Measles Transmission and Vaccine Effectiveness during a Large Outbreak on a Densely Populated Island: Implications for Vaccination Policy

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(See the editorial commentary by Orenstein et al. on pages 320–1)

Background. The Republic of the Marshall Islands (RMI) is a South Pacific nation freely associated with the United States. In 2003, the RMI experienced the largest measles outbreak within the United States or its associated areas for more than a decade, although the reported coverage of 1-dose measles-mumps-rubella (MMR) vaccine was 80%–93%. The outbreak ended only after vaccination of >35,000 persons among a population of 51,000. Of outbreak cases, 41% were reported to have been previously vaccinated. We studied measles attack rates in RMI households to assess vaccine effectiveness and patterns of disease transmission.

Methods. For the household secondary attack rate study, households were selected by convenience sampling of outbreak measles cases. The primary case was defined as the first person with measles in a household. Secondary cases were household members with measles onset 7–18 days after the primary case’s rash onset. Vaccine effectiveness analysis was limited to children aged 6 months to 14 years, with vaccination status verified against written records.

Results. Seventy-two households were included in the study. The median household size was 11 persons, and the median number of persons per room was 5.5. Secondary cases were more likely than primary cases to be infants (46% vs. 13%; P = .03). MMR vaccine effectiveness was 92% (95% confidence interval [CI], 67%–98%) for 1 dose and 95% (95% CI, 82%–98%) for 2 doses.

Conclusions. Measles vaccine effectiveness was high; thus, diminished effectiveness was not the main cause of the outbreak. In communities with high population density and household crowding, very high population immunity is needed to prevent measles outbreaks and to protect infants below the age of vaccination. This may require excellent implementation of a routine 2-dose measles vaccination strategy.

Measles is among the most infectious of the major viral diseases and can cause severe pneumonia, diarrhea, encephalitis, and death. Although an effective vaccine has been available for >30 years, an estimated 30–40 million measles cases and 745,000 deaths occurred in 2001 worldwide, primarily in developing nations where measles vaccine is underutilized [1]. In contrast, <120 measles cases have occurred annually in the United States since 1998 [2, 3]. The success of the US measles program is based on >90% preschool vaccination coverage for 1 dose of measles vaccine and the near-universal requirement of a second dose for school entry [4–6].

The Republic of the Marshall Islands (RMI) is a South Pacific nation freely associated with the United States, which provides much of the RMI’s vaccination funding. The RMI started measles vaccination in 1982 with a single dose of measles vaccine administered routinely at age 9 months, and, in 1998, changed to a 2-dose schedule, administered at ages 12 and 13 months, but implementation of the 2-dose policy was not strongly enforced. During 1994–2002, three supplemental measles immunization campaigns targeting children of different age groups (up to age 14 years) were conducted. From 1989 until 2003, the RMI did not report a single case of measles, and World Health Organization (WHO) cluster surveys showed single-dose vaccine coverage of 93% and
80% among 2-year-old children in 1998 and 2001, respectively, although second-dose coverage lagged behind at 40% in both years.

In 2003, the RMI experienced a widespread measles outbreak, the largest within the United States, its territories, or affiliated nations for ≥1 decade. Despite intensive control efforts that ended with vaccination of >35,000 persons in a population of ~51,000, the outbreak lasted 6 months, resulting in >800 measles cases (23% involved infants who were below the age of routine vaccination), 100 hospitalizations (34% involved infants), and 3 deaths. Of outbreak cases, 41% were reported to have been previously vaccinated [7]. This raised concerns about loss of vaccine effectiveness (VE) in tropical conditions in which the vaccine storage, handling, distribution, and transport requirements (cold chain) might be difficult to maintain. Vaccine failure had been a problem in the past in the RMI; the last outbreak investigation found a lower-than-expected VE, which the authors attributed mainly to improper storage of the vaccine [8].

