Long-Term Immunogenicity of the Pandemic Influenza A/H1N1 2009 Vaccine among Health Care Workers: Influence of Prior Seasonal Influenza Vaccination

Joon Young Song, Hee Jin Cheong, Yu Bin Seo, In Seon Kim, Ji Yun Noh, Won Suk Choi, Jacob Lee, Hye Won Jeong, Sae Yoon Kee, Woo Joo Kim

Division of Infectious Diseases, Department of Internal Medicine, Konkuk University School of Medicine, Seoul, South Korea; Division of Infectious Diseases, Department of Internal Medicine, Cheongju University College of Medicine, Cheongju, South Korea; Division of Infectious Diseases, Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea; Division of Infectious Diseases, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, South Korea; Division of Infectious Diseases, Department of Internal Medicine, Chungbuk National University College of Medicine, Cheongju, South Korea; Division of Infectious Diseases, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, South Korea

Health care workers (HCWs) are at great risk of influenza infection and transmission. Vaccination for seasonal influenza is routinely recommended, but this strategy should be reconsidered in a pandemic situation. Between October 2009 and September 2010, a multicenter study was conducted to assess the long-term immunogenicity of the A/H1N1 2009 monovalent influenza vaccine among HCWs compared to non-health care workers (NHCWs). The influence of prior seasonal influenza vaccination was also assessed with respect to the immunogenicity of pandemic H1N1 influenza vaccine. Serum hemagglutinin inhibition titers were determined prevaccination and then at 1, 6, and 10 months after vaccination. Of the 360 enrolled HCW subjects, 289 participated in the study up to 10 months after H1N1 monovalent influenza vaccination, while 60 of 65 NHCW subjects were followed up. Seroprotection rates, seroconversion rates, and geometric mean titer (GMT) ratios fulfilled the European Union’s licensure criteria for influenza A/California/7/2009 (H1N1) at 1 month after vaccination in both the HCWs and NHCWs, without any significant difference. At 6 months after vaccination, the seroprotection rate was more significantly lowered among the NHCWs than among the HCWs (P < 0.01). Overall, postvaccination (1, 6, and 10 months after vaccination) GMTs for A/California/7/2009 (H1N1) were significantly lower among the seasonal influenza vaccine recipients than among the nonrecipients (P < 0.05). In conclusion, HCWs should be encouraged to receive an annual influenza vaccination, considering the risk of repeated exposure. However, prior receipt of seasonal influenza vaccine showed a negative influence on immunogenicity for the pandemic A/H1N1 2009 influenza vaccine.

Health care facilities can be a source for the rapid spread of influenza, and health care workers (HCWs) are considered the primary source of influenza transmission to their patients. Transmission has been shown to occur from patients to HCWs, from HCWs to patients, and among health care staff (1–4). Vaccines are the primary method of control for influenza and its complications. In fact, generalized vaccination of HCWs has been shown to have a positive impact on absenteeism rates and the economic burden associated with the seasonal epidemic (5). Nevertheless, based on the Advisory Committee on Immunization Practice (ACIP) recommendations, HCWs have one of the lowest influenza vaccine compliance rates (6–8).

During the 2009 influenza pandemic, HCWs were considered an important priority group for influenza vaccination, and it was recommended that they receive both the seasonal and the pandemic vaccines for fear of the emergence of a reassortant virus. However, it is unknown how such a vaccination strategy might affect the immunogenicity of a pandemic vaccine. Moreover, considering that influenza circulates longer during a pandemic (>6 months), there was a concern that a single-dose influenza vaccine for HCWs would be insufficient to provide long-term protection.

In the present study, we evaluated the long-term immunogenicity of the A/H1N1 2009 influenza monovalent vaccine in HCWs aged 18 to 64 years. In addition, we evaluated the impact of prior seasonal influenza vaccination on the immunogenicity of the A/H1N1 2009 influenza monovalent vaccine.

MATERIALS AND METHODS

Study design. Between October 2009 and September 2010, we conducted a multicenter study to assess the immunogenicity of the A/H1N1 2009 monovalent influenza vaccine and its persistence after vaccination among subjects aged 18 to 64 years. The study was performed at four university hospitals in Korea. The primary objective of the study was to investigate both the short-term (1 month postvaccination) and the long-term (6 and 10 months postvaccination) immunogenicities of the influenza vaccine among HCWs compared to the general population (non-health care workers [NHCWs]). The immunogenicity of the A/H1N1 2009 monovalent influenza vaccine among HCWs was further analyzed according to whether or not they had received a seasonal influenza vaccine.

