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Measles Antibody: Reevaluation of Protective Titers

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A school blood drive before a measles outbreak permitted correlation of preexposure measles antibody titers with clinical protection using the plaque reduction neutralization (PRN) test and an EIA. Of 9 donors with detectable preexposure PRN titer ≤120, 8 met the clinical criteria for measles (7 seroconfirmed) compared with none of 71 with preexposure PRN titers >120 ($P < .0001$). Seven of 11 donors with preexposure PRN titers of 216–874 had a ≥4-fold rise in antibody titer (mean, 43-fold) compared with none of 7 with a preexposure PRN titer ≥1052 ($P < .02$). Of 37 noncases with preexposure PRN titer <1052, 26 (70%) reported one or more symptoms compared with 11 (31%) of 35 donors with preexposure PRN titers ≥1052 ($P < .002$). By EIA, no case had detectable preexposure antibody; the preexposure geometric mean titer of asymptomatic donors (220) was not significantly higher than that of symptomatic donors who did not meet the clinical criteria for measles (153) ($P = .10$). The study suggests that PRN titers ≤120 were not protective against measles disease and illness without rash due to measles may occur in persons with PRN titers above this level.

Infection by natural measles virus is believed to induce lifelong immunity. This belief is based on the observations that during an outbreak on the isolated Faroe Islands, the only residents who did not acquire measles were those who had had measles 65 years earlier [1] and that reports of second attacks of measles are rare [2]. It has generally been assumed that infection with live-attenuated or further-attenuated measles vaccine viruses also results in long-term and probably lifelong immunity [3].

The presence of measles antibodies has been used as an indicator of previous infection by natural or vaccine virus, presumably resulting in protection. Measles antibodies have been measured by testing end-point serial dilutions of serum for hemagglutination-inhibition (HI) or virus neutralization using cytopathic effect induced by highly adapted measles virus [4]. The presence of these antibodies has been correlated with clinical protection and their absence considered indicative of susceptibility [5, 6].

Newer serologic techniques, such as EIA [7, 8] or the highly sensitive plaque reduction neutralization test (PRN) [9], have detected antibody in serum found to lack antibodies by traditional assays such as HI [3, 6, 10, 11]. While studies suggest that low titers of antibodies detected by these new assays are specific for measles [9, 10, 12–14], it is not known whether persons with these low levels of antibody are protected against disease.

During an outbreak of measles at Boston University (BU) in 1985, we had access to blood samples from both cases and noncases obtained before presumed exposure. This offered an unusual opportunity to correlate preexposure antibody levels determined by PRN and EIA with clinical protection.

Methods

Background

A measles outbreak with 112 reported cases occurred in the Boston metropolitan area in early 1985; 100 occurred in BU students between 28 January and 20 March 1985 (figure 1). Forty cases were in residents of Warren Towers, a large three-tower dormitory complex (towers A, B, and C, with 512, 498, and 498 residents, respectively). The American Red Cross had held a blood drive at BU from 31 January to 7 February 1985 (6 and 7 February at Warren Towers). This allowed us to obtain preexposure blood specimens from residents who were cases and noncases.

Case Definition

A case of measles was defined as an illness characterized by generalized maculopapular rash of ≥3 days duration; fever ≥38.3°C, if measured, and at least one of the following: cough, coryza, or conjunctivitis [15]. A noncase was defined as an illness that did not meet these criteria or no illness. Routine serologic confirmation consisted

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This paper is dedicated to the memory of Dr. Stephen R. Preblud, whose contributions to the field of vaccines will be sorely missed.

Written informed consent was obtained from study participants; the study was approved by the Boston University Charles River Campus Institutional Review Board.

