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EDITORIAL COMMENTARY

Repeated Seasonal Influenza Vaccination: How Much Is Too Much of a Good Thing?

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(See the Brief Report by Richards et al., on pages 273–7.)

Seasonal vaccination remains the most effective way to protect against influenza virus infections. However, there is accumulating evidence suggesting that repeat seasonal vaccination may, in specific instances, result in reduced antibody responses and diminished vaccine effectiveness. Although the effect of repeat influenza vaccination on the antibody response to influenza has received substantial attention in recent years, much less is known about consequences on the T-cell compartment. In this issue of *the Journal of Infectious Diseases*, Richards et al [1] report that blunted $CD4^+$ T-cell responses resulting from repeat vaccination may underlie previously reported deficits in the antibody response.

The annual reformulation and readministration of the seasonal influenza vaccine remains essential to preventing infections. The vaccine is reformulated annually in an effort to ensure that it provides coverage against the dominant circulating strains of A/H1N1, A/H3N2, and influenza B viruses (Victoria and Yamagata lineages), whose antigenicity evolves rapidly as the population acquires immunity to a given strain [2]. This immunological pressure is mediated primarily by antibodies that bind to hemagglutinin (HA) and neuraminidase—the major viral glycoproteins [3]. In most seasons, only a subset of the vaccine strains are updated. As a result, individuals who are revaccinated annually are often immunized with the same strain over multiple seasons.

Early studies focusing on repeat influenza virus vaccination presented seemingly inconsistent results. Studies by Hoskins et al [3–5] examined vaccine effectiveness in sequentially vaccinated boys over the course of 3 H3N2 outbreaks in 1972, 1974, and 1976. During the 1972 outbreak, no differences were observed in the attack rates between boys who had previously received 1, 2, or 3 prior vaccinations with A/Hong Kong/1/68 (HK/68) [4]. However, during the 1974 outbreak, H3N2 attack rates were elevated in boys previously vaccinated with HK/68 [5]. It is interesting to note that attack rates during the 1976 outbreak were observed to be highest amongs boys who received heterologous vaccination with the 3 previously circulating H3N2 strains [6]. In contrast, a study by Keitel [7] et al analyzed repeat vaccinees involved in a 5-year randomized controlled trial between 1983 and 1987 and concluded that repeat seasonal vaccination provided a protective benefit. In this study, the number of annual seasonal vaccinations was not associated with increased rates of infection. However, in the final year of the trial, a significant reduction in the antibody response and concurrent increase of A/H3N2 viral shedding was observed in individuals who had received 6 prior vaccinations, although no difference in infection rates was observed [7].

The "antigenic distance hypothesis," proposed by Smith et al [8] helps to reconcile these disparate findings and provides a framework for predicting when prior vaccination would be expected to impair vaccine responses. Smith et al [8] postulated that vaccine effectiveness is impacted by the antigenic relatedness between the circulating epidemic strain and the vaccine strains. This hypothesis predicts that negative interference imposed by previous exposures to influenza virus will be most pronounced in seasons where the vaccine strains are very closely related, but the circulating strain is more antigenically distinct [8, 9].

The so-called "Canadian Problem" was one of the most notorious recent examples of a possible increase in risk of infection associated with prior vaccination. Skowronski et al [10, 11] reported that individuals who had been vaccinated in the 2008–2009 season, before the emergence of the 2009 swine flu pandemic, experienced higher rates of infection with the pandemic strain than individuals who were not vaccinated in the preceding year. Similar observations were reported during the 2014–2015 influenza season, where vaccine effectiveness was modestly reduced in individuals who had received the vaccine in the previous season and more substantially reduced in repeat

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vaccinees who had received both the current and prior season's vaccines [12]. Repeat vaccination was also reported to interfere with vaccine effectiveness in a Japanese cohort during the 2016–2017 influenza season, where children immunized in the prior season were found to be more likely to develop influenza [13].

