Long-Lasting Measles Outbreak Affecting Several Unrelated Networks of Unvaccinated Persons

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Despite a population immunity level estimated at ~95%, an outbreak of measles responsible for 94 cases occurred in Quebec, Canada. Unlike previous outbreaks in which most unvaccinated children belonged to a single community, this outbreak had cases coming from several unrelated networks of unvaccinated persons dispersed in the population. No epidemiological link was found for about one-third of laboratory-confirmed cases. This outbreak demonstrated that minimal changes in the level of aggregation of unvaccinated individuals can lead to sustained transmission in highly vaccinated populations. Mathematical work is needed regarding the level of aggregation of unvaccinated individuals that would jeopardize elimination.

In 1994, Canada endorsed the target of measles elimination by year 2000. Elimination was defined as the interruption of endemic transmission and failure to reestablish endemic transmission after importation [1]. After universal 2-dose vaccination programs and catch-up campaigns in 1996–1998, measles is now considered eliminated in Canada [1]. In 2007, a measles outbreak that lasted 25 weeks and affected 94 persons took place in the province of Quebec and spread to 7 of its 18 administrative regions. This article describes the characteristics of this outbreak and discusses its implications for measles elimination.

**Methods.** After the detection of increased measles activity in May 2007, notifications were sent to emergency departments and first-line physicians asking them to look actively for measles in patients presenting with rash and fever. Suspected cases were investigated by the regional public health units. Information was gathered on clinical presentation, age, any epidemiological link to confirmed cases, travels vaccination status, and laboratory confirmation of measles. History of measles immunization was verified with the patient’s immunization record. The outbreak was considered over after 2 incubation periods without any reported case.

Measles cases were defined as either laboratory confirmed or clinically confirmed. Laboratory-confirmed cases were characterized by either measles virus detection, positive serological test for measles immunoglobulin (Ig) M antibody, or a significant increase in the measles-specific IgG antibody titer between acute and convalescent serum samples. Clinically confirmed cases were defined by fever (temperature, \(\geq 38.3\)°C), a generalized maculopapular rash for \(\geq 3\) days, and either cough, coryza, or conjunctivitis. Clinical cases had to be epidemiologically linked to a confirmed case to be included.

Viruses were isolated by viral culture of pharyngeal and/or urine specimens at the Montreal Children’s Hospital Virology Laboratory. Measles viral RNA in pharyngeal and/or urine specimens was also detected by reverse-transcription polymerase chain reaction (RT-PCR) at the National Microbiology Laboratory (Winnipeg, Manitoba) [2]. Measles virus strains were genotyped and compared with reference strains designated by the World Health Organization [2–4].

**Results.** Public health authorities were notified of a first case on 1 May 2007 (Figure 1, week 0). Measles was diagnosed in a 37-year-old male Canadian of Lebanese origin with unknown vaccination status and onset of rash on 19 April. Laboratory confirmation included positive viral culture and positive results of RT-PCR and a measles IgM serologic test. The measles genotype was determined to be D4 (MV/Quebec.CAN/1607/1 [D4]; GenBank accession no. F643601) and was closely related to another measles strain imported from Lebanon into the United States in 2003 (GenBank accession no. DQ390238; Paul Rota, Centers for Disease Control and Prevention, personal communication and Yeung et al [5]). The patient did not recall any recent contact with people who had traveled in the Middle East. He had traveled to Alberta (Canada) but had returned to Quebec 21 days before the rash onset, a delay that exceeded the usual incubation period. Before the index case patient became aware he had measles, he had been to crowded areas and used the public transportation system.
Three second-generation cases occurred. One involved a patient who was an unvaccinated man without any known contact with the index case patient, and 2 involved patients with an epidemiological link: the wife of the index case patient (vaccination status unknown) and a 36-year-old woman (vaccinated without proof) who went to a medical clinic the same day as the index case patient (Figure 2). No epidemiological link could be made between the second and third generations of cases. Among the 3 patients with third-generation cases, a 28-year-old woman transmitted measles to 9 persons: her 2 children (both had received only 1 dose of vaccine), a coworker (vaccinated without proof), and 6 persons with whom she attended a large event (>2000 persons) on 20 May. These 6 persons were all unvaccinated and included her 23-year-old sister and 5 unrelated children aged 9–14 years. One of them, a 9-year-old boy with a positive culture result and rash starting on 9 June, was attending a 175-student alternative school (school 1 in Figure 2) located in another region. This triggered a cluster of 31 confirmed cases, all related to this school (18 pupils and 13 relatives or friends). This number was probably underestimated because some families were reluctant to seek medical attention. Patients with confirmed cases all had rash onset between 18 June and 23 July. Five patients were positive for measles IgM, and the others matched the clinical case definition of measles with an epidemiological link. The vaccine coverage in that school was well below the provincial average, with 47% of persons unvaccinated and 12% having received only 1 dose. Among patients with confirmed measles, 25 (81%) were unvaccinated, 3 (10%) had received 1 dose of measles-containing vaccine, and 1 (3%) had received 2 doses; 2 patients (6%) said they were vaccinated, but the vaccinations could not be traced in their immunization records.

During weeks 5 and 6, measles was diagnosed in 9 more patients who had no apparent epidemiological links (Figure 2). These patients included a 7-year-old unvaccinated boy attending an elementary alternative school (school 2) in another region, completely unrelated to school 1. Seven children attending the same school became sick during the following 3 weeks (6 were not vaccinated; 1 had received only 1 dose). In both schools, the virus was identical to the D4 strain identified in the outbreak index case.

