreased risk of complications ($P < .001$) and of death ($P = .067$); the authors claim that most of these children received vaccination during ORI.

Six papers described outbreaks of measles in Micronesia, islands where measles vaccination coverage ranged from 55%–94%. During 1991–1994, outbreaks of measles moved through this area, ultimately totaling 1353 cases in a population of ~300,000 [25, 26]. With the exception of Guam, the outbreaks were the first in these islands in 20 years. All islands except Guam conducted mass vaccination campaigns targeting all children aged ≥6 months who had been born since the last outbreak; Guam targeted all children aged 6–59 months. In a simple linear regression analysis, time to reach 80% coverage of the target population was significantly associated with duration of outbreaks (β coefficient = .82; $P = .026$), and size of population was positively associated with and time since last outbreak was inversely associated with ($P$ values not given in paper) duration of the outbreak; however, these associations were not statistically significant ($P > .05$). The time required to vaccinate 80% of the population remained significantly associated with the duration of the outbreak, even when controlling for routine measles vaccination coverage in a stepwise linear regression model ($P = .049$) [25].

The aforementioned 1994 measles outbreaks did not affect the Marshall Islands. However, during July–November 2003, after 15 measles-free years, these Micronesian atolls experienced an outbreak with 826 cases in patients aged 2 weeks through 43 years [27–30]; 92% of patients were from the densely populated capital of Majuro. In late August, a mass vaccination campaign targeting children aged 6 months through 15 years who did not have written evidence of 2 doses of measles-mumps-rubella vaccine was implemented. Because more cases were found in older age groups, the target age group for the campaign expanded to include patients aged <40 years and the campaign continued through October, ultimately leading to 93% 1-dose coverage in those aged 6 months through 40 years. Transmission stopped shortly after vaccination activities were concluded. The articles describing this outbreak detail the vaccination activities conducted but do not comment directly on the impact of the ORI. Assessing the impact of this activity is particularly difficult, because it was conducted over many weeks and the population was too small to sustain endemic transmission of measles.

Two articles described outbreaks with ORI in Fiji [31, 32]. However, detailed information on ORI and its impact were only available for the 2006 outbreak. In February 2006, Fiji reported the first laboratory-confirmed measles cases since 1998. From 17 February through 9 June, a total of 132 suspected measles cases were reported. Children aged 6 months to <6 years were targeted for ORI, an activity that began 6 weeks after the first case was reported. By 24 May, 98% of targeted children had been vaccinated. No patients with rash onset after 21 May were reported. The response to ORI was likely attributable to the relative rapidity of the response and the high coverage obtained.

### The Eastern Mediterranean Region

Two papers reported outbreaks in Saudi Arabia [33] and Sudan [34]. Al Wahaibi et al [33] described a school-based study in Riyadh City, Saudi Arabia, where during October 1996–June 1997, 482 cases of measles were reported from 103 schools. In response, school health units nonselectively vaccinated students with measles-mumps-rubella. In the 14 schools able to vaccinate all students, the authors state that vaccination within 10 days after onset of the first case resulted in a preventable fraction. (Preventable fraction (PF) is defined as $PF = (I_0 - I_T)/I_0$ where $I_0$ = rate in the population without intervention and $I_T$ = rate in the population with intervention) of 59.5%, compared with 2.1% in schools that delayed vaccination for ≥19 days.

In early 2004, measles cases were reported among populations displaced by conflict in western Sudan. Among these populations, background measles coverage was estimated to be 46%–77%. ORI targeting children aged 9–59 months was conducted in camps and neighboring communities; current and

