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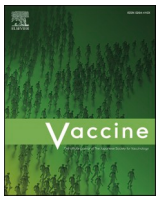

Binding and neutralising antibodies to respiratory syncytial virus and influenza A virus in serum and bronchoalveolar lavage fluid of healthy adults in the United States: A cross-sectional study

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ABSTRACT

Using serum and bronchoalveolar lavage (BAL) fluid collected from 20 healthy adults (23–37 years, 55 % female) in the United States, we measured immunoglobulin (Ig) A, IgG, and neutralising activity against respiratory syncytial virus (RSV) and influenza A (H1N1) virus. RSV-binding IgA and IgG measurements in serum were positively correlated with those in BAL. For influenza A (H1N1) virus, serum and BAL IgA antibodies were positively correlated, whereas IgG antibodies did not show a significant correlation. RSV-specific and influenza A (H1N1)-specific neutralising activity did not correlate between serum and BAL samples. These results demonstrate virus-specific correlations between antibodies in the serum and BAL that may not necessarily reflect correlations in functional activity. Further work is needed to confirm our preliminary observations, and define the immune correlates of neutralising activity to these and other respiratory viruses in the lower respiratory tract.

1. Background

Respiratory viruses, including respiratory syncytial virus (RSV) and influenza, remain a major cause of morbidity and mortality worldwide [1], with vulnerable populations including younger children and older adults who are disproportionately impacted by lower respiratory tract (LRT) complications, such as bronchitis, bronchiolitis and pneumonia [reviewed in [2]]. Although the lungs are an early site of immune interaction with respiratory viruses and the primary setting for pathology in severe viral respiratory disease [reviewed in [3,4]], measuring immunity in the human LRT is challenging due to the need for specialised sampling methods, notably bronchoalveolar lavage (BAL) [5]. Despite these limitations, measurement of immunity against respiratory viruses in the LRT is important for understanding differences between mucosal and systemic immune responses to natural infection and vaccination. Using the unique availability of paired serum and BAL samples from 20 healthy adults in the United States, we measured virus-specific immunoglobulin (Ig) A, IgG, and neutralising activity against RSV and influenza A (H1N1) virus.

2. Methods

As part of a parent research study on primary lung macrophages in cystic fibrosis [6], serum and BAL fluid were obtained from 20 healthy adults (i.e., from the control arm) who were enrolled between 20 January 2015 and 20 January 2016 at Dartmouth-Hitchcock Medical Center (Lebanon, New Hampshire, USA). This study was approved by the Dartmouth Hitchcock Institutional Review Board (protocol #22781). All participants provided written informed consent allowing for future use of samples in ancillary studies, such as the one described in this manuscript. As previously described [6], following local anaesthesia and systemic sedation, BAL fluid was obtained by five lavages, each with

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instillation of 20 mL 0.9 % saline and 10 cc air, into three subsegmental bronchi of the right lung via bronchoscopy, and 100 mL of blood was obtained by peripheral intravenous (IV) catheter. Serum and BAL samples were aliquoted and stored frozen at −80 °C until use. Participants were eligible for inclusion if they: (i) were non-smokers and (ii) had no underlying cardiopulmonary or immunological medical conditions. Participants were excluded if they: (i) were on any immunosuppressive medication, (ii) had received oral or IV antibiotics over the past 28 days, or (iii) had an active upper respiratory tract infection.

Concentrations of total IgA and total IgG, as well as virus-specific IgA and IgG and neutralising activity against RSV and influenza A (H1N1) were evaluated in paired serum and BAL samples.

Samples were tested for antibody binding to recombinant RSV post-fusion F-protein, and influenza A/California/09 (H1N1) using a multiplex assay developed by coupling viral antigens to fluorescently coded magnetic microspheres as reported previously [7]. Data were acquired using a Luminex (Austin, TX, USA) analyser for all but the total BAL IgG, which utilised a Meso Scale Diagnostics (Rockville, MD, USA) reader. Anti-isotype primary antibodies were used to quantify the total amount of each immunoglobulin isotype per sample relative to a purified isotype control (presented in μg/mL) using a sigmoidal curve fit (GraphPad Prism, San Diego, CA, USA). Virus-specific IgA and IgG levels were reported as median fluorescence intensities (MFIs) after subtracting the mean background signal (i.e., the measurement for the assay wash buffer [phosphate buffered saline (PBS, 1×) + 0.1 % bovine serum albumin (BSA) + 0.05 % Tween 20)]). Of note, IgA was measured with goat anti-human IgA (2050–01, Southern Biotech, Birmingham, AL, USA), which detects both monomeric and dimeric IgA.

