Influenza ADCC-antibody responses in vaccinated and infected children as a correlate of protection: abridged secondary publication

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KEY MESSAGES

1. Pandemic haemagglutinin IgG responses are boosted by recent seasonal vaccination and decline within 1 year and reach baseline by 5 years post-vaccination.
2. Correlation is strong between FcR binding and antibody-dependent cellular cytotoxicity function, validating the use of multiplex bead approaches to quantify antibody responses.
3. Vaccination increased IgG1 responses to vaccine and pandemic proteins (HA H3 H1, neuraminidase, nucleoprotein).
4. Unvaccinated uninfected children had increased H1/09 IgG and FcγRIIIA, compared with unvaccinated children who became infected. This indicates that higher baseline pandemic-specific antibodies coincide with protection.
5. Antibody diversity is increased by vaccination and infection, but the diversity does not extend to avian influenza viruses.

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Introduction

Influenza viruses are extremely diverse, and vaccine-mediated protection by available whole-virion inactivated vaccines elicits strain-specific neutralising antibodies as its main protective function. Vaccine efficacy is dependent on haemagglutinin (HA) matching; it varies from 0% to 80% depending on the year and age group. In 2009, seasonal influenza vaccination in children resulted in 47% vaccine effectiveness against H1N1pdm influenza virus.[1] Yet, some classes of antibodies can cross-react among seasonal, pandemic, and avian influenza viruses. These antibodies may play a protective role in limiting the acquisition or severity of influenza virus infection. We aimed to determine whether the magnitudes of antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis responses are enhanced by vaccination and reduce the risk of influenza virus infection with stable responses.

Methods

We utilised a large biobank of immune serum from a randomised control trial of vaccination in children (NCT00792051), whereby children were vaccinated in 2008 with trivalent seasonal influenza vaccines containing H1N1 A/Brisbane/2007 virus or placebo, prior to the H1N1 A/California/2009 pandemic. The cohort was followed over the subsequent 5 years (2009 to 2014) to assess rates of reverse transcription–polymerase chain reaction-confirmed infection.

To quantify influenza-specific antibodies before and after vaccination, and before and after pandemic infection, we used a systems serology approach involving ADCC natural killer (NK) cell-based assays, as well as a multiplex bead approach that couples FcR dimer proteins,[2] diverse HA proteins including HA-stem constructs, and antibody subclasses (IgG1/2/3) and isotypes (IgG/A1). The multiplex bead approach was validated with a flow-cytometric NK cell-based assay[3] to identify influenza-specific ADCC-antibody activities with strong correlations.

Results

Vaccination increased HA-specific antibodies in terms of magnitude and FcR effector functions including antibodies to the pandemic virus H1/2009 HA and neuraminidase proteins. These antibody levels declined within 1 year post-vaccination and then remained stable, similar to other viral proteins. Total H1/2009 HA IgG and IgG2 levels were higher in vaccinated uninfected children than in unvaccinated infected children. This suggests a protective role for cross-reactive HA antibodies. However, although vaccination increased IgG1 responses to the vaccine and related proteins, it did not affect infection status and possibly masked baseline protective effects in unvaccinated uninfected children. There

was strong correlation between FcR binding and ADCC function, validating the use of multiplex bead approaches to quantify antibody responses (data not shown).

We compared the diversities of HA antibody responses to seasonal, pandemic, and avian HA proteins. We also compared total antibody responses to determine the effects of vaccination and infection on cross-reactivity. Antibody effector responses were boosted by vaccination, but vaccine-breakthrough infections occurred despite these increased responses. Therefore, other immune parameters may contribute to virus protection.

Discussion

Seasonal vaccination increased IgG responses to a non-vaccine component (the HA-H1/2009 protein) and resulted in vaccine-mediated protection in 47% of children during the early H1N1 pandemic.[1] Therefore, seasonal vaccination should be encouraged for pandemic viruses where cross-reactivity may provide some residual protection. Baseline elevated HA-H1/2009-specific IgG and FcγRIIIA levels in unvaccinated children coincided with protection from infection, and the sources of elevated baseline protective responses and vaccines that can stimulate these responses should be investigated.

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