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Measles Outbreak Among Previously Immunized Healthcare Workers, the Netherlands, 2014

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Background. We investigated a measles outbreak among healthcare workers (HCWs) by assessing laboratory characteristics, measles vaccine effectiveness, and serological correlates for protection.

Methods. Cases were laboratory-confirmed measles in HCWs from hospital X during weeks 12–20 of 2014. We assessed cases' severity and infectiousness by using a questionnaire. We tested cases' sera for measles immunoglobulin M, immunoglobulin G, avidity, and plaque reduction neutralization (PRN). Throat swabs and oral fluid samples were tested by quantitative polymerase chain reaction. We calculated attack rates (ARs) by vaccination status and estimated measles vaccine effectiveness as $1 - [AR_{vaccinated}/AR_{unvaccinated}]$.

Results. Eight HCWs were notified as measles cases; 6 were vaccinated with measles vaccine twice, 1 was vaccinated once, and 1 was unvaccinated. All 6 twice-vaccinated cases had high avidity and PRN titers. None reported severe measles or onward transmission. Two of 4 investigated twice-vaccinated cases had pre-illness PRN titers of >120 mIU/mL. Among 106 potentially exposed HCWs, the estimated effectiveness of 2 doses of measles vaccine was 52% (95% confidence interval [CI], −207%–93%).

Conclusions. Measles occurred in 6 twice-vaccinated HCWs, despite 2 having adequate pre-exposure neutralizing antibodies. None of the twice-vaccinated cases had severe measles, and none had onward transmission, consistent with laboratory findings suggesting a secondary immune response. Improving 2-dose MMR coverage among HCWs would have likely reduced the size of this outbreak.

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

Measles vaccines, in routine use since the early 1960s, have been very effective in decreasing the incidence of measles and associated mortality [1]. At sufficient coverage, a 2-dose measles vaccination program can eliminate measles from a country (eg, Finland) or region (the Americas) [2, 3]. This success can be attributed to the excellent safety, immunogenicity, and effectiveness profile of currently licensed measles vaccines [4].

Owing to insufficient measles vaccine coverage, however, measles is still endemic in many parts of the world, including several European countries [5]. The measles immune status of healthcare workers (HCWs) is of particular concern in measles control, since they are at increased risk of exposure to measles cases. Also, when infected, HCWs can expose patients, many of whom may be particularly vulnerable to measles and its complications.

In 1976, the Dutch National Immunization Program introduced a single dose of monovalent measles vaccine for 14-month-old children. In 1987, a 2-dose measles, mumps, rubella (MMR) vaccination schedule was introduced for children aged 14 months and 9 years. For 3 years following this introduction, 4-year-old children were also offered a second dose of MMR. The 2-dose MMR vaccine coverage in the Netherlands has been >90% for many years [6]. Despite this, the epidemiologic characteristics of measles in the Netherlands are unusual, reflecting the presence of a socially and geographically clustered subgroup of the population that, on the basis of orthodox Protestant beliefs, refrains from vaccination [7]. Between May 2013 and February 2014, a large measles outbreak occurred among this population [8]. In June 2013, the National Institute for Public Health and the Environment (RIVM) published advice about how to ascertain and ensure measles immunity in HCW based on national seroprevalence studies [9, 10].

The effectiveness of 2 doses of measles vaccines, with age-appropriate receipt of doses, is reported to be 97% [1]. However, waning of vaccine-induced measles immunity is of concern. The extent of it is not well known in twice-vaccinated adults whose immunity is not boosted by exposure to measles. Seroprevalence studies can only provide part of the answers, as antibody concentrations do not necessarily correlate with protection and do not take cellular immunity into account [11].

Laboratory testing of suspected measles in vaccinated individuals can not only confirm measles virus infection, but also aid the

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assessment of whether the infection is due to primary vaccine failure or secondary vaccine failure (SVF). Primary vaccine failure can be identified by low-avidity measles immunoglobulin G (IgG) antibodies following infection [12]. SVF is more difficult to prove, as it requires evidence of an adequate immune response following primary vaccination, which is usually lacking. Sowers et al therefore recently proposed to classify measles cases with a convalescent measles virus neutralizing IgG antibody concentration of ≥40 000 mIU/mL as "reinfections" [13]. However, other indicators, such as the presence of preexisting antibodies before infection and high antibody titers of high avidity shortly after infection can be considered evidence of SVF [14].