Virus-specific neutralising activities were determined using micro-neutralisation assays and recombinant reporter viruses, as previously described [8,9]. Neutralising activity was quantified for RSV using a recombinant RSV-Renilla luciferase virus (rA2-Rluc) [10] in HEp-2 target cells; and for influenza using a luciferase-expressing A/California/04/2009 H1N1 virus (CA/09) [11] in Madin-Darby Canine Kidney cells. Samples were diluted 2-fold (1:4 to 1:128,000) and incubated with a standardised amount of reporter virus prior to adding to the target cells. The titre of neutralising activity was calculated as the reciprocal of the highest sample dilution needed to achieve 60 % neutralisation of a luciferase-expressing virus when compared to virus-only positive controls with no added sample, as described in [8]. Negative controls included wells with no added virus or sample. Undetectable neutralisation titres (i.e., <4) were recorded as 2.

Correlations between immune markers were estimated using Spearman's rank correlation coefficients and visualised as scatter plots on logarithmic scales. Statistical analyses were conducted in Stata (version 18.0, College Station, TX, USA). All *P* values are from two-sided statistical tests, and P values <0.05 were considered to be statistically significant.

3. Results

Twenty healthy adults (age range: 23–37 years; 55 % female) participated in this study. In serum samples, the median total IgA was 380 μg/mL (IQR = 228, 470), and the median total IgG was 12,450 μg/mL (IQR = 11,400, 16,475; Table S1). In the BAL, the median total IgA was 2.85 μg/mL (IQR = 2.22, 3.90), and the median total IgG was 12.08 μg/mL (IQR = 8.48, 13.59), although it is important to note that there is substantial dilution by the buffer in the lavage process (Table S1). For both serum and BAL samples, IgG was measured at higher concentrations than IgA, with a median ratio for total IgG to total IgA of 37.1 (IQR = 27.7, 59.6) in serum and 4.16 (IQR = 1.51, 6.03) in BAL fluid (Table S1).

Serum and BAL RSV-specific IgA levels were positively correlated with each other (rho = 0.46, $p = 0.041$; Fig. 1A, and summarised in Table S2), as were serum and BAL RSV-specific IgG (rho = 0.56, $p = 0.011$; Fig. 1B). In contrast, RSV-specific neutralisation titres were not correlated between individuals' serum and BAL samples (rho = 0.10, $p = 0.68$; Fig. 1C). Notably, RSV-specific neutralising activity in BAL samples was undetectable in 30 % ($n = 6/20$) of participants. In serum, RSV-specific neutralising activity was strongly correlated with IgG (rho = 0.60, $p = 0.006$) but not IgA (rho = 0.24, $p = 0.30$; Fig. 2). The opposite pattern was observed in BAL samples, where RSV-specific neutralising activity was strongly correlated with IgA (rho = 0.70, $p = 0.0009$) but not IgG (rho = 0.29, $p = 0.22$; Fig. 2).

Serum and BAL influenza-specific IgA levels were positively correlated with each other (rho = 0.60, $p = 0.0065$; Fig. 3A, and summarised in Table S3), whereas serum and BAL influenza-specific IgG were not (rho = 0.38, $p = 0.095$; Fig. 3B). Influenza-specific neutralising activity was not correlated between serum and BAL samples (rho = 0.44, $p = 0.055$; Fig. 3C). In serum samples, influenza-specific neutralising activity was strongly correlated with IgG (rho = 0.68, $p = 0.0013$) but not IgA (rho = 0.43, $p = 0.056$; Fig. 4). In BAL samples, influenza-specific neutralising activity was also strongly correlated with IgG (rho = 0.61, $p = 0.0052$), but not IgA (rho = 0.09, $p = 0.70$; Fig. 4).

