Outbreak of Measles Among Persons With Prior Evidence of Immunity, New York City, 2011

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Background. Measles was eliminated in the United States through high vaccination coverage and a public health system able to rapidly respond to measles. Measles may occur among vaccinated individuals, but secondary transmission from such individuals has not been documented.

Methods. Suspected patients and contacts exposed during a measles outbreak in New York City in 2011 were investigated. Medical histories and immunization records were obtained. Cases were confirmed by detection of measles-specific immunoglobulin M and/or RNA. Tests for measles immunoglobulin G (IgG), IgG avidity, measurement of measles neutralizing antibody titers, and genotyping were performed to characterize the cases.

Results. The index patient had 2 doses of measles-containing vaccine; of 88 contacts, 4 secondary patients were confirmed who had either 2 doses of measles-containing vaccine or a past positive measles IgG antibody. All patients had laboratory confirmation of measles infection, clinical symptoms consistent with measles, and high-avidity IgG antibody characteristic of a secondary immune response. Neutralizing antibody titers of secondary patients reached >80 000 mIU/mL 3–4 days after rash onset and that of the index was <500 mIU/mL 9 days after rash onset. No additional cases of measles occurred among 231 contacts of secondary patients.

Conclusions. This is the first report of measles transmission from a twice-vaccinated individual with documented secondary vaccine failure. The clinical presentation and laboratory data of the index patient were typical of measles in a naive individual. Secondary patients had robust anamnestic antibody responses. No tertiary cases occurred despite numerous contacts. This outbreak underscores the need for thorough epidemiologic and laboratory investigation of suspected cases of measles regardless of vaccination status.

Keywords. measles; outbreak; immunity; vaccine failure; waning immunity.

Before the introduction of measles vaccine, >90% of the US population contracted measles by age 15 years [1]. Following the introduction of measles vaccine in 1963, measles incidence declined rapidly [2]. In 1989, the Advisory Committee on Immunization Practices (ACIP) recommended a second dose of measles vaccine, as combined measles-mumps-rubella (MMR) vaccine, for introduction into the routine immunization schedule [3]. Adherence to this recommendation, combined with sustained, high national MMR vaccination coverage, helped eliminate endemic measles transmission by 2000 [4, 5]. Measles remains endemic in many parts of the world, and international travelers with measles may transmit virus to nonimmune individuals in the United States [2]. In 2011, the United States recorded 220 cases of measles, among which 87% of patients were unvaccinated or had undocumented vaccination status, indicating that failure to vaccinate is the most significant cause of measles following importation [6]. The ongoing risk of importations requires sustaining high levels of population immunity to maintain measles elimination in the United States.

The ACIP criteria for presumptive evidence of immunity to measles include documented age-appropriate receipt of live measles virus–containing vaccine, laboratory evidence of immunity, laboratory evidence of

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disease, or birth before 1957 [6, 7]. Although vaccination with 2 doses of MMR vaccine is highly effective and is a proxy for immunity to measles, cases of measles have occurred among persons despite receipt of 2 doses of MMR vaccine [8–13]. Persons with detectable but low levels of neutralizing antibody despite receipt of 2 doses of MMR vaccine are potentially susceptible to infection and disease [14–18]. When measles is introduced into a highly vaccinated population, there are fewer cases of measles; however, among the cases that occur, the relative proportion occurring in vaccinated individuals increases [19]. These cases generally occur in an outbreak or in a setting involving intense exposure to an unvaccinated person with measles, and often exhibit modified symptoms.

Although antibody levels are expected to decline over time, it is unclear what effect the absence of natural boosting (asymptomatic secondary immune response) by circulating virus may have in the future on the maintenance of overall population immunity, including the ability of vaccinated persons to transmit virus [20, 21]. Subsequent spread of disease has not been documented from measles patients with a verified secondary immune response [9, 12, 13].

We report on an outbreak of 5 cases of measles in New York City (NYC) in which a fully vaccinated index patient transmitted measles infection to 4 contacts with presumptive evidence of measles immunity.

