Measles Outbreak in Venezuela: A New Challenge to Postelimination Surveillance and Control?

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The circulation of wild measles virus was interrupted in Venezuela in February 2007 after the catch-up vaccination (1994) and monitoring (1998) and in response to the measles outbreak in 2001. Traditionally, the routine coverage with measles-mumps-rubella vaccine does not exceed 85%. In February 2006, a measles outbreak started by importation in the State Miranda; this extended to 7 states and lasted 50 weeks with an intermediate period of 17 weeks without reported cases. New cases were reported in the States Guarico and Amazon. The pattern of circulation of the silent period was determined through the use of retrospective search for measles; this showed that 57% of suspected cases did not enter the surveillance system. Molecular epidemiology made it possible to identify B3 as only genotype, which also circulated in Spain. The epidemiological and clinical characteristics of measles have been modified; these determine outbreaks identified late, of slow expansion, silent, and with limited case-fatality, compared with classical outbreaks. The outbreak spread by that behavior was not recognized and the classical control measures did not result. The beginning of a broader and intense vaccination was delayed, partly by weaknesses in the sensitivity of the system. It is crucial to recognize the new behavior of measles and the effectiveness of the classical control measures, and especially to establish criteria for interruption of the circulation to control an outbreak in this stage of elimination.

In Resolution CD38.R6 of September 1995, the countries of the Americas committed to eliminating measles [1]. The basic strategies have been catch-up vaccination, follow-up campaigns, and epidemiological and laboratory surveillance. Since then, significant progress has been made; however, the countries have new challenges to face, such as importations and the response to them.

In 1994, Venezuela launched a catch-up campaign, vaccinating the population aged 6 months to 14 years. In 1998, it implemented a follow-up campaign that coincided with the introduction of the combined measles-mumps-rubella (MMR) vaccine in the national child immunization schedule. In 2001, the country dealt with an outbreak by vaccinating children aged <15 years [2]. National MMR coverage by the regular program has been kept at rates of ~85%, with differing levels among the municipalities. The campaigns have been the best strategy for achieving the coverage that made it possible to interrupt endemic transmission of the wild measles virus in 2002.

In February 2006, with an accumulation of susceptible persons estimated at 40% among children aged <5 years and the country in the middle of organizing the adult vaccination campaign to eliminate rubella, an outbreak began in the State Miranda, an area with...
a high population density. Retrospective case-finding was used to determine the behavior of the outbreak.

This article analyzes the factors associated with the epidemiological pattern of the outbreak, the strategies and efficacy of the control and surveillance measures implemented during the outbreak, and the challenges posed by a regional postelimination context that will need to be addressed to prevent the reestablishment of endemic measles transmission.

**METHODOLOGY**

**Strategies of Vaccination**

**Response to the Outbreak.** The first response to a confirmed case was the blockade, defined as vaccination with double viral (mumps and rubella [MR]) of the population aged 6 months–39 years in an area of 5 blocks, or 250 m, around the residence of the case, during the 48 hours after its detection [3]. This measure included places where there were identified suspected cases and persons considered to be at risk because of the presence of contacts. The patterns of the outbreak and the vaccination that did not manage to contain it suggested the need for rapidly implementing mass campaigns, which means that the Ministry stipulated that all the States advance the American Vaccination Week, vaccinating the same aforementioned age group, except the group aged 18–39 years, which only would be vaccinated for confirmed cases. In February 2007, a broad operative in the Municipality Atures was done; Been Amazon vaccinated door to door.

**Campaign of Elimination of Rubella.** The vaccination campaign with measles/rubella-containing vaccine to eliminate rubella was programmed in 2 phases. In 2005, the group aged 12–17 years vaccinated progressively during 2006–2007. The second phase should have been done in 2006, with a target population of men and women aged 18–39 years, but had all the efforts had to be guided toward the vaccination of the populations with greater risk to become ill or to die from measles. Considering that the campaigns of elimination require a detailed process of organization and programming, it was postponed until October 2007.

In August 2007, with a goal of confirming the vaccination condition of the groups aged <17 years, a crossed monitoring of coverage was performed in August: 91% for the group aged 1–4 years, 89% for the group aged 5–11 years, and 86% for the group aged 12–17 years [4].

The campaign of rubella elimination was performed in October and November 2007. It became a valuable opportunity to vaccinate against proof of vaccination to the susceptible persons aged 5–17 years, defined as every unvaccinated person or person who could not demonstrate vaccination. The target population of persons aged 18–39 years, which until that year had not been addressed, was vaccinated indiscriminately. It was confirmed that all health care staff of the public and private sector was vaccinated with MR vaccine.

