Interference of immune globulin with measles and rubella immunization

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Passively acquired antibody may interfere with the active antibody response to live viral vaccines such as measles and rubella. To evaluate the duration of this inhibitory effect, we measured the measles and rubella antibody responses of Apache children immunized with measles, mumps, and rubella vaccine at varying intervals after administration of an immune globulin termed bacterial polysaccharide immune globulin (BPIG). This specific immune globulin contained measles and rubella antibody titers similar to those in standard intramuscularly and intravenously administered immune globulins. Antibody responses to measles vaccine were inhibited for up to 5 months after a BPIG dose of 80 mg IgG per kilogram of body weight, but responses to rubella vaccine were inhibited for only 2 months. Most children who had a decreased measles antibody response to primary measles, mumps, and rubella immunization given 1½ to 4 months after BPIG administration responded to a booster immunization given 6 months after their last BPIG dose. We conclude that high doses of immune globulin (>10 mg/kg) may inhibit the antibody response to measles for more than 3 months. We propose that the interval between administration of immune globulin and measles and rubella immunization be adjusted on the basis of the dose of immune globulin. (J PEDIATR 1993;122:204-11)

In recent years, immune globulins have found increasing application in the prevention and treatment of childhood illnesses.[1,2] A concern about widespread use of IGs is that passively acquired antibodies may interfere with the immune response to active immunization, particularly with live viral vaccines.[3-7] Low antibody responses to measles vaccination in infants have been correlated with the presence of transplacentally acquired measles antibodies.[8-11] Sensitive neutralization assays have demonstrated the persistence of measles antibodies in some children to 12 months of age and older,[12] and consequently measles immunization is not recommended routinely in the United States until 15 months of age.[13]

BPIG	Bacterial polysaccharide immune globulin
ELISA	Enzyme-linked immunosorbent assay
HAI	Hemagglutination inhibition
IG	Immune globulin
MMR	Measles, mumps, and rubella [vaccine]

Because of the concern that viral antibodies in IG would

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also interfere with live viral immunizations, it is recommended that measles, mumps, and rubella vaccine be delayed at least 6 weeks[13] and preferably 3 months after IG administration.[13, 14] Apart from the early use of IG to further attenuate the Edmonston B measles vaccine strain,[15] there is only limited information on the effect of IG administration on the antibody response to immunization with virus vaccines.[3-7, 16, 17]

While conducting efficacy studies of a specific globulin, termed bacterial polysaccharide immune globulin, for preventing *Haemophilus influenzae* type b and pneumococcal infections in Apache children,[18, 19] we had the opportunity to evaluate antibody responses to measles and rubella vaccine given at various intervals after administration of BPIG.

METHODS

Clinical studies. Children of the White Mountain Apache tribe in Whiteriver, Ariz., were enrolled in a double-blind, placebo-controlled trial of BPIG for the prevention of *H. influenzae* type b and pneumococcal infections.[18, 19] All studies were approved by the Joint Committee on Clinical Investigation, Johns Hopkins University School of Medicine; the Indian Health Service; and the Tribal Health Board and the Tribal Council of the White Mountain Apache Tribe. Written informed consent was obtained from parents. During the first phase of the study, BPIG (lots 3 and 4), at a dose of 0.5 ml/kg, or a saline solution placebo, at a dose of 0.5 ml, was given intramuscularly at 2, 6, and 10 months of age.[16] Administration of MMR vaccine was scheduled at 15 months of age, 5 months after the last BPIG or saline solution dose. Blood for measles and rubella antibody determinations was drawn at 15 and 18 months of age.