The exclusion criteria included a history of laboratory-confirmed infection with influenza A/H1N1 2009, prior receipt of an influenza A/H1N1 2009 monovalent vaccine, immunosuppression, hypersensitivity to any component of the vaccines (including eggs), history of Guillain-Barre syndrome, thrombocytopenia or any coagulation disorder contra-indicating intramuscular injection, current febrile illness or another acute illness, administration of gamma globulin during the previous 3 months, and any other vaccination within the past 30 days.

Received 5 December 2012 Returned for modification 17 January 2013 Accepted 25 January 2013 Published ahead of print 30 January 2013 Address correspondence to Hee Jin Cheong, heejinmd@medimail.co.kr. Copyright © 2013, American Society for Microbiology. All Rights Reserved. doi:10.1128/CVI.00725-12
The demographic data collected for the study subjects included age, gender, comorbidities, and history of vaccination for seasonal influenza (2009 to 2010). Each subject received one dose of 15 μg monovalent inactivated vaccine, which was administered intramuscularly into the deltoid muscle. On days 0, 30 ± 7, 180 ± 7, and 300 ± 7 postvaccination, a 10-ml venous blood sample was obtained from each subject.

The study was approved by the ethics committee of each institution involved and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. All subjects provided written informed consent before enrollment.

Vaccines. The influenza A/H1N1 2009 vaccine, a monovalent, nonadjuvanted, inactivated, split-virus vaccine (15 μg hemagglutinin antigen per 0.5-ml prefilled syringe), was produced by Green Cross Corporation (Yongin, South Korea). The seed virus was prepared from reassortant vaccine virus A/California/7/2009 NYMC X-179A, distributed by the National Institute for Biological Standards and Control in the United Kingdom. The vaccine was prepared in embryonated chicken eggs using standard techniques for the production of seasonal trivalent inactivated vaccines.

Immunogenicity assessment. Antibody responses were detected by means of hemagglutination inhibition (HI) assays, according to established procedures and with use of turkey erythrocytes (9, 10), at the Korea University Guro Hospital (Yongin, South Korea). The seed virus was prepared from reasortant vaccine virus A/California/7/2009 NYMC X-179A, distributed by the National Institute for Biological Standards and Control in the United Kingdom. The vaccine was prepared in embryonated chicken eggs using standard techniques for the production of seasonal trivalent inactivated vaccines.

**Results**

Baseline characteristics of study subjects. Of the 360 enrolled HCWs, 289 completed the study up to 10 months after the initial A/H1N1 2009 monovalent influenza vaccination. Among the 79 subjects who dropped out, two were diagnosed with influenza A/H1N1 2009 during the follow-up period, and the others refused follow-up after the initial consent. Sixty of the 65 NHCW subjects were followed up until 10 months postvaccination; the five subjects who dropped out refused follow-up after the initial consent. Among the 289 HCWs, 209 received a seasonal influenza vaccine at least 3 weeks before A/H1N1 2009 vaccination. The baseline characteristics of the study subjects are presented in Table 1.

Immunogenicity of 2009 pandemic influenza vaccine: health care workers versus non-health care workers. Seroprotection rates, seroconversion rates, and GMT fold changes fulfilled the EMA criteria for influenza A/California/7/2009 (H1N1) at 1 month after vaccination in both the HCWs and the NHCWs, without a significant difference (Table 2). Irrespective of previous vaccination for seasonal influenza (P = 0.51), rates of seroprotection and seroconversion met the EMA criteria in the HCWs. However, GMTs for A/California/7/2009 (H1N1) were significantly lower among the seasonal influenza vaccine recipients than among the nonrecipients at 1 month postvaccination (P = 0.01).

Immunogenicity of 2009 pandemic influenza vaccine against 2009-2010 seasonal influenza vaccine strain. We assessed HI titers against the 2009-2010 seasonal influenza A/H1N1 vaccine strain (influenza A/Brisbane/59/2007) with baseline and postvaccination (at 1 month) samples after the pandemic influenza vaccination. GMTs for influenza A/Brisbane/59/2007 (H1N1) did not increase remarkably.