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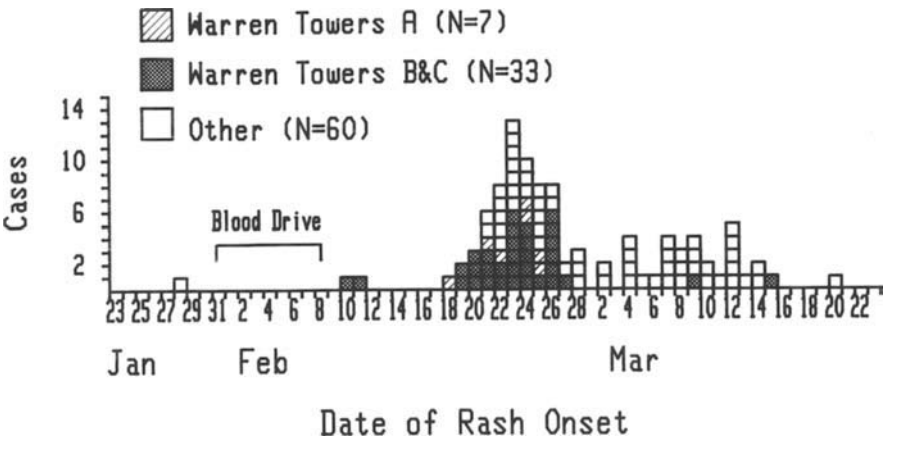

Figure 1. Reported measles cases by date of rash onset, Boston University, 28 January–20 March 1985.

of the demonstration of a fourfold or greater rise in complement fixation or HI antibody titer between acute- and convalescent-phase serum specimens and was done by the Massachusetts Department of Public Health State Laboratory Institute; it was confirmed by PRN in our laboratory.

Study Population

The attack rates in Warren Towers B and C (2.4% and 4.4%, respectively) were the highest observed of all dormitories at BU during the outbreak. Residents of these towers who participated in the blood drive were eligible for the study. Three cases living in other BU dormitories from whom preexposure blood specimens were available were also included. One seroconfirmed case was excluded because only 3 days had elapsed between blood donation and rash onset. The preillness PRN titer of 1:28 in this case may, therefore, have represented an incipient antibody response rather than antibody acquired before this outbreak.

Serologic Tests

Preexposure blood samples, contained in the tubing of the blood donation phlebotomy bag, referred to as "pigtail" specimens, were obtained from the American Red Cross. Sera from the pigtails were diluted with an equal volume of calcium- and magnesium-free Eagle's minimal essential medium (Whittaker MA Bioproducts, Walkersville, MD) to provide adequate volume while preventing clot formation. Postexposure blood samples were obtained during 25 March–19 May from participants not vaccinated during the outbreak. All specimens were stored at 4–6°C. Specimens were coded and tested blindly by PRN, and when quantity was sufficient, by EIA for IgG and IgM antibody.

PRN Test. The PRN test was done as previously described [9]. Sera were heated at 56°C for 30 min to inactivate complement. Two- or fourfold serial dilutions of serum starting at 1:8 (pigtail sera at 1:16) were plated with a low-passage wild strain of Edmonston measles virus and incubated in duplicate onto Vero cell monolayer cultures in 16-mm plastic wells. The PRN titer was defined as the serum dilution that would reduce the number of plaques by 50%. Each PRN titer represents the reciprocal geometric mean titer (GMT) of two assays (the titers for each serum differed by less than twofold). For IgM determination, sera were fractionated on sucrose gradients. Only fractions free of IgG as determined by single radial immunodiffusion assay were used for IgM antibody determination by PRN. The whole serum IgM titer was calculated from the fractional IgM titer, assuming an average serum IgM concentration of 990 μg/ml [16]. An aliquot of reference serum was titered in parallel with each PRN test. Only tests in which the reference titer varied by $\leq$20% from the established mean were considered acceptable.

EIA. The EIA was done as previously described [17] but with antigen prepared from monolayers of Vero cells infected with the Philadelphia 26 strain of measles virus. All sera were tested in duplicate at 1:50 dilution. After the appropriate incubations, the net absorbance of each serum was determined by subtracting the uninfected control well values from the viral well values. A calibration procedure based on the Measelisa assay (Whittaker) was established with calibrated sera in each test plate and an end-point dilution (expressed in reciprocal titer) calculated for each sample by standard linear regression analysis.