During the second phase of the study, IG prophylaxis was evaluated during the second year of age by randomly selecting children to receive BPIG (lot 5 at a dose of 0.5 ml/kg intramuscularly) or saline solution (0.5 ml intramuscularly) at 12, 15, 18, and 21 months of age. Administration of MMR vaccine was scheduled at 14 months of age, 2 months after the 12-month BPIG or saline solution dose. The interval was at least 6 weeks, the minimum interval recommended by the Immunization Practices Advisory Committee.[13]

When serologic evaluation revealed a decreased seroconversion rate to measles vaccine at 14 months of age, the phase 2 protocol was modified by giving the MMR vaccine at 15 months, at least 3 months after the 12-month BPIG or saline solution dose, to conform to the preferred interval recommended by the Immunization Practices Advisory Committee[13] and the Committee on Infectious Diseases of the American Academy of Pediatrics.[14] All BPIG-treated children in the second-phase studies were also reimmunized with MMR vaccine at 27 months of age, at least 6 months after their last BPIG dose, to ensure effective immunization.

Vaccines and immune globulins. Measles, mumps, and rubella vaccine (M-M-R) was obtained from lots licensed by the U.S. Food and Drug Administration and manufactured by Merck Sharpe & Dohme (West Point, Pa.). BPIG is a human IG prepared from the plasma of donors immunized with *H. influenzae* type b, 23-valent pneumococcal and 4-valent meningococcal vaccines by the Massachusetts Public Health Biologic Laboratories, Jamaica Plain, Mass.[20] The globulin contains 14% to 17.5% protein and is formulated for intramuscular administration. Other IGs evaluated for measles and rubella antibodies were intramuscular IG preparations manufactured at the Massachusetts Public Health Biologic Laboratories and intravenous IG preparations manufactured by Sandoz Pharmaceuticals (Basel, Switzerland), Cutter Laboratories (Berkeley, Calif.), or Immuno AG (Vienna, Austria).

Antibody assays. Measles and rubella antibody titers were measured by hemagglutination inhibition assay[21, 22] at the Massachusetts State Laboratory Institute, Jamaica Plain, Mass.

Sera from the cohort of children receiving MMR vaccine 3 months after an IG dose at 12 months of age were also evaluated by an enzyme-linked immunosorbent assay (Measlestat; Whittaker Bioproducts, Walkersville, Md.). The ELISA was calibrated in international units (IU) with the use of serial dilutions of the World Health Organization Measles Reference Serum, obtained from the Statens Seruminstitut (Copenhagen, Denmark). The standard curve was fitted with a four-parameter logistic regression equation (Softmax; Molecular Devices Corp., Palo Alto, Calif.), and unknowns were calculated from this curve. According to the manufacturer's recommendations, samples giving an optical density <80% of the Low Positive Serum Standard should be considered seronegative. The Low Positive Serum Standard contained 0.5 IU measles antibody.

The minimum protective titer of measles antibody is estimated to be 1:120 by plaque reduction neutralization.[23] This titer is equivalent to 0.2 IU measles antibody (personal communication: Dr. Paul Albrecht, Center for Biologics Evaluation and Research, Bethesda, Md., Dec. 4, 1992).

Data analysis. Data organization and analysis were performed on the PROPHET system, a national computer system sponsored by the Chemical/Biological Information Handling Program of the National Institutes of Health. The logarithms of the antibody titers were utilized for statistical calculations. Antibody titers that were below the limits of sensitivity of the HAI assays were assigned values equal to half the lower limit of sensitivity of the assay. The lower

Table I. Measles and rubella antibody titers by hemagglutination inhibition in lots of bacterial polysaccharide immune globulin and standard immune globulins for intramuscular or intravenous administration

	Antibody titer	
	To measles (−1)	To rubella (−1)
Immune globulins*		
BPIG		
Lot 1	20	32
Lot 3	20	16
Lot 4	20	16
Lot 5	20	16
Lot 6	10	16
Lot 7	5	16
IG		
Lot 82B	10	16
Lot 83	10	16
Lot 85	10	16
Lot 86	20	32
Lot 94	10	8
IVIG (Sandoz) (lot 6.369.100.0)	5	16
IVIG (Cutter) (lot 40A02AB)	20	16
IVIG (Immuno) (lot 24268606)	20	16
Measles standards		
WHO/Statens Seruminstitut† (Denmark)	5	—
WHO/NIBSC Standard 66/202†	5	—
U.S. FDA Standard serum lot 176	320	—
Rubella standards		
CDC, reference 82.0136	—	128
CDC, reference 85.0120	—	16