**Table 1** Demographic characteristics of the study subjects

| Parameter                         | HCWs                  | NHCWs                  | P value<sup>a</sup> | Total (n = 289) | NHCWs (n = 60) | P value<sup>c</sup> |
|-----------------------------------|-----------------------|------------------------|---------------------|-----------------|----------------|---------------------|
| Male sex, no. (%)                 | 60 (28.7)             | 24 (30.0)              | 0.83                | 84 (29.1%)      | 13 (21.7%)      | 0.27                |
| Mean age (yr) ± SD                | 34.7 ± 8.2            | 33.1 ± 8.9             | 0.16                | 34.2 ± 8.4      | 36.7 ± 10.2     | 0.07                |
| Age group (yr), no. (%)           | 20–29                 | 70 (33.5)              | 38 (47.5)           | 108 (34.9)      | 20 (33.3)       | 0.23                |
|                                  | 30–39                 | 80 (38.3)              | 23 (28.8)           | 103 (35.6)      | 14 (23.3)       |                     |
|                                  | 40–49                 | 49 (23.4)              | 15 (18.8)           | 64 (22.1)       | 20 (33.3)       |                     |
|                                  | 50–59                 | 9 (4.3)                | 3 (3.8)             | 12 (4.2)        | 6 (10.0)        |                     |
|                                  | 60–64                 | 1 (0.5)                | 1 (0.1)             | 2 (0.7)         | 1 (1.7)         |                     |
| Comorbidities, no.                | 2 (0.96)              | 1 (1.3)                | 0.83                | 3 (1.0)         | 1 (1.7)         | 0.54                |
| Diabetes                          | 1                     | 1                      |                     | 2               | 1              |                     |
| Chronic renal failure             | 0                     | 0                      |                     | 0               | 0              |                     |
| Liver cirrhosis                   | 1                     | 0                      |                     | 1               | 0              |                     |
| Malignancy                        | 1                     | 1                      |                     | 2               | 1              |                     |
| Immunosuppressant treatment       | 0                     | 0                      |                     | 0               | 0              |                     |

<sup>a</sup> HCWs, health care workers; NHCWs, non-health care workers.

<sup>b</sup> Comparison between seasonal influenza vaccine recipients and nonrecipients.

<sup>c</sup> Comparison between HCWs and NHCWs.
TABLE 2 Comparison of short and long-term immunity values for influenza A/H1N1 2009 for seasonal influenza vaccine recipients versus nonrecipients

| Immunogenicity end point | HCWs (n = 209) | Nonrecipients (n = 80) | P value | Total (n = 289) | NHWCs (n = 60) | P value |
|--------------------------|----------------|-----------------------|---------|----------------|----------------|---------|
| Seroprotection rate, % (95% CI) | | | | | | |
| 1 mo postvaccination | 89.5 (84.6–92.9) | 92.5 (84.6–96.5) | 0.51 | 90.3 (86.3–93.2) | 85.0 (73.8–91.8) | 0.25 |
| 6 mo postvaccination | 90.4 (85.7–93.7) | 91.3 (83.0–95.6) | 0.83 | 90.7 (86.7–93.5) | 66.7 (54.0–77.3) | <0.01 |
| 10 mo postvaccination | 53.1 (46.3–59.8) | 68.8 (57.9–77.8) | 0.02 | 57.4 (51.7–63.0) | 61.7 (49.0–72.9) | 0.57 |
| GMT (95% CI) | | | | | | |
| Prevaccination | 12.7 (11.5–13.9) | 14.5 (18.0–271.3) | 0.16 | 13.1 (12.1–14.3) | 10.5 (8.1–13.6) | 0.10 |
| 1 mo postvaccination | 110.7 (94.4–129.9) | 167.1 (124.2–224.9) | 0.01 | 124.1 (107.6–143.1) | 146.1 (97.7–218.6) | 0.45 |
| 6 mo postvaccination | 93.9 (81.8–107.7) | 167.1 (127.8–218.5) | <.01 | 110.1 (90.7–125.0) | 47.4 (33.7–66.7) | <0.01 |
| 10 mo postvaccination | 31.7 (26.7–37.6) | 55.6 (39.9–77.6) | <.01 | 37.0 (31.7–43.3) | 40.9 (29.9–55.9) | 0.60 |
| GMT ratio (95% CI) | | | | | | |
| 1 mo postvaccination | 8.7 (7.4–10.3) | 11.5 (8.4–15.8) | 0.13 | 9.4 (8.1–10.9) | 13.9 (9.1–21.4) | 0.09 |
| 6 mo postvaccination | 7.4 (6.5–8.5) | 11.5 (8.7–15.2) | <.01 | 8.4 (7.4–9.5) | 4.5 (3.2–6.4) | <0.01 |
| 10 mo postvaccination | 2.5 (2.1–3.0) | 3.8 (2.7–5.4) | 0.03 | 2.8 (2.4–3.3) | 3.8 (2.8–5.3) | 0.10 |

