Measles Elimination in the Americas: A Comparison Between Countries With a One-Dose and Two-Dose Routine Vaccination Schedule

Adrienne E. Sever,1,2 Jeanette J. Rainey,2 Elizabeth R. Zell,3 Karen Hennessey,2 Amra Uzicanin,2 Carlos Castillo-Solorzano,4 and Vance Dietz2

1Epidemic Intelligence Service Officer, Office of Workforce and Career Development, 2Global Immunization Division, and 3Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia; and 4Comprehensive Family Immunization Unit, Pan American Health Organization, Washington, D.C.

Background. The Region of the Americas eliminated measles in 2002 through high first-dose routine measles vaccine coverage and vaccination campaigns every 4–6 years; a second routine dose at school entry was added in some countries. The impact of this second routine dose on measles elimination was evaluated.

Methods. Data on socioeconomic factors, demographic characteristics, vaccination coverage, and the estimated proportion of children (<15 years of age) susceptible to measles were compiled. Countries were grouped using propensity score methods, and Kaplan-Meier curves were used to compare time to measles elimination between countries with a 1-dose schedule and those with a 2-dose schedule.

Results. One-dose (n = 14) and 2-dose (n = 7) countries did not differ with respect to median routine first-dose measles vaccine coverage, median coverage for 3 measles campaigns, or estimated percentage of susceptible children after routine first vaccination dose and campaigns. Compared with 1-dose countries, 2-dose countries had higher median gross national income per capita (P = .002), percentage of population living in urban areas (P = .04), and female literacy (P = .01), as well as lower infant mortality (P = .007); however, no differences in time to elimination were found.

Conclusions. One-dose and 2-dose countries had similar times to measles elimination despite socioeconomic differences between their populations. A second routine dose might not have hastened measles elimination, because threshold immunity needed to eliminate measles was achieved with high first routine dose coverage and vaccination campaigns. Further research will be needed to determine the applicability of these findings to other regions.

BACKGROUND

Measles is a highly infectious vaccine-preventable disease and is one of the leading causes of death worldwide among children in developing countries [1]. Because of a global measles mortality reduction program initiated in 2001, first-dose measles vaccination coverage increased from 72% to 82% globally between 2000 and 2007, whereas measles deaths decreased by 74%, from 750,000 deaths in 2000 to 197,000 deaths in 2007. An estimated population immunity of 93%–97% is needed to prevent outbreaks and interrupt endemic measles virus transmission [2–6].

A 2-dose routine strategy is practiced in the United States and Canada, where administration of the first dose at 12 to 15 months of age is recommended; this first dose provides immunity to approximately 95% of children [4, 7]. The second dose is generally provided at school entry [3, 8, 9]. Neither country chose to conduct mass measles campaigns. This vaccination policy, with the addition of a school entry requirement, effectively eliminated endemic measles virus transmission in the United States and Canada by 1998.
In developing countries, where measles incidence and deaths are greatest among children under 5 years of age, measles vaccine is usually administered at 9 months of age, thereby providing immunity to approximately 85% of children vaccinated [2, 3, 8, 10]. Because this schedule leaves some children susceptible, efforts are made to provide all children with a second opportunity to receive measles vaccine through vaccination campaigns or administration of a second routine vaccine dose [3, 8]. Administering a second dose at 12 months of age provides immunity to 97%-99% of children [11–13]. Most countries in the African, American, and Asian regions have focused on providing a first dose through routine immunization services and a second opportunity through vaccination campaigns [14–16].