During March–April 2014, an outbreak of measles affecting twice-vaccinated HCWs occurred in a hospital in the western Netherlands (hospital X) subsequent to the admission of 2 patients with measles in week 12 of 2014. We investigated this outbreak to assess the reasons for and implications of vaccine failure. We characterized the clinical picture, immune responses, and infectiousness of measles in vaccinated HCWs, to inform guidelines for measles prevention in this group. Interestingly, we were able to recall pre-exposure occupational blood samples for some of the HCWs with measles, which allowed us to study correlates for protection. By investigating a cohort of potentially exposed HCWs, we also estimated the effectiveness of measles vaccine.

METHODS

Case Definition

Cases in our investigation were laboratory-confirmed, clinical measles virus infections in HCWs working at hospital X between weeks 12 and 20 of 2014. Clinical measles was defined by fever, maculopapular rash, and at least 1 of the following symptoms: cough, coryza, and conjunctivitis, consistent with European Union case definitions [15].

Case Investigation

Early in the outbreak, HCWs were alerted that measles cases had occurred in the hospital. Cases were ascertained by routine healthcare examination and notified by clinicians and laboratories to Municipal Health Services (MHSs). In addition to case information routinely collected in the notification system, we collected additional information among HCWs with measles, including the severity of measles virus infection, measles exposure, occurrence of secondary cases among contacts, methods of transportation during the infectious period, and recent travel abroad. The vaccination status of cases was ascertained by the MHSs in the national vaccination register and/or patient-held booklets. The chain of transmission among patients and HCWs was deducted from epidemiological and molecular data.

Laboratory Testing

We report the results of laboratory testing performed by the Center for Infectious Disease Research, Diagnostics, and Screening at the RIVM and Leiden University Medical Center. Serum samples obtained after onset of symptoms were tested for measles virus–specific immunoglobulin G (IgG) by a commercial serological assay (CLIA Liaison; Diasorin, Saluggia, Italy). The presence of measles virus–specific immunoglobulin M (IgM) in serum was determined by a capture enzyme immunoassay (MicroImmune, Hounslow, United Kingdom). Avidity of measles virus–specific IgG antibody was tested by a commercially available IgG enzyme immunoassay (EIA), using an avidity index qualification recommended by the manufacturer (EuroImmun, Luebeck, Germany). An avidity index of ≥60% was considered a serum sample with high-avidity antibodies, while an avidity index of ≤40% was considered indicative of low-avidity antibodies. Measles virus–neutralizing antibody titers were assessed with a plaque reduction neutralization (PRN) test performed according to a previously standardized procedure against the WHO Third International Standard for measles virus antibody, containing 3000 mIU/mL (NIBSC code 97/648) [11, 16]. Measles virus RNA extracted from oral fluid and/or nasopharyngeal aspirates was tested by polymerase chain reaction (PCR), whereby positive PCR results were quantitatively expressed as the average cycle threshold (CT) of 2 PCR tests and corrected against the CT value of the positive control in each PCR assay. The samples were then genotyped using primers amplifying a 450-nucleotide fragment of the measles virus nucleocapsid gene.

Pre-exposure serum samples from cases were retrieved among stored samples at hospital X collected for occupational health purposes, including testing of immunity against hepatitis B virus. Pre-exposure serum samples were tested for measles virus neutralizing antibody titers by PRN testing as described above. Tests were performed at least in duplicate, after which a geometric mean titer was calculated. We assumed a PRN titer of at least 120 mIU/mL as protective [16, 17].

Vaccine Effectiveness (VE)

We defined potentially exposed HCWs at hospital X as those having worked in departments where index patients with measles were infectious (ie, 4 days before or after rash onset). Potentially exposed HCWs were identified by examining work rosters of these departments and admission information for measles cases. The vaccination status of all potentially exposed HCWs was retrieved from occupational health records. We calculated attack rates (ARs) by vaccination status and estimated VE against measles as $1 - [AR_{vaccinated}/AR_{unvaccinated}]$, with corresponding 95% confidence intervals (CIs) also determined. Those born before 1965 were considered immune to measles because of past infection and were excluded from the VE estimation.