*Geometric mean titer ratios are the ratios of the antibody level at the day of interest compared to that at day 0. Seroconversion was defined as a prevaccination antibody titer of ≥1:10 and a postvaccination titer of ≥1:40. HI, hemagglutination inhibition; CI, confidence interval; GMT, geometric mean titer; HCWs, health care workers; NHCWs, non-health care workers.

TABLE 3 Comparison of immunity against A/Brisbane/59/2007 (H1N1) for the seasonal influenza vaccine recipients and nonrecipients pre- and postvaccination at 1 month after flu A/H1N1 2009 vaccination

| Parameter | Seasonal influenza vaccine recipients (n = 209) | Seasonal influenza vaccine nonrecipients (n = 80) | P value |
|-----------|----------------------------------------------|-----------------------------------------------|---------|
| GMT (95% CI) | | | |
| Prevaccination | 62.3 (54.4–71.3) | 37.9 (27.5–52.1) | <.01 |
| Postvaccination | 68.6 (62.3–75.5) | 78.6 (64.2–96.1) | 0.23 |
| GMT ratio (95% CI) | 1.1 (1.0–1.1) | 2.1 (1.8–2.3) | 0.01 |

*A/Brisbane/59/2007 (H1N1) is the 2009-2010 seasonal influenza vaccine strain. GMT, geometric mean titer; CI, confidence interval.

In the seasonal vaccine recipients at 1 month after the pandemic influenza vaccination (GMT fold change, 1.1) (Table 3).

Immunologic persistence of 2009 pandemic influenza vaccine: health care workers versus non-health care workers. Pre-vaccination GMTs at and GMTs at 1 month postvaccination were indistinguishable between the HCWs and the NHCWs, whereas GMTs at 6 and 10 months postvaccination were significantly higher in the HCWs than in the NHCWs (P < 0.01). At 6 months after vaccination, the seroprotection rate was more significantly lowered among the NHCWs than among the HCWs (P < 0.01). As for the HCWs, all three EMA criteria were fully met even at 6 months after vaccination. Seroprotection was preserved in more than half of both the HCWs and the NHCWs (57.4% versus 61.7%; P = 0.57) up to 10 months postvaccination.

As for the vaccination status for seasonal influenza, overall postvaccination (1, 6, and 10 months after vaccination) GMTs for A/California/7/2009 (H1N1) were significantly lower among the seasonal influenza vaccine recipients than among the nonrecipients (1 month, P = 0.01; 6 and 10 months, P < 0.01) (Table 2). Though the difference was insignificant up to 6 months after vaccination, there was a significant difference in the seroprotection rates for A/California/7/2009 (H1N1) according to the vaccination status for seasonal influenza at 10 months postvaccination (recipients, 53.1%; nonrecipients, 68.8% [P = 0.02]).

DISCUSSION

This study shows that the 2009 pandemic H1N1 vaccine can induce long-term immunity as assessed by serological assays, which is in line with several previous reports (12–14). Vaccination is the primary tool for the control of influenza. According to a previous study, the overall vaccine effectiveness for influenza A/California/7/2009 (H1N1) was 73.4% in Korea (15). Based on the results of the present study, in accordance with ACIP recommendations, all HCWs should be encouraged to receive an influenza vaccination. During the 2009 pandemic, the A/H1N1 2009 vaccine coverage rate in HCWs was reported to be greater than 90% in Korea, which was remarkably higher than those during interpandemic periods (16).

Another important finding of this study is the negative effect of prior seasonal influenza vaccination on the immunogenicity of the A/H1N1 2009 pandemic vaccine. A reduced HI antibody response against A/California/7/2009 (H1N1) was noted in healthy adults who had previously received a seasonal influenza vaccine. This finding has been presented before in the ferret model (17) as well as in clinical studies (18, 19). The mechanism is still uncertain, but the following hypothesis may be considered. There is a chance that a recent exposure to a seasonal vaccine may hamper...
the production of new antibodies by the pandemic influenza vaccine, which preferentially reactivates previously activated high-affinity memory B cells rather than naive B cells (the hypothesis of original antigenic sin) (20). Contrary to our expectation, GMTs for the 2009-2010 seasonal influenza A/H1N1 vaccine strain (A/Brussels/59/2007) did not increase remarkably in the seasonal vaccine recipients at 1 month after the pandemic influenza vaccination. Another possibility with respect to original antigenic sin is the generation of antibodies of lower affinity against pandemic influenza virus. Allowing for these points, in a pandemic situation with a new influenza virus, routine generalized vaccination for seasonal influenza needs to be reconsidered.