**Table 1. Outbreaks in Which Outbreak Response Immunization Was Reported ($n = 38$)[a,b]**

| Region/Country [REF] | Time to ORI | Selective or nonselective[c] | Target area | Target age | Doses/Coverage | Author's reported impact | Documented impact (our assessment) | Number of outbreaks[a] |
|---|---|---|---|---|---|---|---|---|
| **Western Pacific** | | | | | | | | |
| PNG [23] | ORI1: 9mo after 1st case | Nonselective | Flying clinics in 2 districts | 4mo–14y | 2,000 | Demonstrates that vaccination before rash onset results in decreased mortality & morbidity | Yes, based on decreased mortality & morbidity assuming claim that most vaccinated cases were vaccinated during ORI | 1 |
| | ORI2: 14mo after 1st case | Nonselective | Province | 4mo–NR | NR | | | |
| PNG [24] | N/A | Selective | Hospital | Children | 5558 | NR | Unclear | 1 |
| Micronesia [25, 26] (Kosrae, Palau, Saipan, Guam, Pohnpei, Chuuk) | Various | Nonselective | Multiple islands | Various | Various | Yes, time required to vaccinate 80% of popn significantly associated with o/b duration. Size of popn positively associated with o/b duration, time since last o/b & 1 dose coverage inversely associated [24] | Yes, based on data presented regarding significance of time to achieve 80% coverage | 6 |
| Marshall Islands [27, 28, 29, 30] | ORI1: 3wk after 1st case | Selective | Outer islands and schools | 6mo–15y | NR | NR | Yes, based on >50% reduction in cases 21d after 80% coverage reached in target popn | 1 |
| | ORI2: 6wk after 1st case | Selective | Two major islands | 6mo–40y | >93% | | | |
| Fiji [31] | 2mo | Nonselective | Island-wide (Koro Island) | 1–5y | NR | NR | Unclear | 1 |
| Fiji [32] | 6wk | NR | Island-wide | 6mo–6y | 98% | Last case was reported 8w after ORI | Yes, based on rapid increase in coverage and decrease in cases | 1 |
| **Eastern Mediterranean** | | | | | | | | |
| Saudi Arabia [33] | 14d median from 1st case | Nonselective | 54 schools in Riyadh | School aged children | 14 fully vaccinated schools | Report ORI effective if done promptly: Reported vaccination within 10d of 1st case resulted in a preventable fraction (PF) of 59%; vaccination >19d after 1st case resulted in PF of 2.1% | Yes, based on data presented on preventable fraction | 1 |

**Table 1.** (Continued)

| Region/Country [REF] | Time to ORI | Selective or nonselective[c] | Target area | Target age | Doses/Coverage | Author's reported impact | Documented impact (our assessment) | Number of outbreaks[a] |
|---|---|---|---|---|---|---|---|---|
| Sudan [34] | ORI1: NR | Nonselective | IDP camps | 9mo–5y | 80,000 | Reported that ORI decreased morbidity & mortality | Yes, > 50% reduction in cases 21d after region-wide ORI | 1 |
| | ORI2: 12wk | Nonselective | Region-wide | 9mo–15y | 77% | | | |
| **Americas** | | | | | | | | |
| Mexico [35] | NR | Selective | 70,000 surrounding households | 6mo–39y | NR | NR | Unclear | 1 |
| Mexico [36] | NR | Nonselective | | 6y–11y, high risk groups | 10 million | NR | Unclear | 3 |
| Bolivia [37, 38] | ORI1: 1998 4mo after 1st case | Nonselective | Nationwide | <5y | 85% | Persistent o/b | Yes, after multiple immunization activities | 1 |
| | ORI2: 1999 | NR | House-to-house Nationwide | <5y in most places; <15y in areas of Amazon | 98% | Persistent o/b | | |
| | ORI3: 2000 | NR | House-to-house | <5y | 95% | Transmission stopped | | |
| Haiti [39] | ORI1: <4wk after 1st case | Nonselective | Provincial city | 6mo–14y | 95% | No cases in city within 2w of end of campaign; spread to rest of island | Yes, after multiple activities | 1 |
| | ORI2: NR | Nonselective | Departments | 6mo–14y | 65–95% | No cases after early August in department | | |
| | ORI3: 5-9/00 | Nonselective | Port-au-Prince | 6mo–14y | 82% | | | |
| | ORI4: 11/00-1/01 | Nonselective | Port-au-Prince neighborhood | 6mo–14y | 80 - 90% | Reduced number of cases island-wide | | |
| | ORI5: 9-12/01 | Nonselective | Nationwide | NR | >85% | Measles transmission interrupted | | |
| Venezuela [40] | NR | Nonselective | Statewide | 1–14y | NR | Reported to end o/b | Unclear | 1 |
| Venezuela [40] | ORI1: 1mo after 1st case | Nonselective | Nationwide | <5y | 16/24 states report >100% | Persistent o/b | Yes, transmission eventually stopped | 1 |
| | ORI2: 4mo after 1st case | Nonselective | Nationwide | 6mo–14y & high risk adults | NR | Epi curve shows impact | | |
| Colombia [40, 41] | NR | Nonselective | Nationwide | 6mo–5y & high risk groups | 73% | o/b ongoing when MMWR published | Unclear | 1 |
| Chile [42] | NR | Nonselective | Community-wide | Contacts; <1y & 20–40y | NR | Reported to restrict o/b | Unclear | 1 |
| Argentina [43, 44] | NR | | ''bloqueo'' | NR | NR | Reported to restrict o/b [39] | Unclear | 2 |