For the EIA IgM assay, antigen-coated microtitration plates were prepared as for the IgG assay. Sera were diluted 1:50 and adsorbed with sufficient staphylococcal protein A to remove most IgG and eliminate false positives caused by rheumatoid factor. The test was done as for IgG but with an enzyme-conjugated goat anti-human IgM serum. A similar calibration procedure with IgM-positive and -negative sera was used to express the results as an end-point dilution titer. Seronegative results were recorded as <50. For calculation of EIA GMT, negative specimens were assigned a reciprocal titer of 25.

Clinical and Vaccine History

Information from participants concerning symptoms experienced during the outbreak was obtained by self-administered questionnaires completed during the week of 25 March. Signs and symptoms elicited on the questionnaire included the following: subjective evaluation of fever (temperature not taken), documented fever $\geq$38.3°C, cough, runny nose, red watery eyes or light sensitivity, sore throat, headache, and diarrhea. Only symptoms of >1 day's duration that occurred before vaccination during the outbreak were to be recorded.

Table 1. Cases and noncases reporting symptoms by preexposure plaque reduction neutralization (PRN) titer.

Subject(s)	PRN titer: Pre-exposure	PRN titer: Post-exposure	IgM	Fever, days*	Maximum temperature, °C†	Rash, days*	Cough	Rhinorrhea	Photophobia	Sore throat	Headache	Diarrhea	Age of vaccination‡
Cases													
1	<16	35,363	287	3	39.3	6	x	x	x	x	x	x	12 mo
2	38	17,723	<160	4	40.0	6	x	x	x	x	x		§
3	80	39,268	102	3	38.8	6	x	x	x	x		x	(10 mo)
4	86	NA	NA	x	40.0	x	x		x	x	x		28 mo
5	86	101,339	<48	4	39.6	3	x		x		x		10 mo
6	98	44,661	662	3	≥38.3	3			x	x	x		(11 mo, 11 y)
7	118	14,157	509	3	38.4	3	x	x	x	x	x	x	6 y, 12 y
8	120	13,638	90	2	≥38.3	3			x				8 mo, 10 y
Total, %				100		100	75	50	100	75	75	38	
Noncases, %‖													
n = 37	<1052			35¶		5**	32	27	8	32	27††	16	
n = 35	≥1052			6		3**	17	26	9	17	6	9	
Total, %				37		4	25	26	8	25	17	13	

NOTE. Symptoms lasted >1 day and occurred before vaccination during the outbreak. x indicates symptom present. NA = not available.
* When known.
† Highest recorded in student health clinic chart except for cases 6 and 8, which were based on student history.
‡ Provider-verified unless in parentheses.
§ No history of vaccination; unverified history of disease at age 9 y.
‖ Except for titers.
¶ Noncases with PRN titers <1052 vs. those with titers ≥1052, including undocumented fevers; P = .002, Fisher's exact test.
** Noncases with rash did not meet clinical case definition.
†† P = .02, Fisher's exact test.

Clinical symptoms of ill students who visited the student health clinic were verified from the clinic records. Information on previous vaccine history was obtained from the student, parent, BU student health record, and original vaccine provider (when possible).

Results

Of 996 Warren Towers B and C residents, 139 (14%) participated in the blood drive; 90 (63%) agreed to participate in the study. Preexposure blood samples for testing were located by the American Red Cross for 80 participants (37 tower B, 40 tower C, and 3 nonresident cases).

Cases. Eight donors (10%) who had an illness meeting the clinical case definition for measles were identified. Seven were seroconfirmed (serum was not obtained from one); five had detectable IgM antibody by PRN (table 1). The clinical manifestations of the cases were all consistent with classic measles illnesses with fever, confluent maculopapular rash, and cough, coryza, or conjunctivitis.