Interestingly however, a recent study with ferrets showed that prior seasonal influenza vaccination induced a positive immunologic priming effect on subsequent MF59-adjuvanted A/H1N1 2009 influenza vaccination (21). MF59 adjuvant might enhance the activity of CD4 T cells and memory B cells. Moreover, in the study by Langley et al. (22), subjects immunized first with seasonal influenza vaccine and then with two doses of AS03-adjuvanted pandemic influenza A/H1N1 2009 vaccine had noninferior immune responses to the pandemic strain compared to those subjects receiving two doses of AS03-adjuvanted pandemic influenza A/H1N1 2009 vaccine without previous receipt of seasonal vaccine. Further studies are required to better clarify whether new adjuvants (MF59 and AS03) may overcome the negative impact from prior seasonal influenza vaccination or not.

In this study, the seroprotection rate was more significantly lowered among the NHCWs than among the HCWs at 6 months after vaccination. This might reflect repeated exposure of HCWs to influenza virus. Allowing for these points, the generation of antibodies of lower affinity against pandemic influenza A/H1N1pdm09 vaccine antigen, with and without AS03 adjuvant system, may overcome the negative impact from prior seasonal influenza vaccination or not.

In this study, we observed that the activity of CD4 T cells and memory B cells. Moreover, in the study by Langley et al. (22), subjects immunized first with seasonal influenza vaccine and then with two doses of AS03-adjuvanted pandemic influenza A/H1N1 2009 vaccine had noninferior immune responses to the pandemic strain compared to those subjects receiving two doses of AS03-adjuvanted pandemic influenza A/H1N1 2009 vaccine without previous receipt of seasonal vaccine. Further studies are required to better clarify whether new adjuvants (MF59 and AS03) may overcome the negative impact from prior seasonal influenza vaccination or not.

ACKNOWLEDGMENTS
This research was supported by a grant (09122KFDA578) from the Korean Food and Drug Administration in 2009.
We have no conflict of interest to declare.

