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A mixture model to assess the the immunogenicity of an oral rotavirus vaccine among healthy infants in Niger

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ABSTRACT

Analysis of immunogenicity data is a critical component of vaccine development, providing a biological basis to support any observed protection from vaccination. Conventional methods for analyzing immunogenicity data use either post-vaccination titer or change in titer, often defined as a binary variable using a threshold. These methods are simple to implement but can be limited especially in populations experiencing natural exposure to the pathogen. A mixture model can overcome the limitations of the conventional approaches by jointly modeling the probability of an immune response and the level of the immune marker among those who respond. We apply a mixture model to analyze the immunogenicity of an oral, pentavalent rotavirus vaccine in a cohort of children enrolled into a placebo-controlled vaccine efficacy trial in Niger. Among children with undetectable immunoglobulin A (IgA) at baseline, vaccinated children had 5.2-fold (95% credible interval (CrI) 3.7, 8.3) higher odds of having an IgA response than placebo children, but the mean log IgA among vaccinated responders was 0.9-log lower (95% CrI 0.6, 1.3) than among placebo responders. This result implies that the IgA response generated by vaccination is weaker than that generated by natural infection. Multivariate logistic regression of seroconversion defined by $\geq$ 3-fold rise in IgA similarly found increased seroconversion among vaccinated children, but could not demonstrate lower IgA among those who seroresponded. In addition, we found that the vaccine was less immunogenic among children with detectable IgA pre-vaccination, and that pre-vaccination infant serum IgG and mother's breast milk IgA modified the vaccine immunogenicity. Increased maternal antibodies were associated with weaker IgA response in placebo and vaccinated children, with the association being stronger among vaccinated children. The mixture model is a powerful and flexible method for analyzing immunogenicity data and identifying modifiers of vaccine response and independent predictors of immune response.

1. Introduction

Immunogenicity studies for vaccines are performed to test the response of the immune system to vaccination. Immunogenicity data on a relatively small number of participants can provide information on whether a vaccine generates a response from the immune system. Collection and analysis of immunogenicity data is therefore a critical component of vaccine development, giving a biological basis to support any observed protection against infection or disease.

Immune response to a vaccine is often measured using antigen-specific immunoglobulin assays. The classical approach to assessing immunogenicity compares the concentrations between groups within a randomized trial, analysed as transformed continuous outcomes (geometric mean titre (GMT) or rise in titre using a Wilcoxon or similar non-parametric test [1]), or binary outcomes (seroconversion or seroresponse) using a specified fold rise in titre (e.g. 3-fold rise) or a specified titre post-vaccination (e.g. IgA $\geq$ 20). Classical analysis of continuous GMTs cannot explicitly account for individuals who have undetectable titre, and the standard statistical tests cannot be easily extended to perform multivariate analyses, in particular to control for pre-existing antibodies. Multivariate analyses accounting for the full distribution of the antibody in question (e.g. non-normal distribution,

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samples below the limit of detection) are rare in the literature [2–4]. Binary outcomes are problematic as defining seroconversion with a crude cut-off fails to capture biological variability in antibody titres and assay variability that may be apparent when exploring a continuous range in post-vaccination titres. The thresholds chosen to determine seroconversion and seroresponse have origins in the use of two-fold serial dilution, with a four-fold increase taken as unlikely to be due to assay variability. Different thresholds might be clinically relevant for different assays, but identifying an optimal threshold is not commonly done [5]. Finally, the presence of individuals with elevated titre at baseline complicates the analysis and interpretation of GMT and seroconversion [6]. For example, as the body is limited in how much antibody it can produce, a higher baseline titre might lead to a lower rise in titre for reasons that are unrelated to vaccine interference [7]. In addition, studies that investigate only a small number of unique dilutions may have limited resolution to detect fold changes in titre if baseline titres are elevated.

To overcome some of these limitations, a mixture model has been proposed as a method to analyse immunogenicity data [8–10]. A mixture model describes a population that is composed of distinct groups, in which the response variable's probability distribution is dependent on membership in one of these groups. When analysing immunogenicity data, we can jointly model the probability of being a "seroresponder" vs. a "nonresponder" and the level of seroresponse among seroresponders. There are several advantages to this approach: it avoids reducing a continuous variable to a binary variable, thereby using the full information contained in the data; it allows us to avoid making arbitrary assumptions about what constitutes a significant change in titre and to include baseline titre in a natural way; it allows us to simultaneously examine the probability of having a seroresponse and the level of the immune marker among seroresponders; and it can be easily extended to perform a multivariate analysis. These advantages could allow us to better explore immunogenic markers of protection from disease that are not "all-or-nothing" in their action, but rather confer higher levels of protection with higher titre [11] or for which the titre value is informative beyond its position relative to a threshold [12].