**Table 1.** (Continued)

| Region/Country [REF] | Time to ORI | Selective or nonselective[c] | Target area | Target age | Doses/Coverage | Author's reported impact | Documented impact (our assessment) | Number of outbreaks[a] |
|---|---|---|---|---|---|---|---|---|
| Peru [45] | NR | Nonselective | Community-wide | 6mo–15y | NR | Reported no cases 3w after ORI; 55% susceptibles claimed to be protected by ORI; authors claim that impact of ORI 36d after 1st case attributable to large percentage of susceptibles in child & adult popn & distance between houses slowing spread | Yes | 1 |
| **African** | | | | | | | | |
| Burkina Faso [46] | ORI1: 26 wk after 1st case | Nonselective | Province | Daycare & primary schools | 98% | Reported that impact hard to determine | Unclear | 1 |
| | ORI2: approx 37 wk after 1st case | NR | | <15y catch up | NR | | | |
| Chad [49] | 22wk after 1st case | Nonselective | N'Djamena | 6–59mo | 81% | ORI occurred very late in the o/b | Unclear | 1 |
| Kenya [21] | ORI1: 7mo | NR | 16 most affected districts | 9–59mo | 120% | NR | Unclear | 1 |
| | ORI2: 10mo | NR | 62 remaining districts | 9–59mo | 110% | | | |
| Niger [13, 47, 48, 49, 50] | 24wk after 1st case | Nonselective | Niamey targeting 50% of target age | 6–59mo | 57% of target age children | Median of 7.6% (4.9–8.9) cases were potentially averted because of ORI [46]; Spatial-temporal spread of o/b suggests targeted interventions could have further impacted [47]; 50% of children with no prior measles vaccination received 1st dose during the ORI [49]; ORI occurred very late in the o/b [48];If conducted earlier, likely that many cases would have been averted [12] | Yes | 1 |

**Table 1.** (Continued)

| Region/Country [REF] | Time to ORI | Selective or nonselective[c] | Target area | Target age | Doses/Coverage | Author's reported impact | Documented impact (our assessment) | Number of outbreaks[a] |
|---|---|---|---|---|---|---|---|---|
| Zimbabwe [51] | NR | Selective | | NR | NR | Reported CFR directly correlated with time to recognition of o/b; authors speculate that this is due to inability to vaccinate susceptibles as rapidly in these situations | Unclear | 1 |
| **Southeast Asian** | | | | | | | | |
| Sri Lanka [52] | NR | Nonselective | Refugee camps, welfare centers, preschools, & slums | Children | NR | NR | Unclear | 1 |
| India [53] | Soon after o/b began | Nonselective | Neighborhood | <5y | NR | Reported impact hard to discern | Unclear | 1 |
| India [54] | Soon after o/b began | Nonselective | Neighborhood | NR | NR | NR | Unclear | 1 |
| India [55] | 1 day before (SIAs initiated because of tsunami) | Nonselective | All tsunami-affected areas | 6-60mo | 117% | Not able to document impact of SIA, but possibly limited spread & responsible for rapid decrease in incidence | Unclear | 1 |
| **European** | | | | | | | | |
| Bulgaria [56] | 5wk | Selective | Affected admin regions | 13mo-30y w/o 2 doses MMR | Ongoing | NR | Unclear | 1 |
| Serbia [57] | NR | NR | | Contacts 6mo-25y & children 1–15y not previously vaccinated | NR | NR | Unclear | 1 |
| Turkey [58] | NR | Nonselective | Homes not yet affected by o/b | Children | 123 children | NR | Unclear | 1 |

**NOTE.** NR, not reported; d, day; wk, week; mo, month; y, year; o/b, outbreak; popn, population.

[a] Some outbreaks were reported in multiple papers, while some papers report multiple outbreaks.

