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Features of a Measles Outbreak in the Elimination Era

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Abstract: In 2000, the circulation of indigenous measles was interrupted in Catalonia as a result of the activities of the elimination programme introduced in 1991. However, various transmission chains occurred in the indigenous population after the introduction of an imported case, and this caused a total change in the existing situation of elimination.

The objective of this study was to analyze the epidemiological and clinical characteristics of the measles outbreak in Catalonia in 2006. Cases reported between August 28 2006 and July 8 2007 were collected. Cases were microbiologically confirmed by determination of measles-specific IgM and/or detection of the viral genome in urine samples.

A total of 381 cases of measles were confirmed, representing an incidence of 6.6 per 100,000 inhabitants. Laboratory confirmation was made in 87.1% of the cases and all specimens sequenced belonged to the D4 genotype. A total of 89.5% of the cases occurred in non-vaccinated people, above all in infants aged <16 months.

Keywords: Measles, outbreak, confirmed case.

INTRODUCTION

Measles is a highly contagious disease caused by a virus of the *Morbillivirus* genus of the *Paramyxoviridae* family, that causes substantial worldwide morbidity and mortality. The case-fatality rate is 1 per 1000, but rises to 3-5% in developing countries and, in some areas, between 10 and 30% [1].

Measles is an acute disease whose symptoms in the prodromal period include fever, conjuntivitis, coryza, bronchitis and Köplik spots in the oral mucosa. Between the third and seventh day after disease onset, a characteristic rash of reddish-brown spots appears, initially in the face and later extending to other areas. The rash lasts 4-7 days and may terminate in furfuraceous desquamation. The most frequent complications are otitis media, pneumonia and encephalitis. Subacute sclerosing panencephalitis (SSPE) which occurs in around 1 case per 100,000 is a late sequelae of measles which may appear some years after measles infection.

The measles virus reservoir is exclusively human and transmission is by aerosol transmission or direct contact with pharyngeal or nasal secretions from infected people; aerial transmission or transmission through contact with recently-contaminated objects is less frequent. Measles is one of the most-easily transmittable diseases and a level of population immunity of 90-95% is necessary to interrupt transmission [2, 3].

The incubation period lasts around 10 days, and may vary between 8 and 13 days from exposure to the onset of fever, and 14 days until the onset of rash. The transmission period lasts from just before the prodromal period to four days after the onset of rash, but the risk of infection is considered minimal from the second day after the onset of rash.

Almost all people who have not suffered the disease or have not been immunized are susceptible. The Population immunity acquired by infection is usually lifelong.

The following characteristics of measles make it a potential candidate for elimination from a country or region: an exclusively human reservoir, valid diagnostic tests, and a sufficiently efficient vaccine [4]. Disease elimination consists of a reduction to zero of disease incidence in a defined geographic region as a result of deliberate efforts, although intervention measures should always be continued [5].

The European Region of the World Health Organization (WHO) drew up a strategic plan for the elimination of indigenous measles by 2010. The level of disease control var-

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ies greatly between countries, and although vaccination schedules in most countries now include two doses of the vaccine, coverages are still low. Large outbreaks have occurred in European countries like the Netherlands [6], Germany [7] and the Ukraine [8], amongst others.

In accordance with WHO recommendations, Spain established a measles elimination programme and in 2004 the indigenous transmission of measles was interrupted [9].

In Catalonia, an Autonomous Region (AR) located in the northeast of Spain, with a population of 7, 364, 078, measles, mumps and rubella (MMR) vaccination at 12 months of age was introduced in 1981. In 1987, administration was switched to 15 months and in 1988 a second dose of vaccine at 11 years of age was introduced, substituting the isolated administration of rubella vaccine to 11-year old girls. These changes in vaccination strategy resulted in a very large reduction in cases of measles [10].

In 1991 the programme for the elimination of measles in Catalonia by 2000 was introduced [11]. The main strategies were:

- To improve the immunity of susceptible people by reducing the age of administration of the second dose of MMR from 11 to 4 years, thereby ensuring coverage of cohorts aged 4-10 years.
- To improve epidemiological surveillance by making measles the object of urgent mandatory report (less than 24 hours), with exhaustive follow-up of all cases and contacts, and collection of clinical samples to confirm all cases between the fourth and eleventh day after rash onset.
- To vaccinate susceptible contacts of confirmed cases.