4. Discussion

The findings from this study contribute to the scarce evidence base

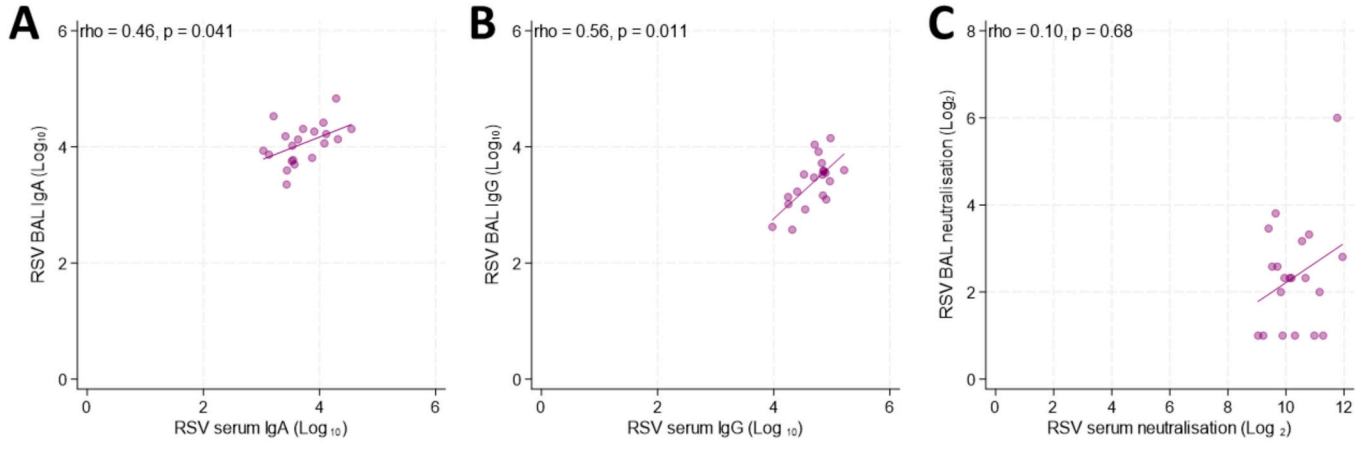

Fig. 1. Correlations between serum and BAL immunoglobulins and neutralising activity against RSV in healthy adults – United States. Correlations between serum and BAL **(A)** IgA MFI, **(B)** IgG MFI and **(C)** neutralising titres against RSV. Correlations estimated using Spearman's rank correlation coefficients. Abbreviations: Bronchoalveolar lavage (BAL), immunoglobulin (Ig), respiratory syncytial virus (RSV), median fluorescence intensity (MFI).