[b] In some cases, multiple rounds of ORI were conducted. In this table, each round is designated by a number.

[c] ''Nonselective'' indicates vaccination of all children in target age group regardless of prior disease or immunization status; ''selective'' indicates vaccination of children in target age who do not have written records of having already received a pre-determined number of vaccine doses.

incoming residents of camps were also vaccinated. However, transmission persisted. In response, a region-wide measles campaign targeting children aged 9 months to 15 years was conducted; this reached 93% of the accessible but only 77% of the total target population. Although cases continued to occur, the epidemiologic curve suggests that the mass campaign greatly reduced transmission. Further evidence of the impact of ORI is the fact that the lowest ORI coverage (44%) was in West Darfur, whereas 51% of cases reported after the campaign were from this area. In contrast, in South Darfur, ORI coverage was 97% and only 12% of all cases reported after the SIA were inpatients from South Darfur.

### The Americas

Thirteen papers described outbreaks in Latin America. Santos et al [35] reported on a Mexican outbreak that occurred in 2000. Since 1999, Mexico has maintained measles vaccine coverage of >95% in children aged 1–10 years. In 2000, 30 measles cases were reported from Mexico City and 3 states; in response, 70,000 households were visited with vaccination of children aged 6–11 months and adults aged 15–39 years at risk of exposure. In 2003, Mexico experienced 44 cases of measles in 3 transmission chains; 10 million children were then vaccinated, as were groups at high risk of transmission [36]. However, the temporal relationship between case detection and vaccination activities is not clear in these reports. It is also difficult to determine whether the limited spread of measles was attributable to ORI or to the very high existing background coverage.

During 1998–2001, Bolivia experienced a nationwide outbreak comprising almost 2500 cases [37, 38]. This outbreak came several years after a nationwide "catch-up" campaign in 1994 and 3 years with few reported cases; during 2 of these years, routine coverage fell by <90%. (The measles elimination strategy used in most countries of the Americas includes "catch-up" campaigns targeting all children aged 9 months–14 years designed to eliminate measles susceptibles, "keep-up" vaccination which entails reaching high vaccination coverage through routine services, and periodic "follow-up" campaigns targeting all children born since the last campaign). In May 1998, the first cases of the epidemic were reported in Yacuiba. In response, vaccination was conducted in Yacuiba and other major cities; however, cases continued to be reported. To halt transmission of measles, 3 nationwide campaigns were conducted in Bolivia in October 1998, during November–December 1999, and during September–December 2000 that targeted children aged <5 years; the campaign in 1999 expanded the upper target age to 14 years in rural settings. In 2002, no measles cases were reported in the country [37].

Haiti also conducted a nationwide catch-up campaign in 1994. This campaign was followed by 6 measles-free years, despite a mean routine vaccination coverage of only 47% among children aged 1 year. In 1999, a follow-up campaign was done, but estimated coverage was only 70%–80% of the target population. In March 2000, measles was confirmed in the Haitian city of Gonaïves. In response, a door-to-door vaccination campaign was rapidly done in the city targeting children aged 6 months to 15 years and reportedly achieving 95% coverage. Within 2 weeks after its completion, no further measles cases were reported from the city. However, measles had spread to nearby cities and to the capital of Port-au-Prince. Measles transmission was halted by the end of August in the department surrounding Gonaïves after additional door-to-door ORI campaigns. In Port-au-Prince, a vaccination campaign targeting children aged 6 months to 15 years achieved only moderate coverage; increasing cases led to an intensive door-to-door repeat vaccination campaign in high-risk areas of the city. Cases decreased sharply after the door-to-door campaign. However, occasional cases of measles continued to be reported until a nationwide door-to-door campaign was conducted in mid-2001. This outbreak highlights the effectiveness of focused, well-supervised campaigns, the futility of poorly run activities, and the need to cover a geographic area beyond which the outbreak was occurring [39].