The circulation of indigenous measles was interrupted in Catalonia in 2000 as a result of the activities of the elimination programme [12]. Between 2000 and 2005, the incidence rate of measles in Catalonia was < 0.3 per 100,000 inhabitants) (Fig. **1**). The outbreaks that occurred were associated with imported cases or families rejecting vaccination who had not received any dose of vaccine, although this did not lead to transmission chains in the indigenous population [13].

On October 11 2006 (week 41), a case of measles in a 10-month-old baby resident in the Vila Olímpica area of Barcelona was reported to the Department of Health. The onset of rash was on October 6 (week 40). The same day, measles-positive IgM were found in samples from a 6-year-old non vaccinated girl of Bosnian origin who lived in a caravan in the Vila Olímpica area. The girl had returned from Italy, where the family had attended a very-large gathering, at the end of August. Rash onset was on August 28. The family attended a health centre on September 4, but the disease could not be confirmed microbiologically at that time. According to the information received, the mother, aged 25-30 years, suffered a similar illness during her stay in Italy, where there was an outbreak of measles, mostly in ethnic gypsies, in the same area at the same time [14]. Due to difficulties in maintaining contact with the girl's family, no measures to avoid the spread of the disease or obtain more information on the case could be taken.

Through personal and family data, the investigation associated the case with two reported suspected cases of measles which could not be confirmed due to absenteeism and refusal, respectively:

- An 11 year-old unvaccinated boy of Bosnian Serb origin, resident in the Costa de Ponent region of Catalonia. The case was reported on September 28; rash onset was on 26 September.
- A 20-month-old unvaccinated boy of Bosnian Serb origin, also resident in the Costa de Ponent region. The case was reported on 9 October; rash onset occurred on 7 October.

The families of the two cases reported that they had both attended a large family funeral on the 24-25 September at the Sancho de Avila crematorium (San Marti district, Barcelona).

From this moment onwards, transmission chains in children who had still not received the first dose of vaccine and were all resident in the Barcelona Health Region, began to be detected. As a consequence, in January 2007, mass vaccination of children aged 9-15 months was begun; the measure was later extended to the Tarragona Health Region when cases appeared there.

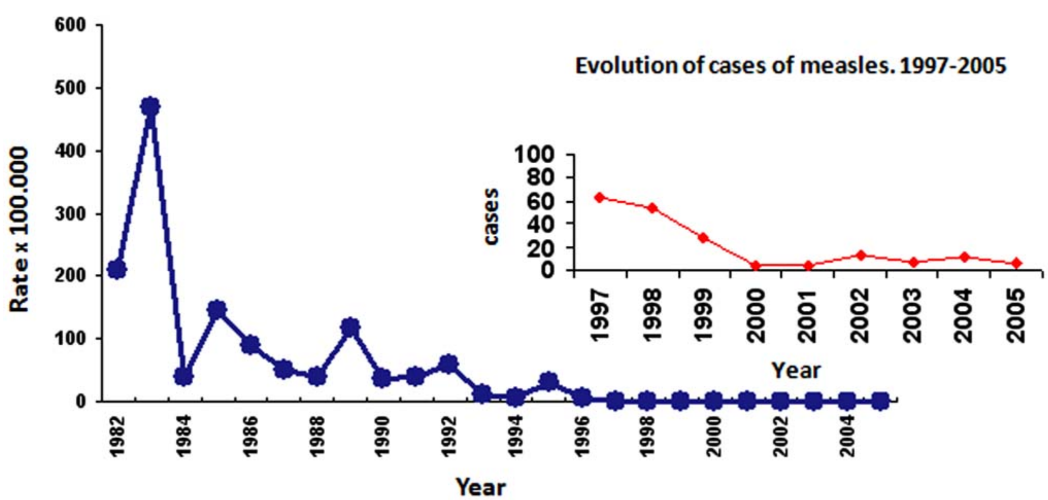

Fig. (1). Evolution of incidence rates of measles in Catalonia, 1982-2005.

The objective of this study is to analyze the clinical and epidemiological characteristics of this measles outbreak in Catalonia at the end of 2006.

MATERIAL AND METHOD

Data were collected from the register of suspected cases of measles reported to the Epidemiological Surveillance Units, Department of Health, Generalitat of Catalonia.

The study period was August 28, 2006 (onset of rash in the index case) to July 8 2007 (two incubation periods of 21 days after the onset of rash in the last confirmed case on June 7, 2007).