REFERENCES
1. Coles FB, Balzano GJ, Morse DL. 1992. An outbreak of influenza A (H3N2) in a well immunized nursing home population. J. Am. Geriatr. Soc. 40:589–592.
2. Ikeda RM, Drabkin PD. 1992. Influenza A outbreaks in nursing homes. J. Am. Geriatr. Soc. 40:1288.
3. Sepkowitz KA. 1996. Occupationally acquired infections in health care workers. Part I. Ann. Intern. Med. 125:826–834.
4. Van Voris LP, Belshe RB, Shaffer JL. 1982. Nosocomial influenza B virus infection in the elderly. Ann. Intern. Med. 96:153–158.
5. Wilde JA, McMillan JA, Serwint J, Butta J, O’Riordan MA, Steinhoff MC. 1999. Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA 281:908–913.
6. de Juanes JR, García de Codes A, Arrazola MP, Jaen F, Sanz MI, Gonzalez A. 2007. Influenza vaccination coverage among hospital personnel over three consecutive vaccination campaigns (2001-2002 to 2003-2004). Vaccine 25:201–204.
7. Mereckiene J, Cotter S, Nicoll A, Levy-Bruhl D, Ferro A, Trindade G, Zanoni G, Berra P, Salmaso S, O’Flanagan D. 2008. National seasonal influenza vaccination survey in Europe, 2008. Euro Surveill. 13:19017.
8. Wilson WR, Rabenau H, Durie S, Altmann R. 2009. Influenza vaccination compliance among health care workers in a German university hospital. Infection 37:197–202.
9. Hannoun C, Megas F, Piercy J. 2004. Immunogenicity and protective efficacy of influenza vaccination. Virus Res. 103:133–138.
10. Kendal AP, Pereira MS, Skehel JJ. 1982. Concepts and procedures for laboratory based influenza surveillance. Viral Disease Unit, World Health Organization, Geneva, Switzerland.
11. European Committee for Proprietary Medicinal Products. 1997. Note for guidance on harmonisation of requirements for influenza vaccines CPMP/WBP/214/96. The Europeen Agency for the Evaluation of Medicinal Products, London, United Kingdom.
12. Ikematsu H, Nagai H, Kawashima M, Wakiwami Y, Tenjinbaru K, Li P, Walravens K, Pillard P, Roman F. 2012. Characterization and long-term persistence of immune response following two doses of an AS03A-adjuvanted H1N1 influenza vaccine in healthy Japanese adults. Hum. Vaccines Immunother. 8:260–266.
13. Song JY, Cheong HJ, Seo YB, Kim IS, Noh JY, Heo JY, Choi WS, Lee J, Kim WJ. 2012. Comparison of the long-term immunogenicity of two pandemic influenza A/H1N1 2009 vaccines, the MF59-adjuvanted and unadjuvanted vaccines, in adults. Clin. Vaccine Immunol. 19:638–641.
14. Walker WT, de Whalley P, Andrews N, Oser C, Casey M, Michaelis L, Hoschler K, Harrill C, Moulds P, Thompson B, Jones C, Chalk P, Kerridge S, John TM, Okike I, Ladhani S, Tomlinson R, Heath PT, Miller E, Faust SN, Snape MD, Finn A, Pollard AJ. 2012. H1N1 antibody persistence 1 year after immunization with an adjuvanted or whole-virus pandemic vaccine and immunogenicity and reactogenicity of subsequent seasonal vaccine: a multicenter follow-on study. Clin. Infect. Dis. 54:661–669.
15. Song JY, Cheong HJ, Heo JY, Noh JY, Jeon HW, Kee SY, Kim WJ. 2011. Effectiveness of the pandemic influenza A/H1N1 2009 monovalent vaccine in Korea. Vaccine 29:1395–1398.
16. Park SW, Lee JH, Kim ES, Kwak YG, Moon CS, Yeom JS, Lee CS. 2011. Adverse events associated with the 2009 H1N1 influenza vaccination and the vaccination coverage rate in health care workers. Am. J. Infect. Control 39:69–71.
17. Kohberger GP, Meunier I, Patel A, Pillet S, Gren J, Stehner S, Leung A, Neufeld JL, Kobasa D, von Messling V. 2010. Assessment of the efficacy of commercially available and candidate vaccines against a pandemic H1N1 2009 virus. J. Infect. Dis. 201:1000–1006.
18. Janjua NZ, Skowronska DM, Hottes TS, Osei W, Adams E, Petric M, Sabaudic S, Chan T, Mak A, Lem M, Tang P, Patrick DM, De Serres G, Bowering D. 2010. Seasonal influenza vaccine and increased risk of pandemic A/H1N1-related illness: first detection of the association in British Columbia, Canada. Clin. Infect. Dis. 51:1017–1027.
19. Skowronska DM, De Serres G, Crowcroft NS, Janjua NZ, Boulinne N, Hottes TS, Rosella LC, Dickinson JA, Gilca R, Sethi P, Ouhammoune N, Willison DJ, Rouleau I, Petric M, Fonseca K, Dews SJ, Rebbapragada A, Charest H, Hamelin ME, Boivin G, Garidy JL, Li Y, Kwint JD, Patrick DM, Brunham RC. 2010. Association between the 2008-09 seasonal influenza vaccine and pandemic H1N1 illness among children aged <5 years in a subarctic community, Nunavut, Canada. Clin. Infect. Dis. 50:838–843.
20. Dormitzer PR, Gali G, Castellino F, Golding H, Kurana S, Del Giudice G, Rappuoli R. 2011. Influenza vaccine immunology. Immunol. Rev. 239:167–177.
21. Del Giudice G, Stittelaar KJ, van Amerongen G, Simon J, Osterhaus AD, Stohr K, Rappuoli R. 2009. Seasonal influenza vaccine provides priming for A/H1N1 immunization. Sci. Transl. Med. 1:12re1.
22. Langley JM, Frenette L, Chu L, McNeil S, Halperin S, Li P, Vaughn D. 2012. A randomized, controlled non-inferiority trial comparing A(H1N1)pdm09 vaccine antigen, with and without AS03 adjuvant system, co-administered or sequentially administered with an inactivated trivalent seasonal influenza vaccine. BMC Infect. Dis. 12:279.