Preexposure antibody titers: comparison of cases and noncases. The interval between blood donation and onset of rash was 12–36 days (median, 16). Only one of the eight cases had undetectable preexposure PRN antibody (≤16); the other seven had titers of 38–120. In comparison, participants who did not have clinical measles had PRN antibody titers ranging from 56 to 20,658; all except one were >120. The GMT of cases was 63 compared with 1157 for noncases (P < .0001, t test). The highest preexposure titer among cases was 120; using this cutoff, 8 of 9 donors with a PRN titer ≤120 met the Centers for Disease Control case definition for measles compared with 0 of 71 with a PRN titer >120 (P < .0001, Fisher's exact test).

By EIA, no case had detectable antibody in the pigtail specimen, whereas the GMT for noncases was 183 (range, 0–1390; P < .0001, t test). Three of the 72 noncases had undetectable preexposure EIA antibody. No EIA IgM antibodies were detected in any pigtail specimen.

Pre- and postexposure antibody titers: noncases. We compiled information on symptoms of noncases (table 1). The preexposure PRN GMT of those with one or more symptoms, 871, was significantly lower than that of those who remained asymptomatic, 1549 (P < .04, t test). By EIA, the preexposure GMTs in symptomatic noncases (153) were lower than those of asymptomatic students (220), but this difference was not statistically significant (P = .10, t test).

To determine a titer that appeared to protect against other potential manifestations of measles virus infection, we examined pre- and postexposure blood specimens of noncases. Of 36 noncases who were not vaccinated during the outbreak control program, 18 (50%) agreed to be assayed for postexposure antibody. Seven of 11 with preexposure PRN titers of 216–874 had a fourfold or greater boost in antibody (mean, 43-fold; table 2), compared with 0 of 7 with titers ≥1052 (P < .02, Fisher's exact test). Among five students with adequate postexposure sera for testing, IgM antibody was detected in

Table 2. Prexposure plaque reduction neutralization (PRN) titers and seroconversion, noncases.

Donor	PRN titer: Pre-exposure	PRN titer: Postexposure IgG	PRN titer: Postexposure IgM	Fold titer rise*	Interval (pre- to post-exposure, days)	Age of vaccination†
1	216	1240		6	47	13 mo, 8 y
2	270	9500	<12	35	46	12 mo, 10 y
3	282	370		–	72	12 mo, 11 y
4	286	38,710		133	46	4 y, 11 y
5	390	7520		19	47	(17 y)
6	526	19,400	104	37	96	10 mo, 10 y
7	546	1110	<15	–	78	10 mo, 14 y
8	568	19,400		34	47	10 mo, 8 y
9	620	830		–	47	20 y
10	636	1820	<12	–	46	(12 mo, 11 y)
11	874	31,540	<12	36	46	8 mo, 6 y
12	1052	750		–	46	9 mo, 10 y
13	1076	620		–	95	12 mo, 2 y
14	1988	1220		–	46	(14 mo)
15	2998	1830		–	47	2 y
16	3684	4300		–	47	<6 mo, 10 y
17	3742	1610		–	47	(14 y)
18	5548	1160		–	96	(12 y)

* More than fourfold.
† Provider-verified unless in parentheses.

one with preexposure PRN titer of 526. Postexposure sera were not tested by EIA due to insufficient quantity.

Using PRN titer of 1052 suggested by the above analysis as a cutoff, 26 (70%) of 37 noncases with preexposure PRN titers <1052 reported at least one symptom compared with 11 (31%) of 35 donors with titers ≥1052 ($P < .002$, χ^2 test). Except for photophobia, all symptoms were more common in individuals with titers <1052 (table 1). However, the differences were significant only for fever and headache ($P < .01$ and $P = .02$ by Fisher's exact test, respectively).

Vaccination history. Seven of the eight cases occurred in students who had received live measles vaccine, including five with provider verification. All seven noncases with more-than-fourfold boost in convalescent PRN titer reported previous vaccination, six with provider verification. Table 3 compares the vaccination history of students with a preexposure PRN titer ≤120, 121–1051, and ≥1052. The proportion in each titer range who had received one dose of measles vaccine at <12 months, one dose at 12–14 months, or at least one dose at ≥15 months of age did not differ significantly, regardless of provider verification.

