Measles Epidemic in Romania, 1996–1998: Assessment of Vaccine Effectiveness by Case-Control and Cohort Studies

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A measles epidemic occurred in Romania with 32,915 cases and 21 deaths reported between November 1996 and June 1998, despite high vaccination coverage since the early 1980s. Most cases were unvaccinated children aged <2 years and vaccinated school-aged children. A case-control study among preschool children and a cohort study among primary-school children were conducted to estimate effectiveness of Romanian-produced measles vaccine, and to evaluate age at vaccination and waning immunity as risk factors for vaccine failure. Both studies indicated that measles vaccine was highly effective. One dose reduced the risk for measles by 89% (95% confidence interval (CI) 85, 91); two doses reduced the risk by 96% (95% CI 92, 98). Children vaccinated at <1 year of age were not at increased risk for measles compared with children vaccinated at ≥1 year. Waning immunity was not identified as a risk factor since vaccine effectiveness was similar for children vaccinated 6–8, 9–11, and 12–14 years in the past. Because specific groups were not at risk for vaccine failure, an immunization campaign that targets all school-aged children who lack two doses may be an effective strategy for preventing outbreaks. A mass campaign followed by increased first-dose coverage should provide the population immunity required to interrupt indigenous measles virus transmission in Romania. Am J Epidemiol 1999;150:1250–7.

disease outbreaks; immunity; immunization programs; measles; measles vaccine; vaccination

A large measles epidemic occurred in Romania with 32,915 measles cases and 21 deaths reported between November 1996 and June 1998, despite high measles vaccination coverage since the early 1980s. Romania introduced routine measles vaccination in May 1979 with an imported live attenuated Schwarz measles vaccine administered to children aged 9–15 months through biannual campaigns held in public clinics. Clinic staff use birth registries to compile a list of children eligible for each biannual campaign and inform parents when their child should be brought to the clinic for vaccination. In 1981, the Cantacuzino Institute in Bucharest in collaboration with the Pasteur Institute, France, began producing live attenuated Schwarz measles vaccine, which has been used exclusively since then. Each batch of vaccine is tested for purity and potency by an independent Romanian regulatory agency. In 1994, a two-dose measles immunization strategy was introduced by administering a second dose of measles vaccine to schoolchildren aged 7 years (children in grade 1) in December; by the beginning of the 1997–1998 school year, schoolchildren in grades 2–4 had received two doses of measles vaccine. To reduce the age of receipt of the first measles dose, administration of the first measles vaccine dose changed from biannual campaigns to monthly campaigns which targeted children aged 9–11 months. Currently, virtually all measles immunizations are administered through the public sector.

During 1983–1997, reported coverage with one dose of measles vaccine by 18 months of age averaged 93 percent and coverage with the second dose in each school entry cohort has been approximately 95 percent. These high coverage rates have led to a >90 percent reduction in measles incidence and >95 percent reduction in measles mortality compared with the incidence in the pre-vaccine era; however, periodic outbreaks continue to occur (figure 1).

Preliminary analysis of surveillance data for the 1996–1998 outbreak showed the highest number of
cases were reported among unvaccinated children <1 year of age and among vaccinated persons 10–18 years of age (1). To identify reasons why such a large outbreak occurred in a highly vaccinated population, studies were conducted to estimate the effectiveness of Romanian-produced measles vaccine and to evaluate age at initial measles vaccination and duration of immunity as possible risk factors in this outbreak.

MATERIALS AND METHODS

Measles surveillance

In Romania, reporting of a physician-diagnosed measles case became compulsory by law in 1954. Cases are reported from all 41 district-level public health departments every 3 months to the National Immunization Program in Bucharest. Reports are made in a line list format and include date of rash onset, age, sex, vaccination status, and complications. All cases from this epidemic with onset during November 1996 to March 1997 (n = 4,056) were entered into a surveillance database. Because of the magnitude of the outbreak, only every fifth case with onset during April 1997 through December 1998 was entered into the database. Analysis of surveillance data includes cases reported during November 1996 through June 1998.

Measles attack rate by year of age for 1997 was calculated by using surveillance data to obtain number of cases with onset in 1997 per birth cohort (cases with onset during April to December 1997 were weighted as five cases) and using census data to obtain size of the birth cohort.