Prior to the global measles mortality reduction program, in 1994, the Pan American Health Organization (PAHO) set a goal of eliminating endemic measles in the Western Hemisphere by 2000 [14, 17, 18]. By late 2002, transmission of measles virus was successfully interrupted through a strategy consisting of an initial mass-vaccination campaign targeting children aged 9 months to 14 years (“catch-up campaign”), continuation of routine vaccination of children aged 12 months (“keep-up” vaccination), and additional mass-vaccination campaigns among children every 4–6 years (“follow-up” campaigns) for children 1–5 years old [18, 19]. Although not formally recommended or monitored by PAHO, some countries in the region introduced a second routine dose of measles-containing vaccine (MCV2) to their routine vaccination schedule at school entry in addition to providing a second dose through vaccination campaigns. The presence of a routine second dose in some countries but not in others provided a unique opportunity to evaluate whether a second routine measles vaccination dose aided in eliminating measles in the Region of the Americas. Understanding the impact of a second routine dose may help guide measles elimination strategies in other regions.

**METHODS**

**Countries Included in This Study**
The region of the Americas includes 35 countries and 13 territories and is demographically and economically diverse; public health policy in the region is guided by PAHO. Countries and territories in the English-speaking Caribbean, French, and Dutch territories, and Bermuda (n = 24) were excluded from the analysis because of small population size and geographic isolation. The United States (including Puerto Rico) and Canada were also excluded, because vaccination policy in these countries differed from that in the rest of the countries in the region. This analysis focused on the remaining 21 countries in Latin America and the Caribbean. These countries were categorized into whether they added a second routine dose of measles vaccine (“2-dose country”) or not (“1-dose country”) according to the routine vaccination schedule in place at least 3 years prior to the last endemic case of measles in the country (Figure 1).

**Data Sources**
Country-level programmatic and administrative vaccination data were obtained from the Immunization Unit of the Family and Community Health Area of PAHO. The following immunization variables were used for this analysis: first routine dose of measles-containing vaccine (MCV1) coverage, supplemental immunization activity (SIA) coverage, SIA frequency (followed recommendations to conduct a follow-up campaign every 4–6 years or not), first and third doses of diphtheria-tetanus-pertussis vaccine (DTP1 and DTP3) coverage, and measles and DTP3 dropout rates. MCV1, DTP1, and DTP3 coverage were based on the average reported coverage from the 3 years (1999–2001) preceding the interruption of endemic measles virus transmission in the region. SIA coverage was estimated as the average coverage achieved during the 3 SIAs implemented in each country for measles elimination efforts. DTP3 and measles dropout rates were calculated using standard definitions [20]. MCV2 coverage information was not available. The percentage of surveillance sites reporting measles cases on a weekly basis was the only consistently reported indicator available for surveillance quality and was averaged from 1999 through 2001.

Socioeconomic and demographic variables were collected from the PAHO Basic Indicators and the United Nations Educational, Scientific, and Cultural Organization databases [21, 22] to represent access to health care, socioeconomic determinants of health care or vaccination coverage, or relation to measles virus transmission [23–28]. Selected variables included population density, proportion of the population living in urban areas, female literacy, gross national income (GNI) per capita, percentage of gross domestic product (GDP) spent on health care, net primary school enrollment, doctor and nurse ratio per 1000 population, and infant mortality.

**Definitions for Measles Elimination and Time to Elimination**
Three definitions for measles elimination year (MEY) were used: (1) a case-based MEY was defined as the year after which the last endemic (nonimported) measles case was reported, (2) a population-based MEY was defined as the year measles incidence of <1 laboratory-confirmed case per 1 million population was achieved and sustained, and (3) a combination MEY was defined as the year in which both the case-based and population-based definitions were met. The case-based definition was used because this encompasses the traditional definition for measles elimination, in which no further endemic cases exist; in addition, the population-based definition was included because this is one of the current factors being assessed globally and used by the World Health Organization as a requirement for measles elimination.
Time to elimination was calculated as the difference between 1992 (the year in which the first countries introduced MCV2 and in which the first vaccination campaigns occurred) and the year of measles elimination. For each country, time to measles elimination was evaluated for each of the 3 definitions for measles elimination given above.

