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Serum Cross-Reactive Antibody Response to a Novel Influenza A (H1N1) Virus After Vaccination with Seasonal Influenza Vaccine

As of May 19, 2009, a total of 5,469 confirmed or probable cases* of human infection with a novel influenza A (H1N1) virus had been documented in 47 states and the District of Columbia (*1,2*). In addition, the virus had spread to 41 countries (*3*), with a total of 4,774 cases reported in countries outside the United States. Because producing a novel influenza A (H1N1) virus vaccine will take several months (*4*), determining whether receipt of seasonal influenza vaccine might offer any protection against the novel influenza A (H1N1) virus is important. Therefore, using stored serum specimens collected during previous vaccine studies, CDC assessed the level of cross-reactive antibody to the novel influenza A (H1N1) virus in cohorts of children and adults before and after they had been vaccinated with the 2005–06, 2006–07, 2007–08, or 2008–09 influenza season vaccines. The results indicated that before vaccination, no cross-reactive antibody to the novel influenza A (H1N1) virus existed among children. Among adults, before vaccination, cross-reactive antibody was detected in 6%–9% of those aged 18–64 years and in 33% of those aged >60 years. Previous vaccination of children with any of four seasonal trivalent, inactivated influenza vaccines (TIV) or with live, attenuated influenza vaccine (LAIV) did not elicit a cross-reactive antibody response to the novel influenza A (H1N1) virus. Among adults, vaccination with seasonal TIV resulted in a twofold increase in cross-reactive antibody response to the novel influenza A (H1N1) virus among those aged 18–64 years, compared with a twelvefold to nineteenfold increase in cross-reactive antibody response to the seasonal H1N1 strain; no increase in cross-reactive antibody response to the novel influenza A (H1N1) virus was observed among adults aged >60 years. These data suggest that receipt of recent (2005–2009) seasonal influenza vaccines is unlikely to elicit a protective antibody response to the novel influenza A (H1N1) virus.

Serum specimens were provided to CDC from academic, government, and industry partners for use as part of the public health response to the emergence of the novel influenza A (H1N1) virus. The specimens had been collected from healthy human participants, with written, informed consent. All participants had been vaccinated either 1) intramuscularly with licensed TIV developed for the northern hemisphere 2005–06, 2006–07, 2007–08, or 2008–09 influenza seasons or 2) intranasally with licensed LAIV developed for the northern hemisphere 2005–06 or 2006–07 influenza seasons. The serum specimens were grouped for influenza serology testing by the age of participants and formulation of the vaccines.

Microneutralization (MN) and hemagglutination inhibition (HI) assays were performed at CDC, according to standard MN and HI procedures (*5,6*). As with vaccine production, the seasonal influenza A (H1N1) viruses used in this study (A/New Caledonia/20/1999 [2005–06 and

*Case definitions available at http://www.cdc.gov/h1n1flu/casedef.htm.

INSIDE

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2006–07], A/Solomon Islands/3/2006 [2007–08], and A/Brisbane/59/2007 [2008–09]) were propagated in embryonated chicken eggs. The novel influenza A (H1N1) virus used in the study was A/California/04/2009, which was grown in Madin-Darby canine kidney cells. All procedures were performed in a biosafety level 2 laboratory using biosafety level 3 practices.[†] The HI assay was performed using 0.5% turkey red blood cells. Serum specimens were treated with receptor-destroying enzymes. Sera containing nonspecific agglutinins were heme-adsorbed and tested at an initial dilution of 1:10. For the MN assay, serum specimens were heat inactivated (at 133ºF [56ºC], for 30 minutes) and tested at an initial dilution of 1:10. For calculation of geometric mean titer (GMT) estimates, a titer of <10 was assigned a value of 5, and a titer of ≥1280 was assigned a value of 1280. Statistical significance was determined using a paired t-test.

An initial comparison between the HI and MN assays was made for panels of sera from children aged 6 months to 9 years (n = 28), adults aged 18–59 years (n = 30), and adults aged >60 years (n = 42). Although the estimated correlation between HI and MN titers was high (r = 0.82) for the seasonal vaccine strains, the MN assay generally yielded higher titers and detected more seroconversions (i.e., fourfold or greater increases in antibody titers) to A/California/04/2009 than the HI assay. Therefore, the MN assay was used to assess the level of cross-reactive antibody to A/California/04/2009 in populations before and after vaccination with seasonal influenza vaccines. Although serum HI antibody titers of 40 are associated with at least a 50% reduction in risk for influenza infection or disease in populations (*7*), no such correlate of protection exists for MN antibody titers. Therefore, a linear regression model was used to predict the MN titer for seasonal influenza A (H1N1) viruses that corresponded to an HI titer of 40 and to measure titer achievement against the seasonal vaccine strain and the novel influenza A (H1N1) virus. In the pediatric population, an HI titer of 40 corresponded to an MN titer of 40, whereas in the adult population the corresponding MN titer was ≥160.

