Complexities in predicting the immunogenicity of live attenuated influenza vaccines

Benjamin B. Lindsey[1,2], Katja Höschler[3] & Thushan I. de Silva[1,2,4]

1. Vaccines and Immunity Theme, Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Atlantic Road, PO Box 273, Banjul, The Gambia.
2. Department of Medicine, Imperial College London, St Mary's Campus, London, W2 1PG, UK.
3. Virus Reference Department, Reference Microbiology Services, Public Health England, Colindale Avenue, London NW9 5HT, UK.
4. The Florey Institute for Host-Pathogen Interactions and Department of Infection, Immunity and Cardiovascular Disease, University of Sheffield, Beech Hill Road, Sheffield, S10 2RX, UK.

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Corresponding author: Thushan de Silva, Vaccines and Immunity Theme, Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Atlantic Road, PO Box 273, Banjul, The Gambia. Email: tdesilva@mrc.gm; Telephone: +44(0)7976605320.

Alternate corresponding author: Benjamin Lindsey, Vaccines and Immunity Theme, Medical Research Council Unit The Gambia at the London School of Hygiene and Tropical Medicine, Atlantic Road, PO Box 273, Banjul, The Gambia. Email: benjamin.lindsey08@gmail.com

Dear Editor,

We read with interest the findings from Matrajt *et al*.[1], who propose a novel approach to live attenuated influenza vaccine (LAIV) strain selection based on results from mathematical models. They suggest vaccine strains should be antigenically distant enough from pre-existing immunity to allow vaccine replication, while remaining antigenically close enough to circulating strains to protect from infection. We fully agree this approach is worth exploring, not only for strain selection, but also for decisions about the optimal age and frequency of childhood immunization with LAIV. However, there are a number of complexities to LAIV immunogenicity worth highlighting that cannot be ignored if such strategies were to be used in practice.

The proposed model assumes that pre-existing serum antibodies from prior infection or vaccination are the main driver of LAIV 'take' and immunogenicity. Our own data using Russian-backbone LAIV in Gambian children aged 24-59 months partially support this, with pre-immunization serum haemagglutination inhibition (HAI) titre (but not T-cell response or mucosal IgA) being the key determinant of LAIV shedding[2]. We have recently stratified this cohort based on seropositivity to the H3N2 strain included in the vaccine (A/Hong Kong/4801/2014; A/HK), and two older H3N2 strains antigenically similar to those potentially encountered during the children's lifetime (A/Switzerland/9715293/2013; A/Sw or A/Texas/50/2012; A/Tex). Children who were A/HK+ (HAI titre ≥1:10) at baseline (n = 169) were less likely to shed H3N2, compared to those seropositive to A/Sw or A/Tex (but A/HK seronegative, n = 28), or children seronegative (<1:10) to all three H3N2 strains (n = 45, Figures 1A and 1B)). Shedding was not significantly different between seronegative children and those seropositive to A/Sw or A/Tex only.

However, the immunogenicity data reveal a more complex pattern. While HAI seroconversion is significantly lower in A/HK+ children and reflects patterns of shedding, the T-cell and mucosal IgA responses follow different trends (Figure 1C). A ≥2-fold CD4+ T-cell response is generated most often in children seronegative to all three strains, but at similar levels in A/HK+ or A/Sw+/A/Tex+ (A/HK-) children. In addition, prior serostatus has no impact on the likelihood of a ≥2-fold mucosal IgA response. This is in keeping with our findings that shedding increases the odds of seroconversion and a T-cell response, but not mucosal IgA responses[2]. Furthermore, ~50% of children generated a T-cell response to A/HK Haemagglutinin despite being A/HK seropositive, challenging the view that giving LAIV may not be worthwhile in the face of pre-existing serum antibody immunity to vaccine strains. Similar T-cell data are observed for matrix and nucleoprotein (data not shown). Interpreting any such data is of course limited by the lack of a correlate of protection for LAIV, although both T-cells and IgA have been shown to protect in the absence of seroconversion and are likely to be co-correlates of protection, along with serum antibodies[3-7].

The approach taken by Matrajt *et al*.[1] to improve LAIV effectiveness is promising. Well-designed immunogenicity studies in children to both inform and test further models could help refine our approach to LAIV use in the future.