RESULTS

Index Cases

Two index patients with measles were admitted to hospital X with suspected pneumonia/influenza on the same day during

week 12 of 2014 and were hospitalized for 3 days. The vaccination status of index patient 1 could not be confirmed, as they could not produce their vaccination booklet and were not listed on the national vaccination register, while index patient 2 was confirmed as unvaccinated. Within 24 hours following admission, both index patients were suspected of having measles and were cared for in isolation. Genotyping results revealed that index patient 1 was infected with genotype B3 measles virus (strain MVs/Den.Haag/12.14; WHO Measles Nucleotide Surveillance [MEANS] identifier 47791; GenBank accession no. KJ690783), with a sequence indistinguishable from that of strain MVs/Tonbridge.GBR/5.14 [B3] (GenBank accession no. KJ650198). This strain has been identified in several concurrent outbreaks in the Netherlands and the United Kingdom [18]. Index patient 2 was infected with the same Tonbridge virus but with a specific mutation (Tonbridge C339 T variant; strain MVs/Den Haag.NLD/15.14 [B3] > C339T; WHO/MEANS identifier 47814; GenBank accession no. KJ690847). This mutation allowed the deduction of 2 separate chains of transmission among HCWs in hospital X (Figure 1).

Measles in HCWs

Unvaccinated HCWs who did not report a history of measles and were working in departments with patients who had measles were excluded from work for 21 days. During weeks 14 and 15 of 2014, 5 HCWs who had contact with the 2 index patients developed measles. Three of these HCWs were twice vaccinated, 1 was once vaccinated, and 1 (HCW4) was unvaccinated. The unvaccinated HCW, who had not been recognized earlier as being unvaccinated and exposed to measles, presented twice to the emergency department of hospital X with atypical symptoms. Upon the second presentation in week 15, HCW4 was