*All IGs were diluted to a final protein concentration of 1% before assay.
†Assayed at a dilution containing 1 IU/ml.
IVIG, Intravenously administered immune globulin; *WHO*, World Health Organization; *NIBSC*, National Institute for Biological Standards and Control; *FDA*, Food and Drug Administration; *CDC*, Centers for Disease Control.

limits of sensitivity were 1:5 for measles and 1:8 for rubella antibodies by HAI. The calculated measles antibody concentration, measured by ELISA in international units, was used for statistical purposes even for values <0.4 IU/ml. Seroconversions were defined as achievement of a detectable HAI titer (≥1:5) or ELISA antibody concentration (≥0.4 IU/ml).

Comparisons of means or geometric means were performed by the two-sided *t* test for normally distributed values and by the Mann-Whitney test for non-normally-distributed values. Comparisons of proportions were performed by a two-sided Fisher Exact Test.

RESULTS

Antibody titers in human IGs. Antibody titers by HAI to measles and rubella viruses in BPIG lots resembled the titers in standard IGs prepared from nonimmunized donors (Table I). Titers varied over a fourfold range in both BPIG and standard IG lots.

Measles antibody responses after use of IG. When MMR vaccine was given 2 months after IG treatment, measles antibody responses were markedly lower than in saline solution–treated control subjects (Table II). Two thirds of the children failed to make detectable antibody by HAI, compared with 14% of concurrent saline solution–treated control subjects ($p < 0.01$). The geometric mean titer was more than sixfold lower in IG recipients than in saline solution recipients ($p < 0.01$).

The HAI assay was not sufficiently sensitive to detect residual measles antibody from the IG dose given 2 months previously. Thus none of the 15 IG recipients had detectable antibody, and yet 10 of these children failed to respond to measles immunization. When MMR vaccine was given 3 months after IG, measles antibody responses were still significantly impaired (Table II). Forty-three percent failed to make detectable antibody by HAI, compared with 8% of concurrent control subjects ($p = 0.008$), and the geometric mean titer was reduced by about half in BPIG recipients relative to placebo recipients ($p = 0.038$).

To verify the results with the HAI assay, we also evaluated this group by ELISA (Measlestat). When postimmunization sera were tested, the correlation between the results of ELISA and those of HAI was high ($r = +0.94$). There was also a high level of concordance for negative responses. All 12 sera with negative HAI results also had negative ELISA results. All but 1 of 13 sera with negative ELISA results also had negative HAI results. From the equation for the regression, a concentration of 1 IU measles antibody was equivalent to an HAI titer of 1:8. Direct assay of the measles standard sera gave HAI titers of 1:5 for dilutions containing 1 IU/ml (Table I).

As with the HAI assay, a lower proportion of IG recipients than placebo recipients had seroconversion by ELISA ($p < 0.05$, Table III). Like the HAI assay, the ELISA was not sufficiently sensitive to detect the residual measles antibody from the IG dose 3 months previously. The geometric mean antibody levels before MMR immunization were similar in BPIG and placebo recipients, as were the ranges of values (Table III). In the 10 IG recipients without seroconversion, measles antibody levels (geometric mean +0.16 IU/ml) were similar to those in the 13 who did seroconvert (geometric mean = 0.19 IU/ml). This suggests that ELISA antibody concentrations less than 80% of the low positive standard serum (0.4 IU/ml) represent nonspecific variations in background, rather than measles antibody, and

Table II. Antibody response of Apache children to measles and rubella immunization given at various times after administration of bacterial polysaccharide immune globulin or placebo