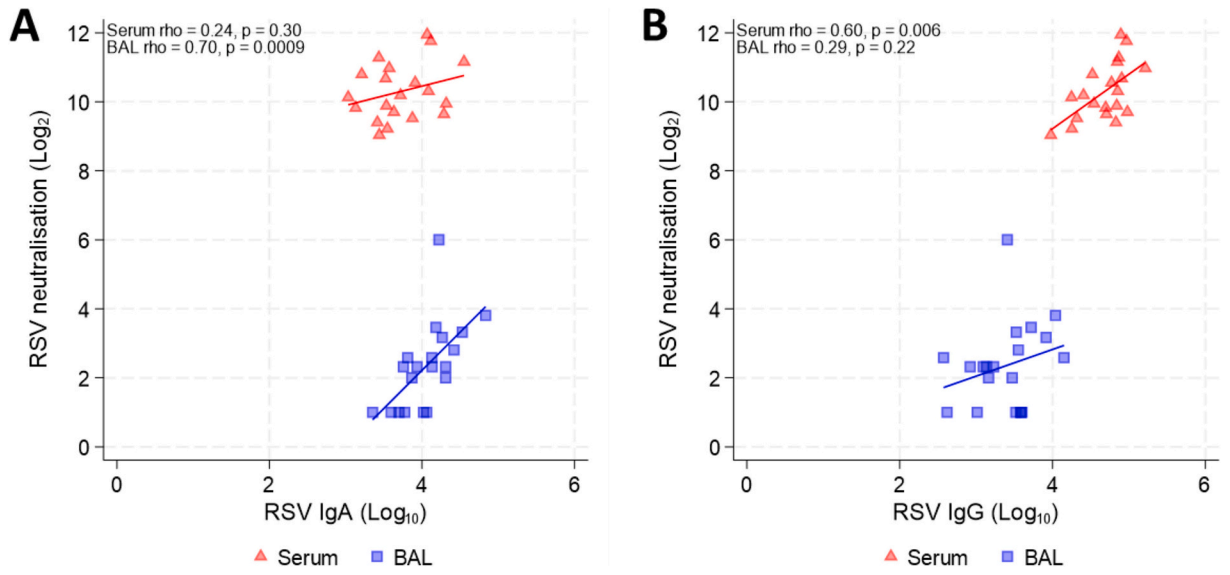

Fig. 2. Correlations between immunoglobulins and neutralising activity against RSV in the serum and BAL of healthy adults – United States. Correlations between **(A)** IgA MFI and **(B)** IgG MFI and neutralising titres against RSV in the serum and BAL. Correlations estimated using Spearman's rank correlation coefficients. Abbreviations: Immunoglobulin (Ig), bronchoalveolar lavage (BAL), respiratory syncytial virus (RSV), median fluorescence intensity (MFI).

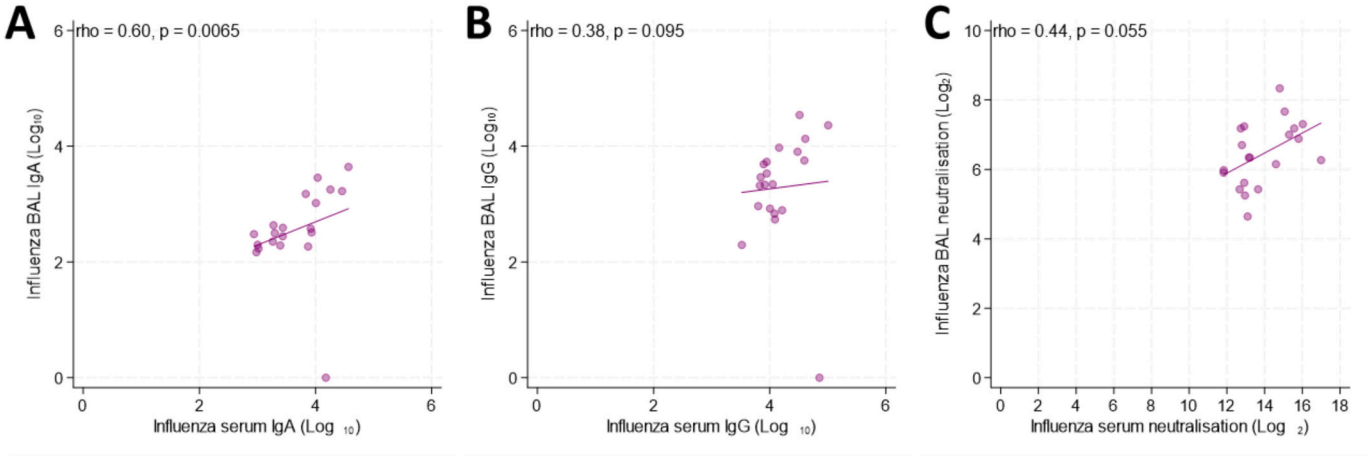

Fig. 3. Correlations between serum and BAL immunoglobulins and neutralising activity against influenza virus A (H1N1) in healthy adults – United States. Correlations between serum and BAL **(A)** IgA MFI, **(B)** IgG MFI and **(C)** neutralising titres against influenza virus A (H1N1). Correlations estimated using Spearman's rank correlation coefficients. Abbreviations: Bronchoalveolar lavage (BAL), immunoglobulin (Ig), median fluorescence intensity (MFI).

that has directly investigated binding and neutralising antibodies in the LRT secretions of humans. Leveraging paired serum and BAL samples, we measured total and virus-specific binding antibodies as well as functional neutralising activity against RSV and influenza A (H1N1), both of which may replicate in epithelial cells of the lower respiratory tract [reviewed in [3,4]]. Although the sample size and statistical power of the current study are limited due to the methodological challenges of sampling the LRT in humans, our findings identify both similarities and differences in the serum and BAL antibody patterns between RSV and influenza A (H1N1) and provide evidence that the functional anti-viral antibody responses in the LRT may not necessarily reflect those associated with systemic immunity.

Our results demonstrate detectable levels of both IgA and IgG in mucosal secretions from the LRT of healthy adults. Given the dilution that inevitably occurs during the BAL procedure, we were unable to determine immunoglobulin levels representing those in situ, which will be considerably higher than the measured concentrations, and were limited to defining relative levels of IgA and IgG in BAL fluid. Consistent with earlier research, we observed that IgG appeared to be the dominant immunoglobulin isotype in the serum [12] and to a lesser extent in the LRT [reviewed in [13]], with a median ratio for total IgG to total IgA of 37.1 in serum and 4.2 in BAL fluid.

