Large Outbreak of Measles in a Community with High Vaccination Coverage: Implications for the Vaccination Schedule

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Background. Attempts to eliminate measles from a country or region may be disrupted by an imported case that affects indigenous persons. The objective of this study was to analyze epidemiological and clinical characteristics of a measles outbreak in Catalonia, Spain, in 2006.

Methods. Data on cases of measles reported to the Department of Health, Generalitat of Catalonia, during the period 28 August 2006 through 8 July 2007 were collected. Suspected cases were confirmed by determination of measles-specific immunoglobulin M antibodies and/or detection of virus genome. Incidences were calculated using the estimated population of Catalonia for 2006, and 95% confidence intervals were determined assuming a Poisson distribution. The association between proportions was determined using the $\chi^2$ test and Fisher’s exact test. The level of statistical significance was set at $p < 0.05$.

Results. A total of 381 cases were confirmed, for an incidence of 6.6 cases per 100,000 persons. A total of 89.5% of cases occurred in nonvaccinated persons, mainly those aged ≤15 months (incidence, 278.2 cases per 100,000 persons; mean age of patients, 12 months). Indigenous subjects accounted for 89.8% of cases, and laboratory confirmation of results was obtained for 87.1%. Measles genotype D4 was identified in all sequenced samples.

Conclusions. The age distribution of cases of measles among children aged ≤15 months suggests that the first dose of vaccine should be routinely administered at the age of 12 months.

Measles is a highly contagious disease caused by a morbillivirus that results in substantial morbidity and mortality worldwide [1] and has a case-fatality rate of ~1 death per 1000 persons [2]; in developing countries, the case-fatality rate may reach almost 100 cases per 1000 persons [3]. In 2005, it was estimated that there were >20 million cases of measles and >300,000 associated deaths worldwide, the majority of which were in Southeast Asia and in Africa; measles control is difficult in this setting, where there is also a high prevalence of HIV infection [4, 5].

The virus is highly transmissible, and 90%–95% of the population must be immune to interrupt transmission [6, 7]. Therefore, the rate of vaccination coverage (with 2 doses of vaccine) must be maintained at >90% [8].

Given the characteristics of the disease, the lack of an animal reservoir, and the availability of valid diagnostic tests and of a safe, effective vaccine, experts considered measles to be potentially eradicable [9]. The European Region of the World Health Organization (WHO) designed a strategic plan to eliminate indigenous measles in the region by 2007, but in 2003, after analyzing the evolution of the disease and the difficulties in implementing national plans, the objective of elimination of endemic measles was postponed to 2010 [8]. The success in controlling the disease varies be-
tween countries, and although most national vaccination schedules already include administration of 2 doses of vaccine, cover-
age rates are still suboptimal [10]. Large outbreaks of measles in Europe have occurred, with >1000 cases and some deaths in The Netherlands in 1999 [11] and in Germany [12], in Ukraine [13], and among Romanian gypsies [14] in 2006.

In accordance with the recommendations of the European Region of the WHO, Spain launched a measles elimination program in 2001, and in 2004, the circulation of indigenous measles was interrupted [15]. However, until worldwide eradication is achieved, elimination of measles from a country or region is potentially reversible, because the virus can be reintroduced and cause epidemics that can substantially affect the indigenous population [16, 17].

Catalonia, a region in northeastern Spain with ∼7 million inhabitants, >14% of whom are immigrants [18], began re-
quiring the administration of 1 dose of the measles, mumps, and rubella (MMR) vaccine at the age of 12 months in the routine vaccination schedule in 1980. In 1987, the timing of the administration of the first dose shifted to 15 months of age, and in 1988, a second dose of MMR vaccine was added to the schedule at 11 years of age, to replace the rubella vaccine administered to girls [19]. To ensure that the proportion of vaccinated children aged <10 years was >95% and to achieve elimination of the disease by the year 2000, children aged 4 years began to receive the second dose of vaccine starting in 1998 [20].

During the period 2000–2005, the incidence of measles in Catalonia was very low, and outbreaks were either related to imported cases or affected families that had not received any dose of the vaccine for philosophical reasons. No transmission chains involved the indigenous population [21]. On 11 October 2006 (week 41), a case of measles in a girl (age, 14 months) born in Catalonia was reported to the Department of Health of Catalonia (Barcelona). Three related cases were detected among immigrants of Bosnian origin, 1 of whom had been in Italy during the incubation period. All of the patients resided in the Barcelona region. Given the successive transmission chains that were detected among children who had still not received the first dose of vaccine, in January 2007, mass vaccination of children aged 9–15 months in the Barcelona region was initiated. Mass vaccination was subsequently extended to the Tarragona region when cases appeared there. The objective of the present study was to analyze the epidemiological and clinical characteristics of the measles outbreak that began in Catalonia at the end of 2006.