The brigades of vaccination workers applied blue stickers to indicate that people living in the marked houses and apartments were completely vaccinated and orange stickers to indicate the need to return to conclude vaccination. Each establishment confirmed daily its progress through rapid monitoring of coverage. This made it possible to identify areas where 100% of the population was vaccinated or not, because they were marked with different colors on the map monitored by corresponding health posts.

The Ministerial Resolution authorized the vaccination schedules in ports and international airports, where posts were installed to vaccinate travelers. The vaccination of every person >6 months of age, whether Venezuelans, or foreigners living in Venezuela who traveled outside the Americas was declared compulsory.

**Monitoring Crossed Coverage (MCC).** MCC (Protocolo de certificación de las coberturas de la Campaña Nacional de Vacunación para eliminar la rubéola, síndrome de rubéola congénita y sarampión en Venezuela. MPPS. Agosto 2007) was performed at the end of the campaign in the 368 municipalities of the country for the group aged 18–39 years. Each municipality was sectorized in geographical units, localities, or neighborhoods where the population was concentrated, and the sample size and number of conglomerates proportional to the size of its population was assigned to each. The parameters for the sample calculation established 95% confidence intervals, coverage expected of 95%, precision of ±3%, and effect of design of 2. Overall, 6115 selected conglomerates were randomly surveyed. To ensure objectivity and avoid information biases, we ensured that the personnel of an establishment were exchanged with those at neighboring establishments.

Planning, execution, and final report were the responsibility of the epidemiologist and regional coordinator of immunization of every state, accompanied by a national supervisor.

**Epidemiological Surveillance.** With the measles outbreak confirmed, epidemiological surveillance was intensified through the preparation of national guidelines for case reporting, investigation, and follow-up that were disseminated and implemented in all states. For each confirmed or suspect case, active case-finding of other cases and contacts was conducted during the probable period of exposure to the investigated case. Contacts were defined as every person living in the home or sharing other enclosed spaces with the suspect case during the period of communicability (4 days before and 4 days after rash onset). In every location where contacts were found, a list of them was made so they could be monitored for up to 21 days for the timely detection of fever, rash, or respiratory symptoms (cough, runny nose, or conjunctivitis).

In addition to the established definition of a suspect case in joint MR surveillance, every contact with fever was also
considered to have a suspect case. In addition, interdisciplinary rapid intervention teams were formed and outbreak situation rooms were established at the national, state, and district levels in the affected areas.

All border states were informed that they should report every suspect case of measles to the neighboring country if it occurred in a border community. Because of the presence of confirmed cases in the municipality of Atures, in Amazonas state on the Colombian border (an area that because of its sociopolitical conditions has historically been characterized by low coverage), a Colombian–Venezuelan containment plan was established.

**Laboratory.** For any suspect case of measles, a serum sample was obtained during the acute phase for IgM enzyme-linked immunosorbent assay serologic examination purpose [3]. Every case for which the sample tested positive or cases with epidemiological links to another laboratory-confirmed case was considered to be a laboratory-confirmed measles cases. Serum samples were processed in regional laboratories. As part of quality control, positive cases were sent to the virology laboratory of the Rafael Rangel National Institute of Hygiene (INHRR) in Caracas.

At the first contact with the patient, nasopharyngeal swab specimens were obtained for isolation and virus detection, in an attempt to obtain isolates for each chain of transmission or every certain period of weeks since the outbreak began. The isolated viruses in INHRR were sent to the Centers for Disease Control and Prevention (Atlanta, GA) for molecular characterization [5].

**Chain of Transmission.** To identify potential areas of measles circulation, the chain of transmission was then identified by identifying case contacts from 14 days before to 7 days after the rash onset. This was also used for the indiscriminate vaccination of contacts and/or identification of potential new cases in all the places where a confirmed case had been detected. Logistical and operational difficulties and a lack of human resources did not permit this activity to continue.

**Active and Retrospective Case-Finding.** Active case-finding was done door-to-door and for each suspect case during perimeter vaccination. Retrospective case-finding was proposed to determine the circulation pattern during the outbreak’s period of epidemiological silence between epidemiological weeks (EWs) 27/2006 and 43/2006. This would answer the question of whether we were dealing with the same or a new outbreak. Case-finding began in the states of Amazonas and Guárico, because confirmed measles cases began there in EW 44/2006. The states of Apure and Bolivar were then included in a second round, because they are border states and are linked through common overland access routes; in addition, there had been heavy migration of persons for work and trade toward the compromised areas since EW 44. Finally, case-finding was undertaken in Zulia and Carabobo, the last 2 states with confirmed measles cases before the period of epidemiological silence.