				Measles antibody*						Rubella antibody†				
		Mean interval from BPIG to MMR		Geometric mean titer^{-1}			Children without seroconversion			Geometric mean titer^{-1}			Children without seroconversion	
Group	n	Days	Range	Before	After	p‡	No.	%	p‡	Before	After	p‡	No.	%
Interval of 2 mo														
BPIG	15	60	(42-74)	2.50	4.77	<0.01	10/15	67	0.008	4.19	33.5	0.026	1/15	7
Placebo	14	61	(42-77)	3.05	31.2		2/14	14		4.00	90.5		0/14	0
Interval of 3 mo														
BPIG	23	99	(85-119)	2.58	8.60	0.038	10/23	43	0.008	4.13	105.	0.358	2/21	10
Placebo	24	100	(90-119)	2.50	17.3		2/24	8		4.00	170.		0/22	0
Interval of 5 mo														
BPIG	48	156	(126-217)	2.50	20.0	0.304	7/48	15	0.062	4.00	83.7	0.645	4/44	9
Placebo	43	162	(123-245)	2.50	29.4		1/43	2		4.00	88.0		2/42	5

*Measured by hemagglutination inhibition assay. The lower limit of sensitivity is a titer of 1:5. Titers <1:5 were coded as 2.5 for purposes of calculating geometric means.
†Measured by hemagglutination inhibition assay. The lower limit of sensitivity is a titer of 1:8. Titers <1:8 were coded as 4 for purposes of calculating geometric means.
‡Significance: BPIG values versus placebo values.

Table III. Postimmunization measles antibody concentrations by ELISA in Apache children immunized 3 months after receiving bacterial polysaccharide immune globulin or placebo

		Measles antibody concentration (IU/ml)							
		Before		After			Children without seroconversion†		
Group	n	GM	Range	GM	Range	p*	No.	%	p
BPIG	23	0.18	0.06-0.36	1.18	0.06-0.18	NS	10/23	43	0.022
Placebo	25	0.15	0.05-0.37	3.01	0.15-0.13		3/25	12	

GM, Geometric mean; *NS*, not significant.
*Significance: BPIG values versus placebo values.
†0.4 IU is 80% of the measles antibody concentration of the low positive standard serum in the Measlestat ELISA. Values below this level are considered seronegative according to the manufacturer's instructions.

should be considered seronegative as recommended by the manufacturer.

When MMR vaccine was given 5 months after IG or placebo, the proportion of nonresponders was still higher in IG than in placebo recipients (15% vs 2%; $p = 0.062$) (Table II). All seven children without seroconversion to measles antibodies 5 months after IG had received BPIG lot 4, a relatively high-titer lot. The actual intervals between IG and MMR vaccine administration in these seven children ranged from 126 to 168 days.

Relationship between measles seroconversion and interval after IG administration. Because the actual intervals between IG and MMR vaccine varied within each of the three study groups, a pooled analysis of antibody responses was performed in 30-day intervals (Figure). The geometric mean titer and the rate of seroconversion to measles increased progressively with increasing intervals from a 30- to 59-day interval to a 150- to 179-day interval.

Measles antibody responses to reimmunization. When BPIG-treated children who received MMR vaccine at 15 months of age (3 months after IG administration) were given an MMR booster at 27 months (at least 6 months after IG), their preimmunization titers were significantly lower ($p < 0.01$) than those of saline solution–treated control subjects and the proportion of the BPIG-treated children without measles antibody was significantly higher ($p = < 0.05$) than the proportion of control subjects without measles antibody (Table IV). The IG-treated children responded well to reimmunization (preimmunization vs postimmunization titers, $p < 0.01$); their postimmunization measles antibody titers thus no longer differed significantly from titers of placebo-treated control subjects.