The following case definitions were used:

- Suspected or clinically compatible: fulfilment of the clinical case definition (maculopapular rash, fever >38°, cough, conjuntivitis and/or coryza).
- Laboratory-confirmed case: suspected case with laboratory-confirmed diagnosis (measles-specific IgM and/or detection of measles virus genome in urine sample).
- Epidemiologically-confirmed case: suspected case epidemiologically linked with a confirmed case.
- Discarded case: suspected case not laboratory or epidemiologically confirmed or which does not comply with the clinical case definition [15].
- Imported case: person infected by a source outside Catalonia, with rash onset within 18 days of arrival in Catalonia and with no association with an indigenous transmission chain.
- Indigenous case: cases which have not been shown to be imported.
- All persons born in Catalonia, including those whose parents were born outside Catalonia, were considered to be indigenous.

To avoid false-negative results, blood samples were obtained ≤72 hours after rash onset [16] and urine samples within the first week after rash onset [17].

Measles-specific IgG and IgM antibodies were determined by enzyme immunoassay (Measles ELISA IgG and Measles ELISA IgM Vircell®, Granada, Spain) at the Microbiology Laboratory, Hospital Clinic of Barcelona. Urine samples for detection of the virus were frozen to - 40ºC until despatch to the National Microbiology Centre, Carlos III Health Institute, Madrid. Detection was made using multiplex nested polymerase chain reaction (PCR) designed to detect measles, rubella and parvovirus B19 simultaneously; if the PCR was positive for the measles virus, the result was confirmed by analysis of a second aliquot of the specimen by measles-specific nested PCR [18, 19].

Vaccination status was determined by review of vaccination cards and medical records or by determination of serum levels of IgG. If the vaccination status could not be determined, the subject was considered as non-vaccinated.

Contacts were studied by following-up people exposed to a suspected case during the infective period (four days before to four days after rash onset). Vaccination status was investigated and non-vaccinated susceptible people and those who had only received one dose of MMR received one MMR dose if the exposure had occurred < 72 previously, or of non-specific gamma globulin if > 72 hours but > 6 days had passed.

Incidence rates were calculated in accordance with the estimated population of the regions affected in 2006. The confidence intervals (CI) were calculated assuming a Poisson distribution. The chi-square and Fisher's exact tests were used to compare the differences between proportions. Statistical significance was established as $\alpha = 0.05$.

RESULTS

During the study period (August 28 2006 to July 8 2007) 538 suspected cases of measles were reported in Catalonia, of which 381 (70.8%) were confirmed and 157 discarded (29.2%). The highest case incidence was between the last week of 2006 and the last week of February 2007, with a total of 176 confirmed cases; the second week of 2007 had the greatest number of cases (49). The temporal distribution of confirmed cases is shown in Fig. (**2**).

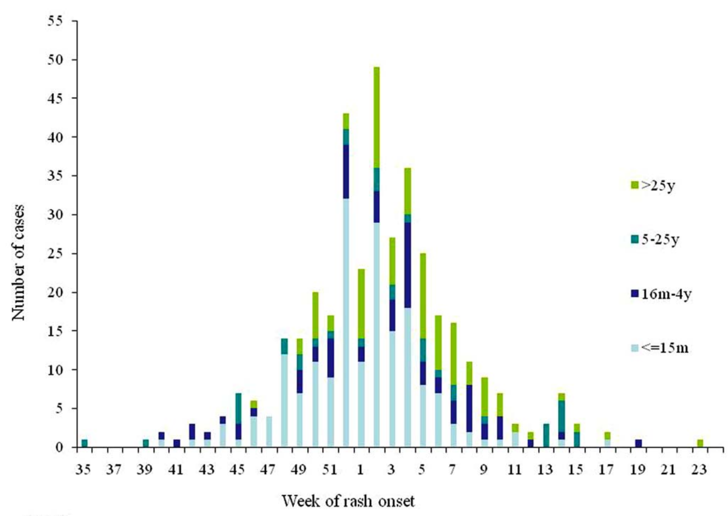

Fig. (2). Distribution of confirmed cases according to age and rash onset.

By age group, incidence rates ranged from 278.2 per 100,000 (95%CI: 233-312) in infants aged < 15 months to 0.70 per 100,000 (95%CI:0.4-1.0) in people aged > 34 years. The global incidence rate was 6.6 per 100,000 inhabitants (95%CI: 5.8-7.1) (Fig. **3**).

The mean age of the 381 confirmed cases was 15 months (range 1 month – 50 years). The mean age of cases in the < 15 months age group was 12 months: cases were much more frequent after 8 months of age (Fig. **4**). A total of 51.5% of cases were male and 49.5% female.

