Reply to Skowronski

To the Editor—We thank Skowronski et al for encouraging further discussion of the effect of seasonal trivalent inactivated influenza vaccination (TIV) on the risk of pandemic H1N1 (pH1N1) infection [1]. Using the original data from our paper (made available on the corresponding author’s homepage [2]) the crude odds ratio [OR] for pH1N1 infection among TIV versus placebo recipients was 3.04 (95% confidence interval [CI]: 1.04 – 8.91) and the corresponding relative risk was 2.42 (95% CI: .99 – 5.95). We found that infection with seasonal influenza was associated with a reduced risk of pH1N1. This effect was statistically significant in all participants combined (Table 6 [2]) and of a similar magnitude although not statistically significant in randomized participants, possibly because of reduced power with a smaller sample size (Table 7 [2]). After adjustment for prior seasonal infection, the effect of TIV was not statistically significant.
with a point estimate of 2.74 (95% CI: 0.84–8.91). Although the point estimate is large [1], we caution against overinterpretation of nonsignificant effects. The infection-block hypothesis is sufficient to explain the excess risk of pH1N1 in TIV recipients in our study.

Nevertheless, we agree with Skowronski et al that a true OR greater than 2 could be difficult to explain by the infection-block hypothesis alone [1]. However, we are wary of overinterpretation of our results for 2 reasons. Firstly, the confidence interval on our estimated OR for pH1N1 in TIV recipients was wide (although always greater than 1) and consistent with a wide range of true ORs. The 95% CI around our estimated OR reflects a plausible range for the true OR, and we would not expect our estimate of the OR to match the true OR exactly. We also note that ORs approaching 2 could be obtained by modification of the illustrative calculation of Skowronski et al [1] to account for pre-existing immunity to seasonal influenza in some children (data not shown). In such circumstances, a true OR between 1 and 2 would be consistent with our findings. Secondly, few infections indicated by serology could be confirmed by virologic testing of nose and throat swabs collected during illness episodes [2]. Further work is needed to explore how imperfect sensitivity and specificity of serology as a measure of infection, such as for the seasonal H3N2 virus in 2009 [3], could be accounted for to permit more accurate measures of seasonal and pandemic influenza infection in our study and other cohort studies [4].

We agree with Skowronski et al that the infection-block hypothesis is not the only possible scenario that could explain an increased risk of pH1N1 infection in TIV recipients. It is important for further studies to test the hypothesis that TIV could increase susceptibility to pH1N1 infection via antibody-dependent enhancement or other mechanisms [1]. It would also be important to determine whether any such effect is specific to certain vaccines, and whether any effect is specific to the 2009 pH1N1 virus or applies to many influenza viruses. Finally, regarding the infection-block hypothesis, further work is needed to characterize immunity following influenza virus infection.

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