Retrospective case-finding included institutional and community case-finding. The first involved case identification in public health and private services. To this end, various sources of information were reviewed: daily morbidity records, hospital discharges, emergency consultations, medical histories, and laboratory reports in areas identified at greater risk for virus circulation. Community case-finding was performed through interviews with key informants, such as health care workers, members of community committees and councils, and indigenous leaders.

For retrospective case-finding, operational definitions were established. A suspect case was any case in a person who, according to health facility records or a verbal report by a key community informant, presented with fever and rash. The medical record was reviewed and a home visit was made to all patients with suspect cases to ultimately classify them as clinically compatible, if, in addition to fever and rash, they had a cough, runny nose, or conjunctivitis or the physician had considered measles as the diagnosis. The case was considered to be ruled out when it did not meet any of the aforementioned criteria, its clinical manifestations were attributable to another diagnosis (dengue, roseola, rubella, allergy, or other), or if the person had a history of measles vaccination at some time from 1 year of age to 21 days before the onset of symptoms. It was verified whether all suspect cases were included in the integrated measles and rubella information system (MESS); every case not entered into this system was considered to be a surveillance failure.

Retrospective case-finding was expanded to all states to confirm the absence of measles cases after the last confirmed case in Amazonas. To this end, teams were trained in all states and, supported by national-level supervisors, identified, analyzed, and investigated suspect cases with use of a protocol and standardized collection and analysis tools.

**RESULTS**

**Vaccination Incidence and Coverage**

In Venezuela, measles incidence showed a downward trend from 1980 through 2007 (Figure 1). Outbreaks, occurring every 3–4 years during the 1980s, continued with 5–6-year interepidemic cycles after the catch-up campaign in 1994. The size of the outbreaks reported during the 1980s, with figures of 38382 cases and 124 deaths in 1981, decreased to 2495 cases during 2001–2002 and 122 cases during the 2006–2007 outbreak.

This outbreak began in a context of low coverage. In January 2006, the country had an estimated 843742 susceptible children aged <5 years, equivalent to 40% of that age group. The follow-up campaign conducted in 2006 to cover the population aged 6 months to 4 years attained national administrative coverage of 95%, but coverage was not uniform among the states.
Finally, in October 2007, Venezuela conducted a national campaign to eliminate rubella that provided a valuable opportunity to elevate measles immunity in the population aged 18–39 years. Administrative coverage of 100% was attained through this activity. At the end of the campaign, verification of coverage was done by clusters in every municipality in the country, showing mean results of 97%. Three hundred fifty-seven (98%) of 365 municipalities attained coverage ≥95%.

Characteristics of the Outbreak
The last measles case in the Venezuelan outbreak was confirmed in EW 7/2007 in the municipality of Atures. In total, 122 cases were confirmed from the onset of the outbreak; 39 cases (32%) occurred in children aged 1–4 years, and 37 cases (30.3%) occurred in persons aged 18–39 years. The highest rate was among children <1 year of age (236 cases per 100,000 population), followed by children aged 1–4 years, with a rate of 74 case per 100,000 population (Figure 2). Only 4 (3.3%) of the 122 had a history of vaccination; all of them were aged 1–4 years. Clinically, the cases did not present the classical signs and symptoms described in the literature. No complications or deaths were reported.

The outbreak spread to 7 states (Figure 3); it had 3 periods: 2 active periods and 1 intermediate period of silence.

First Active Period
The first active period began during EW 9/2006 in Miranda. The index case was a 33-year-old Venezuelan airplane pilot who had flown to Madrid on 1 February 2006 and returned to Venezuela on 13 February; his rash began on 23 February. There were 41 confirmed measles cases in this state; the last case occurred during EW 18/2006. In each case, perimeter vaccination was done (indiscriminate vaccination 5 blocks around), the chain of transmission was identified, and active and retrospective case-finding were conducted. Most cases were epidemiologically linked. Genotype B3 virus was isolated, corresponding to the virus that was circulating in Madrid, Spain, at that time. The most recent circulating genotypes in America were B3 in Mexico during 2005–2006 and D4 in Brazil during 2006–2007, both of which were associated with imports [6].

In the capital city of Caracas, 4 cases were confirmed, the last during EW 15/2006. During EW 12 and 13/2006, 4 confirmed cases were reported in Nueva Esparta, a Venezuelan island with heavy tourist traffic. The outbreak spread to Carabobo in EW 20/2006 and remained active until EW 26/2006, with a total of 29 cases. During weeks 22 and 24, 4 cases were confirmed Zulia.