Definitions

A measles case was defined as physician-diagnosed measles. Vaccine effectiveness was calculated using the formula:

$$VE = \left[1 - \left(\frac{AR_v}{AR_u}\right)\right] \times 100,$$

where VE is vaccine effectiveness as a percent, ARv is the measles attack rate among vaccinated persons, and ARu is the measles attack rate among unvaccinated persons (2). In the case-control study, the matched odds ratio was used as an approximation to the risk ratio to calculate vaccine effectiveness (2).

Case-control study

To estimate vaccine effectiveness and identifying risk factors for measles among pre-school children, a case-control study was conducted in Bucharest and Maramures districts. Children born during 1991–1996, aged from 9 months to 6 years, with measles onset between January 1, 1997 and July 15, 1997, were eligible for the study. At each of the district-level health
departments, all eligible cases were identified and sorted by clinic. Clinics with the largest number of cases were visited first and then in descending order until 50 cases were enrolled. For each case, six age-matched controls were selected from the clinic's birth register by selecting the first three eligible children registered immediately before and after the case. Children who were noted in the register to have left the district were not eligible to be controls. Dates of measles vaccination and information regarding risk factors for measles were abstracted from clinic medical records and obtained from clinic staff for both cases and controls. To evaluate if young age at vaccination was a risk factor for measles, a subset of children who received one dose of measles were analyzed; the odds of measles among children vaccinated at <1 year of age was compared with the odds of measles among children vaccinated at ≥1 year of age. Risk factors associated with acquiring measles were identified by matching analysis using conditional logistic regression modeling. Risk factors independently associated with measles disease were identified by adjusting for potential confounding variables using multivariate conditional logistic regression. Analyses were performed using Statistical Analysis Software (SAS) (3).

Retrospective cohort study

To estimate one- and two-dose vaccine effectiveness in primary school-aged children, a retrospective cohort study was conducted in primary schools in Dolj district with >10 measles cases. Dolj district was selected as a study site because it had a large number of school outbreaks. All children in classes that had ≥1 measles case with onset during October–December 1997 were included. Medical records were reviewed for history of vaccination and previous measles. Attack rates, vaccine effectiveness, and 95 percent confidence intervals were calculated using Epi Info, Version 6 software (4).

RESULTS

Surveillance

During November 1996 to June 1998, a total of 32,915 measles cases were reported; only 131 measles cases were reported in the 4 months prior to November 1996, and 223 cases were reported in the remainder of 1998 (figure 2). The increase in reported measles cases began in November 1996 and peaked in April–June 1997. Cases continued to be reported through March 1998 but at lower levels compared with Spring 1997.
Of the 32,915 measles cases reported, 9,647 (29 percent) were included in the surveillance database and are described here. Vaccination status and age distribution of cases are shown in table 1. Overall, 65 percent of cases occurred among school-aged children (5–18 years of age), 74 percent of whom were vaccinated with at least one dose of measles vaccine. Of the 1,130 cases <1 year of age, 258 (23 percent) were aged <6 months, 416 (37 percent) were aged 6–8 months, and 456 (40 percent) were aged 9–11 months. Among the cases 9–11 months of age, 423 (93 percent) were unvaccinated; among the 492 cases who were 12–23 months of age, 314 (64 percent) were unvaccinated. The 21 cases who died had a median age of one year (range: 6 months–18 years), 71 percent were female, 62 percent were unvaccinated, and 38 percent had received one dose of measles vaccine.

Of the 22,823 cases reported in 1997, 7,510 (33 percent) were included in the surveillance database. The overall measles attack rate for 1997 was 101 measles cases per 100,000 population and ranged from 22 to 287 per 100,000 population among the 41 districts. Measles attack rates by year of age show children <1 year of age and those 1 year of age had the highest attack rates, more than 1,100 and 500 cases per 100,000 children, respectively (figure 3). The next highest attack rates were observed in school-aged children aged 7–18 years, except for those aged 8–9 years (the two cohorts targeted by the two-dose strategy).

Case-control study

A total of 98 cases and 588 matched controls were included in the analysis of vaccine effectiveness. Two cases and their matched controls were excluded; one because the case was vaccinated 10 days prior to rash onset and the other due to measles onset before January 1997.

