Two Case Studies of Modified Measles in Vaccinated Physicians Exposed to Primary Measles Cases: High Risk of Infection But Low Risk of Transmission

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In 2009, measles outbreaks in Pennsylvania and Virginia resulted in the exposure and apparent infection of 2 physicians, both of whom had a documented history of vaccination with >2 doses of measles-mumps-rubella vaccine. These physicians were suspected of having been infected with measles after treating patients who subsequently received a diagnosis of measles. The clinical presentation was nonclassical in regard to progression, duration, and severity. It is hypothesized that the 2 physicians mounted vigorous secondary immune responses typified by high avidity measles immunoglobulin G antibody and remarkably high neutralizing titers in response to intense and prolonged exposure to a primary measles case patient. Both of the physicians continued to see patients, because neither considered that they could have measles. Despite surveillance for cases among contacts, including unvaccinated persons, no additional cases were identified.

In the United States, limited measles outbreaks continue to occur after importation of measles, and the cost of conducting follow-up investigations and case containment can be substantial [1]. Prior to a diagnosis of measles, a patient may be seen in multiple health care facilities, resulting in numerous exposures of patients and health care workers. In hospitals, there are often immunocompromised patients and other persons for whom infection with measles can have severe consequences. For this reason, health care workers born after 1957 are generally required to have documentation of having received 2 doses of measles-mumps-rubella (MMR) vaccine and/or demonstrate immunity to measles by serological testing.

The laboratory plays a critical role in case classification when rash and fever develop in persons who have possibly been exposed to measles. To complicate matters, nonclassic cases of measles in vaccinated persons may be identified, which must be investigated. Often the symptoms are mild and resolve rapidly and, outside of the context of an outbreak or known exposure to a measles case patient, the nonclassic presentation might not raise suspicion of measles [2–4]. However, the consequences of possible spread from such cases, and particularly from cases among health care workers, puts tremendous pressure and demands on those who are responsible for outbreak control.

In this report, we describe 2 instances in which physicians developed rash and fever following treatment of a confirmed measles case despite a history of receipt of >2 doses of MMR vaccine. The laboratory findings from the 2 suspected cases were consistent with a secondary immune response (SIR) to measles. The relevance of immunoglobulin (Ig) M detection for case confirmation in such circumstances and the implications for outbreak investigations are discussed. The absence of spread cases from the 2 physicians suggests

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that such cases, although not asymptomatic, have a very low potential for infecting others, compared with cases in fully symptomatic individuals.

CASE REPORT: MEASLES OUTBREAK WITH EMERGENCY DEPARTMENT EXPOSURE TO PHYSICIAN, PENNSYLVANIA, MARCH 2009

A 37-year-old female emergency department physician in Pennsylvania with mild symptoms was suspected of being infected with measles in the course of an outbreak investigation in which the initial case of measles was not immediately recognized. The physician had a history of having received 3 doses of MMR vaccine, 2 of which were documented, with the most recent dose being administered in 2003. The reason given for the additional dose was failure to show immunity to rubella. The physician had evaluated a 10-year-old child in the emergency department on 10 March 2009 who was suspected to have Kawasaki disease. The child had arrived from India on 8 March and had developed a rash on 9 March. A review of medical records led the investigators to reconsider the rash illness in the 10-year-old child as a possible measles case following the laboratory confirmation of measles by IgM testing on 30 March in 3 family members who had been in the same emergency department on 10 March for an unrelated complaint. The family members, comprising 2 unvaccinated male siblings (23 months of age and 4 years of age) and their father (33 years of age) had developed rash illnesses 13–16 days after the emergency department visit. Viral samples collected from the 2 children were positive for measles by reverse-transcriptase polymerase chain reaction (RT-PCR), and genotype D8 was identified, which was consistent with importation of the disease from India [5]. The clinical sample obtained from the father, who reported having received 1 dose of MMR vaccine as a child, had negative RT-PCR results. The description of his symptoms included a rash on the face and the trunk, cough, and coryza, but the highest recorded temperature was 99°F (37.22°C). Because of the positive IgM result, the father was confirmed as having a measles infection but no additional cases occurred, even though the father continued to work while potentially infectious. The 10-year-old child from India was determined to be the index case patient after a serum sample that was collected 24 days after rash onset had test results that were positive for measles IgM (Table 1). One additional case was confirmed in an 11-month-old infant (who was unvaccinated) who had also been in the same emergency department on 10 March.