A total of 356 (93.4%) of cases occurred in residents of the Barcelona Health Region, with an incidence rate of 6.8 per 100,000 inhabitants (95% CI: 6.1-7.6). Nineteen (5.2%) cases occurred in residents of the Tarragona Health Region, with an incidence rate of 3.5 per 100,000 inhabitants (95% CI: 1.95-5.4). Two cases occurred in the Lerida Health Region and four in the Catalonia Central Health Region: however, these patients had attended a hospital in the Barcelona Health Region, where they were infected, but did not produce transmission chains in their respective regions, and therefore were not considered in the calculation of incidence rates.

Of confirmed cases, 89.5% (341/381) occurred in non-vaccinated people, the majority of whom were infants aged < 15 months (55%; 188/341): 9.2% of cases (35/381) had received one dose of MMR and 1.3% (5/381) two doses. Of the cases in adults, 11 were in health workers aged between nineteen and thirty-seven years of age: all were not vaccinated, except for one case who had received one MMR dose.

Laboratory confirmation was obtained in 333 cases (87.4%), of which 140 (42%) were confirmed by determination of measles-specific IgM, 64 (19%) by positive genome detection by PCR in urine and 129 (39%) by both techniques (Table **1**). Of the sequenced samples, 114 corresponded to the D4 genotype and no other genotype was detected in the samples analyzed. Of the 48 remaining cases, 40 (10.5%) were confirmed by epidemiological link and 8 were classified (2%) as clinically compatible due to the impossibility of collecting samples and the lack of confirmation of direct contact with a confirmed case.

Table 1. Laboratory-Confirmed Cases

Type of Test	Nº of Cases	%
Determination of IgM	140	42%
PCR in urine	64	19%
IgM + PCR	129	39%
TOTAL	333	100%

There were complications in 91 cases (24.5%) and 61 cases (16.2%) required hospitalization. The most-frequent complications were diarrhoea and/or vomiting [56 cases (15.2%)], otitis [20 cases (5.4%)] and pneumonia [8 cases (2.1%)]. The highest frequency of hospitalization was in the 25-34 years age group (28.8%). Complications were signifi-

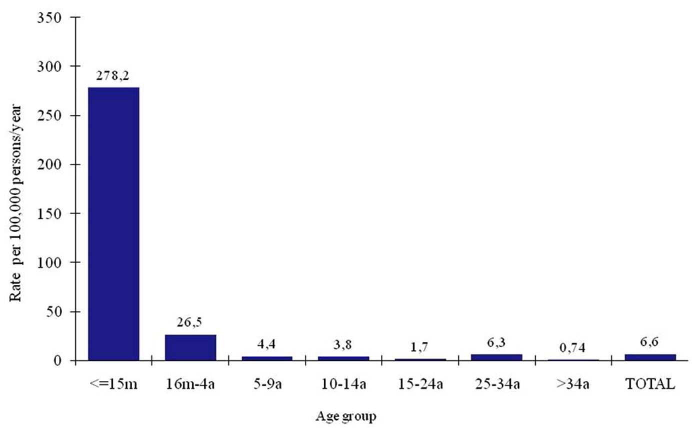

Fig. (3). Incidence rates of confirmed cases according to age group.

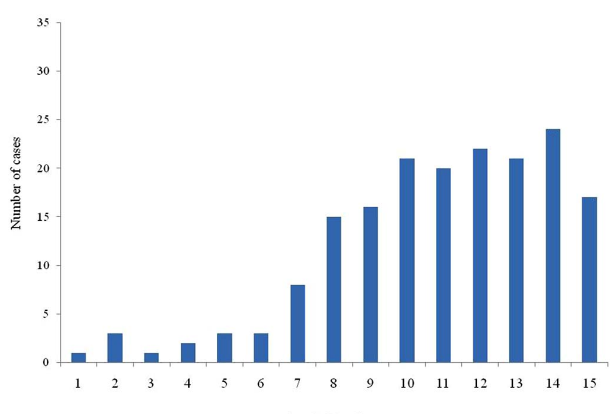

Fig. (4). Distribution of confirmed cases aged ≤ 15m according to age in months.

cantly higher ($p < 0.001$) in non-vaccinated subjects [85/151 (56%)] compared with those who had received at least one dose of vaccine [4/34 (12%)]. There were no cases of encephalitis and no deaths occurred.