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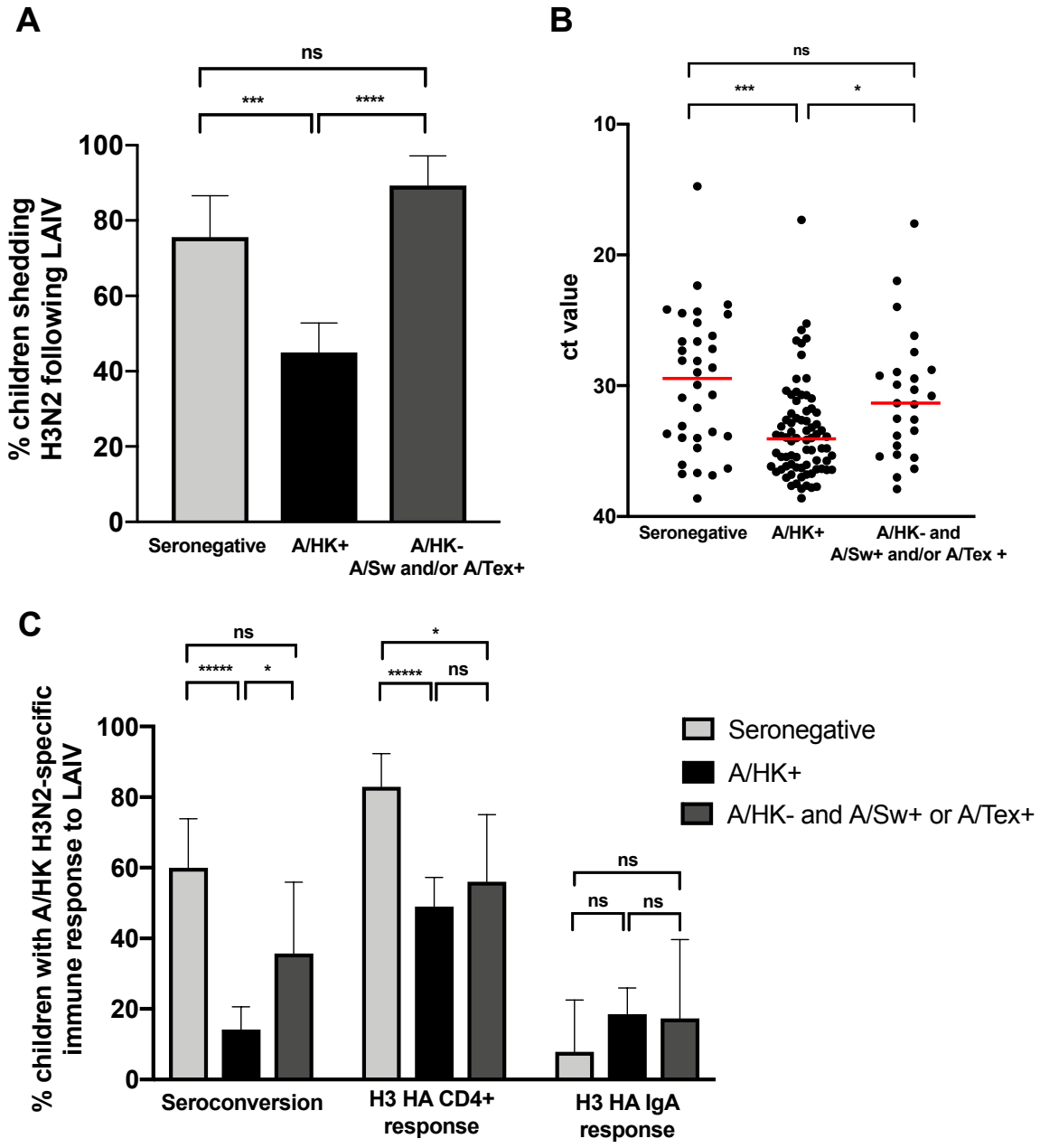

Figure 1. Shedding and immunogenicity to Russian-backbone LAIV in Gambian children aged 24-59 months, stratified by pre-existing serum antibodies to H3N2 strains. A. Percentage of children shedding H3N2 at day 2 following LAIV. **B.** Cycle threshold (ct) from H3 haemagglutinin (HA)-specific reverse-transcriptase polymerase chain reaction assays on nasopharyngeal swabs as a marker of viral load at day 2 following LAIV. **C**. Immune responses to LAIV determined by responses at day 21 following immunization (definition of responses

described previously[2]). T-cell response denotes H3 HA-specific CD4+ T-cells producing IFN-γ and/or IL-2. A/HK = H3N2 A/Hong Kong/4801/2014, A/Sw = H3N2 A/Switzerland/9715293/2013, A/Tex = A/Texas/50/2012, Seronegative = haemagglutination inhibition titre <1:10 to A/HK, A/Sw and A/Tex, H3 HA = A/HK haemagglutinin, IgA = immunoglobulin A. **** p <0.0001, *** p<0.001, *p<0.05. ns = not significant at p<0.05. Proportions compared with Fisher's exact test. Ct values compared using Kruskal-Wallis test with Dunn's post-test.