Vaccine effectiveness estimates were similar between Bucharest and Maramures, therefore, analyses are presented for the two districts combined. Univariate analysis showed that being unvaccinated and being a child of itinerant parents (roms) were significant risk factors for measles among preschool children (table 2). These factors remained significant after adjusting for potential confounding variables (vaccination status or ethnicity, medical exposure, type of housing, and day-care use). After adjustment for potential confounding variables, single-dose vaccine effectiveness was 94 percent (95 percent confidence interval (CI) 86, 98) and two-dose effectiveness (based on only one case) was 99 percent (95 percent CI 87, 99). Among the study participants who had received one dose of measles vaccine, receipt of this dose at <1 year of age compared with ≥1 year of age was not associated with an increased risk for measles (adjusted matched odds ratio = 0.5; 95 percent CI 0.2, 1.4).

Retrospective cohort study

Five primary schools with 197 measles cases that had rash onsets between October 13, 1997 and December 10, 1997 were included in the study. These cases were selected from 112 classes with a total of 2,561 study children. Study children had a median age of 11 years (range: 6–15 years); 51 percent were female. Fourteen study children were vaccinated during the outbreak; all 14 were vaccinated after classroom exposure to a measles case, and therefore these vaccinations were not counted.

The measles attack rate among children who received zero, one, or two doses was 48.2 percent, 5.5 percent, and 1.9 percent, respectively (table 3). Single-dose vaccine effectiveness was 89 percent (95 percent CI 73, 95) and two-dose effectiveness (based on only one case) was 99 percent (95 percent CI 87, 99).
FIGURE 3. Measles attack rates by year of age, Romania, 1997. Of the 22,823 cases reported in 1997, 7,510 (33%) were included in the surveillance database; cases with onset during April to December 1997 were weighted as 5 cases.

TABLE 2. Risk factors for measles among preschool children, case-control study, Bucharest and Maramures, Romania, 1997

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Cases (n = 98)</th>
<th>Controls (n = 588)</th>
<th>OR*</th>
<th>95% CI*</th>
<th>Adjusted† OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles vaccination, by no. of doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>47</td>
<td>73</td>
<td>12.4</td>
<td>†</td>
<td>†</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>50</td>
<td>491</td>
<td>83.5</td>
<td>0.04</td>
<td>0.02, 0.09</td>
<td>0.06</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>24</td>
<td>4.1</td>
<td>0.01</td>
<td>0.001, 0.07</td>
<td>0.01</td>
</tr>
<tr>
<td>Rroma</td>
<td>37</td>
<td>74</td>
<td>12.6</td>
<td>5.4</td>
<td>3.1, 9.3</td>
<td>2.2</td>
</tr>
<tr>
<td>Medical exposure§</td>
<td>21</td>
<td>84</td>
<td>14.3</td>
<td>1.8</td>
<td>1.0, 3.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Lives in apartment</td>
<td>54</td>
<td>346</td>
<td>58.8</td>
<td>0.8</td>
<td>0.4, 1.9</td>
<td>1.2</td>
</tr>
<tr>
<td>In day care§</td>
<td>13</td>
<td>137</td>
<td>23.3</td>
<td>0.4</td>
<td>0.2, 1.8</td>
<td>0.6</td>
</tr>
</tbody>
</table>

* OR, matched odds ratio; CI, confidence interval.
† Independent variables included measles vaccination status, ethnicity, medical exposure, type of housing, and day care.
‡ Reference category.
§ Defined as having visited a hospital or clinic 7–18 days prior to rash onset.
¶ In day care for at least half-day.

CI 85, 91); two-dose vaccine effectiveness was significantly higher at 96 percent (95 percent CI 92, 98). Single-dose vaccine effectiveness estimates were statistically similar between children vaccinated 6–8 years, 9–11 years, and 12–14 years in the past; all had overlapping 95 percent confidence intervals (table 4). However, children vaccinated ≤5 years in the past had a significantly lower vaccine effectiveness estimate than children vaccinated 6–8 years in the past. Single-dose vaccine effectiveness was similar for children who were vaccinated between 9–11 months, 12–15 months, and 16–24 months of age (table 5). Children vaccinated between 6–8 months of age also had a similar vaccine effectiveness estimate but had a wider 95 percent confidence interval compared with the age groups mentioned above. Children vaccinated with
their first measles dose after 24 months of age had lower vaccine effectiveness than children vaccinated at younger ages.