A single dose of measles vaccine administered at age 9–12 months has an effectiveness of 85%–95% [9, 10]. Because of this high effectiveness, the WHO has recommended attaining high rates of routine immunization by providing the first dose of measles vaccine to all infants. A second opportunity for measles vaccination—either through a 2-dose routine schedule or through supplementary campaigns conducted periodically—is also recommended. Under conditions of high population density, such as in schools, >95% coverage with a single dose may be insufficient to prevent outbreaks, as experience in the United States has revealed [11, 12]. Whether some community settings facilitate measles transmission as efficiently as schools is unclear. We studied measles attack rates within RMI households to assess VE and patterns of disease transmission.

**METHODS**

**Setting.** The RMI consists of 29 atolls and 5 major islands scattered in the Pacific Ocean. The study was conducted on the Majuro atoll, home to half of the country’s population and to >90% of outbreak cases. Most of Majuro’s population lives in closely packed buildings grouped within a 16-km portion of the 48-km-long island, producing a densely populated area of 2584 persons per square km (cf. Chicago, 2195 persons/km²) [13]. Extended families are common, and family members, particularly children, often move among family dwellings for variable periods. Immunizations are provided through a network of public health clinics that maintain written immunization records and a centralized electronic database.

**Design.** We used a household secondary attack rate (SAR) study to evaluate VE. In the period after exposure to a household member with measles, rates of subsequent measles disease were compared for vaccinated and unvaccinated exposed household contacts.

**Definitions.** A measles case was defined as a person who either (1) met the WHO clinical case definition for measles (fever, generalized maculopapular rash, and cough, coryza, or conjunctivitis) [14] or (2) had a positive test for measles IgM antibody by any serologic assay with the absence of vaccination 6–45 days before testing. A household was defined as all persons residing in the same physical dwelling. A primary case was defined as the first case of measles in a household. Household contacts were defined as persons residing in the household for at least 1 day during the primary case’s infectious period (from 4 days before rash onset to 4 days after). For the purposes of this study, contacts were dichotomized into secondary cases (with measles rash onset 7–18 days after primary case’s rash onset) and noncases (with no clinically apparent disease within 18 days after primary case’s rash onset). A contact was considered vaccinated if there was documented record of measles vaccination administered >4 days before the rash onset of the primary case [15]. A contact was considered unvaccinated if no record of measles vaccination meeting the criteria could be found in any written or electronic immunization records. A contact was considered to have an unknown vaccination status if no immunization card could be found and if the person’s name could not be found in any other immunization record. The SAR represents the proportion of secondary cases among household contacts exposed to the primary household case.

**Sample size calculations.** Assuming a vaccination rate of 80% and a VE of 90%, we sought a study population of ≥200 contacts to estimate VE within 20%, using 95% CIs.

**Subject selection.** Households were selected for study enrollment by convenience sampling of measles cases reported in Majuro from 13 July to 7 November 2003.

**Data collection.** By use of a standardized questionnaire, data on clinical features were collected through interviews with household members during home visits. All vaccination histories were verified against all available written and electronic immunization records. For a subset of households, we collected information about the number of household rooms.

**Data analysis.** For VE analysis, we excluded (1) persons with unknown vaccination status, (2) persons aged <6 months (the minimum age for vaccination during the outbreak), and (3) persons aged ≥15 years. The upper age limit was chosen because older persons had inadequate documentation of immunization and may have had prior disease-acquired immunity. VE was assessed using the Orenstein method [16]: VE = [(SARv − SARu)/SARv] × 100%, where SARv is the SAR among unvaccinated persons, and SARu is the SAR among vaccinated persons.

**Human subjects.** As part of the outbreak-control investigation, this study was designated exempt from the Centers for Disease Control and Prevention human subject policy [17].
Measles Transmission and Vaccine Effectiveness

Figure 1. Age distribution of primary cases (n = 72) (top) and secondary cases (n = 39) (bottom) in the secondary attack rate study of the Marshall Islands measles outbreak, July–November 2003. mos, Months; yrs, years.