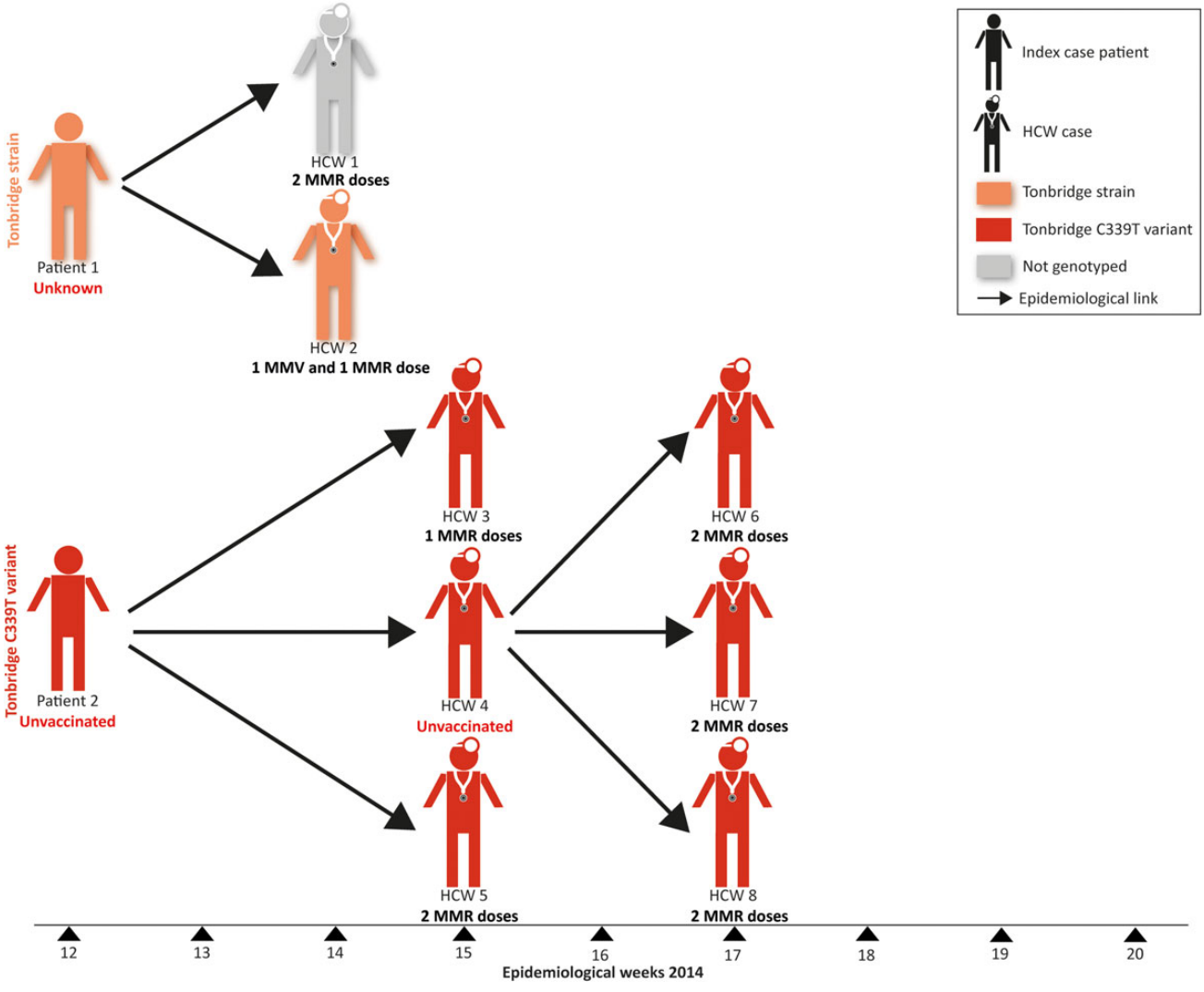

Figure 1. Measles cases in 2 index patients and 8 healthcare workers (HCWs), by week of admission and onset, respectively, hospital X, the Netherlands, weeks 12–20, 2014. Abbreviations: MMR, measles, mumps, rubella vaccine; MMV, monovalent measles vaccine.

hospitalized for further observation. Two days following admission, HCW4 developed rash and received a diagnosis of measles. In week 17, 3 twice-vaccinated HCWs who had been in contact with HCW4 received a diagnosis of measles. Of the 8 cases in HCWs, 1 had measles virus strain MVs/Tonbridge.GBR/5.14 [B3], 1 (HCW1) had insufficient sample for genotyping but had an epidemiologic link with index patient 1, while 6 were infected with measles virus containing the C339T mutation (ie, the Tonbridge C339T variant; Figure 1). The measles vaccine status for all twice-vaccinated cases was further verified in patient-held vaccination booklets or the national vaccine register. For the once-vaccinated case (HCW3), measles vaccination information was obtained from the patient, since no records were available.

The median age of the 8 HCWs with measles was 27 years (range, 25–43 years); 4 were women. The diagnosis in 8 HCWs with measles was based on positive PCR results, and all 5 cases for whom a convalescent serum sample was available had a ≥4-fold rise in PRN titers (Table 1). Symptoms from all 8 cases matched the clinical case definition for measles except those for HCW6, who had a rash and fever but no cough, conjunctivitis, or coryza. All 6 twice-vaccinated cases had high pre-illness and/or per-illness avidity measles IgG antibody, and all 5 with a per-illness serum specimen available tested negative for IgM (Tables 1 and 2). However, the per-illness sera were all collected at the day of rash onset or 1 day later, which is not a sensitive time point for detecting IgM antibodies. Convalescent PRN titers for 4 of 6 twice-vaccinated cases were >40 000 mIU/mL. All 4 twice-vaccinated cases with information on the course of disease reported mild-to-moderately severe symptoms; none were hospitalized. However, 1 twice-vaccinated case developed adult-onset Still disease 4 weeks following measles virus infection. The once-vaccinated case had fairly severe measles, with a chest infection and mild diarrhea, but did not require hospitalization. The unvaccinated case had severe measles requiring hospitalization for pneumonia, pleurisy, oliguria, and hypotension, with abnormal findings of liver biochemical tests.

Quantitative PCR results suggested a relation between the vaccination history and the viral load: the unvaccinated case had the highest viral load (lowest CT value), the once-vaccinated case had an intermediate value, whereas the 6 twice-vaccinated cases had CT values indicating relatively low viral loads (Table 1). Although this is a molecular estimate obtained at only 1 time point and dependent on the specimen quality, these results are consistent with data on infectiousness. None of the once- or twice-vaccinated cases were known to have infected others, even though, during their infectious period, 2 cases travelled abroad, 3 cases used public transportation, and 3 cases worked at the hospital. The unvaccinated HCW travelled abroad and infected 2 individuals outside of the hospital setting, in addition to the 3 HCWs reported above (Figure 1).