Transmission decreased significantly after week 12 (Figure 1). The last 12 measles cases all occurred in the Montreal area between weeks 17 and 25. Eight cases belonged to a cluster that started on week 18, involving 4 unvaccinated children 5–9 years old attending a third school (school 3). No epidemiological link was found with the previous cases. In 4 patients, serological findings were positive, but the virus could not be isolated. In week 17, a new virus strain was isolated by culture from a 2-year-old boy, a D4 strain that differed from the outbreak strain by 9 nucleotides (98% sequence identity; MVi/Quebec.CAN/33.07 [D4]; GenBank accession no. FJ643602). That same strain was later found in week 21, in a 3-year-old boy from the same region with no epidemiological link to the other child. The older brother of the second child also acquired measles after his mother refused vaccination and postexposure prophylaxis. Judging by the timing and the recovery of the same second strain, these 3 cases were probably linked. None of the patients had a history of travel or known contact with someone with a similar disease. Because no virus was identified for the school
3 cluster and no epidemiological link was found between that school and the main outbreak, it is unclear whether that cluster belonged to the initial outbreak or the second importation. However, these cases were included in the statistics presented below, but not the 3 cases associated with the second strain.

Among the 94 confirmed cases, 50 cases (53%) were laboratory confirmed, and 44 (47%) were clinical cases with an epidemiological link to a laboratory-confirmed case. The virus was detected in 15 patients (by RT-PCR only in 9, and by culture [with or without RT-PCR] in 10), and 25 patients were only IgM positive.

The outbreak affected mostly children: 75 (80%) of the patients were <20 years old (none were <1 year old). Eight patients (8%) were hospitalized, but no complications were documented. Sixty-eight patients (72%) were unvaccinated, 11 (12%) had received only 1 dose, 4 (4%) had received 2 doses, and 6 (6%) were reportedly vaccinated without written proof. Information on vaccination was missing for 5 cases. In the vast majority of unvaccinated patients, vaccination was objected to for religious or philosophical reasons. No case was exported to another province, but 1 patient’s symptoms developed while he was traveling in Austria, where measles infection was diagnosed. During its 23 weeks of activity, this outbreak had 12–17 generations of spread, assuming 10–14 days between each generation. The incidence of measles was 12.6 cases per 1 million population (97 cases per 7.7 million population).

**Discussion.** Four of the 6 regions of the world have now committed to eliminating measles [6]. Developed countries that successfully eliminated measles have high vaccine coverage, with 2 doses of vaccine administered through routine system or mass campaigns [7]. In all of these countries, however, despite intense efforts, a small proportion of children remain unvaccinated because of parental objections, most based on religious or philosophical beliefs. In the United States, the 3 largest outbreaks since 1998 occurred mainly in unvaccinated individuals and involved <35 cases [8–10]. During the same period, Canada has had 1 outbreak with 155 cases in 2000 and this 94-case outbreak in 2007 [1]. The first outbreak was mostly restricted to a specific religious group unfavorable to immunization, although the latter was characterized by its long transmission in unvaccinated individuals belonging to unrelated networks dispersed in the population. This outbreak raises the possibility that even a small proportion of unvaccinated individuals scattered in the population may jeopardize elimination of measles.

Epidemic modeling predicts that elimination can be reached and maintained if >93% of the entire population is immune [11]. In Quebec, the vaccine coverage is likely to provide such
a high level of immunity. After the school-based vaccination campaign in 1996, 97% of children 5–17 years of age had received ≥1 dose, and 85% had received 2 doses [12]. In 2005, a survey in preschool children showed that 95% had received ≥1 dose of measles vaccine by 24 months of age, and 87% had already received a second dose [13]. Because some of these children will be vaccinated before school entry, the proportion of completely unvaccinated school-aged children is estimated to be <3%. The level of immunity in children 1–19 years of age could therefore be estimated at ~95%, which is greater than the elimination threshold.

An important assumption of mathematical models predicting elimination, however, is the random distribution of susceptible persons in the population. In reality, unvaccinated individuals are not distributed at random. Religious groups opposed to vaccination are often tightly knit communities. Our outbreak involving 2 unrelated alternative schools attended by children whose parents were resistant to vaccination on philosophical ground demonstrated that these persons also aggregate. The spontaneous interruption of this outbreak, despite the current level of aggregation in unvaccinated children, suggests that endemcity was not likely to be reestablished in this population. The continued propagation throughout many generations of cases, however, raised the possibility that a minimal change in the overall vaccine coverage in the population or in the level of aggregation of unvaccinated individuals can lead to sustained but protracted transmission despite an immunity level near 95%. If confirmed, this latter possibility would have important implications for the success of an initiative for global elimination of measles. In fact, much larger outbreaks have occurred in countries with similar level of immunity [14].

This outbreak also raised questions regarding our capacity to assess properly the extent of measles transmission. Despite active investigation, we could not find any epidemiological link for many cases. Transmission may have happened in public settings, but it is also possible that several cases were missed despite the enhanced surveillance. The source of importation was not found for the index case and for the cases with the distinct strain diagnosed near the end of the outbreak. The true sensitivity of our surveillance system was unknown, but our ability to detect sporadic cases and small clusters indicate that it was reasonably good. However, not all cases had an identified source, which indicates that not all cases and importations were detected. This imperfect sensitivity limits the capacity to monitor elimination status in a country, because such monitoring depends on the ability to identify the source of importations and length of chains of transmission secondary to importations [15].

In conclusion, this analysis of a measles outbreak suggests that, despite high vaccine coverage, measles transmission may persist for >10 generations among unvaccinated individuals dispersed in the population but with a certain level of aggregation. Mathematical work is needed regarding the level of aggregation of unvaccinated individuals that would jeopardize elimination.

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