We then compared virus-specific binding and neutralising antibodies between and within serum and BAL samples. For both RSV and influenza A (H1N1), we observed: (i) virus-specific serum and BAL IgA levels were positively and statistically significantly correlated, (ii) virus-specific serum and BAL neutralising activities were not statistically significantly correlated, and (iii) within serum samples, virus-specific neutralising activity was strongly correlated with IgG, but not IgA. In contrast between the viruses, we also found: (i) IgG was positively and statistically significantly correlated between serum and BAL for RSV, but not for influenza A (H1N1) and (ii) within BAL samples, virus-specific neutralising activity was more strongly correlated with IgA in the case of RSV and IgG in the case of influenza A (H1N1).

We hypothesise that the discrepancies in neutralising and immunoglobulin-class specific antibodies against RSV and influenza A (H1N1) likely reflect differences in participants' routes of prior exposure to these respiratory viruses. At the time of sample collection (i.e., 2015

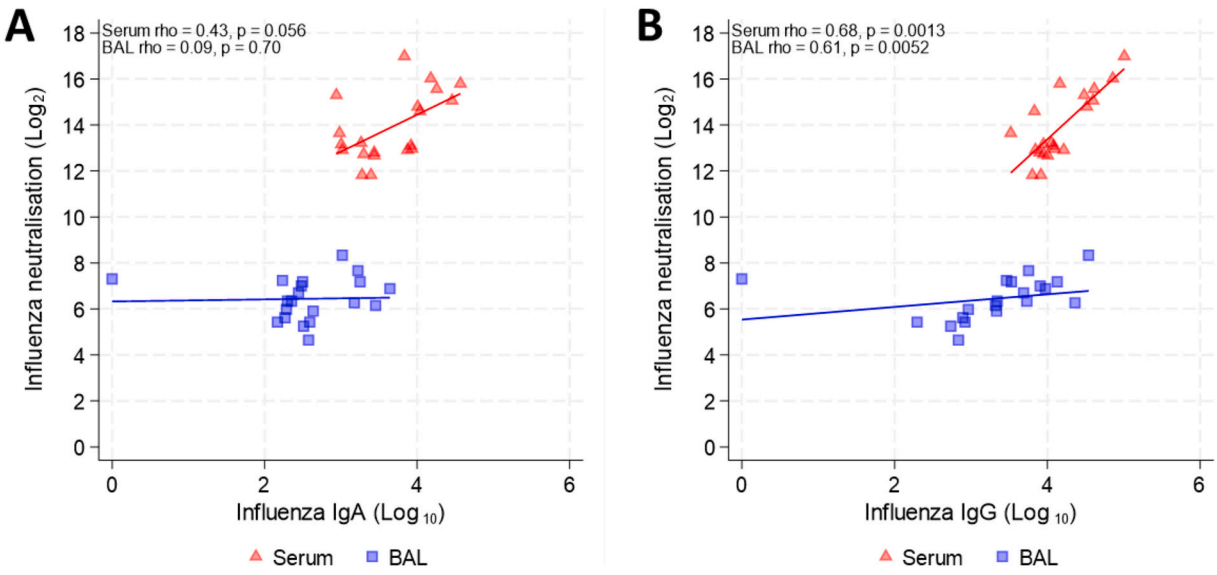

Fig. 4. Correlations between immunoglobulins and neutralising activity against influenza virus A (H1N1) in the serum and BAL of healthy adults – United States. Correlations between **(A)** IgA MFI and **(B)** IgG MFI and neutralising titres against influenza virus A (H1N1) in the serum and BAL. Correlations estimated using Spearman's rank correlation coefficients. Abbreviations: Immunoglobulin (Ig), bronchoalveolar lavage (BAL), median fluorescence intensity (MFI).