Table 1. Laboratory Results and Clinical and Epidemiological Characterization of Measles Cases in 8 Healthcare Workers (HCWs), Hospital X, The Netherlands, March–April 2014

Case	Birth Year; Age, y	Measles Vaccine Doses Received, No.	Week of Rash Onset	Serum Sample 1			Serum Sample 2			Avidity Index, %	CT Value[b]	Measles Severity	Infected Others	Hospitalized
				Days From Rash to Collection	IgM Finding	PRN Titer,[a] mIU/mL	Days From Rash to Collection	IgM Finding	PRN Titer,[a] mIU/mL					
HCW1	1987; 26	2	14	1	Neg	3670	84	NA	66 020	87 (high)	37.5[c]	Mild	No	No
HCW2	1982; 31	2	14	1	Neg	7970	NA	NA	NA	88 (high)	26.6	NA	No	No
HCW3	1985; 29	1	15	0	Pos	1080	73	NA	7750	36 (low)	23.3	Severe	No	No
HCW4	1970; 43	0	15	−1	Neg	50	80	NA	19 110	NA	17.2[c]	Severe	Yes	Yes
HCW5	1988; 25	2	15	NA	NA	NA	NA	NA	NA	NA	29.4	NA	No	No
HCW6	1987; 26	2	17	0	Neg	6940	26	NA	200 640	89 (high)	28.1	Mild-moderate	No	No
HCW7	1987; 26	2	17	0	Neg	5970	72	NA	107 150	84 (high)	26.5	Mild	No	No
HCW8	1990; 23	2	17	2	Neg	46 100	NA	NA	NA	95 (high)	33.7	NA	No	No

Abbreviations: IgM, immunoglobulin; NA, not available; Neg, negative; Pos, positive.

[a] Data denote measles virus neutralizing antibodies determined by the plaque-reduction neutralization (PRN) test.

[b] Cycle threshold (CT) values were obtained from a quantitative polymerase chain reaction analysis of throat swabs (for HCW1, HCW2, and HCW4–HCW8) or saliva (for HCW3).

[c] Results are from Leiden University Medical Center.

Table 2. Results of Serological Tests Performed Before Illness Onset Among 5 Healthcare Workers (HCWs) With Measles

Case	Year of Birth, Age	Measles Vaccine Doses Received, No.	Serum Sample Collection Date	Time of Rash Onset	Time Between Serum Sampling and Onset of Rash	PRN Test GMT,[a] mIU/mL	Avidity Index, %
HCW1	1987, 26 y	2	23 Jul 2013	Week 14, 2014	8.3 mo	115	72 (high)
HCW4	1970, 43 y	0	19 Sep 2013	Week 15, 2014	6.6 mo	51	NA
HCW5	1988, 25 y	2	12 Dec 2013	Week 15, 2014	3.9 mo	146	81 (high)
HCW6	1987, 26 y	2	16 Apr 2006	Week 17, 2014	8 y	525	83 (high)
HCW7	1987, 26 y	2	23 May 2006	Week 17, 2014	8 y	85	64 (high)

Abbreviation: NA, not available.

[a] Data denote geometric mean titer (GMT) of measles virus neutralizing antibodies determined by the plaque-reduction neutralization (PRN) test.

Estimated Vaccine Effectiveness (VE)

Of 106 potentially exposed HCWs at hospital X, 83 were born after 1965 and included in the VE estimate. Of these 83 HCWs, 4 were unvaccinated, and 8 and 50 were once and twice vaccinated, respectively. Two HCWs were thrice vaccinated. For 19 potentially exposed HCWs, the vaccination status was unknown. The 4 unvaccinated HCWs were older than the twice-vaccinated HCWs (median age, 36 years [range, 26–43] vs 29 years [range, 24–40 years]; $P = .05$)). Six cases occurred among 50 twice-vaccinated HCWs (AR 12%). One case occurred among 8 once-vaccinated HCWs (AR 13%) and 1 case occurred among 4 unvaccinated HCWs (AR 25%). The three potentially exposed unvaccinated HCWs who did not develop measles were found to have no detectable IgG antibodies. The estimated VE for 2 doses of measles vaccine was 52% (95% CI, −207%–93%). When comparing vaccination schedules among twice-vaccinated HCWs born in 1978–1982 (who received monovalent measles vaccine plus MMR), the AR was 8% (1 of 13), whereas among those born in 1986–1990 (who received 2 doses of MMR), the AR was 23% (5 of 22; $P = .3$).