Therefore, formal informed consent was not requested, but participation by study subjects was entirely voluntary.

RESULTS

Study population. Seventy-two households were identified; all agreed to participate. A total of 857 persons lived in these households, and the median household size was 10.5 persons (range, 4–28 persons). We examined living space in 25 households, in which the median household size was 12 persons (range, 4–28 persons), the median number of rooms was 2 (range, 1–4 rooms), and the median number of persons per room was 5.5 (range, 2–9 persons/room). Acute measles infection was laboratory confirmed in 19.4% of the cases identified. Of the remaining clinically diagnosed cases, 88% had a duration of rash ≥3 days.

Transmission patterns. Among the 857 household members were 72 primary cases and 785 household contacts, of whom 39 became secondary cases. Secondary cases occurred in 24 (33.3%) of the 72 households. Overall, secondary cases were younger than primary cases; the median age of secondary cases was 1.4 years (range, 12 weeks to 35 years), compared with 11.3 years (range, 2 weeks to 36 years) for primary cases. A higher proportion of secondary cases than of primary cases were infants below the age of routine vaccination (46% vs. 13%; P = .03); by contrast, 36% of primary cases were aged ≥15 years (figure 1).

VE. In the 72 households, there were 280 exposed contacts aged 6 months to 14 years; vaccination status was available for 219 (78.2%), and they represent the VE study population (table 1). Of these, 198 (90%) had received at least 1 dose of measles vaccine, including 150 (68%) who had received ≥2 doses. Among the 219 contacts, 17 contracted measles. VE for 1 and 2 measles-mumps-rubella (MMR) vaccine doses was 92% (95% CI, 67%–98%) and 95% (95% CI, 82%–98%), respectively. We examined the effect that the exclusion of children aged 6–8 months had on VE; point estimates did not differ meaningfully (1 dose: VE, 94%; 2 doses: VE, 93%), so we decided to present the results with these children included in the analysis.

The attack rate for persons with unknown vaccination status was 5% (3 of 61). This is far less than the attack rate for unvaccinated persons (52% [11 of 21]) but comparable to that for vaccinated persons (3% [6 of 198]).

DISCUSSION

During a large outbreak on a densely populated island, measles vaccine was highly effective: a single dose reduced the risk of measles disease by 92%, a result consistent with previous studies of measles VE [4, 15, 18, 19]. Two doses reduced measles risk by 95%, which suggests increased protection, although our study lacked the power to distinguish VE between 1 and 2 MMR vaccine doses. We have no evidence that diminished VE contributed to the size or duration of the RMI outbreak. In contrast to a previous Marshall Island measles outbreak [8], vaccine storage and handling did not appear to contribute to the 2003 outbreak.

Despite that the vaccine was highly effective, the vaccine apparently failed for 41% of cases [7]. During this outbreak, efforts were focused on vaccination rather than on coverage surveys. However, using a standard outbreak screening method, one can estimate the proportion of the population vaccinated if the proportion of cases vaccinated and VE are known [20]. For 41% vaccine failure among cases and 92% VE, the estimate for the population-based vaccination coverage would be 88%. This estimate is consistent with previous WHO coverage surveys in the RMI (in 1998, 93%; in 2001, 80%) and with the 90% single-dose coverage rate obtained in our convenience sample of households. Such single-dose coverage would exceed

Table 1. Vaccination status of contacts aged 6 months to 14 years, secondary attack rate (SAR), and vaccine effectiveness (VE) in a study of the Marshall Islands measles outbreak, July–November 2003.