After measles was diagnosed among the secondary cases, the physician recalled having flu-like symptoms, including myalgia, cough, and fever that lasted 4–5 days, prior to the appearance of a rash on the abdomen, which spread to the neck. The rash appeared on 26 March, 16 days after contact with the index case patient, and had resolved within 24 h. The physician continued to work and saw >100 patients during her infectious period, including unvaccinated infants; however, no spread cases were detected. The laboratory results are summarized in Table 1.

CASE REPORT: SPORADIC MEASLES CASE WITH ACUTE CARE FACILITY EXPOSURE TO PHYSICIAN, VIRGINIA, APRIL 2009

In contrast to the first case report, the exposure of a 39-year-old male physician in Virginia to measles was recognized within a few days after seeing the patient. However, the physician had a history of having received 5 doses of MMR vaccine (2 in childhood and 3 in medical school), and his immunity to measles had been verified in December 2004. The reason given for receipt of the multiple doses was failure to demonstrate seroconversion to ≥1 of the antigens. On 14 April 2009, the

Table 1. Centers for Disease Control and Prevention Laboratory Results for 6 Measles Cases Including an Emergency Department Physician in Pennsylvania, March 2009

Case description, rash onset date	Vaccine history	Interval, rash onset to serum collection	IgM result	IgG result	PRN titer	Avidity
Index case patient, 9 March	Unknown	24 days	Positive	Positive	3644	Low
Sibling 1, 23 March	No MMR	7 days	Positive	Positive	9503	Low
Sibling 2, 26 March	No MMR	S1: 5 days S2: 7 days	S1: Positive S2: Positive	S1: Negative S2: Positive	S1: 2332 S2: 10,564	Not done
Father, 26 March	1 MMR dose (no record)	4 days	Positive	Positive	168,640	High
11-Month-old infant, 27 March	No MMR	6 days	Positive	Positive	2395	Not done
Physician, 26 March	3 MMR doses	S1: 6 days S2: 20 days	S1: Ind S2: Negative	S1: Positive S2: Positive	S1: 248,628 S2: 206,580	High

NOTE. The S1 (physician) was determined to be immunoglobulin (Ig) M positive at the Pennsylvania Bureau of Laboratories. Ind, indeterminant; MMR, measles-mumps-rubella vaccine; PRN, plaque reduction neutralization.

physician had examined a 25-year-old patient who presented to his clinic with fever and rash. Blood samples were collected from the 25-year-old patient on 17 April and again on 20 April, at which time the diagnosis of measles was confirmed by IgM detection. Because there was no recent travel and no other cases had been identified, the IgM results for the 25-year-old patient were confirmed by additional laboratory tests. Because the first serum sample collected had test results that were negative for measles IgG, seroconversion was demonstrated (Table 2). Also, viral samples collected on 17 April were positive for measles by RT-PCR (data not shown).

On 29 April, 15 days after seeing the measles case patient, the physician noticed that he had developed a rash. However, he had removed a tick from himself 2 days earlier and attributed the rash either to the tick bite or to taking doxycycline. A blood sample was drawn on 29 April, which was tested at a commercial laboratory and found to be IgM negative and IgG positive for measles. The physician continued to see patients during his infectious period because he considered himself to be protected from measles. Because the first blood sample collection date was the first day of the rash (and therefore possibly yielded a false-negative result), a second blood sample was obtained on 8 May. No viral samples were collected. The second blood sample was sent to a different commercial laboratory, and the sample was found to be IgM positive and IgG positive. The symptoms reported by the physician were temperature to 103°F (39.44°C) and headache prior to rash, but no coryza, conjunctivitis, or cough were reported. The physician also had an unvaccinated 3-month-old child at home who remained well, as did the child's mother (whose vaccination status was unknown). No additional cases were reported. Another serum sample was collected on 12 May. The blood samples collected on 8 May and 12 May were submitted to the Centers for Disease Control and Prevention (CDC) for testing and were found to be IgM negative, at which time the physician was ruled out as a case patient. However, a second aliquot of the serum, dated 12 May, arrived later and a positive result for measles IgM was obtained. The laboratory results are summarized in Table 2.