Outbreaks followed by ORI were also described in Venezuela, Colombia [40, 41], Chile [42], and Argentina [43, 44]. Despite measles vaccination coverage of only 58% in 2001, Venezuela was able to stop an outbreak of 37 cases from growing by conducting a statewide ORI for children aged 1–14 years; coverage for this ORI was not reported. Later in the same year, it attempted to contain another outbreak with a nationwide campaign targeting children aged 1–4 years; many pockets were missed, and the outbreak expanded to 2397 cases before being stopped by another nationwide campaign, this one targeting children aged 1–14 years and adults at high risk and reported to have achieved >100% coverage. The outbreak spread to Colombia. With routine coverage >78%, Colombia was able to stop ongoing transmission after 139 cases were reported through a nationwide campaign targeting children aged 6 months to 5 years and adults at high risk. Similar to Colombia, Chile was able to contain its outbreak to 19 cases of measles, reportedly due to a combination of high background immunity and a community-wide vaccination program.

One article also describes a Peruvian outbreak [45] that occurred from 22 July through 21 September 1993 in a remote, sparsely populated village. This serologically confirmed outbreak was the first in 20 years despite a lack of routine vaccination services and poor coverage (<10%) during outreach activities. It affected 27% of the population in the area, with 44% of cases in adults aged 16–40 years. ORI targeting children aged 6 months to 15 years was conducted 35 days after onset of illness in the index patient. Only 2 cases occurred ≥2 weeks after ORI, and both of these were in children aged <6 months. The large inter-household distances may have helped ORI to be effective despite the presence of susceptibility to measles in older age groups.

### African Region

Soula et al [46] described an outbreak in Houet, a province of Burkina Faso with measles vaccine coverage of 50%. This epidemic lasted from October 1995 through May 1996, with most cases occurring after January 1996. Fifty-eight percent of cases were in children aged <5 years. The outbreak was noted to begin in 2 suburban and 1 central starter zones in Bobo Dioulasso but did not spread rapidly until it reached high population density areas in the third week of January. Beginning in April, 95% of children in daycare centers and primary school were vaccinated. The authors comment that ORI was conducted late after outbreak detection and that the target age group appeared to be inappropriate because of the age distribution of cases; they do not comment on the effect of the vaccination activities, although the epidemic curve appears to show impact [46].

An outbreak in Niamey, Niger, was reported by Grais et al [13, 47, 48, 49] and Dubray et al [50]. The campaign, targeting all children aged 6–59 months, began 23 weeks after outbreak onset and reached 57% of the targeted population. Dubray's epidemic curve shows a decrease of ~50% in cases beginning 2 weeks after ORI. Grais et al used mathematical modeling to assess the number of averted cases and the difference that would have been made had the target age group been expanded to children aged 6 months to 15 years or had the campaign begun earlier. These analyses showed that timely implementation of ORI could result in substantial numbers of cases averted and that the proportion of cases averted was associated both with coverage achieved and the number of birth cohorts targeted in the ORI. The authors conclude that more cases can be averted through early intervention targeting a wide age range even if vaccination coverage is low, compared with the number of cases that can be averted through higher coverage with a later intervention.

Vaccination response was mentioned in articles on Zimbabwe [51] and Kenya [21]; however, the impact of these activities was not described.

### Southeast Asian Region

Puvimanisinghe et al [52] summarized an explosive measles epidemic of >15,000 suspected cases experienced in Sri Lanka during 1999–2001. Nationwide, background coverage with 1 dose of measles vaccine was high at 90%. In response to the outbreak, vaccination was offered to children aged <10 years without evidence of vaccination; in addition, an extra dose of vaccine was administered to all children in welfare centers, refugee camps, preschools, and urban slums. However, Puvimanisinghe et al [52] does not discuss the impact of these vaccination activities, nor can it be easily deduced from the epidemic curve. Thakur et al [53] and Ratho et al [54] reported 2 measles outbreaks with ORI in India. Thakur et al describes response immunization for children aged <5 years in a focused geographic area in December 1998, with persistent measles cases reported in January 1999. Proximal areas did not conduct vaccination activities and reported new measles cases in February. Ratho et al mentions ORI but does not discuss impact.

