Defining Repeated Vaccination Effects for Influenza

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Background

Repeated influenza vaccination effects have been studied for more than 50 years, yet remain incompletely described and explained. Repeat vaccination effects refer specifically to the negative impact of recipients of prior vaccination on the efficacy or effectiveness of influenza vaccination in the current year, with the reference group being individuals vaccinated in the current year but not in preceding years.

Repeated vaccination effect

This effect is particularly evident when individuals receive vaccinations consecutively for two years, especially for A(H3N2) strains. Although some studies observed an inverse association between current VE and the number of prior vaccinations, there are no constant reductions in VE along with consecutive years of vaccination. Immunological studies consistently demonstrate a negative association between repeated vaccination and post-vaccination titers and fold rises.

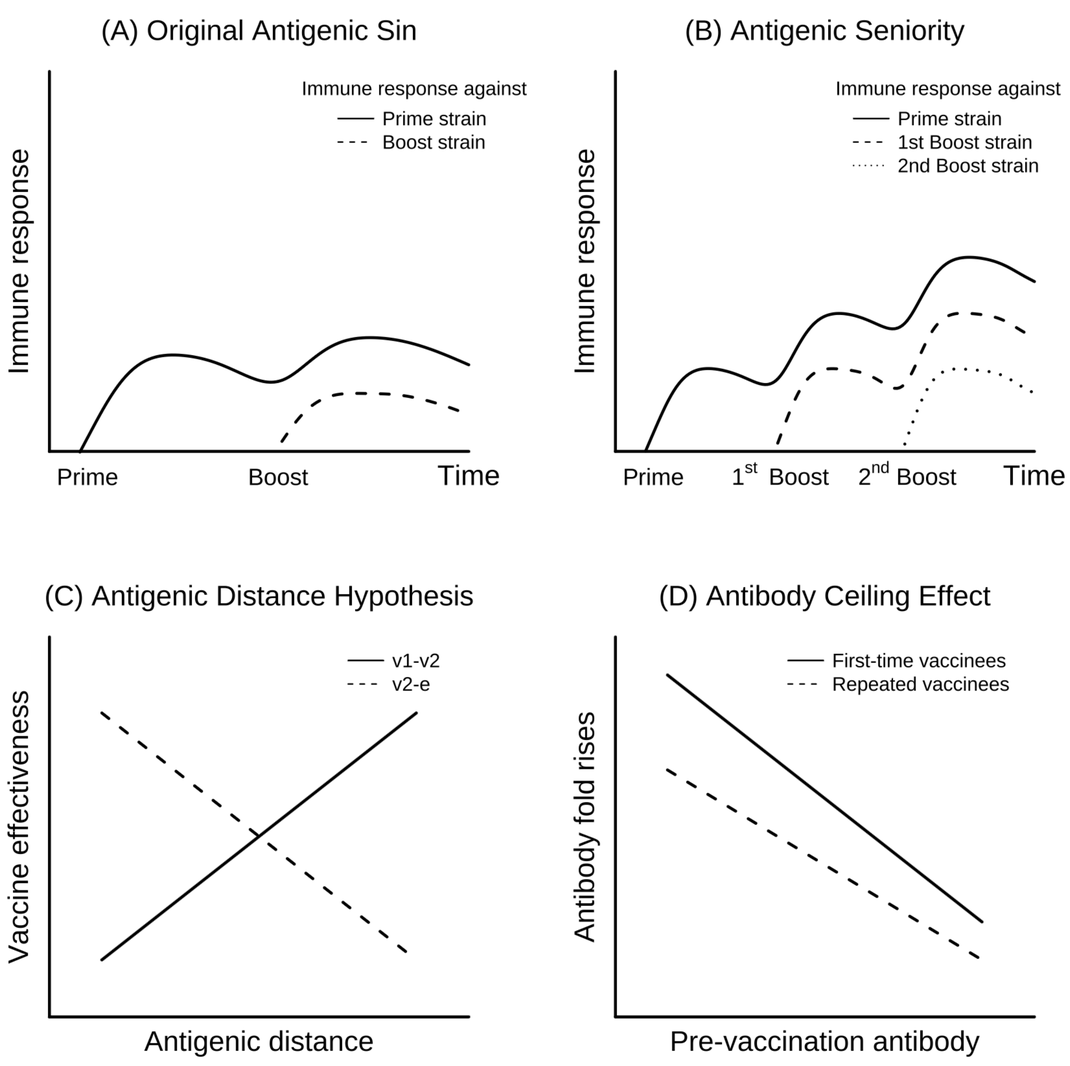

Figure 1. Illustration of hypotheses for repeated vaccination effects. (A) Original antigenic sin: exposure to drifted homologous strain boosts a higher immune response to the older strain encountered in early life than the current strain. (B) Antigenic seniority: every exposure to drifted homologous strain back-boosts immunity to the previous strains, resulting in a hierarchical response based on the exposure sequence. (C) Antigenic distance hypothesis: vaccine effectiveness against the current vaccine strain (v2) could be more impaired when v2 closely resembles the previous vaccine strain (v1), and significantly differ from the circulating strain (e). (D) Antibody ceiling effect: refer to the negative slope in both lines, but studies have consistently shown that repeat vaccinees have weaker fold rises for any level of pre-vaccination titer compared to first-time vaccinees.

Hypothesis

There are several hypotheses for observed effects. **The original antigenic sin hypothesis** suggests that immune response tends to be more effective against the antigen encountered in early life than the current vaccine strains (Figure 1A). This phenomenon may result in reduced protection against antigenically drifted influenza strains, which has been widely used to explain age cohort-associated trends in infection risk or immune response.

The antigenic seniority hypothesis supplements that each encountered strain back-boost immunity to the previous strains, resulting in a hierarchical response based on the exposure sequence. Notably, while some evidence conducted among different populations support this hypothesis, the antibody response to newly encountered virus strains were not always hampered at a cost (Figure 1B).

The antigenic distance hypothesis proposes that if the current vaccine strains closely resemble the previous vaccine strains but significantly differ from the circulating strains, the detrimental impact of repeated vaccination becomes more pronounced (Figure 1C). This hypothesis offers valuable immunological perspectives for interpreting the effects of repeated vaccination, while the specific influence of receiving vaccinations for more than a single prior season remains unexplored.

The infection block hypothesis is proposed based on the observations that recent infections are associated with higher immunogenicity and effectiveness of the current vaccination. Therefore, the protection of current vaccination are expected to be higher in non-repeated vaccinees, who tend to have higher number of infections in the previous seasons compared to the repeated vaccinees.

The antibody ceiling effect describes the phenomenon that higher pre-vaccination antibody titer is associated with lower immune response to subsequent vaccinations (Figure 1D). This effect can be partly attributed to pre-existing antibody that neutralizes vaccine antigens, thereby reducing the effective dose. Besides, the germinal center tends to amplify memory B cells for immunodominant epitopes at the expense of the expansion of other B cells for new-encountered epitopes. This masking effect of immunodominant epitope could be the underlying mechanism for the uneliminated repeated vaccination effect after adjusting the pre-vaccination antibody titers.

Conclusions

Despite these hypotheses, none of them fully explain the repeated vaccination effect. Further investigations are needed to gain a comprehensive understanding of this effect and uncover its underlying mechanisms.

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