<table>
<thead>
<tr>
<th>No. of MMR vaccine doses</th>
<th>No. of contacts</th>
<th>No. of secondary cases</th>
<th>SAR, %</th>
<th>VE, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21</td>
<td>11</td>
<td>52</td>
<td>…</td>
</tr>
<tr>
<td>1</td>
<td>48</td>
<td>2</td>
<td>4</td>
<td>92 (67–98)</td>
</tr>
<tr>
<td>2</td>
<td>106</td>
<td>3</td>
<td>3</td>
<td>95 (82–98)</td>
</tr>
<tr>
<td>≥3</td>
<td>44</td>
<td>1</td>
<td>2</td>
<td>…</td>
</tr>
<tr>
<td>Total</td>
<td>219</td>
<td>17</td>
<td>…</td>
<td>…</td>
</tr>
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NOTE. MMR, measles-mumps-rubella.
the 80% threshold thought to provide measles herd immunity in US communities outside of schools [21]. Our study data agree with previous WHO coverage surveys that second-dose coverage, in contrast, was relatively low (40%–68%).

Our findings also suggest that community conditions in Majuro facilitated transmission of the highly infectious measles virus. Household sizes were large (median, 11 persons), the number of persons per room was large (median, 5.5), and a high overall population density was found in the outbreak zone. Such community conditions may facilitate viral transmission as efficiently as school environments. In US schools, high coverage with a routine 2-dose schedule has been necessary to prevent outbreaks [6]. In Majuro, the outbreak did not end until more than two-thirds of the population had received additional doses.

In this study, we found that older siblings or adults brought the measles virus into the household and exposed infants, who contracted the disease. This finding highlights the need to protect infants below the age of routine vaccination, who have the highest morbidity and mortality associated with measles infection [22]. In the RMI outbreak, infants accounted for 23% of cases and 34% of hospitalizations, more than any other age group [7]. Most infants have some protection from measles by passively acquired maternal antibodies at birth. Measles had not been reported in the RMI since 1989, and mothers who have not had measles do not transfer measles antibody to their infants. Vaccine-induced antibody titers are typically lower than those induced by natural infection. Thus, for infants born to vaccinated mothers, the level and duration of maternal protection is lower than for those born to mothers who sustained the disease [23–25]. Because documentation of measles vaccination was not available for persons aged >14 years and because information on measles history was unreliable, we were not able to assess whether this high attack rate among infants in the RMI was the result of lack of maternal measles antibody or low maternal antibody.

Countries such as the United States that achieve high vaccination coverage protect unvaccinated infants from exposure to the virus through herd immunity effect. This allows routine vaccination to be delayed until after the first birthday, providing a substantial increase in the effectiveness of vaccine. In countries with lower rates of coverage, infants are at high risk of exposure. In such situations, policy makers usually lower the age of first vaccination to <12 months, despite the consequence of diminished VE. Fortunately, the lower VE may be increased by providing a second dose of vaccine [26–28]. This suggests that the second-dose strategy may mitigate the lower VE obtained with early vaccination, and every effort should be made to ensure a 2-dose policy.

Our study had a number of limitations. We used a clinical case definition for measles that did not include rash duration, and not all cases were laboratory confirmed. Because of convenience sampling, our household size and density findings may not have been representative of the overall Majuro population. Our study was not powered to distinguish the typical 5% difference in effectiveness between 1 and 2 doses of measles vaccine. However, the results of high VE are robust because they were obtained from a household contact study, the most stringent test of vaccine performance because of the intensity and duration of exposure [29].

Our findings suggest that, even with a highly effective vaccine, large outbreaks can occur because of the high transmissibility of measles virus in crowded communities—with transmission possibly as efficient as in a school environment. Recent measles outbreaks in European countries are a reminder that, even in developed countries with a routine 2-dose measles vaccination schedule, low vaccination coverage can allow susceptible persons to accumulate and thus sustain measles virus transmission, with the resulting morbidity and mortality [30–33]. If measles vaccination in the population aged ≥12 months falls to levels that permit measles virus transmission, the infant population is at a particularly high risk of measles and its complications. Policy makers need to consider whether aggressive implementation and maintenance of high routine 2-dose measles vaccination coverage may be needed to avert outbreaks in similar communities elsewhere and to protect infants below the age of vaccination.

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Potential conflicts of interest. All authors: no conflicts.

References