DISCUSSION

Romania experienced a large and prolonged measles epidemic between November 1996 and June 1998 despite >90 percent single-dose vaccination coverage since the early 1980s and use of a second dose at school entry since 1995. Because surveillance data indicated that many cases were vaccinated, decreased vaccine effectiveness of Romanian-produced measles vaccine was investigated as one of the possible explanations for this large epidemic. We employed two different study designs which led to the same conclusion that measles vaccine used in Romania is highly effective. Based on the results from the cohort study, a single dose of vaccine reduced the risk of measles by 89 percent. Among primary school-aged children targeted to receive two doses, the second dose provided significantly higher protection, reducing measles risk by 96 percent.

The availability of detailed vaccination records in clinics and schools in Romania offered the opportunity to evaluate young age at vaccination and duration of immunity as possible risk factors for decreased vaccine effectiveness. Young age at vaccination is of interest because presence of maternal antibody interferes with the immune response to measles vaccine and is associated with primary vaccine failure (5). Several studies (6-10) have reported that children vaccinated at <12 months of age were at increased risk for measles; other studies (11-13) have found no increased risk for measles among this age group. We found in both the case-control and cohort studies that vaccination between 9-11 months of age was not associated with increased risk for measles. Results from a serologic study conducted among 66 children in Bucharest in the early 1980s (14) found that all study children lost maternal antibodies by the age of 8 months. Therefore, both epidemiologic and serologic data support the current strategy of starting vaccination at 9 months of age for Romanian children. Studies that have identified vaccination at <12 months of age as a risk factor for measles either may have included a higher proportion of younger infants, who are more likely to have maternal antibodies, or may have been conducted in populations that experienced a slower decay in maternal antibodies (15).

It is not clear why single-dose vaccine effectiveness estimated from the cohort study was lower among children vaccinated after 24 months of age compared with children vaccinated earlier. Children who received their first measles dose after 24 months of age were not vaccinated as part of the routine schedule and may represent children at higher risk for disease or vaccine failure.

There is debate about the importance of waning vaccine-induced immunity, also referred to as secondary vaccine failure, as a cause of increased susceptibility to measles among school-aged children (16). No evidence of waning immunity was found from the cohort study of primary school children as single-dose vaccine effectiveness estimates were similar for children vaccinated 6-8 years, 9-11 years, and 12-14 years in the past. This finding is consistent with the preponder-

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**TABLE 3. Measles attack rates and vaccine effectiveness (VE) by number of doses of vaccine, primary school cohort study, Dolj district, Romania, 1997**

<table>
<thead>
<tr>
<th>No. of doses</th>
<th>No. of cases</th>
<th>Total</th>
<th>Attack rate</th>
<th>VE</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>80</td>
<td>166</td>
<td>48.2</td>
<td>t</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>109</td>
<td>1,982</td>
<td>5.5</td>
<td>89</td>
<td>85,91</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>412</td>
<td>1.9</td>
<td>96</td>
<td>92,98</td>
</tr>
</tbody>
</table>

* CI, confidence interval.  
† Reference category.

**TABLE 4. Measles attack rates and single-dose vaccine effectiveness (VE) by years since vaccination, primary school cohort study, Dolj district, Romania, 1997**

<table>
<thead>
<tr>
<th>Years since vaccination</th>
<th>No. of cases</th>
<th>Total</th>
<th>Attack rate</th>
<th>VE</th>
<th>95% CI*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not vaccinated</td>
<td>80</td>
<td>166</td>
<td>48.2</td>
<td>t</td>
<td></td>
</tr>
<tr>
<td>&lt;35</td>
<td>8</td>
<td>59</td>
<td>13.6</td>
<td>72</td>
<td>45,86</td>
</tr>
<tr>
<td>6-8</td>
<td>24</td>
<td>565</td>
<td>4.3</td>
<td>91</td>
<td>87,94</td>
</tr>
<tr>
<td>9-11</td>
<td>53</td>
<td>862</td>
<td>6.1</td>
<td>87</td>
<td>83,91</td>
</tr>
<tr>
<td>12-14</td>
<td>24</td>
<td>498</td>
<td>4.8</td>
<td>90</td>
<td>85,93</td>
</tr>
</tbody>
</table>

* CI, confidence interval.  
† Reference category.