to 2016), RSV-specific binding antibodies would have exclusively reflected participants' prior natural seasonal infections. In contrast, influenza-specific binding antibodies among the young adult participants would have reflected a potential combination of both natural seasonal infections and intramuscular (i.e., systemic) vaccination, the latter of which is known to induce robust humoral responses but have a limited impact on mucosal antibodies [reviewed in [13]] [14]. For the 2015–16 season, influenza vaccination coverage in the USA was 32.3 % among 18–49 years olds [15], with a 2011 systematic review and meta-analysis reporting cumulative incidences of influenza for healthy working adults to be 5.4 % among unvaccinated individuals and 1.2 % among vaccinated individuals [16]. Additionally, infection with respiratory viruses, such as influenza, RSV, coronavirus and adenovirus, are associated with the formation of inducible bronchus-associated lymphoid tissue (iBALT), which is important for both humoral and cellular immune responses to pathogens [reviewed in [17]]. However, it remains unclear whether systemic vaccination against these respiratory viruses are able to induce the formation of iBALT [18], which may in part explain some of the differences seen between responses to RSV and influenza A (H1N1) in our study.

While participants' prior infection histories were not available in this study, we hypothesise that it would be unlikely that there were substantial discrepancies in the incidence and recency of natural seasonal RSV and influenza infections within the study population. Although evidence on the comparative incidence of RSV and influenza in healthy adults remains scarce, a community-based study of older adults (≥60 years) in Belgium, the Netherlands, and the United Kingdom reported approximately similar cumulative incidences between the viruses during two seasons (2017–2018 and 2018–2019) of 4.2 % and 7.2 % for RSV and 2.7 % and 3.7 % for influenza A [19].

There may also be potential intrinsic factors that explain the differences observed in our study. Clear differences have been reported between RSV and influenza virus in the induction of innate and adaptive immunity in the lungs [reviewed in [20]]. Specifically, defects in IgA memory responses to RSV are postulated to contribute to recurrent RSV infection [21]. Our cross-sectional study did not permit examination of changes in RSV-specific IgA in BAL over time, nor did we know the interval since last exposure to the virus. However, we found evidence of RSV-specific IgA binding in BAL samples from all participants, most likely reflecting recent respiratory exposure to the virus [22]. Although RSV-specific functional neutralising activity in BAL samples was only detected in 70 % of participants, we did observe a correlation between the level of RSV-specific IgA and neutralisation in the BAL, suggesting the possibility of a functional contribution of mucosal IgA in controlling RSV replication in the LRT. A similar correlation was not found between RSV-specific IgA and neutralisation in serum samples, emphasizing distinctions between the systemic and LRT compartments following natural infection. Additionally, we found correlations between neutralisation of RSV and RSV-specific IgG in serum but not BAL samples. A prior report found that high titres of RSV-specific serum IgG and neutralising activity and nasal IgA were associated with protection from natural infection in adults [23].

In contrast to RSV infection, influenza infection induces long-lived strain-specific IgA and IgG memory responses in the lungs [reviewed in [20]]. In BAL samples, we only found correlation between influenza-specific IgG and neutralisation. However, the extent to which influenza-specific IgG is induced locally in the LRT or is transported from the serum into the LRT remains uncertain. The lack of correlation between influenza-specific IgA and neutralisation in the BAL is consistent with prior research reporting that vaccination with an inactivated influenza vaccine does not effectively induce nasal IgA responses [14]. In serum samples, we found correlations between influenza-specific IgG and IgA and neutralisation, which are consistent with exposure to influenza either through infection and/or vaccination [24,25].

Overall, these results open avenues for further exploration and contribute to our understanding of mucosal immunity to respiratory pathogens in the LRT. Although the small number of participants and lack of exposure history limits our study, our findings provide preliminary evidence that there are important differences in anti-viral immunity to respiratory viruses as measured in serum and BAL fluid. It does not appear from our results that measurement of serum antibody, even if immunoglobulin class-specific, can definitively predict functional adaptive immunity in the LRT.

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CRediT authorship contribution statement

Amber I. Raja: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Ruth I. Connor:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Alix Ashare:** Writing – review & editing, Resources, Methodology, Investigation. **Joshua A. Weiner:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Wendy F. Wieland-Alter:** Writing – review & editing, Validation, Methodology, Investigation, Data curation. **Audrey Godin:** Writing – review & editing, Visualization, Methodology, Formal analysis. **John F. Modlin:** Writing – review & editing. **Margaret E. Ackerman:** Writing – review & editing, Methodology, Investigation. **Elizabeth B. Brickley:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Methodology, Formal analysis, Conceptualization. **Peter F. Wright:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplemental data

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2025.126936.

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