Discussion

Protective levels of antibody. The presence of detectable measles antibody as measured by traditional serologic assays has been thought to indicate that an individual would be protected from clinical disease if exposed to the measles virus.

Table 3. Vaccination history of students with different preexposure plaque reduction neutralization (PRN) titers.

Vaccination history	PRN titer range ≤120 (n = 9)	121–1051 (n = 36)	≥1052 (n = 35)
Provider-verified			
1 dose at <12 mo	1 (11)	2 (6)	2 (6)
1 dose at 12–14 mo	1 (11)	4 (11)	4 (11)
≥1 dose at ≥15 mo	3 (33)	19 (53)	14 (40)
Other or unknown	4 (44)	11 (31)	15 (43)
All vaccinations			
1 dose at <12 mo	2 (22)	1 (3)	2 (6)
1 dose at 12–14 mo	0	1 (3)	0
≥1 dose at ≥15 mo	7 (77)	27 (75)	28 (80)
Other or unknown	0	7 (19)	5 (14)

NOTE. Data are number of students (%).

This study, using a highly sensitive PRN assay, suggests that a titer >120 was required for protection from classic measles illness. Reinfection and disease may occasionally occur in individuals whose immunologic system had previously been primed by wild [18] or vaccine measles virus [19–24]. With the exception of a case of atypical measles [21], none of these studies showed that measles could occur when antibody was present immediately before exposure.

The conclusion that persons with low levels of measles antibody may not be protected depends on the pigtail specimens having been collected prior to exposure and PRN titers being specific for measles. The exact time course of production and detection of EIA or PRN antibodies is not known. In children >1 year of age, HI and cytopathic effect neutralization antibodies are detectable between the first and third day after onset of rash during a typical measles illness [4]. In this study, the shortest interval between donation and rash onset was 12 days. One case occurred in an individual with a PRN titer of 98, in a specimen obtained 36 days before rash onset, which was clearly long before exposure. The absence of IgM antibody by EIA in pigtail specimens is additional evidence that the subjects were not in the process of making a primary immune response when the specimen was obtained [25].

Sensitivity and specificity of PRN and EIA antibody. The neutralization antibody test, which measures the serum dilution capable of preventing 50% of plaque formation induced by measles virus in cell cultures, has been considered the most reliable criterion for the serologic evaluation of measles immunity [9, 26]. In this study, the EIA, unlike the PRN assay, did not detect preexisting antibodies in the pigtail specimens of the measles cases. In two other outbreaks where preexposure sera from cases were available, antibodies were not detected by another EIA [27] or by a less-sensitive neutralization test [6]. This discrepancy in antibody detection may be due to the increased sensitivity of the PRN test. The PRN test is ~220-fold, 60-fold, and 10-fold more sensitive than

the complement fixation test, the standard HI test, and the cytopathic effect neutralization test, respectively [9, 14].

Several studies suggest that antibodies detected by the PRN assay, including low titers, are specific. Three studies found an inverse relationship between the level of maternal PRN antibody detected in infants and seroconversion after administration of measles vaccine [12, 28, 29]. Another study examined the immune response following revaccination of students with little or no PRN antibody [14]. Students without detectable prevaccination PRN antibody were significantly more likely to make IgM detected by either the HI or PRN technique; of 16 with initial PRN titers <4, 14 made PRN IgM, while only 1 of 68 with initial PRN titers ≥4 made PRN IgM.

In the present study, good correlation between preexposure PRN titer and postexposure boosting was observed (table 2); persons with preexposure PRN titers ≥1052 consistently failed to show fourfold or greater boost in antibody. This lends further support for the specificity of PRN antibodies. However, further studies may be needed to define the significance of low titers of PRN antibodies.