Preillness Serological Results

For 5 of 8 cases, preillness sera were available. Three of these specimens were obtained <1 year before onset of measles, whereas for 2 others, sampling took place several years earlier. The unvaccinated cases' level of neutralizing antibodies before illness was low (51 mIU/mL), which is below the estimated cutoff for clinical protection (120 mIU/mL [17]). All 4 twice-vaccinated cases with preillness serological results had measurable measles virus–specific antibodies, consistent with the presence of high-avidity antibodies in their preillness and per-illness sera (Table 2). Interestingly, 2 of 4 twice-vaccinated cases with preillness sera had relatively high PRN titers of 146 and 524 mIU/mL, with samples collected 3.9 months and 8 years before illness, respectively. When assuming a mean decline of measles IgG levels in the steady-state period of 7.1% per year, both preillness PRN titers were well above 120 mIU/mL at acquisition of infection [19].

DISCUSSION

We presented results of a measles outbreak investigation in a hospital that included 8 HCWs with measles, of whom 6 were twice vaccinated with measles vaccine. Quantitative virological and serological results of the twice-vaccinated cases were available at multiple time points before and subsequent to measles virus infection, allowing detailed characterization of vaccine failure. All 6 twice-vaccinated HCWs had high-avidity measles IgG antibodies, indicative of a secondary immune response to natural measles virus infection. Negative results of IgM tests and high convalescent IgG titers were consistent with this. Four of 6 cases could be classified as SVF, based on the documented evidence of vaccination and the presence of measurable measles virus–specific PRN titers before infection. For the remaining 2, unfortunately no pre-exposure sera were available. The secondary immune response to natural measles virus infection in twice-vaccinated cases is instrumental in the rapid clearance of the virus, thereby reducing virulence, clinical severity, and contagiousness among patients. Indeed, none of our twice-vaccinated cases infected others, consistent with their low viral loads, and none had severe measles. The occurrence of measles in twice-vaccinated individuals is nevertheless an important concern for measles elimination efforts, which rely on a 2-dose measles vaccination schedule [4].

Outbreaks of measles among twice-vaccinated individuals have been reported previously, albeit infrequently [20, 21]. Rosen et al described an outbreak of 5 measles cases in persons with prior immunity, whereby the index case was twice vaccinated [20]. The authors state that the index case had evidence of SVF. This conclusion was only based on the high-avidity antibodies detected in the serum samples after onset of rash. However, this case showed very low antibody concentrations (81 mIU/mL) and rather poor development of virus neutralizing antibodies (402 mIU/mL), which contrasts with the high levels in other cases of SVF and even with levels found in unvaccinated individuals with acute measles [13, 22]. Thus, it is more likely that this index case had primary vaccine failure, and avidity testing alone should be interpreted with caution here.

An interesting aspect of our investigation was the availability of pre-exposure sera for 4 vaccinated cases. Two of these, both with symptoms matching the clinical case definition for measles and positive PCR results, had pre-exposure PRN titers greater than the currently assumed correlate for protection against

symptomatic measles of 120 mIU/mL [16, 17]. This is of some concern, since it questions the validity of assessments of the population's immunity, which are usually based on this correlate [10, 23]. In previous studies, it was shown that antibody levels of >1000 mIU/mL correlate with full protection from infection. Persons with antibody titers of 120–1000 mIU/mL were shown to be susceptible to infection, and while many of these also showed symptoms of illness, none met the clinical case description for measles [17, 24].