MATERIALS AND METHODS

Data were collected from the register of clinically suspected cases of measles reported to the epidemiological surveillance units of the Department of Health of the Generalitat of Catalonia (Barcelona). The study period was from 28 August 2006 (the date of the onset of rash in the index case) to 8 July 2007 (2 maximum incubation periods [21 days] after the onset of rash in the last confirmed case on 7 June).

A suspected or clinically compatible case was defined as a case of measles that met the clinical case definition (maculo-
papular rash, fever [temperature, >38°C], and cough, conjunctivitis, and/or coryza). Laboratory-confirmed cases were defined as suspected cases in which a virological diagnosis was confirmed by presence of IgM and/or detection of measles virus genome in a urine specimen. Epidemiologically confirmed cases were defined as suspected cases that had been epidemiologically linked to a confirmed case. Cases in persons who had undergone recent vaccination (i.e., vaccination ≤45 days prior to the onset of rash) were considered to be confirmed cases on the basis of genotype D4–positive results of PCR of urine specimens or by epidemiological link to a confirmed case, if the urine specimen yielded negative PCR results or was not available.
Table 1. Distribution of confirmed cases of measles, according to age group and vaccination status.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No. of cases</th>
<th>Vaccination status</th>
<th>Vaccination status</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indigenous population</td>
<td>Immigrant population</td>
<td>Indigenous population</td>
</tr>
<tr>
<td>≤15 months</td>
<td>179&lt;sup&gt;a&lt;/sup&gt;</td>
<td>11&lt;sup&gt;a&lt;/sup&gt;</td>
<td>176</td>
</tr>
<tr>
<td>16 months–4 years</td>
<td>59</td>
<td>7</td>
<td>33</td>
</tr>
<tr>
<td>5–9 years</td>
<td>11</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>10–14 years</td>
<td>9</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>15–24 years</td>
<td>8</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>25–34 years</td>
<td>57</td>
<td>11</td>
<td>52</td>
</tr>
<tr>
<td>&gt;34 years</td>
<td>19</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>342</td>
<td>39</td>
<td>303</td>
</tr>
</tbody>
</table>

<sup>a</sup> P = .007.

RESULTS

During the study period, 538 suspected cases of measles were reported in Catalonia. Three hundred eighty-one of the cases were confirmed, and 157 were eliminated; 6 of the cases eliminated from further study involved vaccine reactions. The highest incidence of cases occurred between the last week of December 2006 and the first week of February 2007, when a total of 203 confirmed cases occurred; the greatest number of cases (n = 49) occurred during the second week of January 2007. Figure 1 shows the time distribution of confirmed cases.

The global incidence of the 2 affected regions, the Barcelona

Table 2. PCR results for laboratory-confirmed and discarded cases of measles, according to date of collection of the urine sample.

<table>
<thead>
<tr>
<th>Case, time of sample collection&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PCR result</th>
<th>Percentage of PCR results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
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<tr>
<td>Confirmed cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 days</td>
<td>54</td>
<td>6</td>
</tr>
<tr>
<td>1–3 days</td>
<td>94</td>
<td>12</td>
</tr>
<tr>
<td>4–6 days</td>
<td>35</td>
<td>7</td>
</tr>
<tr>
<td>7–10 days</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>194</td>
<td>31</td>
</tr>
<tr>
<td>Discarded cases</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 days</td>
<td>...</td>
<td>16</td>
</tr>
<tr>
<td>1–3 days</td>
<td>...</td>
<td>47</td>
</tr>
<tr>
<td>4–6 days</td>
<td>...</td>
<td>25</td>
</tr>
<tr>
<td>7–10 days</td>
<td>...</td>
<td>14</td>
</tr>
<tr>
<td>&gt;10 days</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>...</td>
<td>103</td>
</tr>
</tbody>
</table>

<sup>a</sup> Times are no. of days after onset of rash.