Of confirmed cases, 342 (89.7%) occurred in indigenous subjects and 39 (10.3%) in immigrants, of which two, both aged >25 years, had received one dose of vaccine.

The source of infection was identified in 178 cases: in 56 cases the source was in the home, in 65 in day-care centres or kindergartens, in 37 in a health centre and in 20 in the community.

DISCUSSION

As a result of the measles elimination programme implemented in Catalonia in 1991, the incidence of measles infections was reduced to >1 per 100,000 inhabitants. The last reported indigenous case in Catalonia was recorded in 2000. Since then, the region has been free of measles with the exception of a few imported cases, mainly in non vaccinated adults [12, 13].

During the last five years, the incidence has been <1 per 100,000 and all cases have been imported or secondary to imported cases [6]. The outbreak of measles studied here is the largest in Catalonia since the introduction of routine immunization. Thanks to the large number of clinical samples available for the study of molecular epidemiology, it can be stated that all cases belonged to the same outbreak. The first cases were clearly imported, but various transmission chains (10-15) occurred in the indigenous population: this resulted in a total change in the situation of measles elimination that existed in Catalonia since July 2000.

Although immigrants are able to access the same health services as indigenous people, coverages of the MMR vaccine are lower in immigrants (93.3%) than in indigenous subjects (98.9%). This, together with pockets of susceptible people in some population groups and the increased mobility of European residents, many of whom are also immigrants, may explain why there was a population large enough to sustain the succession of the series of transmission chains that were observed [20].

This outbreak shows that high vaccination coverages alone are not sufficient to guarantee that elimination is maintained. In the Netherlands, with a national vaccination coverage of 96%, a measles outbreak in 1999 in groups who reject vaccination caused almost 3,000 cases [6]. In Spain, an outbreak in 1995 affected >300 people; vaccination coverage was 95% [21]. More recently, in Andalusia, with a vaccination coverage >95%, another outbreak of almost 200 cases occurred [22].

In 37 cases of the outbreak discussed here, exposure occurred in a health centre. This suggests that in addition to promoting the immunization of health workers, hospitalization of cases should be limited to those in which it is warranted because of severity and that when an outbreak occurs, home care should be promoted.

The age distribution of cases clearly shows that children below the age when the first dose of vaccine is administered (15 months) were the most affected. Only 23% of cases occurred in adults. In the Madrid outbreak in 2006, which caused 59 cases, nearly 60% were adults, but normally, in large outbreaks, the proportion of adults is lower than that of children [22]. It is difficult for cases in adults to have the capacity to maintain sustained community transmission [23]. Therefore, it is essential to ensure that coverage with two vaccine doses is high and that these are distributed homogenously to avoid pockets of susceptible people.

The striking role of infants aged < 15 months in this outbreak suggests that measles antibodies transferred passively by the mother are not sufficient to stop the circulation of the virus in children who have not yet been vaccinated. For this reason, and taking expert opinion into account [24], the first dose of vaccine should be routinely administered at 12 months of age.

In addition, if there is evidence that transmission is occurring in children younger than 12 months, mass vaccination should be carried out as soon as possible, even though these children would still have to be vaccinated again with the first routine dose at 12 months.

ACKNOWLEDGMENTS

The other members of the Study Group of the Measles Outbreak in Catalonia are:

P. Godoy and J. Batalla (Department of Health, Generalitat of Catalonia, Barcelona; and CIBER Epidemiology and Public health [CIBERESP], Spain); J. Alvarez, R.Urbano, C. Arias, J. Torres, N. Camps, L. Urbitzondo, J.M. Jansà, and A. Plasencia (Department of Health, Generalitat of Catalonia); J. Guix (Public Health Agency, Barcelona); A. Guarga and X. Sintes (Barcelona Health Region); E. Zabaleta and G. Jodar (Catalan Health Institute, Barcelona); M.V. Martinez and I. Peña-Rey (National Epidemiology Centre, Madrid, and CIBERESP); T. Castellanos (National Epidemiology Centre); and J.E. Echevarria and F. de Ory (National Microbiology Centre, Madrid, and CIBERESP).

We thank the reporting physicians and the technicians of the Epidemiological Surveillance Units of the Department of Health and the Public Health Agency of Barcelona for their collaboration.

This work was partially funded by CIBER Epidemiology and Public Health (CIBERESP), Spain.

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Received: November 20, 2009 Revised: November 25, 2009 Accepted: November 25, 2009