Mohan et al [55] described measles transmission after the 2004 tsunami in India. A cluster of cases occurred in tsunami-affected and unaffected villages, and supplementary immunization activities targeting children aged 6–60 months were conducted in tsunami-affected areas. These SIAs were in response to the emergency rather than the outbreak. Their timing relative to the reporting of the first measles case is not clear. Tsunami-affected areas showed lower measles incidence than non-tsunami areas; however, measles transmission persisted longer in these areas.

### European Region

Three articles reported outbreaks with ORI (Marinova et al [56], Seguliev et al [57], and Ceylan et al [58]). However, the impact of these activities was not described.

## DISCUSSION

This article reviews data published during 1995–2009 to systematically examine the potential impact of measles vaccination campaigns in response to measles outbreaks. Various approaches to examining impact of vaccination activities were used by the articles that we reviewed, including length of outbreak [25],, persistence of measles after immunization activities both locally and nationally [26, 37, 39, 45], shape of epidemic curve [34], measles cases prevented [45], and preventable fraction [33]. Although some articles presented clear evidence of the impact of ORI, in others, available data were more difficult to interpret or were inadequate to permit objective evaluation. As in the case of Darfur, a high-coverage, wide–age-range vaccination campaign may have an impact easily detected in the epidemic curve [34]; delay in implementing or more prolonged delivery of vaccine, as in the Marshall Islands, may have a much less obvious impact [28]. Vaccination may also be offered when the reported number of cases is already decreasing, as in the Burkina Faso report [46], leading to difficulty determining the relative contributions of immunization and the exhaustion of remaining susceptible persons due to acquisition of measles. Measles outbreaks eventually burn out when most susceptible persons are exhausted; when ORI is conducted late in isolated communities or in those with high background vaccination coverage, ORI may appear to be successful when, in fact, the outbreak would have ended even without it.

Most of the outbreak responses that we considered to have demonstrated impact were nonselective, with the sole exception being that in the Marshall Islands. However, the self-contained nature of these small islands, access to records from several sources, and the multiple rounds of immunization may have ensured that, in this setting, unvaccinated individuals were not accidentally missed.

These reports highlight the variable benefits and challenges of ORI and emphasize the importance of considering a variety of outbreak-specific factors in determining whether to conduct ORI, including the country's measles control goals, background vaccination coverage, age distribution of cases, population movement, population density, case-fatality ratios, and ability to conduct a timely response. The Americas, a region with a measles elimination goal, has taken an especially aggressive approach to ORI. The Haitian experience emphasizes both the success that a well-conducted and planned ORI may have in stopping transmission locally, as in Gonaïves, and the challenges of stopping disease spread to other regions when background vaccination coverage is low [39]. The challenge of achieving population impact with ORI in settings of low coverage recurs in the reports from Bolivia and Venezuela [37, 40].

Papers from Peru and the Marshall Islands indicate the relationships of population density, target population, and the success of ORI. Both the Peruvian village and the Marshall Islands had populations too small to sustain endemic disease; isolation had, in both cases, resulted in many measles-free years despite extensive population susceptibility. Although 44% of all Peruvian cases were in those aged >15 years, a high-coverage ORI targeting only children aged 6 months to 15 years stopped the outbreak. However, in the Marshall Islands, with a similar proportion of older cases, transmission was not stopped until vaccination was extended to those aged <40 years. The Peruvian village had exceptionally low population density, whereas that of Majuro was very high at 6692 persons/mi$^2$ [28, 45].

Guris et al [25] demonstrated the association between time to vaccinate 80% of the target population and length of outbreak. Similarly, Al-Wahaibi et al [33] found a strong association between time to achieve full vaccination of a school and preventable fraction of cases. Grais et al [47] also emphasized the importance of timely vaccination in concluding that more cases could be averted through early intervention targeting a wide age range, even if vaccination coverage is lower than can be averted through higher coverage with a later intervention.