METHODS

Patient and Contact Ascertainment and Investigation

The index patient was identified through routine surveillance at the NYC Department of Health and Mental Hygiene (DOHMH). Patients with measles were identified by mandatory healthcare provider reports and electronic laboratory notification of positive measles immunoglobulin M (IgM) and/or RNA results. Provider reports of immunization records and measles immunoglobulin G (IgG) titers done before the onset of illness were reviewed for all patients, if available; verbal reports were not accepted as documentation of immunity. Clinical information and lists of exposed contacts were obtained from a review of medical records and through patient interview. The 2009 Council of State and Territorial Epidemiologists case definition was used to classify confirmed cases [22]. A list of contacts was developed based on identifiable individuals at known exposure sites in NYC. Documented immunization records and measles IgG titers of identified contacts were reviewed and immunity to measles was determined based on ACIP criteria [7]. Contacts were informed about symptoms of measles and were instructed to contact the DOHMH if they developed measles symptoms. Follow-up with nonimmune contacts was conducted again at the end of the incubation period to assure that contacts remained asymptomatic. Exposures occurring outside of NYC were not included in this evaluation.

Laboratory Testing

Initial serological and virological testing was performed in several commercial and public health department laboratories. Subsequently, all specimens were sent to the MMR Laboratory at the Centers for Disease Control and Prevention (CDC) for confirmation. Only results from the MMR laboratory at CDC are presented.

Serum specimens were tested for measles-specific IgM antibodies using an IgM capture enzyme immunoassay (EIA) as previously described [23]. Measles-specific IgG was tested using an in-house indirect EIA assay incorporating the measles nucleoprotein as the antigen [23]. IgM/IgG index ratios were derived by dividing the net absorbance values measured for IgM by IgG [24]. The IgM/IgG ratio was compared among patients as a measure of primary vs secondary immune response to infection. Index ratios >1 suggested a primary immune response to measles, and ratios <1 were consistent with a secondary response [24].

Avidity of measles-specific IgG antibody was tested by modification of a commercial measles IgG EIA (Captia Measles IgG, Trinity Biotech, Jamestown, New York), as previously described [25]. Measles neutralizing antibody titers were measured using a plaque reduction neutralization (PRN) test performed as previously described [26–28]. Serum specimens were run in parallel with the World Health Organization (WHO) Second International Standard Anti-Measles serum (coded 66/202, supplied by National Institute for Biological Standards and Control, South Mimms, United Kingdom). According to the run validation parameters, a titer of 1:8 corresponded to 8 mIU/mL. Seropositivity was defined as PRN concentrations ≥8 mIU/mL and seroprotection ≥120 mIU/mL [28].

Reverse transcription polymerase chain reaction (RT-PCR) and genotyping were performed. RNA was extracted from nasopharyngeal swab specimens using the QIAamp Viral RNA Mini Kit (Qiagen, Gaithersburg, Maryland). Measles virus RNA was detected by using a real-time RT-PCR assay targeting the measles nucleoprotein gene as previously described [29]. The measles genotypes were determined following RT-PCR and sequencing using the approach recommended by WHO [30–32].

RESULTS

The index patient was a 22-year-old female resident of NYC with a past medical history only significant for mitral valve prolapse. She developed a generalized rash, cough, conjunctivitis, coryza, sore throat, and subjective fever and presented to an emergency room for medical care but was not hospitalized. She had documentation of receipt of MMR vaccination at 3 years and

Table 1. Medical History, Immunity History, and Clinical Presentation for Patients in a Measles Outbreak in New York City, 2011