DISCUSSION

Physicians are often exposed to patients at a very infectious stage of measles disease, during the prodrome when fever is present or at onset of rash [6]. Persons with preexisting antibody levels that would be clinically protective against disease (or would asymptomatically boost) after a lesser or ''casual'' exposure, may be mildly to moderately symptomatic upon prolonged exposure in close quarters, such as an examination room. The vaccination history of the 2 physicians and the high avidity antibody were consistent with designation of these cases as having a SIR. Furthermore, the symptoms reported were modified or nonclassic; they were less severe and/or of shorter duration than what is typically observed in a primary infection. In the absence of a known exposure to a measles case patient, the possibility of measles would likely not have been considered.

Laboratory testing of serum samples from asymptomatic or mildly ill contacts of a measles case patient can detect an immunologic response to measles infection [3, 7]. As reported by Helfand et al [3], many persons who were exposed to a measles case patient on a 3-day bus trip had a detectable IgM response, regardless of having received previous vaccination or, for some, having a history of natural measles infection. In addition, the microneutralization titers measured from the exposed persons on the bus in which the measles case patient traveled were significantly higher than those obtained from persons who traveled on the second bus in the caravan. The clinical presentations of the exposed persons with detectable antibodies and/or measles-neutralizing antibodies, however, did not meet the measles clinical case definition [3].

In addition to IgM testing and IgG avidity testing, the serum samples collected from the 2 physicians and the index case patients (and other case patients in the Pennsylvania outbreak) were tested using a plaque reduction neutralization (PRN) assay [7]. The magnitude of the titers obtained from the PRN test from acute-phase serum samples collected from the primary measles case patients (who were identified as having low avidity or having initial IgG-negative test results) did not exceed 10,564 (Tables 1 and 2). In contrast, at comparable intervals after rash (4–9 days), PRN titers from the 2 physicians (as well as from the father in the Pennsylvania outbreak) were 10–168 times higher, reflecting a robust booster response. Concomitant with high

Table 2. Centers for Disease Control and Prevention Laboratory Results for the Index Case Patient and Exposed Physician in Virginia, April 2009

Case description, rash onset date	Vaccine history	Interval, rash onset to serum collection	IgM result	IgG result	PRN titer	Avidity
Index case patient, 14 April	Unknown	S1: 3 days S2: 6 days	S1: Positive S2: Positive	S1: Negative S2: Positive	S1: 341 S2: 1472	Not done
Physician, 29 April	5 MMRs	S1: 9 days S2.1: 13 days S2.2: 13 days	S1: Negative S2: Negative S2: Positive	S1: Positive S2: Positive S2: Positive	S1: 81,916 S2: 129,424 S2: 128,043	High

NOTE. Two serum samples (S2.1, S2.2) were received with collection date of 12 May (13 days after rash onset). The second sample that was received (S2.2) tested positive for immunoglobulin (Ig) M. MMR, measles-mumps-rubella vaccine; PRN, plaque reduction neutralization.

PRN titers in acute phase serum samples, a very strong reaction in the IgG enzyme immunoassay was observed, compared with that obtained from the primary case patients (data not shown). High levels of IgG can interfere with IgM assays because of insufficient removal of the IgG from the serum, giving rise to false-positive results, as well as to false-negative results [8].

Intensified surveillance for rash illnesses in an outbreak setting has frequently presented dilemmas for outbreak control when vaccinated persons with modified illness are identified as suspected case patients. Although detection of IgM is the recommended method for measles confirmation, it is an unreliable marker for measles infection in persons with an SIR. The father of the 2 unvaccinated siblings in the Pennsylvania outbreak (who had a history of having received 1 MMR vaccine dose in childhood) was confirmed as a measles case patient by IgM testing performed on serum samples collected 4 days after rash. However, the IgM was weakly positive, and 3 replicates of the serum run in the same test were IgM indeterminate (data not shown). Similarly, inconsistent results for IgM were obtained from serum samples obtained from the 2 physicians (Tables 1 and 2), possibly attributable to the very high levels of IgG and/or relatively low levels of IgM [8].