Grais et al [13] was also able to document the persistence of measles outbreaks in Kinshasa for >20 weeks in the absence of ORI. In this city, a measles epidemic lasted >16 weeks before it reached certain neighborhoods. The authors speculate that slow spread of disease may have been attributable to limited internal mobility and a lower-than-expected effective reproductive ratio (The effective reproductive ratio is the average number of secondary cases resulting from a single infectious individual in a partially immunized population). These data suggest that, because of the length of outbreaks in the absence of ORI, even delayed vaccination could have an impact.

In some cases (eg, the report by Thakur et al [53] of ORI in India), response was limited to the directly affected population. In others, such as ORI reported from Bolivia and Venezuela [37, 40] and from Sudan [34], ORI targeted a much broader geographic area. Epidemiologic considerations would suggest that the latter approach would be successful; this appears to be borne out in the literature.

Paradoxically, the low-coverage settings where ORI may be least likely to stop transmission are the environments where it may offer greatest benefit. Because of the high percentage of persons susceptible to measles in such settings, each ORI dose delivered has a much higher chance of producing needed immunity than in a high-coverage population where most individuals are already immune. Historically, settings where high background coverage existed tended to be those where the greatest political will to conduct ORI was greatest, as in Mexico [35, 36]. Recent investments in nationwide catch-up campaigns in Africa and Asia and increases in routine coverage could therefore raise the profile of subsequent measles outbreaks and increase the political pressure to conduct ORI.

The articles that we summarize report the occurrence of measles outbreaks and corresponding ORI. However, they did not report on such critical issues as government funding for measles control, priority given to outbreak response, trained personnel available and mobilized, and ready availability of vaccine, syringes, and cold chain equipment. In most cases, these are reflected in the time elapsed between outbreak detection and ORI and clearly play a critical role in the success of ORI.

Our study was limited by inability to obtain a small percentage of papers identified through our literature search. In addition, it is possible that manuscripts showing a positive impact of ORI were more likely to be published than were those that did not. The articles reviewed presented data from such divergent settings as hospitals and community-based investigations, as well as using disparate methods of documenting the impact of ORI, thus making comparisons between outbreaks difficult. Finally, because few relevant papers providing insight into the impact of ORI were found from the European or SouthEast Asian Regions, our findings are based predominantly on experiences in the Western Pacific, Eastern Mediterranean, American, and African Regions.

## CONCLUSIONS

The articles that we reviewed generally demonstrate a decrease in morbidity associated with ORI and document the impact achieved by rapidly reaching high coverage in the population targeted. They reveal the difficulty of preventing spread to other geographic areas and emphasize the importance of considering age distribution of cases, potential timeliness of ORI, population density, and population movement in planning a vaccination response. Furthermore, the recent outbreaks described demonstrate that epidemics may last months in limited geographic areas and that spread of disease may be especially slow in areas with little population movement and low disease reproductive ratio. This is contrary to previous assumptions that, after

a measles outbreak is detected in a population with low measles immunity, it is too late to implement ORI because of the rapid spread of disease. Many reports did not provide sufficient information to allow us to judge the impact of ORI. Nonetheless, in 16 (42%) of 38 outbreaks in which ORI was used, we believe that there was substantial evidence that ORI had a clear impact.

These findings generally support use of ORI in middle- and low-income countries, particularly if ORI can be implemented soon after outbreak detection. However, considerations such as limited availability of funds, vaccine, syringes, and vaccinators may present serious logistical constraints to conducting high-coverage ORI, particularly in wide geographic areas. For these reasons, the decision to conduct an ORI and the nature and extent of vaccination response still needs to be made on a case-by-case basis, taking into account epidemiologic and operational factors. To support countries in rapidly implementing ORI, as is currently recommended, the global measles community should consider outbreak preparedness, response planning, and fund raising. Whether immunization is conducted, outbreak response should include enhanced surveillance, efforts to limit case contact with susceptible persons, and case management, particularly treatment with vitamin A. Finally, although outbreak response immunization can be effective in controlling measles outbreaks, the best and most cost-effective approach to outbreak control is the primary prevention of epidemics entirely by ensuring high coverage with 2 doses of measles vaccine for all children [19].

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