Among 79 children ranging in age from 6 months to 9 years, little evidence was found of prevaccination cross-reactive antibodies to A/California/04/2009 (Table 1). In addition, after vaccination with seasonal TIV, no seroconversions to A/California/04/2009 virus were detected, whereas seroconversions to the seasonal vaccine strains were detected in 67%–100% of children. Children vaccinated with LAIV also had no seroconversions to the A/California/04/2009 virus.

[†] Biosafety level information is available at http://www.cdc.gov/od/ohs/biosfty/bmbl5/bmbl5toc.htm.

TABLE 1. Cross-reactive microneutralization (MN) antibody response to novel influenza A (H1N1) virus* in pediatric recipients (aged 6 months–9 years) of seasonal influenza vaccines

Vaccine	Influenza season	Influenza virus	Age group	No.	% with fourfold or greater increase in antibody titer†	% with MN titer of ≥40§		Geometric mean titer (GMT)¶		
						Prevaccination	Postvaccination	Prevaccination (95% CI**)	Postvaccination (95% CI)	Postvaccination to prevaccination ratio
TIV††	2005–2007§§	A/New Caledonia/20/1999	6 mos–9 yrs	33	67	42	94	31 (21–46)	255 (172–378)	8
		A/California/04/2009			0	0	0	5 (4–6)	6 (6–7)	1
	2007–08	A/Solomon Is/3/2006	5–9 yrs	13	85	54	100	42 (22–80)	575 (303–1093)	14
		A/California/04/2009			0	8	8	10 (7–15)	12 (8–17)	1
	2008–09	A/Brisbane/59/2007	6 mos–3 yrs	9	100	0	100	5 (4–7)	285 (202–402)	57
		A/California/04/2009			0	0	0	5 (—)	5 (—)	1
LAIV¶¶	2005–2007§§	A/New Caledonia/20/1999	6 mos–9 yrs	24	25	46	79	33 (17–63)	73 (38–139)	2
		A/California/04/2009			0	0	4	5 (4–6)	6 (5–7)	1

* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In pediatric populations, an HI titer of 40 corresponds with an MN titer of 40.
¶ A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.
§§ 2005–06 and 2006–07 influenza seasons.
¶¶ Live, attenuated influenza vaccine.

Consistent with previous reports (*4*), vaccination of adults with seasonal TIV resulted in seroconversion to the seasonal influenza A (H1N1) vaccine strain in 74% of adults aged 18–64 years, 78% of adults aged 18–40 years, and 54% of adults aged >60 years (Table 2). In contrast, seroconversion to the A/California/04/2009 virus was detected in 19% of adults aged 18–64 years and 3% of adults aged >60 years who received the 2007–08 vaccine and in 12% of adults aged 18–40 years who received the 2008–09 vaccine. Compared with responses to the seasonal influenza A (H1N1) vaccine virus, postvaccination to prevaccination GMT ratios for the response to A/California/04/2009 virus were fivefold to tenfold lower among all adults. However, 6% of adults aged 18–40 years, 9% of adults 18–64 years, and 33% of adults aged >60 years had prevaccination MN titers of ≥160. After vaccination with seasonal vaccine, 7% of adults aged 18–40 years, 25% of adults aged 18–64 years, and 43% of adults aged >60 years had postvaccination titers of ≥160 to A/California/04/2009. The prevaccination GMT of adults aged >60 years against the novel 2009 H1N1 strain was significantly higher than against the seasonal 2007–08 H1N1 vaccine component ($p<0.001$).

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Editorial Note: The results in this report suggest that vaccination with recent (2005–2009) seasonal influenza vaccines is unlikely to provide protection against the novel influenza A (H1N1) virus. Although vaccination of adults with seasonal TIV generally resulted in a small increase in antibodies against the novel influenza A (H1N1) virus, whether such levels of cross-reactive antibody provide any protection against infection with novel influenza A (H1N1) virus is unknown. These results are consistent with the substantial degree of genetic divergence of the novel influenza A (H1N1) virus of swine origin from recent seasonal human H1N1 viruses; A/California/04/09 shares only 72%–73% amino acid identity in the HA1 portion of the hemagglutinin molecule with the seasonal viruses used in this study. For comparison, the amino acid sequence identity in the HA1 portion among seasonal vaccine strains used in this study is 97%–98%.