The ability to detect IgM among persons with an SIR following an exposure to measles will depend on the magnitude and kinetics of the individual immune response (current and previous), the timing of the serum sample collection, and the sensitivity of the assay [9]. In addition, because of the rapid boosting of IgG, it may not be possible to demonstrate a 4-fold rise in titer among SIR cases. However, when clinical samples are collected in a timely manner, real-time RT-PCR testing may detect virus in persons with modified illness. For example, during a measles outbreak in 2007 [10], 2 vaccinated college students (cases 6 and 7 in [10]) were identified in the course of follow-up investigations of contacts of an acutely ill measles case patient. Both of the students had some rash and fever, but neither of the students presented with cough, coryza, or conjunctivitis. Only 1 of the students had a detectable IgM response; the other case was confirmed by virus detection using RT-PCR [10]. The PRN titers obtained from the students were very high (119,287 and 217,812), and the avidity was also high, consistent with a SIR (cases 2 and 3 in [7]). No spread cases from the 2 students were identified.

Modified measles infections may also resemble other rash illnesses, including rubella, which is a situation that can be confusing, because serum from measles-infected persons can cause interference in rubella IgM assays, producing false-positive results [11]. This occurred during a measles outbreak in 2006, when several persons with a mild rash illness were identified. Because the serum samples were negative for measles IgM (and the case patients had symptoms that were suggestive of rubella), the samples were tested for rubella IgM. Although 3 of 4 serum samples sent to the CDC for confirmatory testing were weakly positive for rubella IgM, the avidity index for 3 of the samples (1 sample was IgG negative) was either intermediate or high and, therefore, was inconsistent with a current rubella infection. In addition, 2 of the case patients with viral samples available for testing had positive results when later tested for measles by real-time RT-PCR, including the 1 sample with results that were negative for rubella IgG, and could not be ruled out by avidity testing (CDC, unpublished data).

As suggested by Chen et al [12], immunity to measles may not be absolute but, depending on the levels of preexisting antibody, reflect a continuum of clinical illness. In addition to the level of preexisting antibody, the intensity of exposure (ie, the dose of virus received) is an important risk factor for breakthrough infection and one that could not be quantified in studies that retrospectively determine the protective titer against symptomatic infection. The absence of circulating virus and the periodic boosting that may have provided additional protection from infection may alter the paradigm of lifelong (asymptomatic) immunity after vaccination or disease. As pointed out by Helfand et al [3], the rate of nonclassic infection is likely to increase as measles control improves in a population, because boosting from exposure to wild-type measles virus will be rare. This may also occur among older persons who have a history of natural disease, although prior disease is difficult to document. One such case occurred in 2008 in a 55-year-old man who was born outside of the United States and who claimed to have had measles in childhood. He had traveled to his home country and was exposed to children who had measles. Initially, the case was not strongly suspicious for measles because of the nonclassic presentation and disease progression. However, the case was confirmed as measles by IgM detection and by an RT-PCR result positive for measles. The avidity was high, and the PRN titer was >160,000 (CDC, unpublished data).

Despite ample opportunities for transmission of virus, the 2 physicians in this report did not infect any patients, including many patients who were unvaccinated. The determination of whether a vaccinated individual who is exposed to measles (who develops symptoms that are suggestive of measles) represents a case patient and therefore a potential source of infection for others often hinges on a laboratory test result as the deciding factor. Reliance on the absence of IgM to rule out a case may be unjustified under these circumstances. In the future, more of these difficult cases will be confirmed by detection of measles RNA. Additional studies are needed to determine whether persons with modified measles can infect others. The absence or reduced severity of respiratory symptoms, particularly a cough, may result in lower infectivity relative to a classic measles infection [13, 14]. The ability to discern measles infection in persons with an SIR, however, is valuable for surveillance purposes in support of measles eradication efforts.

The absence of spread cases from the 2 physicians in this report suggests that there may be limited replication of virus in

vaccinated persons with mild or short-lived symptoms. Although this report may raise questions regarding case classification for persons with a mild rash illness detected during a measles outbreak (eg, should positive laboratory results trump the clinical case definition?), the limitations of standard methods for confirmation (ie, IgM detection) in cases of modified or nonclassic measles may be better appreciated. The collection of viral samples in addition to serum samples is strongly recommended. An investigation into the timing of the rise and fall of neutralization titers in previously vaccinated persons with modified measles is underway.

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