Case	Age, y	Prior Evidence of Immunity: MMR, Year	Prior Evidence of Immunity: Measles IgG, Year	Medical History and Clinical Presentation: Medical History	Rash[a]	Rash Duration, d	Fever	Cough	Conjunctivitis	Coryza	Other
1 (index)	22	1991; 1992	. . .	Mitral valve prolapse	Y	8	Subjective	Y	Y	Y	Sore throat
2	25	1987 1990	. . .	Ulcerative colitis, immunosuppressive medication, cerebral palsy	Y	Unknown	38.9°C	Y	Y	Y	Diarrhea; Koplik spots
3[b]	20	1992 1996	. . .	None	Y	4	38.9°C	N	N	N	Sore throat
4	35	. . .	2006	None	Y	3	38.3°C	Y	N	N	N
5[c]	52	. . .	1993	Hypothyroid on Synthroid	Y	5	Subjective	Y	N	N	N

Abbreviations: IgG, immunoglobulin G; MMR, measles-mumps-rubella.

[a] Generalized.

[b] Case was reported to the New York City Department of Health and Mental Hygiene (NYC DOHMH) but investigated by the jurisdiction of residence, Baltimore County Department of Health.

[c] Case was reported to the NYC DOHMH but investigated by the jurisdiction of residence, Westchester County Department of Health.

4 years of age. There was no travel during the incubation period and no known sick contacts. However, the index patient worked at a theater frequented by tourists. Eighty-eight exposed contacts aged 20–65 years were identified in NYC during her infectious period, of whom 66 (75%) had documentation of immunity, 10 (11%) were not immune to measles at the time of exposure, and 12 (14%) had unknown immune status.

Subsequently, 4 additional patients were identified among contacts of the index patient (Table 1). Three of the secondary patients (cases 2, 4, and 5) were healthcare workers at a clinic

Table 2. Laboratory Results From Serologic and Virologic Testing of Patients in a Measles Outbreak in New York City, 2011

Case	Serum Sample No.: Days From Rash Onset to Collection	IgM Result	IgG Result	IgM/IgG Index Ratio[a]	IgG Avidity (etAI)[b]	PRN Titer, mIU/mL	RT-PCR	Genotype
1	Serum 1: 2 d	Positive	Positive	. . .	Intermediate (63%)	81	Positive	D4
	Serum 2: 9 d	Positive	Positive	9.7	High (100%)	402		
2	Serum 1: 0 d	Negative	Negative	. . .	Not done	1367	Positive	D4
	Serum 2: 4 d	Positive	Positive	. . .	High (83%)	150 219		
	Serum 3: 11 d	Positive	Positive	0.3	High (79%)	175 563		
3[c]	Serum 1: 3 d	Positive	Positive	. . .	High (82%)	87 155	Positive	Not done
	Serum 2: 6 d	Positive	Positive	. . .	High (70%)	221 291		
	Serum 3: 11 d	Positive	Positive	0.2	High (73%)	168 036		
4	Serum 1: 3 d	Positive	Positive	. . .	Intermediate (62%)	107 712	Negative	Not done
	Serum 2: 10 d	Positive	Positive	0.24	High (70%)	94 860		
5[d]	Serum 1: 3 d	Negative	Positive	. . .	High (92%)	94 860	Positive	Not done
	Serum 2: 7 d	Negative	Positive	0.02	High (97%)	171 632		

Abbreviations: etAI, end-titer avidity index; IgG, immunoglobulin G; IgM, immunoglobulin M; PRN, plaque reduction neutralization; RT-PCR, reverse transcription polymerase chain reaction.

[a] IgM/IgG index ratio calculated on latest serum available for each patient (7–11 days); index ratios >1 suggest a primary immune response to measles and ratios <1 suggest a secondary response.

[b] Avidity classified as low (etAI ≤30%), intermediate (etAI 31%–70%), and high (etAI ≥70%); intermediate and high avidity suggest past immunologic experience with measles through vaccination or natural measles infection.

[c] Case reported to the New York City Department of Health and Mental Hygiene (NYC DOHMH) but investigated by the Baltimore County Department of Health.