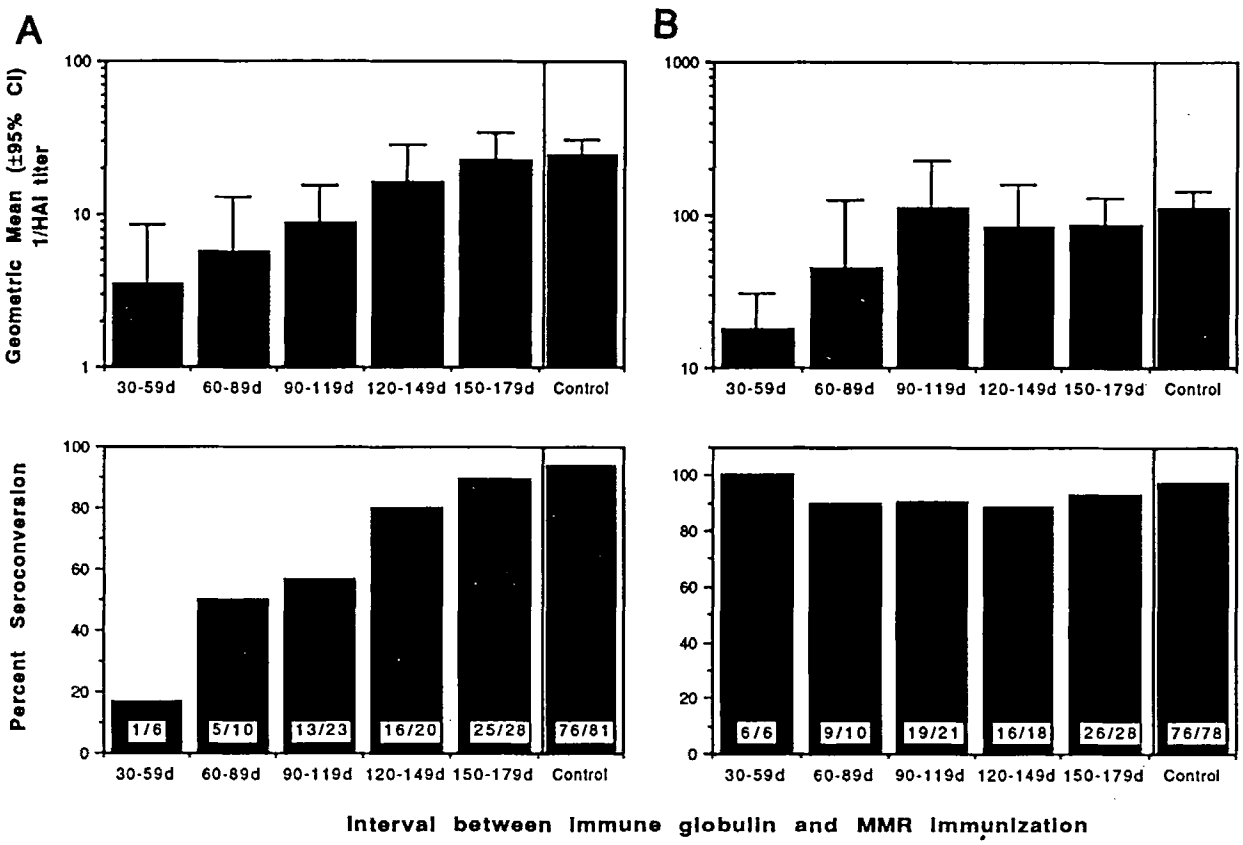

Figure. Geometric mean HAI antibody titers ±95% confidence interval *(CI)* and seroconversion rates to measles antibodies (A) and rubella antibodies (B) in children receiving MMR vaccine at various intervals after BPIG. *d*, Days.

Table IV. Antibody concentrations to measles and rubella after reimmunization with measles, mumps, and rubella vaccine at 27 months, at least 6 months after administration of bacterial polysaccharide immune globulin

		Measles antibody*						Rubella antibody†					
		Geometric mean titer^{-1}		Undetectable antibody				Geometric mean titer^{-1}		Undetectable antibody			
				Before		After		Before	After	Before		After	
Group	n	Before ($^{-1}$)	After ($^{-1}$)	No	%	No	%	($^{-1}$)	($^{-1}$)	No.	%	No.	%
BPIG	15	8.31	21.9	6/15	40	2/15	13	15.3	25.4	1/15	7	0/15	0
Placebo‡	15	23.0	—	1/15	7	—		15.3	—	0/15	0	—	
p Value		<0.01		<0.05									

*Measured by hemagglutination inhibition assay. The lower limit is 1:5. Titers <1:5 were coded as 2.5 for purposes of calculating geometric means.
†Measured by hemagglutination inhibition assay. The lower limit is 1:8. Titers <1:8 were coded as 4 for purposes of calculating geometric means.
‡The placebo group was not reimmunized with MMR vaccine.