The PRN titers were measured by assessing neutralization of the vaccine strain (genotype A). Of note, PRN testing is known to suffer from variability in results. Our findings nevertheless raise the question of whether particular wild-type strains of measles virus may be neutralized less efficiently. There is currently no evidence of wild-type strains that can fully resist neutralization by antibodies that were generated by the measles vaccine strain, as both constitute conserved neutralizing epitopes of the measles virus H protein that are required for receptor binding [25, 26]. However, some resistance to antibody-mediated neutralization has been reported for wild-type strains of measles that were related to particular mutations in their H, F, and M proteins affecting other epitopes involved in virus neutralization [27–29]. Also, it may be that differences in the capacity to neutralize different genotypes only become apparent at relatively low levels of vaccine-induced IgG, particularly when there is intense exposure, such as reported here for the measles virus B3 strain. It is striking that, during the large outbreak of infection due to measles virus strain D8 in the Netherlands during 2013–2014, 181 patients with measles were admitted to the hospital, and only 2 cases of measles in vaccinated hospital HCWs were reported (T. Woudenberg, personal communication). This may indicate differences between the D8 and B3 strains in terms of pathogenicity or capacity to overcome vaccine-induced immunity. B3 strains are now globally the most common genotype found [5]. Further research into the correlates of serological protection against distinct wild-type strains is required, especially in the context of low levels of vaccine-acquired antibodies.

By defining a cohort of potentially exposed HCWs in the hospital, we estimated VE for 2 doses of MMR. The estimated VE (52%), albeit imprecise because of low numbers of unvaccinated HCWs in the cohort, was much lower than the 94% found in a systematic review [30]. The AR among once-vaccinated HCWs was unexpectedly high (13%). Unvaccinated HCWs were older than vaccinated HCWs, but all were found to be susceptible when screened for IgG. This is consistent with national seroprevalence data, which do not show evidence of natural immunity in birth cohorts born after 1976, the year of introduction of measles vaccination [10]. The exposure to measles is unlikely to be related to vaccination history. However, by chance, exposure among unvaccinated HCWs in our cohort may have been less frequent, artificially reducing the VE. A more precise definition of the exposed cohort might have improved the validity of our VE estimate. However, in a hospital setting, it is difficult to ascertain which HCWs attended to which patient.

A high intensity of exposure coupled with possibly a more pathogenic strain, as discussed above, could have contributed to this outbreak of measles among twice-vaccinated HCWs. Another explanation may be the relatively long period since individuals in our cohort received their most recent MMR dose, allowing for increased waning of immunity. If waning was the only explanatory factor, however, we would have expected a relatively higher attack rate in older HCWs. Yet, there were relatively few cases among the first birth cohorts having been offered monovalent measles and MMR vaccine (1978–1982), compared with the later birth cohort, which is offered 2 doses of MMR (since 1987). We did not find a difference in effectiveness between these schedules, but this comparison lacked power owing to the low number of cases.

Our outbreak investigation encountered some limitations. Our assessment of correlates for protection was restricted to serum specimens obtained from vaccinated HCWs before measles onset, which we were able to retrieve from the hospital because serum samples had been collected from HCWs earlier for immunity screening purposes. We also encountered difficulties following up all HCWs with measles, owing to their schedules, and some questionnaire responses may be prone to recall bias. Furthermore, we may have missed mild measles cases among contacts of cases, since there was no systematic follow-up of contacts.

Results of long-term follow-up studies of measles virus immunity among twice-vaccinated cohorts who have not been exposed to wild-type measles virus show considerable waning of immunity, raising the question whether a booster MMR vaccination is necessary [19, 31]. Recent results by Fiebelkorn et al, however, suggest that administering a third dose of MMR to twice-vaccinated individuals has a limited long-term effect on the height and quality of the immune status [32]. Larger studies to further explore the effects of MMR-3 are urgently needed. The timely diagnosis of measles, with subsequent immediate isolation procedures, and the furloughing of HCWs potentially exposed to measles who develop symptoms remain key interventions to limit the spread of measles in hospitals. Testing pre-exposure sera for antibody levels and postexposure sera for the dynamics of the antibody response is important to characterize vaccine failure in HCWs with measles. However, the first priority remains improving the 2-dose MMR vaccination status among HCWs. Adhering to this would have likely reduced the size and severity of the outbreak we reported. Enhanced surveillance and detailed laboratory characterization of measles vaccine failures will be crucial to establish the long-term effectiveness of measles vaccination programs.

Notes

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