NOTE. Data are no. of cases, unless otherwise indicated.
Table 3. Distribution of confirmed cases, according to age group, hospitalization, vaccination status, and complications.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Hospitalized patients</th>
<th>Nonhospitalized patients</th>
<th>Hospitalized patients</th>
<th>Nonhospitalized patients</th>
<th>Hospitalized patients</th>
<th>Nonhospitalized patients</th>
<th>Hospitalized patients</th>
<th>Nonhospitalized patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 months&lt;sup&gt;a&lt;/sup&gt;</td>
<td>25 (13.2)</td>
<td>165</td>
<td>25</td>
<td>162</td>
<td>...</td>
<td>3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>16 months–4 years&lt;sup&gt;d&lt;/sup&gt;</td>
<td>5 (7.6)</td>
<td>61</td>
<td>4</td>
<td>35</td>
<td>1</td>
<td>26</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>5–9 years</td>
<td>4 (30.8)</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10–14 years</td>
<td>0 (0)</td>
<td>10</td>
<td>...</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>4</td>
</tr>
<tr>
<td>15–24 years</td>
<td>3 (30.0)</td>
<td>7</td>
<td>3</td>
<td>7</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>25–34 years&lt;sup&gt;e&lt;/sup&gt;</td>
<td>19 (27.9)</td>
<td>49</td>
<td>17</td>
<td>44</td>
<td>2</td>
<td>5</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>≥34 years</td>
<td>4 (16.7)</td>
<td>20</td>
<td>4</td>
<td>20</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>60 (15.7)</td>
<td>321</td>
<td>56</td>
<td>283</td>
<td>3</td>
<td>34</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

NOTE. Data are no. (%) of patients.

<sup>a</sup> Respiratory complications included pneumonia and bronchitis.

<sup>b</sup> Three nonhospitalized patients presented with otitis and diarrhea, and 1 patient presented with bronchitis and diarrhea.

<sup>c</sup> Thrombocytopenia.

<sup>d</sup> Four nonhospitalized patients presented with diarrhea and otitis.

<sup>e</sup> One nonhospitalized and 3 hospitalized patients presented with diarrhea and otitis, 1 nonhospitalized patient presented with diarrhea and hepatitis, 1 hospitalized patient presented with diarrhea and pneumonia, and 1 hospitalized patient presented with diarrhea, otitis, and pneumonia.

and Tarragona health regions (population, 5,684,454 inhabitants), was 6.5 per 100,000 inhabitants (95% CI, 5.9–7.2 per 100,000 inhabitants) The incidence, according to age group, ranged from 0.74 cases per 100,000 persons (95% CI, 0.5–1.1 cases per 100,000 persons) among persons aged >34 years to 278.2 cases per 100,000 persons (95% CI, 239.5–321.3 cases per 100,000 persons) among children aged ≤15 months (figure 2). Of the 381 cases, 355 (93.2%) occurred in the Barcelona health region (incidence, 6.9 cases per 100,000 inhabitants; 95% CI, 6.2–7.6 cases per 100,000 inhabitants), and 19 cases (5.0%) occurred in the Tarragona health region (incidence, 3.5 cases per 100,000 inhabitants; 95% CI, 1.95–5.4 cases per 100,000 inhabitants). Six cases occurred among residents of other health regions who had attended hospitals in the Barcelona health region, where they were contacts of cases; there were no resulting transmission chains of infection in their respective regions.

Of the 381 confirmed cases, 342 (89.8%) occurred among indigenous subjects. A total of 340 (89.2%) of 381 cases occurred among nonvaccinated subjects, 187 (55.2%) of whom were mainly aged ≤15 months; 36 individuals (9.4%) had received 1 dose of MMR vaccine, and 5 (1.3%) had received 2 doses. The titers of measles-specific IgG antibodies were determined and/or urine PCR was performed for the 5 patients with confirmed (IgM-positive) cases who had received 2 doses of vaccine. In 2 cases, positive urine PCR results indicated infection; in the other cases, urine specimens were not available, and the analysis of IgG antibodies yielded inconclusive findings. Therefore, these cases were classified as confirmed cases, because they fulfilled clinical criteria and were set within the context of the outbreak.

A total of 51.5% of the cases occurred in men, and 48.5% occurred in women. No statistically significant differences were observed in the proportion of cases among vaccinated men (21 of 193 cases; 18 men had received 1 dose of vaccine, and 3 had received 2 doses) and of cases among vaccinated women (18 of 185 cases; 16 women had received 1 dose, and 2 had received 2 doses; \( P = .5 \)).