**Analysis**

**Descriptive Analysis.** Using all 3 MEY definitions, bivariate statistics were calculated to evaluate overall trends in the region and to assess whether any of the socioeconomic or demographic variables were associated with achieving measles elimination. Immunization program variables were divided categorically for bivariate analyses. Immunization coverage was divided into 4 categories (≥95%, 90–94%, 80–89%, <80%) so that countries that achieved high coverage (>95%) could be delineated more clearly. SIA frequency was divided into 2 categories (followed recommendations to conduct campaigns every 4–6 years or not) and surveillance quality—defined as the percent of surveillance sites reporting weekly—was divided into 4 categories (≥90%, 80–89%, 70–79%, and <70%); the remainder of the variables were divided into quartiles. Countries were divided into early (before 2000, which was the year originally chosen as a goal for regional elimination) and late (2000 or after) elimination categories. The Kruskal-Wallis test was used to compare the medians of 1- and 2-dose countries, and Fischer’s exact test was used to evaluate the association between each of the variables and measles elimination.

**Propensity Score Methods.** Because of a low number of observations and a high number of covariates [29], propensity score methods were used to identify a subset of 1-dose and 2-dose countries that were similar for selected characteristics to reduce bias in comparing time to measles elimination [29–31]. Logistic regression was used to generate a propensity score for each country based on the conditional probability of experiencing an event (having a 1-dose routine measles vaccination policy) given a set of potential confounders (known covariates associated with both the routine measles vaccination policy and measles elimination or with transmission risk factors) [30]. Countries with similar propensity scores have similar covariate patterns and can, therefore, be more comparable.

The variables chosen for this model were MCV1 coverage, measles vaccination campaign coverage, measles vaccination campaign schedule, population density, percentage of population residing in urban areas, and surveillance quality. The propensity score model was developed through the use of Bayesian logistic regression [32]. The distributions of propensity scores for 1- and 2-dose countries were assessed to identify countries that had covariate patterns similar to those of a country in the other group. Countries with no comparable counterpart were omitted. The resulting reduction in bias was assessed by evaluating changes in the absolute difference in the t statistic for each variable included in the model, utilizing all countries, compared with the selected subset. The subgroup of countries chosen was redefined until the best overall balance in variables was achieved.

**Time to Elimination.** Kaplan-Meier curves were generated to visualize the time to elimination for 1- and 2-dose countries, and curves were compared using log-rank tests for all 3 time-to-measles-elimination definitions [33]. Two-dose countries were further stratified into early (1992) and late (1997–1998) introduction according to the implementation date of the second routine dose. Mean and median time to elimination were also calculated using each time-to-elimination definition.

**Measles Susceptibility**

Estimates of measles susceptibility were calculated for each country for persons <15 years of age, which encompasses the age groups most at risk for measles virus infection and those targeted by both campaigns and routine immunization programs. Susceptibility by cohort was estimated by multiplying the number of persons in the birth cohort by first-dose vaccine coverage and vaccine efficacy (VE). To obtain the most-conservative estimates of susceptibility, natural measles immunity was not included in the models. Eighty-five percent VE was assumed for vaccination in first year of life, because most countries still administered the first routine dose at 9 months of age during the time period, and 95% VE was assumed for vaccination of those in the second year of life or older. All vaccination opportunities were assumed to be independent events. In addition, because routine second-dose coverage data were not available, we estimated the immunity gained from this additional dose by assuming 50% and 75% coverage for countries where this was applicable.

An alpha level of 0.05 was used to assess statistical significance. All analyses were conducted using SAS, version 9.1 (SAS Institute).

**RESULTS**

**Descriptive Analysis**

Of the 21 countries included in the analysis, 7 were classified as 2-dose policy countries and 14 were classified as 1-dose policy countries (Table 1). Compared with 1-dose countries, 2-dose countries had lower infant mortality (P = .007), higher female literacy (P = .01), higher GNI per capita (P = .002), and a higher proportion of the population residing in urban areas (P = .04) (Table 2). Other socioeconomic and demographic characteristics and immunization program indicators were similar between 1-and 2-dose countries, including first-dose routine measles vaccine coverage and coverage for the 3 SIAs.

