Reply to Sambhara

To the Editor—We are pleased to respond to the interesting questions raised in Sambhara’s letter regarding our article [1]. How has prior exposure to 2009 pandemic influenza A virus subtype H1N1 (A[H1N1]pdm09) or previous vaccination influenced the A(H1N1)pdm09-specific vaccine responses? In Norway, mass vaccination was initiated before the peak of the pandemic, and healthcare workers (HCWs) were prioritized for early vaccination [2]. Hospital policy was that all HCWs who experienced respiratory symptoms were required to have a A(H1N1)pdm09-negative result of polymerase chain reaction analysis before returning to work. None of our HCWs reported experiencing an influenza-like illness prior to or after vaccination. All subjects (10 controls and 2 low responders) who had prevaccination hemagglutination
Inhibition (HI) titers of 9–63 worked on the infectious diseases ward and may, thus, have acquired a subclinical infection during patient care. We found slightly lower HI responses after A(H1N1)pdm09 vaccination in subjects vaccinated in the previous season, compared with HCWs who were not vaccinated (Figure 1A). As previously reported [3], 2008–2009 seasonal vaccine did not boost the A(H1N1)pdm09-specific HI responses.

There was a trend toward higher HI responses in controls with prevaccination titers, compared with those with no prevaccination titer, although this difference was not statistically significant (Figure 1B). However, the responses of all controls were significantly higher than those in the low responders 21 and 90 days after vaccination. Because serum antibodies are secreted by plasma cells, prevaccination HI titers may not reflect the frequencies of cross-strain–specific memory B and T cells responsible for recall/memory responses, but rather indicate exposure to A(H1N1)pdm09 or a related strain. It can be argued that the controls (ie, responders) elicited a more rapid response than low responders, because by day 7 after vaccination HI titers of >40 were found in 84% of responders (21 of 25) and only 43% of low responders (3 of 7), but by day 14 all except 1 subject had HI titers of >40. Furthermore, the controls had higher frequencies of A(H1N1)pdm09-specific immunoglobulin G (IgG)–expressing antibody-secreting cells (ASCs) and higher ratios of IgG to immunoglobulin M at day 7. ASC frequencies can only be measured transiently in peripheral blood, but they generally peak 7 days after vaccination [4] and were therefore evaluated at this time point. Although an association between ASCs and HI titers would be expected, a correlation is not always observed [4, 5]. In a recent study, peak frequencies of influenza virus–specific ASCs correlated significantly with HI responses, but were observed at different time points, from 5–8 days after vaccination [6]. Thus, a kinetics study may have revealed a correlation between peak ASC frequencies and HI responses in the re-vaccinated subjects. Importantly, the ASCs displayed in Figure 3C of our article [1] were activated influenza virus–specific memory B cells, which were measured by an enzyme-linked immunosorbent assay after polyclonal activation, which thus accounted for the high frequencies of influenza virus–specific ASCs (these were not an overestimation of responses by a factor 10). Memory B-cell frequencies after revaccination correlated significantly with HI titers [1] and were in agreement with findings after trivalent seasonal influenza vaccination [7]. Therefore, our study illustrates the importance of monitoring vaccinees to identify low responders and the potential of protecting these by an extra vaccine dose.

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**Figure 1.** Influence of previous seasonal influenza vaccination or prevaccination hemagglutination inhibition (HI) antibody titers on serological responses to 2009 pandemic influenza A virus subtype H1N1 (A[H1N1]pdm09) vaccine. A. Receipt of 2008–2009 seasonal influenza vaccination was not associated with higher HI titers following A[H1N1]pdm09 vaccination. Subjects were divided on the basis of previous receipt of 2008–2009 seasonal influenza vaccination or no receipt of seasonal influenza vaccination, and the HI antibody responses were measured in sera obtained 21 days after A(H1N1)pdm09 vaccination. No statistically significant differences were observed between the 2 groups (P = .06, by the unpaired Student t test). B. Pre-vaccination HI-seropositive vaccinees in the control group had the highest postvaccination HI titers, although titers were not significantly different from those of the prevaccination seronegative individuals. At days 21 and 90, both control groups had significantly higher HI titers than the low responder group. The HI geometric mean titer (GMT) after 1 dose of AS03-adjuvanted A(H1N1)pdm09 vaccine is shown, with 95% confidence intervals indicated by error bars. *P < .05, by an unpaired Student t test. Abbreviations: C+, control healthcare worker with detectable HI titers before vaccination; C−, control healthcare worker with no detectable HI titers before vaccination; LR, low responders who required a second dose of vaccine.
Note

Potential conflicts of interest. All authors: No reported conflicts.

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