Although the number of sera from children tested in this analysis was small, results indicate that U.S. children are largely serologically naïve to the novel influenza A (H1N1) virus and that vaccination with seasonal TIV or LAIV does not elicit any measurable level of cross-reactive antibody to the novel virus. Results among adults suggest that some degree of preexisting immunity to the novel H1N1 strains exists, especially among adults aged >60 years. One possible explanation is that some adults in this age group have had previous exposure, either through infection or vaccination, to an influenza A (H1N1) virus that is genetically and antigenically more closely related

TABLE 2. Cross-reactive microneutralization (MN) antibody response to novel influenza A (H1N1) virus* in adult recipients of seasonal influenza vaccines

Vaccine	Influenza season	Influenza virus	Age group (yrs)	No.	% with fourfold or greater increase in antibody titer†	% with MN titer of ≥160§		Geometric mean titer (GMT)¶		
						Prevaccination	Postvaccination	Prevaccination (95% CI**)	Postvaccination (95% CI)	Postvaccination to prevaccination ratio
TIV††	2007–08	A/Solomon Is/3/2006	18–64	134	74	28	92	48 (40–59)	561 (462–682)	12
		A/California/04/2009			19	9	25	28 (23–34)	53 (43–66)	2
	2008–09	A/Brisbane/59/2007	18–40	83	78	20	88	29 (22–38)	546 (418–713)	19
		A/California/04/2009			12	6	7	11 (9–14)	21 (16–26)	2
	2007–08	A/Solomon Is/3/2006	>60	63	54	14	54	31 (22–42)	143 (105–194)	5
		A/California/04/2009			3	33	43	92 (71–121)	97 (74–127)	1

* A/California/04/2009.
† A fourfold or greater increase in antibody titer indicates seroconversion (a response to the vaccine).
§ A linear regression model was used to predict the MN titer for seasonal H1N1 viruses that corresponded to a hemagglutination inhibition (HI) antibody titer of 40. (Serum HI antibody titers of 40 are associated with at least a 50% decrease in risk for influenza infection or disease [7]). In adult populations, an HI titer of 40 corresponds with an MN titer of ≥160.
¶ A titer of 1280 was used for all samples with a titer of ≥1280. The dilution of sera in the first well is based on the combination of a 1:10 serum dilution with an equal volume of diluted virus for a final serum dilution referred to as 1:10. In the statistical models, study participants were treated as random effects sampled from a larger population of study participants, and duplicate samples were treated as random effects nested within each study participant.
** Confidence interval.
†† Trivalent, inactivated influenza vaccine.

to the novel influenza A (H1N1) virus than are contemporary seasonal H1N1 strains. Ongoing assessment of the cross-reactive antibody response among persons in different age groups might identify a particular age group that would allow further clarification of the cross-reactive serologic response. Development of a strain-specific vaccine against the novel influenza A (H1N1) virus is needed for optimal protection against the virus among persons of all ages.

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Federal and State Cigarette Excise Taxes — United States, 1995–2009

On April 1, 2009, the largest federal cigarette excise tax increase in history went into effect, bringing the combined federal and average state excise tax for cigarettes to $2.21 per pack and achieving the *Healthy People 2010* (HP2010) objective (27-21a) to increase the combined federal and average state cigarette excise tax to at least $2 per pack (*1*). This report summarizes changes in the federal excise tax, as well as state excise taxes for all 50 states and the District of Columbia (DC) from December 31, 1995 to April 1, 2009.* The findings indicate that the federal excise tax increased from 24 cents per pack in 1995 to $1.01 per pack in 2009, and the average state excise tax increased from 32.7 cents per pack to $1.20 per pack during the same period.† These increases represent a 321% increase in the federal excise tax and a 267% increase in the average state excise tax since 1995. Price increases should be combined with other evidence-based policy and clinical

* For this report, DC is included among results for states.
† The federal tax of $50.33 for cigarettes is levied per 1,000 cigarettes. When calculated per pack of 20 cigarettes, this is $1.0066 per pack. For this study, this fractional tax is referred to as $1.01 per pack.