Higher surveillance quality was associated with all 3 definitions of measles elimination (P = .03 for all 3 definitions). No other significant associations were detected between any socioeconomic,
demographic, and immunization program variables and measles elimination.

**Propensity Scores**

The propensity score model identified a subset of 15 countries (Argentina, Belize, Bolivia, Brazil, Chile, Costa Rica, Cuba, Dominican Republic, Ecuador, El Salvador, Panama, Paraguay, Peru, Uruguay, and Venezuela) with similar scores. The achieved reduction in corresponding absolute values of the \( t \) statistics demonstrated the potential reduction in bias when analyzing time to elimination.

**Time to Elimination**

Mean and median time to elimination were similar for 1- and 2-dose countries when all countries were analyzed and for the subset of propensity score–selected countries (Table 3). When analyzed for all countries, Kaplan-Meier curves (as demonstrated in Figure 2A for the case-based definition) were similar for 1-dose and 2-dose countries for all 3 elimination outcomes (case-based: \( \chi^2 = 0.07, P = .79 \); population-based: \( \chi^2 = 0.61, P = .44 \); combination: \( \chi^2 = 0.28, P = .60 \)). When stratified into early and late introduction for MCV2, time to elimination remained statistically similar between 1-dose and 2-dose countries. Time-to-elimination analyses were repeated using the subset of propensity score–selected countries, and Kaplan-Meier curves (as demonstrated in Figure 2B for the case-based definition) were similar for all 3 definitions (case-based: \( \chi^2 = 0.44, P = .51 \); population-based: \( \chi^2 = 0.01, P = .91 \); combination: \( \chi^2 = 0.44, P = .51 \)).

**Measles Susceptibility**

The estimated proportion of persons <15 years of age who were susceptible to measles for both 1-dose (mean susceptibility, 7.4% [95% confidence interval [CI], 5.5%–9.2%]; median susceptibility, 7.1%) and 2-dose (mean susceptibility, 5.9%; 95% CI, 3.9%–7.9%; median susceptibility, 5.5%) countries were similar after the first routine vaccination dose and vaccination campaign doses (Figure 3). The estimated percentage of susceptible persons aged <15 years was lower in 2-dose countries than in 1-dose countries, assuming MCV2
coverage of 50% (mean susceptibility, 4.1%; 95% CI, 2.3%–5.8%; median susceptibility, 3.5%) and 75% (mean susceptibility, 3.3%; 95% CI, 1.5%–5.0%; median susceptibility, 2.5%).

**DISCUSSION**

Findings from this analysis suggest that, in the Region of the Americas, countries that added a second routine measles dose to

Table 2. Mean and Median Values for Socioeconomic, Demographic, and Program Indicators by Routine Vaccination Schedule, Region of the Americas, 1992–2002

<table>
<thead>
<tr>
<th>Indicator</th>
<th>2-Dose countries (n = 7)</th>
<th>1-Dose countries (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean value (95% CI)</td>
<td>Median value (range)</td>
</tr>
<tr>
<td><strong>Socioeconomic and demographic indicators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Population density (people per km²)</td>
<td>37 (17–58)</td>
<td>40 (13–77)</td>
</tr>
<tr>
<td>Population in urban areas, %</td>
<td>76 (63–89)</td>
<td>75 (56–92)</td>
</tr>
<tr>
<td>Female literacy, %</td>
<td>94 (91–97)²</td>
<td>96 (89–98)</td>
</tr>
<tr>
<td>GNI per capita, USD</td>
<td>473 (309–637)</td>
<td>486 (206–747)</td>
</tr>
<tr>
<td>Percent of GDP spent on health care</td>
<td>7.3 (5.7–8.9)</td>
<td>7.0 (5.1–10.1)</td>
</tr>
<tr>
<td>Net primary school enrollment, %</td>
<td>90 (79–100)</td>
<td>90 (67–99)</td>
</tr>
<tr>
<td>Doctor and nurse ratio (per 10 000 population)</td>
<td>97 (86–108)</td>
<td>96 (72–107)</td>
</tr>
<tr>
<td>Infant mortality (per 1000 live births)</td>
<td>17 (12–22)²</td>
<td>18 (9–23)²</td>
</tr>
<tr>
<td><strong>Immunization program indicators</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MCV1 coverage</td>
<td>91 (85–97)</td>
<td>94 (80–96)</td>
</tr>
<tr>
<td>Measles SIA coverage</td>
<td>88 (80–95)</td>
<td>91 (77–97)</td>
</tr>
<tr>
<td>DTP1 coverage</td>
<td>95 (92–97)</td>
<td>94 (92–96)</td>
</tr>
<tr>
<td>DTP3 coverage</td>
<td>87 (80–94)</td>
<td>88 (74–92)</td>
</tr>
<tr>
<td>Measles dropout</td>
<td>4.3 (–2.9–11)</td>
<td>3.2 (–6.7–19)</td>
</tr>
<tr>
<td>DTP dropout</td>
<td>6.7 (0.45–13)</td>
<td>3.3 (1–20)</td>
</tr>
<tr>
<td>Surveillance quality</td>
<td>80 (62–99)</td>
<td>90 (44–97)</td>
</tr>
</tbody>
</table>