Silent Period
From EW 27/2006 through EW 43/2006, 493 files were entered in the Measles Surveillance System (MESS); 120 of them were confirmed. These cases were reported by 7 of the 24 states; the remaining 17 states had no suspected or confirmed cases during that period.

Second Active Period
In EW 44/2006, a measles case was reported in Camagüey, a town in the state of Guácire, located on the overland route to the state of Amazonas. The Camagüey index case was a 39-year-old woman who developed a rash on 2 November 2006; subsequently, her 3 children, aged 5, 3, and 1 year of age, and 2 grandchildren (11 months and 4 years of age) became ill.
None had a history of vaccination. The intensification of surveillance and case-finding made it possible to confirm a total of 15 cases at this locality, the last of which occurred in EW 51/2006.

In EW 49/2006, confirmed measles cases were reported in Amazons. The index case’s source of contagion could not be identified; through EW 05/2007, 21 cases were confirmed. The main source of transmission was identified as the regional hospital and family and community contact. The genotype isolated in this second period in the Camagüey and Amazons cases was B3, the same detected in the first period.

In the Amazons, which is predominantly rural, coverage had historically been low; all the cases occurred in Atures municipality, capital of the state of Amazons, a city with heavy
traffic by indigenous persons of various ethnicities, traveling to the interior of the Amazon jungle or neighboring states.

Because of the threat of transmission, a mass vaccination campaign was launched with the aim of achieving ≥95% coverage among persons aged <18 years through vaccination based on documentation, and the national MR vaccination campaign targeting the population aged 18–39 years programmed for October 2007 was moved up to February 2007. As a strategy, the first stage was vaccination in the urban area of Atures and towns located along the access roads; the second stage covered the municipalities in the interior. This kept the virus from spreading to the remote indigenous areas of Amazonas state and Colombia.

The intervention in Atures municipality concluded with a final evaluation of coverage done through cluster sampling. The results indicated coverage of 96% (95% confidence interval, 95%–97%) in the population aged 6 months to 39 years, with figures ≥95% in all age groups (6 months–4 years, 5–11 years, 12–17 years, and 18–39 years). Colombia did not report any cases.

Retrospective Case-Finding
A total of 185 suspect measles cases were identified: 80 with fever and rash, 51 with physician-diagnosed measles, 27 with a rubella diagnosis, 16 with dengue with rash, and 11 with exanthema subitum. Of the 185 cases identified, 105 (57%) had not been reported to the surveillance system, nor were they investigated.

With use of the clinical and epidemiological information, the cases were classified according to the established definitions. Fourteen cases compatible with measles were added that had occurred during the outbreak’s period of epidemiological silence; this closed the information gap during the weeks that the virus was circulating in the country (Figure 4).

DISCUSSION
The vaccination strategies that were implemented have altered the epidemiology of measles and led to a substantial decrease in the incidence of measles cases and to a shift in the age groups affected [7]. We also have seen changes in the behavior of the outbreaks. They are no longer explosive, rapidly spreading, and accompanied by fatalities, such as the outbreaks that occurred in Peru [8] (1992–1993) and Brazil (1997–January 1998) [9, 10]. Recent outbreaks have shown several idiosyncrasies: they are produced by imported cases, and case numbers are few. Because of the low level of suspicion, there is a delay in identifying the first and subsequent case; this can result in periods of silence, such as occurred in Uruguay (1998) [9] and Venezuela (2001 [9] and 2006 [5]), which can be interpreted as the outbreak having been controlled. No case fatalities were reported, and the cases spread slowly; in Venezuela, there were 122 cases with 0 deaths. Moreover, the information from field observations is that, clinically, the cases were not the typical ones described in the literature and were not severe; neither severe complications nor sequelae were reported in the Venezuelan
outbreak. The outbreak lasted 50 weeks, with a period of 17 weeks without confirmed cases in the surveillance system; this constituted a 2-phase pattern, which raised the possibility of 2 different outbreaks or the same outbreak with constant transmission. The results of the retrospective case-finding made it possible to establish that there had been deficiencies in the epidemiological surveillance and that this had been a single outbreak. This proved to be a valuable procedure for evaluating the quality of surveillance; this kind of investigation is useful for identifying suspect cases, although not necessarily confirmed cases. It should be done systematically, especially in epidemiologically silent areas and when a confirmed case presents.