The mean age of the 381 patients with confirmed cases was 15 months (range, 1 month to 50 years). The distribution, by age group, is shown in table 1. Of the patients aged ≤15 months, 52.2% were indigenous children, and 28% were immigrants (\( P = .007 \)).

Of the adults, 11 were health care workers (age range, 19–37 years), none of whom had been vaccinated, with the exception of 1 person who received 1 dose of MMR vaccine. Three hundred forty-two (89.8%) of the 381 cases occurred in the indigenous population, and 39 (10.2%) occurred among immigrants, 2 of whom (age, >25 years) had received 1 dose of MMR vaccine.

Laboratory confirmation was obtained in 330 cases (86.6%). One hundred forty (42.4%) of the 330 cases were confirmed by determination of measles-specific IgM antibodies, 65 (19.7%) were confirmed by PCR detection of measles virus genome in urine specimens, and 129 (39.1%) were confirmed by both techniques. A total of 328 urine samples were analyzed (accounting for 61.0% of 538 suspected cases), of which 194 (59.1%) yielded positive PCR results and 134 yielded negative results (table 2). Of these results, 118 corresponded to the D4 genotype. No other genotype was detected in the samples an-
alyzed, and only 3 differed in 1 or 2 nucleotides, with respect to the main sequence of the 456 nucleotides sequenced.

Of the 51 remaining cases, 41 (80.4%) were confirmed by epidemiological link, and 10 (19.6%) were classified as clinically compatible because samples were unavailable or there was evidence of direct contact with a confirmed case.

Sixty patients (15.7%) required hospitalization. Complications occurred in 91 cases (23.9%), of which 35 required hospitalization; 25 were ambulatory cases. The most common complications were diarrhea and/or vomiting (56 cases [14.7%]), otitis (20 cases [5.2%]), and pneumonia (8 cases [2.1%]). No significant differences in the type of complication were observed between patients aged <15 years and older patients. The highest frequency of hospitalization (30.8%) was observed for patients aged 15–24 years, and a significant difference was observed in the hospitalization rate between patients aged <15 years (12.2%) and those aged ≥15 years (26.2%) (P = .001). Complications were significantly more common among unvaccinated patients (87 [25.7%] of 339 unvaccinated persons) than among patients who had received ≥1 dose of vaccine (4 [10%] of 40 patients; P < .04) (table 3). There were no deaths. The source of infection was identified in 181 cases (family environment, 56 cases; day-care or preschool centers, 68 cases; health care centers, 37 cases; and the neighborhood, 20 cases).

**DISCUSSION**

This outbreak of measles was the largest in Catalonia in the 20 years since the introduction of routine vaccination. The first cases were clearly imported but gave rise to various transmission chains in the indigenous population, changing the situation of measles elimination that had existed in Catalonia since 2000. In Catalonia, the great majority of immigrants come from underdeveloped countries with poor vaccination coverage. Although immigrants are offered the same health care services as the indigenous population, the rate of MMR vaccination coverage is only 93.3% among immigrants, compared with 98.9% for the indigenous population [27]. This, together with the existence of susceptible individuals in some population groups and the enormous mobility of European residents, many of whom are immigrants, may explain why there are enough susceptible subjects to ensure the succession of various transmission chains [28]. Theoretically, the rejection of vaccination for philosophical reasons may also have contributed to this outbreak, but in our experience, outbreaks associated with this reason are self-limiting [29], and this particular outbreak would not have occurred without the previously mentioned circumstances.

This outbreak shows that high national and regional vaccination coverage rates do not, in themselves, guarantee maintenance of elimination. Parker et al. [30] reported an outbreak of 43 cases in Indiana in 2005; the rate of vaccination coverage among the schoolchildren was 98%. Ehresmann et al. [31] described a similar phenomenon. In The Netherlands, where the national rate of coverage is 96%, an outbreak in 1999 caused almost 3000 cases among people who rejected vaccination for religious reasons [11]. In Spain, Castell et al. [32] reported an outbreak that affecting >300 people in 1995; the rate of vaccine coverage was 95%. More recently, an outbreak of almost 200 cases occurred in Andalusia, Spain, where the vaccination coverage rate was >95% [16]. The proportion of cases requiring hospitalization (15.8%) is situated between the 8.8% rate reported in the Indiana outbreak [30] and the 51% rate reported in the Ukraine outbreak [13]. Other studies have also reported differing figures [11, 32, 33]. Hospitalization of patients with measles probably has more to do with how cases are managed than with their severity; therefore, this may not be a good parameter for evaluating the magnitude and severity of an outbreak. In addition, there is a risk of nosocomial cases occurring both among patients visiting the hospital for other reasons and among health workers; this could increase disease transmission [16, 30, 34, 35].