**NOTE.** CI, confidence interval; DTP, diphtheria-tetanus-pertussis vaccine; SIA, supplemental immunization activity.

- For median values, significant (P < .05) Kruskal-Wallis test comparing 1-dose and 2-dose countries.
- For mean values, significant nonoverlapping 95% CI between the 1-dose and 2-dose countries.
- MCV1 coverage is defined as average measles-containing vaccine coverage during the period 1999–2001, SIA coverage is defined as the average coverage of 3 SIAs, DTP1 coverage is defined as the average DTP first-dose vaccine coverage during 1999–2001, DTP3 coverage is defined as the average DTP third-dose vaccine coverage 1999–2001, surveillance quality is defined as the average percentage of weekly reporting by site, 1999–2001.

Table 3. Median Time to Elimination by Definition for 1-Dose and 2-Dose Countries for All 21 Countries in the Study and the Subset of 15 Countries Identified Through Propensity Score Methods, Region of the Americas, 1992–2002

<table>
<thead>
<tr>
<th>Routine vaccination policy</th>
<th>Number of countries</th>
<th>Case-based time to elimination</th>
<th>Population-based time to elimination</th>
<th>Combination time to elimination</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Median years</td>
<td>IQR</td>
<td>Median years</td>
</tr>
<tr>
<td>All 21 countries</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>14</td>
<td>7</td>
<td>5–9</td>
<td>5.5</td>
</tr>
<tr>
<td>2 early</td>
<td>4</td>
<td>8</td>
<td>6–8</td>
<td>8</td>
</tr>
<tr>
<td>2 late</td>
<td>3</td>
<td>9</td>
<td>9–10</td>
<td>8</td>
</tr>
<tr>
<td>All 2 dose</td>
<td>7</td>
<td>8</td>
<td>8–9</td>
<td>8</td>
</tr>
<tr>
<td>Propensity score subset</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 dose</td>
<td>10</td>
<td>8</td>
<td>5–9</td>
<td>6.5</td>
</tr>
<tr>
<td>2 early</td>
<td>4</td>
<td>8</td>
<td>6–8</td>
<td>8</td>
</tr>
<tr>
<td>2 late</td>
<td>1</td>
<td>9</td>
<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>All 2 dose</td>
<td>5</td>
<td>8</td>
<td>8–8</td>
<td>8</td>
</tr>
</tbody>
</table>