Recent efforts have been made to provide a more detailed characterization of the effects of repeat vaccination on the antibody response. To better understand the relatively low efficacy of seasonal influenza vaccines against H3N2, a group from the Centers for Disease Control and Prevention vaccinated ferrets with 1 or both of the 2016–2017 and 2017–2018 Northern Hemisphere inactivated influenza vaccines. Although animals who received both vaccines had equal or greater antibody titers (as measured by HI and enzyme-linked immunosorbent assay) against H3N2 than those who received the current season vaccine only, they also shed more virus and experienced increased morbidity [14]. This led the authors to propose that antibody quality, and not quantity, might explain reduced protection in repeatedly vaccinated individuals [14]. In line with this hypothesis, another study examined the impact of sequential vaccination on the avidity of the antibody response in individuals who had been vaccinated with FluBlok, FluCelvax, or Fluzone in the 2015–2016 and 2016–2017 influenza seasons [15]. Individuals who were vaccinated in both seasons experienced a reduction in antibody avidity irrespective of the vaccine formulation [15]. Furthermore, a longitudinal study between 2011 and 2016 found that repeat vaccination with the A/H1N1pdm09 strain led to increased rates of antibody waning, from a half-life of 32 months after 1 vaccination to only 9 months after 7 sequential vaccinations [16].

$CD4^+$ T cells play a critical, and often overlooked, role in the development of antigen-specific B-cell responses to vaccination. Previous work from the Sant and Nayak [17, 18] groups has established a direct positive correlation between antigen-specific $CD4^+$ T cells and the magnitude of the antibody response against A/H1N1pdm09 and A/H5N1 vaccination. Although these studies did not specifically examine sequential vaccination, they suggest that blunted antibody responses could result from impairments in the $CD4^+$ T-cell compartment.

In the current issue, Richards et al [1] collected serum and peripheral blood mononuclear cells from a cohort of adults after the administration of seasonal influenza vaccine across 2 successive seasons (2015–2016 and 2016–2017). Based on self-reported vaccination status, participants were grouped by those that received the seasonal vaccine in the previous season ("vaccinated") or those that had not been vaccinated in the previous season ("unvaccinated"). Richards et al [1] observed that previously vaccinated individuals had lower postvaccination titers of HA-specific antibodies against all strains tested. Expansion of $CD4^+$ and T follicular helper cells (Tfh), a specific subset of $CD4^+$ T cells, was also reduced after vaccination in the previously vaccinated group. The Tfh are known to play an important role during T cell-dependent B-cell responses to influenza vaccination and infection [19–21]. The strong correlation observed by Richards et al [1] between the antibody response and elicitation of $CD4^+$ T cells suggests that the dampening of the antibody response observed in repeat vaccine recipients may be a consequence of diminished $CD4^+$ T-cell responses.

The observations reported by Richards et al [1] are well aligned with the established paradigm that high pre-existing antibody titers before vaccination reduce the magnitude of the vaccine-induced antibody response [22, 23]. High levels of circulating antigen-specific antibody can lead to antigen clearance or epitope masking, thereby preventing B-cell activation. However, $CD4^+$ T-cell activation generally occurs upstream of B-cell activation, and, thus, the mechanism through which high levels of circulating antibody inhibit CD4 T-cell responses requires further elucidation. It is interesting to note that an earlier study that compared a cohort of annually vaccinated cystic fibrosis patients with unvaccinated healthy children found that the annually vaccinated children had a defect in age-associated expansion of virus-specific $CD8^+$ T cells, whereas $CD4^+$ T cells and antibody titers were similar to those of the control group [24]. Therefore, repeat vaccination may affect both $CD4^+$ and $CD8^+$ T-cell compartments in specific instances.

The results reported by Richards et al [1] add to a growing body of evidence that raises important questions about the way in which seasonal vaccines are formulated and administered. Although this study did not directly address whether the observed reduction in $CD4^+$ T-cell responses and antibody titers affected vaccine effectiveness, there have now been multiple reports wherein effectiveness appears to be reduced in repeat vaccinees, as outlined above. However, a systematic review and meta-analysis of 5 randomized, controlled trials and 28 observational studies found no reduction in vaccine effectiveness after repeat influenza vaccination [25]. Therefore, more studies are needed to define whether repeat vaccination is problematic from the standpoint of vaccine effectiveness.

Most current seasonal influenza vaccine formulations activate T cells poorly [26]. However, seasonal vaccines remain the best way to prevent influenza virus infection. Therefore, considerable efforts should be made to more comprehensively understand (1) whether repeat seasonal influenza vaccination is problematic and (2) the immunological basis for this phenomenon. This would facilitate the development of strategies to maintain the benefits of seasonal influenza vaccination, while mitigating potentially negative consequences. One simple strategy could be the development of seasonal vaccines of varying valency, wherein unchanged strains could be omitted from the formulations offered to repeat vaccinees. The development of "universal" influenza virus vaccines would greatly reduce the need for repeat annual vaccinations, and it seems increasingly clear that an effective universal influenza virus vaccine will need to sufficiently engage both the T-cell and B-cell compartments.

Notes

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