**TABLE 5. Measles attack rates and single-dose vaccine effectiveness (VE) by age at vaccination, primary school cohort study, Dolj district, Romania, 1997**

<table>
<thead>
<tr>
<th>Age in months at vaccination</th>
<th>No. of cases</th>
<th>Total</th>
<th>Attack rate</th>
<th>VE</th>
<th>95% CI†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not vaccinated</td>
<td>80</td>
<td>166</td>
<td>48.2</td>
<td>t</td>
<td></td>
</tr>
<tr>
<td>6-8</td>
<td>2</td>
<td>49</td>
<td>4.1</td>
<td>92</td>
<td>67,96</td>
</tr>
<tr>
<td>9-11</td>
<td>32</td>
<td>550</td>
<td>5.8</td>
<td>88</td>
<td>82,92</td>
</tr>
<tr>
<td>12-15</td>
<td>36</td>
<td>807</td>
<td>4.5</td>
<td>91</td>
<td>87,94</td>
</tr>
<tr>
<td>15-24</td>
<td>17</td>
<td>353</td>
<td>4.8</td>
<td>90</td>
<td>84,94</td>
</tr>
<tr>
<td>&gt;24§</td>
<td>22</td>
<td>222</td>
<td>9.9</td>
<td>79</td>
<td>66,87</td>
</tr>
</tbody>
</table>

* Analysis excludes children who received 2 doses of vaccine (n = 412) and one child missing date of vaccination; no children were vaccinated prior to 6 months of age.  
† CI, confidence interval.  
‡ Reference category.  
§ Range: 24 months to 11 years; median = 3 years.

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This type of "catch-up" campaign has been conducted years of age had high measles attack rates and that 93 transmission of measles virus (22, 25). community and through living in extended families. measles, possibly due to higher contact rates in the future outbreaks may be to conduct a mass immunization because they were born prior to introduction of 1979-1987) missed the second dose recommenda-

dation and will have the highest levels of susceptibility to measles given the current vaccination schedule and has provided the rationale for two-dose immunization strategies. A routine two-dose immunization schedule or a routine single-dose sched-

ule followed by a mass campaign achieves higher pop-

ulation immunity by immunizing persons who missed the first dose or experienced primary vaccine failure. The changing epidemiology of measles in Romania has now reached a unique stage for accelerating measles control. A large proportion of persons >18 years of age have natural immunity against measles because they were born prior to introduction of measles vaccine. Persons aged 10-18 years (born during 1979-1987) missed the second dose recommendation and will have the current vaccination schedule and coverage levels. Because our study did not identify specific groups at high risk for primary or secondary vaccine failure, an effective strategy for preventing future outbreaks may be to conduct a mass immunization campaign that would target all school-aged children who have not received at least two doses of measles vaccine. Such a campaign should include strategies to immunize children who may not attend school, because findings from the case-control study suggest that rroma children are at increased risk of measles, possibly due to higher contact rates in the community and through living in extended families. This type of "catch-up" campaign has been conducted in other countries with an aim to eliminate indigenous transmission of measles virus (22, 25).

National surveillance data showed that children <2 years of age had high measles attack rates and that 93 percent of measles cases aged 9-11 months and 64 percent of cases aged 12-23 months were unvaccinated. A mass immunization campaign among school-aged children should interrupt measles transmission to an extent that would reduce the risk of exposure among children <2 years of age. Nevertheless, increasing on-
time routine vaccination coverage is essential for reducing the level of measles susceptibility in this age group. Achieving >95 percent on-time coverage with the first dose of measles vaccine throughout each of Romania's 41 districts should prevent outbreaks among preschool children in the years following the campaign. Romania plans to increase on-time first-dose coverage by encouraging each district to achieve at least 95 percent coverage in the cohorts aged 9-11 months. To monitor district level coverage, districts began reporting first-dose coverage among cohorts aged 9-11 months to the National Immunization Program in November 1998 on a monthly basis. If coverage can be maintained at this level for both the first and second doses of measles vaccine, Romania should achieve the high population immunity required to maintain interruption of indigenous transmission of measles virus.

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