


COMMENTARY



Immunodominance hierarchy of influenza subtype-specific neutralizing antibody response as a hurdle to effectiveness of polyvalent vaccine

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ABSTRACT

Strengthening of immunodominance hierarchy of influenza subtype-specific neutralizing antibody response by annual polyvalent vaccinations could increase the variation of vaccine effectiveness by subtype. Therefore, we suggest the assessment of neutralizing antibody titer prior to seasonal vaccination and recommend the inoculation of only strains lower than protective levels.

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Introduction

The World Health Organization reports the composition of influenza virus vaccines annually, and we vaccinate according to their recommendation based on three virus subtypes (A/H1N1, A/H3N2, and B). Although this has been shown to be an effective method to prevent infections, we question whether it is best to inoculate the three subtypes at the same time annually. In April 2016, a systematic review containing test-negative design studies to evaluate the vaccine effectiveness (VE), which is calculated as $100\% \times (1 - \text{attack rate in vaccination} / \text{attack rate in non-vaccination})$,¹ revealed that trivalent vaccination provided substantial protection against H1N1pdm09 (VE = 61%; 95% confidence interval (CI), 57 to 65), pre-2009 H1N1 (VE = 67%; 95% CI, 29 to 85) and type B (VE = 54%; 95% CI, 46 to 61), and reduced protection against H3N2 (VE = 33%; 95% CI, 26 to 39).² Here, we suggest a hypothesis to explain the different VE by subtype and new guidelines for seasonal vaccination.

Hierarchy of immune response between strains in trivalent vaccine

Previous studies have investigated the hierarchy of immune response to different antigens of virus.^{3,4} Using the same principles, trivalent influenza vaccination could induce an immune competition between influenza strains and establish the hierarchy of strain-specific immunity. Therefore, we suggest that the different VE by subtype depends on hierarchy of influenza subtype-specific neutralizing antibody response. Reduced VE of H3N2 might be the result of the trivalent influenza vaccine.

Immunodominance hierarchy of strain-specific hemagglutination inhibiting antibody response

Since hemagglutination inhibiting (HI) antibody, which blocks the viral attachment to host cells,⁵ correlates with real protection from influenza infection,⁶ we focused on HI antibody response to assess the hierarchy of immune response linked to VE. The differences of HI antibody titer between strains after trivalent vaccination have already been identified in healthy adults and children.^{7,8} Next, to prove the immunodominance hierarchy, the inhibition of strain-specific HI antibody response in trivalent vaccination should be verified compared to monovalent vaccination. Although we could not find direct evidence in clinical studies, previous non-clinical studies showed that trivalent vaccine in mice induced higher HI antibody titers against H1N1 and H3N2 relative to each of the monovalent vaccines but lower for type B.⁹ This result demonstrates that B-specific HI antibody response is inhibited by immune competition between three virus strains.

Strengthening of immunodominance hierarchy in repeated trivalent vaccination

If B cell immunodominance hierarchy is also determined by antigen dose and antigen-specific precursor cell number as a CD8 T cell response,¹⁰ the hierarchy of strain-specific neutralizing antibody response will be further strengthened by annual vaccination.

Persistence of strain-specific memory response until next year's vaccination

Surprisingly, at 18 months after vaccination in healthy adults, the percentage of HI titer ≥ 32 for type H3N2 and B was

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reported as 89.1 and 95.6, respectively.¹¹ This means that the persistence of hierarchy in strain-specific memory response could affect the vaccination after one or two years. Moreover, based on the systematic review reporting no difference in VE of trivalent vaccine between matched (VE = 65%; 95% CI, 54 to 73) or mismatched strains (VE = 52%; 95% CI, 37 to 63),¹² previous strain-specific HI antibodies could prevent the infections of other strains in the same subtype. Therefore, memory response could influence the next strain-specific immune response. Consequently, the differing memory response, which depends on hierarchy at the time of vaccination, could strengthen the hierarchical difference.

Strengthening of immunodominance hierarchy might reduce the VE for H3N2

A systematic review containing observational studies to evaluate the VE from database inception to 2016 showed that compared to prior season vaccination only, vaccination in both seasons was associated with greater protection against influenza H1N1 (Δ VE = 26%; 95% CI, 15 to 36) and B (Δ VE = 24%; 95% CI, 7 to 42), but not H3N2 (Δ VE = 10%; 95% CI, -6 to 25).¹³ Although not statistically significant, we also found that the tendency of decreased VE for H3N2 (Δ VE = -12%; 95% CI, -27 to 4) in both seasons vaccination compared to current season only in this report.¹³ This demonstrates that prior trivalent vaccination might increase the variation of VE for each subtype and reduce the VE for H3N2 in current season vaccination.

New vaccination guidelines to avoid the immunodominance hierarchy

The increasing vaccine dose of low immunogenic subtype virus could overcome the limitation of polyvalent vaccine as the result of animal experiments.⁹ However, this would be almost impossible because we have already been exposed to influenza antigens and established the differing memory response.¹⁰

Assessment of strain-specific HI antibody response prior to vaccination

Hemagglutination inhibition assay should be performed to assess the strain-specific HI antibody response before vaccination. After that, the strain lower than protective level (HI titer ≥ 40)¹⁴ among the recommended seasonal strains could be selected and inoculated to avoid the unnecessary immune competition.

Discussion

Why is trivalent influenza vaccination performed every year? The first reason is the shortening of neutralizing antibody response after vaccination; however, the neutralizing antibody response persisted for over 18 months in most healthy persons.¹¹ Next is the change of recommended strain annually, although the VEs of trivalent vaccine between matched and mismatched strains were not statistically different.¹² On the contrary, unnecessary strain vaccination could suppress the

necessary immune boosting. Therefore, we suggest the assessment of HI antibody titer prior to seasonal vaccination and recommend the inoculation of only strains lower than protective levels. It is necessary to change the method of vaccination according to individual immune state for influenza viruses. In addition, if genetic background¹⁵ is found to contribute to the variable VE by subtype, especially H3N2, future vaccination may involve the design of a personal influenza vaccination plan beginning at birth.

Disclosure of potential conflicts of interest

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