Rubella antibody responses. Even when MMR vaccine was given within 2 months of IG, all but 1 of 15 children had seroconversion to rubella by HAI assay (Table II). The geometric mean rubella titer, however, was reduced approximately threefold ($p < 0.05$). When MMR vaccine was given 3 months or 5 months after IG, no detectable inhibition of rubella antibody responses was observed. Administration of rubella vaccine in the second and third months after IG reduced geometric mean titers without affecting seroconversion rates (Figure).

Table V. Suggested interval between use of IG and immunization against measles

Reason for use of IG or IgG	IG				IgG dose (mg/kg)	Suggested interval (mo)
	Type	Dose	Route	Indication		
Prophylaxis						
Tetanus	Tetanus IG	250 units	IM		<10	3
Hepatitis A	16.5% IG	0.02 ml/kg	IM	For contacts	<10	3
		0.06 ml/kg	IM	For international travel	10	3
Hepatitis B	Hepatitis B IG	0.06 ml/kg	IM		10	3
Chickenpox	Varicella-zoster IG	125 units/10 kg	IM		40	5
Measles	16.5% IG	0.25 ml/kg	IM	For healthy contacts	40	5
		0.50 ml/kg	IM	For contacts with compromised immunity	80	6
Replacement of humoral immunodeficiencies	5% IG	3.2 ml/kg	IV		160	7
	5% IG	6.4 ml/kg	IV		320	8
Treatment of idiopathic thrombocytopenic purpura	5% IG	12.8 ml/kg	IV		640	9
Treatment of Kawasaki disease	5% IG	≥25.6 ml/kg	IV		≥1280	≥10

IM, Intramuscular route; *IV*, intravenous route.

Rubella antibody titers in the IG-treated children immunized with MMR vaccine at 15 months of age, 3 months after IG administration, were similar to those in saline solution–treated children at 27 months (Table IV). After booster immunization, rubella antibody titers rose (n = 7), fell (n = 2), or remained unchanged (n = 6).

DISCUSSION

Successful immunization with live viral vaccines such as MMR vaccine requires the active replication of the vaccine viruses in the recipient. The presence of preexisting immunity, presumably antiviral antibody, may inhibit viral replication and thus reduce or prevent the antibody response. The attenuated measles vaccine strains are particularly susceptible to inhibition by antibody. The Attenuvax strain of measles licensed in the United States failed to produce consistent seroconversion in children ≤12 months of age primarily because of persistent maternal antibodies.[9-12] The level of maternal or cord antibodies was the major factor predicting the age of seroconversion to vaccination or susceptibility to natural measles in Haiti[8] and other countries.[24] Rubella vaccine strains may be less susceptible to inhibition by the levels of transplacental antibodies persisting beyond 6 months of age.[25]

The evidence that IG administration may inhibit antibody responses to MMR vaccine is limited. Concurrent administration of the partially attenuated Edmonston B vaccine strain with a measles IG containing a standardized titer of measles neutralizing antibody reduced side effects associated with this vaccine.[15-17] The rate of seroconversion with this and several other attenuated strains[16, 17] was not reduced but the geometric mean titer achieved was diminished by twofold. High intramuscular doses of IG (7.5 to 20 ml), selected for high levels of rubella antibodies, inhibited the antibody response to the Cendehill rubella vaccine strain in children[6] or to experimental rubella challenge in male volunteers.[7] Lower doses (2 ml) of Rh IGs given to women at delivery did not inhibit the antibody responses to rubella vaccine.[26, 27]

Our findings indicate that an intramuscular dose of IG of 80 mg/kg inhibited seroconversion rates to measles antibodies for 5 months. In contrast, rubella antibody responses were significantly reduced 2 months, but not 3 or 5 months, after IG administration. Although the geometric mean antibody titers to rubella were reduced when MMR vaccine was given during the second and third months after IG administration, the seroconversion rate was not reduced.

The HAI assay and ELISA used to measure measles antibodies in this study were not sufficiently sensitive to measure the low levels of measles antibodies that may inhibit replication of the vaccine strain. Thus the minimum antibody concentration capable of inhibiting measles vaccine responses could not be estimated. When a more sensitive plaque reduction neutralization assay is used, the minimum antibody level capable of preventing natural measles infection has been estimated to be 1:120 (0.2 IU/ml).[23] This level is at one fifth of the lower limit of sensitivity of the HAI and at half the lower limit of the ELISA used in our study.