In Mexico, 2 outbreaks were reported in 2003 and 2004 [11], with 44 and 64 confirmed cases, respectively; in both cases, H1 virus was isolated. We found a similar pattern, because we confirmed that, in both outbreaks, B3 virus was isolated, which corroborated that it was a single outbreak and there were deficiencies in the surveillance system. For this reason, we believe that it is very important in this new context that molecular epidemiology be obtained for samples [12] every 4–12 weeks for viral detection and genotyping as long as the outbreak lasts [13].

Ring vaccination did not prove to be effective, which we attribute to the new characteristics of dissemination of measles in this postelimination phase and also to a delay in analysis and decision-making. With every confirmed case, control should begin with a wide blockade; however, it will also be necessary to establish the risk of spread. This risk analysis must be based on the following elements: analysis of historical coverage, accumulation of susceptible, population dynamics, monitoring of surveillance indicators, spatial distribution of cases, and resource availability. These criteria will help to define the breadth of the vaccination strategy in this phase and they will help the outbreaks not be extensive and minimize the risk of endemic recirculation. This procedure was applied in Amazonas state with the aforementioned results.

Imported cases from other regions where measles is still circulating will continue to occur, but if adequate levels of immunity and sensitive surveillance systems are maintained, these outbreaks will not spread.

The challenge in the first period stemmed from the failure to analyze the virus circulation pattern. The measures adopted opposite to an outbreak relate to strategies of vaccination, strengthening of the vigilance, availability of resources, and political support. All of these measures are important but, in our experience, because of the characteristics of the aforementioned outbreak, it will be important, in terms of eradication, to know when circulation of the wild measles virus can be considered to have been interrupted. We propose determining this if the following criteria are met:

1. The absence of confirmed measles cases for 7 incubation periods, considering a period of 12 days as a maximum [7] 12 weeks after the last confirmed case. This period is proposed because up to 4 incubation periods are expected between a first and second case, from which monitoring of at least 3 chains of transmission would then start.
2. MR and/or MMR vaccination coverage >95%, confirmed by rapid coverage monitoring conducted by external evaluators.
3. Active case-finding to confirm the absence of cases and the sensitivity of the system.
4. Maintain negative weekly reporting in 90% of reporting units.
5. Ensure complete and timely investigation of every suspect case, including recreation of the chain of transmission, especially for the first cases.
6. Monitoring for up to 30 days of suspect cases and contacts identified in the chain of transmission.

The first cases in this outbreak had diagnoses unrelated to measles; this was attributable to the low level of suspicion of measles among physicians, either because they had never seen a case because of the low frequency of the disease and this diagnosis did not occur to them or because the symptoms were mild and they expected to see classical cases of measles. The positive predictive value of a case definition decreases considerably in situations of low incidence; [14] this situation can improve if a reporting rate for suspect cases by state is established [15] and there is regular reporting on this disease to all health care workers, in hopes of maintaining a high level of suspicion. In addition, the eradication issue should be regularly kept on the political agenda. These combined elements will help to maintain an active and sensitive surveillance system. In this outbreak, many states let their guard down when it comes to suspecting and investigating cases.

In addition, maintaining the achievements of the elimination should be a public health priority, which will require ongoing advocacy and sensitization of political and health authorities.

The rubella elimination strategy of using the MR vaccine substantially helps to establish measles elimination because adolescent and adult populations are vaccinated. The sustainability of this initial impact is based on maintaining uniform routine coverage (≥95%) in all municipalities; this administrative coverage should be confirmed through monitoring at municipal level. It is necessary to evaluate the need to offer a second vaccination opportunity, either through follow-up or routine campaigns [15]. The campaign of MR vaccination leaves various lessons learned at the central and regional level that are very useful to strengthen the regular program considered as the necessary support for elimination; in 2008, the MPPS initiated a broad process to improve the program initially addressing the increase in coverage, information system, epidemiological surveillance, and logistical system.
The epidemiology of measles has changed, and until worldwide elimination occurs, importation will continue to pose a threat to the gains achieved. This makes it necessary to keep the system sensitized, including professionals and political authorities and, in each confirmed case, to adopt vigorous control measures of sufficient breadth and depth to permit rapid control, preventing periods of prolonged circulation that could lead to the reestablishment of endemic circulation [16]. Pattern analysis, active and retrospective case-finding, molecular epidemiology, and laboratory surveillance are elements that should always be considered. Finally, the absence of cases alone is not sufficient to consider discontinuous the circulation of the wild virus of the measles.

**Funding**

The active case search was funded by the Pan American Health Organization.

**Acknowledgments**

We thank the political and technical authorities of the Ministry of Popular Power for Health and of the state and local surveillance and immunization teams and the social sectors and communities who got involved and firmly supported the activities that made it possible to interrupt measles virus circulation in Venezuela.

**References**