**NOTE.** Case-based elimination year is defined as the year after which last endemic (nonimported) measles case occurred through 2002, population-based elimination year is defined as the year measles incidence of <1 laboratory-confirmed case per 1 million population was achieved and sustained, and combination elimination year is defined as the year following the last endemic measles virus cases after which measles incidence of <1 case per 1 million population was sustained. Two early refers to countries that introduced a second routine dose in 1992, and 2 late refers to countries that introduced a second routine dose during 1997–1998. IQR, interquartile range; NA, not applicable.
the “catch-up, keep-up, follow-up” strategy did not hasten measles elimination, compared with countries that did not have a second routine vaccination dose, despite apparent socioeconomic advantages in countries with a second routine dose. This is the first study to evaluate the impact of a second routine measles vaccination dose on measles elimination in countries that used a vaccination campaign strategy in addition to routine vaccination for administration of the first MCV dose. Although factors such as high GNI per capita, high literacy rate, and high first-dose MCV coverage make the PAHO region unique, there are lessons that are transferable to other regions. In particular, the Region of the Americas represents a diverse group of countries in which regional level commitment, expertise, and support were instrumental in organizing measles vaccination campaigns and ensuring uniformly high-quality routine vaccination activities in all countries in the region, thereby minimizing the impact of having a lower level of socioeconomic development on achieving regional measles elimination objectives.

Possible explanations for the lack of impact of a second routine measles vaccine dose in the Region of the Americas are the high overall population immunity achieved with high-quality implementation of the PAHO measles elimination strategy [34] and the age of MCV2 administration (4–6 years of age). The PAHO measles elimination strategy included vaccination campaigns that were often synchronized in multiple countries and which led to a rapid increase in overall population immunity. In addition, high first-dose measles vaccine coverage through routine vaccination resulted in a low number of accumulated susceptible persons throughout the region. With the population immunity achieved through this strategy at or near the herd immunity threshold, it is likely that the addition of a second routine dose had little overall effect on measles elimination. Furthermore, the second routine dose in country childhood vaccination schedules was administered at 4–6 years of age, after children had received a first routine dose and a vaccination campaign dose. Thus, for many children, the
second routine dose represented a “third opportunity” for vaccination. In the Region of the Americas, as well as in the United States, Canada, and most of Europe, administration of the second routine dose at 4–6 years of age is effective because the majority of measles virus infections occur after 5–6 years of age [2, 14]. However, in developing countries, where transmission rates are higher among preschool-aged children [2, 35], the second dose should be administered in the second year of life, as is done in countries of the Asian and Eastern Mediterranean regions [8, 36, 37].

In our study, propensity score methods were used, in addition to descriptive analyses, to identify a subset of 1-dose and 2-dose countries with similar characteristics, which made them more comparable with one another. This approach is applicable for analyses in which the use of traditional multivariate logistic regression models would have been difficult because of the small number of observations in relation to the number of possible covariates [29]. Although other relevant covariates might not be accounted for in this model, the propensity score method reduced bias related to confounders, which would not have been feasible with traditional methods. Nevertheless, the lack of a statistical difference in time to measles elimination in 1-dose and 2-dose countries could also reflect the small sample size and our inability to completely control for confounding. A total of 21 countries were included in the analysis, and only 15 of these were selected through the propensity score methods. However, we looked at several different time-to-elimination outcomes and estimated susceptibility for 1-dose and 2-dose countries. Results were consistently similar, which suggests that the findings are robust.

Although no impact of a second routine dose was found in the Region of the Americas, these findings might not be applicable to other countries and regions. In particular, a second routine dose might have greater impact when administered at 2 years of age and in countries with lower measles vaccine coverage than was achieved in the Region of the Americas from routine vaccination and from vaccination campaigns. As other regions and countries come closer to achieving measles elimination goals, research or modeling is needed to determine the most-effective means and timing of delivering a second routine dose of measles vaccine. In addition, future research should focus on the role a second routine dose may have in sustaining measles elimination.

Acknowledgments

We thank Dr Carolina Donavaro, Christina Marsigl, Pamela Bravo, and others at PAHO, for their contributions and assistance with gathering regional data; Dr Brent Burkholder, Dr Steve Cochi, Dr Hardeep Sandhu, Dr Kathleen Wannemuehler, and others in the Global Immunization Division at the Centers for Disease Control and Prevention as well as Dr Peter Strebel and others at the World Health Organization, for their insight and comments provided to the project.

References