Although we studied a specific intramuscular IG preparation made from a small number of donors, our results are likely to apply to standard intramuscular and intravenous IG preparations, because these contain similar measles and rubella HAI antibody titers. Our studies were done in Apache children but should extend to other racial groups because the non-IG-treated Apache had the expected seroconversion rate of about 95%.

In children whose tests failed to show seroconversion to measles because they were immunized at ≤12 months of age, reimmunization produces poor responses in up to 50% and only transient responses in a portion of those with seroconversion.[28-31] However, we noted that most children who had responded poorly to their first MMR immunization, 3 months after BPIG was given, responded well to reimmunization 6 months after their last dose of BPIG.

The current recommendation of the Immunization Practices Advisory Committee on measles prevention is that "measles vaccine should not be given for at least 6 weeks and preferably 3 months after a person has been given IG, whole blood or other antibody-containing products."[13] The Committee on Infectious Diseases of the American Academy of Pediatrics recommends that MMR vaccination be deferred for at least 3 months after IG administration regardless of the IG dose given.[14] When IG prophylaxis is given for measles exposure at a dose of 0.25 to 0.5 ml/kg intramuscularly (~40 to 80 mg/kg) or 100 to 400 mg/kg intravenously, active measles immunization is recommended after 3 months.[14] Our results indicate that these intervals are too short when large doses of IG (≥10 mg/kg) have been given.

Appropriate intervals between IG administration and measles immunization can be estimated from our results (Table V). The assumptions for these estimates are (1) that standard IG preparations contain concentrations of measles antibody similar to those of the IGs used in our study, (2) that an IgG dose of 80 mg/kg reduces seroconversion rates to measles after 5 months but not after 6 months, and (3) that the half-life of passively administered IgG class measles antibodies is approximately 1 month.[1] It is apparent that 3 months is an appropriate interval for measles immunization after IG doses recommended for hepatitis A prophylaxis, hepatitis A being the most common indication for IG prophylaxis in children. However, the interval should be increased to 5 or 6 months after the larger IG doses used for measles and chicken pox prophylaxis (40 to 80 mg/kg), and to 7 or 8 months after the usual intravenous replacement doses of IG in B-cell immunodeficiencies (200 to 400 mg/kg). The pharmacologic intravenous doses of IG used for treating immunologic diseases such as idiopathic thrombocytopenic purpura and Kawasaki disease raise circulating IgG to levels equal to or higher than those in healthy adults. Consequently, the estimated interval to effective measles immunization resembles that of term neonates receiving a full complement of transplacental antibody (i.e., 12 to 15 months).

The application of these guidelines is subject to several caveats. The first is that in any particular individual, the persistence of measles antibody may vary with the measles titer in the IG lot used and with the half-life of measles antibody. Our limited evaluation of IGs indicate that measles antibody titers vary at least fourfold from one lot to another. The half-life of IgG may also vary substantially in healthy individuals and may be accelerated in many diseases, including febrile illnesses, malnutrition, burns, and other conditions associated with protein loss (see reference 1 for review). Thus the measles titer of some individuals may fall below that necessary to prevent or attenuate natural infection within the recommended intervals.

A second caveat is that both the measles antibody assays used in these studies were not sufficiently sensitive to detect the minimum level of measles antibody estimated to be protective in acute exposures (0.2 IU/ml). Consequently we may have underestimated the proportion of children who achieved protective measles antibody levels after MMR immunization, at least for the short term. Physicians may therefore wish to shorten the interval between IG administration and MMR immunization if the risk of measles exposure is considered high. As shown in the Figure, a varying proportion of children will have seroconversion to measles antibodies when immunized at shorter intervals after IG administration. If this strategy is adopted, the antibody response could be checked and the nonresponders reimmunized after the recommended interval. Alternatively, all such children could be reimmunized empirically after the recommended interval.

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