

Time to Peak Serum Antibody Response to Influenza Vaccine

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The time to the appearance of a peak serum antibody response to influenza virus vaccine is not clearly defined. We compared the most commonly used time intervals described in the literature—4 and 6 weeks after vaccination. We studied 118 elderly patients from three different geographic sites. The 1992 to 1993 trivalent inactivated influenza virus vaccine containing influenza virus A/Beijing/353/89 (H3N2), influenza virus A/Texas/36/91 (H1N1), and influenza virus B/Panama/45/90 was used. No statistically significant differences were found at the 4- and 6-week intervals after vaccination.

Serum hemagglutination inhibition (HI) titers of 40 or greater are closely correlated with protection from infection with influenza virus A (4). At the present time, a difference of opinion exists as to the precise time interval for the development of a peak serum antibody response to influenza virus vaccine. Gravenstein and colleagues state that 6 weeks is the optimal time interval to determine the peak serum HI antibody response to influenza virus vaccine (3). Some investigators have used 4 weeks for assessing the development of peak antibody response (1, 5). Few investigators have compared the 4- and 6-week intervals simultaneously (8).

In this study, we monitored a group of elderly patients at 4 and 6 weeks after influenza virus vaccination to determine which time interval was associated with the development of the highest HI titer.

Elderly patients between 65 and 93 years of age were enrolled from three sites: the Geriatric Clinics at Cornell Medical School, New York, N.Y.; the Medical College of Pennsylvania, Philadelphia, Pa., and the Woodcrest Center Nursing Home, New Milford, N.J. From the New York group, 60 healthy elderly patients were enrolled; from Philadelphia, 35 healthy and 9 infirm patients were enrolled; and from New Jersey, 14 infirm patients were enrolled.

Patients were given the 1992 to 1993 commercially available trivalent influenza virus vaccine manufactured by Connaught and Company. The vaccine contained influenza virus A/Beijing/353/89 (H3N2), influenza virus A/Texas/36/91 (H1N1), and influenza virus B/Panama/45/90. The vaccine was given by intramuscular injection in the deltoid muscle. It was administered from mid-October through mid-November, 1992.

Three blood specimens were obtained—one at the time of vaccination and the other two 4 and 6 weeks after vaccination. Serum HI antibody titers were determined in microtiter plates as previously described (5). All three specimens were tested simultaneously for each vaccine strain so that comparison of the values at the 4- and 6-week intervals would be valid. The

specimens from all study sites were tested simultaneously against each strain so that intersite comparison would also be valid for each strain. The specimens were tested in the Diagnostic Virology Laboratory, Hackensack Medical Center, Hackensack, N.J.

Statistical analyses were performed with the Systat, Inc., program. Group means were compared by using Student's *t* test. Dichotomous variables were compared by using the chi-square test. When one of the cell entries was less than 5, Fisher's exact test was used.

The trivalent influenza virus vaccine was effective in inducing an HI antibody response in both the healthy as well as infirm groups. Most subjects had an increase in antibody titer equal to or greater than 1:40, a value that is generally considered to correlate with protection.

For all three influenza virus strains, no statistically significant differences were observed between the geometric mean HI titers for the 4- and 6-week postvaccination blood specimens. The level of HI antibody that developed at 4 weeks was comparable with the HI titers that were present at 6 weeks for most groups. Some differences, however, were observed (Table 1). When we examined the percentage of patients with serum HI titers equal to or greater than 40 at 4 and 6 weeks after vaccination, similar minor differences were noted.

We were unable to find a difference in serum HI antibody levels when we compared 4- and 6-week postvaccination specimens. Some titers were higher at 4 weeks, and some were higher at 6 weeks; however, no regular trend for the numbers obtained was found.

In our study, for each virus strain, we tested all samples from all sites simultaneously. This was done to avoid errors when comparing results at different sites. It is not clear whether this has been done in other studies.

The number of patients studied was high enough to find a significant difference. For a predicted difference of 20% or greater, when a type I error is set at the 0.05 level and the power of the test is set at 0.80, 58 to 107 patients would have to be studied (2). We studied 118 patients. This group size should be sufficient to help us avoid a type II error.

While the peak titer after influenza virus vaccination is assumed to occur 4 to 6 weeks later, we did not collect blood

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TABLE 1. Comparison of reciprocal serum HI antibody responses 4 and 6 weeks after immunization with the 1992 to 1993 trivalent influenza virus vaccine

Vaccine strain and health status ^a	Geometric mean titer:			% with HI titer \geq 40:	
	Before vaccine	4 wk after vaccine	6 wk after vaccine	4 wk after vaccine	6 wk after vaccine
Healthy group (95 patients)					
Influenza virus A/Texas/36/91 (H1N1)	18	35	35	63	68
Influenza virus A/Beijing/353/89 (H3N2)	29	58	63	78	82
Influenza virus B/Panama/45/90	29	65	66	89	89
Infirm group (23 patients)					
Influenza virus A/Texas/36/91 (H1N1)	19	51	46	85	75
Influenza virus A/Beijing/353/89 (H3N2)	30	63	48	74	74
Influenza virus B/Panama/45/90	20	65	77	82	88

^a The healthy group had a mean age of 74 years (range, 65 to 89 years), 76% had been previously vaccinated, and 46% were men. The infirm group had a mean age of 82 years (range 65 to 93 years), 88% had been previously vaccinated, and 38% were men.

specimens before or after the 4- to 6-week period to determine the peak period with certainty. Peak titers have been reported to occur as early as 2 weeks and as long as 16 weeks after vaccine administration (7). The longer intervals of 8 to 16 weeks occur when adjuvants are added to the vaccine (6). Whether peak periods differ by influenza virus type or subtype and by age or risk group cannot be stated from our study and is not clear in the literature.

In conclusion, from this limited study of 118 patients, it appears that no difference exists between the heights of the serum HI antibody titers when blood specimens are drawn at 4 or 6 weeks after influenza virus vaccination.

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