Although the rate of hospitalization was moderate in the outbreak we describe, exposure in a health care center affected

<table>
<thead>
<tr>
<th>Complications</th>
<th>Gastrointestinal</th>
<th>Respiratory</th>
<th>Otitis</th>
<th>Hepatitis</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized patients</td>
<td>2</td>
<td>20</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Nonhospitalized patients</td>
<td>1</td>
<td>10</td>
<td>1</td>
<td>...</td>
<td>...</td>
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<tr>
<td>Hospitalized patients</td>
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<tr>
<td>Nonhospitalized patients</td>
<td>...</td>
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</tbody>
</table>
37 persons (10%). In addition to supporting the recommenda-
don of vaccination of health care workers, this event suggests
tion of who were younger than the age of administration of the first
dose of vaccine (15 months) were the most affected, accounting
cases. The incidence rate of 278.2 cases per 100,000 persons was greater than the incidence reported in an
outbreak in Ireland (158 cases per 100,000 persons) [37]. In
the outbreak in Andalusia, this age group accounted for 25% of
cases, with an incidence rate of 552 cases per 100,000 persons
[38]. The fact that only 11 cases were reported among immi-
grant children aged ≤15 months may be because these children
are more likely to stay at home than to attend a day care center.

Only 25.6% of the cases occurred in adults. In a recent out-
break of 18 cases in Scandinavia, adults accounted for 72% of
cases [39], and in an outbreak of 59 cases in Madrid, adults
accounted for almost 60% of cases. However, in large outbreaks,
the proportion of cases among adults is normally much lower
than that among children [16]. As Orenstein et al. [40] suggest,
it is difficult to believe that adult patients can sustain a trans-
mismission chain in the general population. Likewise, several au-
thors suggest that, if there are high coverage rates among
schoolchildren, it is difficult for the outbreak to propagate in
the community, even if there are susceptible adults [30, 31].
Therefore, we consider high rates of coverage with 2 vaccine
doses for children to be essential, and the rates should be dis-
tributed homogeneously, avoiding pools of susceptible children.
The important role played by children aged ≤15 months in the
outbreak suggests that measles antibodies transferred pass-
vively by the mother were not sufficient to combat the circu-
lation of the virus in as-yet-unvaccinated children. For this
reason, in accordance with expert opinion [10, 41], we suggest
lowering the age at which the first dose of MMR vaccine is
administered to 12 months.

In this outbreak, 87% of cases were laboratory confirmed,
similar to the 96% rate for the outbreak in Andalusia [38, 42]
and the 88% rate for the outbreak in Madrid [151] but much
higher than the proportion found in other countries. In the
United States, Parker et al. [30] found that 41% of cases were
confirmed, and Ehresmann et al. [31] reported that 64% of
cases were confirmed. The proportion of laboratory-confirmed
cases was 32% in a study from Italy [43], 33% in a study from
Germany [12], 20% in a study from Ireland [37], and 18% in a
study from The Netherlands [36].

Although laboratory confirmation is not essential to confirm
a case during an outbreak, it does reflect an improvement of
disease surveillance that involves not only the laboratory and
epidemiological surveillance units, but also attending physi-
cians, and should thus be encouraged. In addition, if a large
number of clinical samples are available for molecular epide-
miological study, it can be determined whether all cases oc-
curred as part of the same outbreak.

Finally, timely reporting of cases to avoid delays in investi-
gating and managing the outbreak is essential. In this outbreak,
the index case was not detected until 6 weeks after the onset
of symptoms (29 August 2006), and this, together with the
interval between reporting of the first cases and the initiation
of mass vaccination of all children aged 9–15 months in the
region (second week of January 2007), contributed to a greater
spread of the outbreak. Logically, the sooner mass vaccination
is initiated, the sooner circulation of the virus can be inter-
rupted. However, the problem lies in evaluating the capacity
of diffusion during the initial phases of the outbreak. Therefore,
we suggest that, in communities where the wild virus has not
immunized women of childbearing age, as in Catalonia, the
first dose of the vaccine should be administered routinely at
12 months of age. In addition, if there is evidence that trans-
mismission is occurring in children who are younger than this age,
mass vaccination of children aged <12 months should be per-
fomed as soon as possible, although these children should still
receive the first routine vaccine dose when they reach 12 months
of age.

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