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Preview

Teach 'em young: Influenza vaccines induce broadly neutralizing antibodies in children

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Antibodies against the influenza virus hemagglutinin stalk afford broad protection against antigenically drifted viruses. In this issue of *Cell Reports Medicine*, Yegorov et al.[1] identify that current vaccine formulations induce neutralizing stalk antibodies in children—a highly vulnerable population.

Vaccines remain the gold standard for protection against influenza viruses, but antigenic variability and poor immunogenicity pose challenges for vaccine effectiveness. Influenza viruses have a remarkable ability to evade the human antibody response, by accumulating mutations in the surface glycoprotein hemagglutinin (HA), the key viral protein required for infection. This necessitates annual reformulation of seasonal vaccines, which are often mismatched to currently circulating influenza virus strains. Seasonal vaccines primarily elicit strain-specific responses to the antigenically variable HA head domain, further contributing to viral escape. When vaccine-elicited, strain-specific antibodies are unable to neutralize antigenically drifted strains, the result is low vaccine efficacy and susceptibility to infection.[2]

The induction of broadly neutralizing antibodies (bnAbs) by vaccines represents a promising avenue for universal protection against drifted influenza viruses. Antiviral bnAbs have been described for influenza virus, HIV-1, Ebola virus, SARS-CoV-2, and others[3] and target viral epitopes that are often functionally conserved. Influenza bnAbs most commonly target the conserved HA stalk domain. However, HA stalk bnAbs are exceedingly rare within the germline repertoire, and antibodies to the variable HA head domain are immunodominant, hindering antibody generation to the stalk.[4]

Since individuals have been exposed to different variants of influenza virus throughout their lifetime, complex immune histories pose an additional barrier for bnAb induction. In 1960, an essay by Thomas Francis, Jr. first described the concept of "original antigenic sin" (OAS): the notion that antibody responses to childhood influenza viruses are preferentially recalled later in life upon exposure to antigenically drifted viral strains.[5] This phenomenon was interpreted as "sinful" because it was assumed that children generated narrow antibody responses that would not protect against drifted viruses encountered later in life. It was Francis' hope that someday vaccines would be comprised of antigens that confer broad immunity, in anticipation of all future exposures.

In the following years, it became well-established that pre-existing B cell memory generated by past influenza virus exposures shapes protective responses upon subsequent vaccination or infection. Our understanding of OAS has evolved as we continue to unravel memory B cell (MBC) responses to influenza viruses in humans. The concept of "antigenic imprinting" has been recently described to account for the hierarchical nature of MBC bias upon sequential exposures and considers both positive and negative outcomes: MBCs to conserved HA epitopes are continually boosted following diverse exposures and may recognize conserved, neutralizing, or non-neutralizing viral epitopes. Factors such as antigen accessibility, serum epitope masking, age, T cell help, and immune history to distinct viral subtypes will bias the ever-evolving MBC repertoire. As a result, several studies have published examples of imprinting that suggest context-dependent protection or susceptibility to influenza.[6,7]

Despite these hurdles, there is widespread consensus in the field: universal vaccines are urgently needed, and if delivered in early childhood, they could imprint the immune system toward broadly neutralizing epitopes, ultimately circumventing the complications described above. However, little is known regarding pediatric antibody responses to influenza viruses. It remains unclear whether infants or young children generate bnAbs, or whether they predominantly mount strain-specific responses. Investigating antibody responses to influenza in children is paramount for determining effective vaccination regimens that can imprint the immune system to conserved, neutralizing HA epitopes. Moreover, children represent a high-risk group for severe infection and therefore contribute largely to transmission.

In this issue of *Cell Reports Medicine*, Yegorov et al.[1] present evidence that group 1 influenza virus HA stalk bnAbs are generated in a pediatric cohort upon repeated vaccination or after administration of inactivated influenza virus (IIV) or live-attenuated influenza virus (LAIV) in a cluster randomized control trial. The repeated influenza virus vaccination cohort was comprised of 37 children aged 3–15 years from the 2008–2011 flu seasons and 31 control participants who had received the hepatitis A vaccine or no vaccine. To compare bnAb responses upon distinct vaccine formulations, the authors investigated antibody responses in 35 IIV vaccinees and 37 LAIV vaccinees aged 3–15 years from the 2014–2015 flu season.

The authors first analyzed influenza A serum and mucosal nasal swab antibody responses to a chimeric influenza virus expressing an avian group 1 H5 influenza A head, and an H1 stalk derived from A/Puerto Rico/8/1934. As H5 represents an antigenically divergent HA head from a zoonotic reservoir, individuals should have little to no pre-existing immunity to this antigen. Therefore, the antibodies analyzed to HA should largely be directed against conserved H1 stalk epitopes. To quantify serum antibody responses to the stalk, the authors used microneutralization (MNT) assays and enzyme-linked immunosorbent assay (ELISA) to detect anti-stalk immunoglobulin G (IgG) and IgA.

In response to vaccination across three consecutive seasons, the authors identified increased serum MNT_{50} titers to cH5/1 virus relative to controls, but not increased hemagglutination inhibition titers, suggesting antibody boosting to the conserved stalk and not the antigenically divergent H5 head. Moreover, they found that both IIV and LAIV could elicit anti-stalk IgG and IgA to similar magnitudes, with anti-stalk IgG and MNT_{50} declining slightly with age. It remains unclear whether age, immune history, or both could contribute to the age-dependence of anti-stalk antibody titers in this cohort, though both likely play a role. As immune exposures to influenza viruses accumulate with age, a hierarchical imprinting phenomenon could occur in which antibodies target other conserved, non-neutralizing epitopes on the stalk. In addition, pre-existing serum antibodies to the broadly neutralizing stalk epitope could mask boosting to this epitope or prevent *de novo* responses.[8] In contrast to these findings, other studies have noted an increase in HA stalk bnAbs in aged cohorts, likely influenced by historical patterns of influenza virus circulation and the boosting of memory responses over a lifetime.[9] Longitudinal studies analyzing antibodies following influenza virus vaccination or infection in distinct age groups are needed to shed light on this mechanism, in addition to single-cell studies investigating imprinting to distinct epitopes.

LAIVs represent a promising avenue for universal vaccination in children, as they are administered through the nasal mucosa and more closely recapitulate natural infection. Mucosal antibody responses to LAIVs have been historically difficult to study due to difficulty obtaining nasal swab and bronchoalveolar lavage samples. In addition, LAIVs are not approved in children under 2 years due to adverse reports of wheezing, though further attenuation may decrease side effects.[10] To conclude their work, Yegorov et al. collected nasal swabs from children vaccinated with LAIVs or IIVs and determined that both vaccine types induce anti-stalk IgG and IgA to a similar extent, though they did not measure neutralization titers. More studies are needed to determine whether LAIVs induce more bnAbs in children, as they may be advantageous in their ability to induce "beneficial imprinting" responses through establishment of tissue-resident memory and secretory IgA.

DECLARATION OF INTERESTS

H.L.D. is an employee of Adimab, LLC, and may hold shares in Adimab, LLC. P.C.W. is a consultant for Adagio Therapeutics, Inc.

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