IgM antibodies. The presence or absence of IgM antibodies has been used to define primary or secondary immune response following viral infection by wild or vaccine virus [30, 31]. In this study, IgM was detected in several measles cases (table 1) and one noncase (table 2). On average, the serum IgM titer constituted ~1.5% of the combined IgG and IgM titer and never >3.6% of the titer. In contrast, titers of IgM 3 weeks after primary measles vaccination constitute 4%–15% of the total PRN titer (unpublished data). Nagy et al. [32], using a fluorescent antibody assay, also found many measles cases with prior history of vaccination had detectable IgM antibodies in convalescent blood samples at levels "unusually low" compared with those of unvaccinated measles patients. These results suggest that with more sensitive assays IgM may be detectable in measles patients with a secondary immune response, albeit at low IgM to IgG ratios.

Modified measles illness. In this study, we found significant differences in preexposure PRN GMTs between participants without clinical measles who remained completely asymptomatic and those who developed some symptoms; a trend was found for differences by EIA. These data suggest that some levels of preexisting antibody may protect against classic measles but not against mild clinical infections. Further, the data suggest that immunity to measles may not be absolute but rather a continuum of clinical illness.

Other studies have shown that when infection occurs in partly protected individuals, such as those with maternal antibody [33] or who have had immune globulin administration as prophylaxis [25], a modified form of measles can occur. Mild, nonclassic measles, resembling modified measles, also has been described among children previously vaccinated with live attenuated vaccine [19, 20, 34]. Measles illness without rash, however, was not observed in another study; 15% of grade-school children reporting nonspecific illness had serologic evidence of recent measles infection compared with 16% of asymptomatic children [30]. The older age of our study population may have permitted detection of less specific illnesses missed in younger children.

Whether individuals with measles illness without rash can transmit virus is unknown. Individuals with higher levels of antibodies may inhibit virus replication more than those with low levels and therefore be less likely to effectively shed virus. While the intensive booster response in students with medium-range preexposure titers (220–1000) suggests that viral replication may have occurred and raises the possibility that they may be unidentified transmitters of disease, one study suggests that if such transmission occurs, it is probably not important in outbreak propagation [35].

Waning vaccine-induced immunity. Antibody titers immediately after measle vaccination were not known for the participants in our study. Therefore, we do not know the initial responses to measles antigen in our cases. It is possible that they never made a protective immune response and were primary vaccine failures. Alternatively, they may have responded adequately to the initial vaccination with a subsequent decline in antibody titers over time (secondary vaccine failure).

Our data suggest that earlier serologic studies in which antibody declined over time may be subject to reinterpretation. Krugman [3] reported that 25 (36%) of 70 institutionalized residents not exposed to wild virus lost detectable HI antibody (to levels <8) 16 years after seroconverting with further-attenuated measles vaccine. Sixteen serum specimens with HI titers <2–4, obtained 6–15 years after successful immunization, were tested by our PRN assay. Sera were found to have PRN titers of only 4–46, substantially below the titer of 120 believed to be associated with protection on the basis of this study. This suggests that at least some of these persons may have lost protection over time.

Most epidemiologic evidence suggests that such secondary vaccine failures do not play a significant role in measles outbreaks [36, 37]. In one recent outbreak, however, a 5% attack rate among persons who had seroconverted after vaccination 10 years earlier was reported [23]. A two-dose measles vaccination schedule has recently been recommended in the USA [38, 39]. Such a schedule should reduce the accumulation of susceptibles from primary vaccine failures. Whether a second dose will also have a significant impact on secondary vaccine failures is unclear as the booster response may be short-lived [40]. Also, as the relative importance of waning immunity remains poorly understood [41], the optimal age for the second dose remains controversial. It is interesting to note that three (two provider-verified) of the eight cases in this study reported receiving two doses of measles vaccine, but the small numbers makes interpretation difficult. Further studies of vaccine-induced immunity are needed.

Conclusion. The traditional belief has been that once the immune system is stimulated against wild measles virus, im-

munity will persist life-long, and it is assumed that this holds true for further-attenuated measles vaccine virus as well. Our data suggest that some persons can make an immune response against measles antigens, including low levels of apparently specific neutralizing antibodies, and subsequently become susceptible to measles if their PRN titers fall to 120 or below. Illness without rash may also occur after exposure to measles in persons with PRN titers above this level.

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