[d] Case reported to the NYC DOHMH but investigated by jurisdiction of residence, Westchester County Department of Health.

where the index patient received care and were exposed to the index patient on her day of rash onset. The other secondary patient (case 3) was a coworker of the index patient and was exposed to the index patient 2 days prior to her rash onset. The secondary patients had no epidemiologic links to any other patient with measles in NYC. These secondary patients had a generalized rash with onset between days 12 and 16 after exposure to the index patient and ranged in age from 20 to 52 years (median, 30 years). Two of the secondary patients had 2 documented doses of MMR vaccine and 2 had prior positive measles IgG antibody results (Table 1). One patient (case 2) had a medical history of immunosuppression and presented with rash, fever, cough, coryza, and conjunctivitis (Table 1). All other secondary patients presented with either rash and fever (case 3) or rash, fever, and cough (cases 4 and 5). None were hospitalized and there were no complications (Table 1).

An additional 231 contacts were identified as exposed to the secondary patients in NYC. Among these exposed contacts, 157 (68%) were considered to be immune to measles or received postexposure prophylaxis, 5 (2%) were not immune, and 69 (30%) had unknown immune status. No tertiary cases were identified among these contacts.

All cases were laboratory confirmed by a positive measles IgM result, detection of measles RNA by measles RT-PCR, or both (Table 2). Measles IgM was detected in serologic specimens collected 3 or more days after rash onset from 4 of the 5 patients. Measles IgG was detected in all serum samples except 1 sample collected on day 0 from case 2, although the PRN titer from the same serum sample was 1367 mIU/mL and by day 4 IgG was positive and the PRN titer had increased by >100-fold. The ratio of IgM to IgG in the day 9 serum from the index patient was 9.7, whereas the other 4 patients had ratios <1.0 (Table 2). Measles RT-PCR was positive from nasopharyngeal specimens from 4 of the 5 patients, 2 of which were sequenced and identified as genotype D4 (Table 2).

The initial serum samples collected from the index patient and case 4 had IgG avidity measured in the intermediate range (end-titer avidity index: 63% and 62%, respectively). However, all of the patients had high-avidity IgG in follow-up serum samples (Table 2). The PRN titer obtained from the index patient was 81 mIU/mL in serum collected 2 days after rash and 402 mIU/mL in the follow-up serum collected 7 days later. The 4 secondary patients had PRN titers of >80 000 mIU/mL in serum collected at ≥3 days after rash onset.

DISCUSSION

An unusual outbreak of measles was investigated in which all of the patients had either 2 documented doses of MMR vaccine or a positive result recorded for measles IgG antibody in the past. The index patient had 2 documented doses of MMR vaccine before infection and subsequently transmitted disease to 4 contacts. Although other outbreaks have been reported in which persons with a history of MMR vaccination were confirmed with measles, this is the first report in which a person with a verified secondary vaccine failure despite receipt of two doses of MMR was demonstrated to be capable of transmitting disease to other individuals [8–13, 33].

The laboratory results of intermediate or high-avidity IgG antibody indicate that the index patient and all of the secondary patients had past immunologic experience with measles through vaccination or natural measles infection. However, the index's relatively high IgM to IgG ratio was typical of a primary response, whereas those of the 4 secondary patients were consistent with a secondary immune response [14, 24]. Although the detection of IgM among measles patients had long been presumed to be a characteristic of the first exposure to measles antigen (ie, primary immune response), it has since been recognized that IgM can be elicited by persons with either a symptomatic or asymptomatic secondary immune response, albeit at lower IgM to IgG ratios [14, 24]. Despite high-avidity IgG, the index patient did not develop the typical high neutralizing antibody titers that have been observed among previously immunized patients [12, 13]. Previous studies have noted that extremely high PRN titers in acute-phase serum from vaccinated persons with suspected measles infection might serve as a biomarker for patients with a secondary immune response [12, 13]. The 4 secondary patients all had an early and robust antibody response within a few days after rash onset, with PRN titers 6–60 times higher than those observed after primary infection with natural disease or following measles vaccination [12, 13]. Despite >200 exposures identified through investigations following notification of the 4 secondary patients, no additional cases were detected. This is in agreement with other published investigations describing a lack of transmission by documented cases of secondary vaccine failure [12, 13]. In each of the secondary patients, neutralizing antibody may have waned sufficiently to allow symptomatic infection, but the anamnestic response upon reexposure to measles generated a rapid and robust memory response that may have reduced their infectious period. However, in the setting of high population-level immunity, it is challenging to evaluate transmissibility. In contrast, the index patient's lower neutralizing antibody titer after infection provides a biologically plausible explanation for her ability to transmit virus.

Previous outbreaks in which symptomatic patients with measles who were later confirmed to have a secondary immune response generally involved patients with modified clinical presentations that could easily have been misdiagnosed in the absence of another confirmed case of measles [12, 13]. However, based on the clinical information available, the index patient and 3 of the 4 secondary patients had typical clinical

presentations of a generalized rash with duration of 3 or more days with fever, and either cough, conjunctivitis, or coryza.

An understanding of the duration of measles immunity is important for ensuring continued success with global measles elimination. Demonstration of waning immunity requires measurement of neutralizing antibody titers before revaccination or infection and at time points subsequent to the antigenic stimulation. Detection of IgG is a proxy for immunity, not an absolute correlate of protection from disease. Similarly, the inability to detect measles-specific IgG should not be construed as a lack of immunity in persons who have been previously vaccinated, as cellular immunity and antibody functionality play important roles in protection [17, 34–37]. Neutralizing antibody titers have the closest correlation with immunity to measles, but assays that measure measles neutralizing antibody are not widely available, and tests of cellular immunity are challenging to perform [36, 38].

With the achievement of measles elimination, boosting of immunity from exposure to wild-type measles virus is uncommon [20]. It is unknown if boosting of immunity among vaccinated individuals by exposure to circulating virus had previously played an important role in maintaining protective levels of antibody, raising questions about the duration of population immunity to measles. In one report of schoolchildren in a postelimination environment, measles neutralizing antibodies persisted for 10 years after receipt of a second dose of MMR. Although no seronegative results were detected after 10 years, titers did decline over time, with 4.7% (18/382) of the children considered potentially susceptible to infection, given PRN titers in the range of 8–120 mIU/mL; however, 72% of those with low titers after 10 years had been in the lowest quartile of titers prior to the second MMR dose [17].

There are limitations to this evaluation. Although provider documentation of MMR vaccination was obtained, it is not possible to know about the quality of the vaccine received. Inappropriate storage conditions could alter the effectiveness of vaccine. It is possible that the patients never responded adequately or only achieved minimal titers following vaccination; however, the laboratory results of high-avidity IgG antibody demonstrate that all the patients had responded previously to measles virus and are not primary vaccine failures.

As we move forward on global efforts to eliminate measles, it remains critical that we maintain high population immunity and vigilance for disease. International importations of measles continue to occur in the United States [6]. The current 2-dose MMR vaccination strategy has successfully maintained measles elimination in the United States for nearly 20 years, despite continued importations. Now that the United States has been free of endemic measles for more than a decade and natural boosting of infection is uncommon, it will be important to better understand the duration of immunity [20, 39, 40]. However, this outbreak probably represents a series of rare events, and waning immunity among previously vaccinated persons is unlikely to threaten the ability to sustain measles elimination.

Surveillance also plays a vital role in monitoring the status and duration of population immunity by identifying instances of disease in individuals with prior immunity and conducting investigations of their exposed contacts. Although 3 of the 4 secondary patients described in this report had typical clinical presentations, it is important to note that previous outbreaks in which measles patients with a secondary immune response were identified generally involved patients with modified clinical presentations that could easily have been misdiagnosed in the absence of a thorough investigation [12, 13]. A single episode of transmission from an individual with prior evidence of immunity does not justify a change in current measles control and elimination strategies; however, this case clearly underscores the need to maintain sensitive surveillance activities.

Notes

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