In this study we analyse immunogenicity data from a cohort of children in Niger enrolled in a vaccine efficacy trial [13] using a mixture model. We demonstrate the approach with this data set because it is large, includes placebo and vaccinated participants, and has data on maternal antibodies measured at baseline that can be used to address a common question in rotavirus immunology: that of whether maternal antibodies interfere with vaccine response. We apply a mixture model to measurement of serum IgA with several aims: to determine whether vaccination is associated with an increased IgA response compared to placebo; to identify predictors of IgA response that are independent of vaccination; and to identify factors that modify the effectiveness of vaccination in generating an IgA response. Finally, we consider what additional information the mixture model can provide over a traditional immunogenicity analysis.

2. Methods

2.1. Study population

Details of the study population have been published elsewhere [13] In brief, healthy infants were enrolled in Maradi, Niger and randomized in a 1:1 ratio to receive three doses of a heat-stable, live, oral bovine rotavirus pentavalent vaccine (Rotasiil, Serum Institute of India), or three doses of placebo at 6, 10 and 14 weeks of age. The primary efficacy analysis included 3508 children. An immunogenicity sub-study was carried out among a subset of children who received all three doses of vaccine or placebo per protocol (n = 1525) to assess differences in serum IgA following administration of vaccine or placebo. Serum was collected from infants in the immunogenicity sub-study pre-dose 1 (6–8 weeks from birth, henceforth "baseline") and 28 days post-dose 3 (18–23 weeks from birth, henceforth "post-vaccination") to measure IgA response to the vaccine. Infant serum IgG and mother's breast milk IgA pre-dose 1 were also collected.

2.2. Outcome definition and assay description

The outcome of interest was log IgA titre at the post-vaccination visit. An individual whose IgA titre fell below the lower limit of detection (LOD) of 7.5 AU/ml was censored. Immunology analyses were performed in Cincinnati Children's Hospital Medical Center in Cincinnati. Serum rotavirus IgA, serum rotavirus IgG, and breast milk rotavirus-IgA were measured by Enzyme Immunoassay (EIA): 96-well microtitre plates were coated with anti-rotavirus IgG rabbit hyperimmune serum raised against a pool of Rotavirus (strains SA-11, RV3, RV4, RV5, and ST3), and simian SA11-strain Rotavirus added as antigen, as previously described [14]. IgA/IgG was detected using peroxidase-conjugated secondary antibody followed by orthophenyenediamine reaction to measure antibody concentration (AU/mL).

2.3. Mixture model

For the mixture model, we assumed that the population comprised two unobserved groups defined by their post-vaccination IgA response: those who truly had no exposure to rotavirus or response to vaccination ("non-response"), and those who had some exposure and/or response ("response") [8]. Among responders, the log IgA titre follows a gamma distribution, representing the strength of response to a previous exposure. The response is censored below at the LOD.

We derive the likelihood of this model as follows. Let Y = log (IgA) post-vaccination and Y_0 = log(IgA) at baseline, and let the mean response for a responder i be

$$E[Y_i] = \mu_i = Y_{0i} + \sum_{j=1}^{r} \gamma_j X_{ij}.$$

μ_i represents the mean of a gamma distribution with shape parameter $\sigma > 0$, and the γ parameters represent associations between covariates X_{ij} and change in log(IgA) from baseline. Being a responder is determined by a Bernoulli distribution with probability p_i, which links to a different set of covariates X'_{ij} with a logistic model

$$logit(p_i) = \sum_{j=1}^{r'} \beta_j X'_{ij}.$$

Assuming that the population consists of n individuals with IgA $\geq$ LOD post-vaccination and m individuals with IgA < LOD post-vaccination, the log likelihood of the model given the data is

$$l(\beta, \gamma, \sigma) = \sum_{i=1}^{n} \ln(p_i f(x_i)) + \sum_{i=n+1}^{n+m} \ln([1 - p_i + p_i F(LOD)]).$$

Parameter estimation was done by maximizing the log-likelihood using Bayesian MCMC. Estimates are presented alongside the 95% credible interval estimated from the posterior likelihood.

Pre-dose 1 IgA is censored below the LOD, meaning that we do not have full exposure information for such children. Therefore, a value must be chosen for children with IgA < LOD, commonly set to LOD, LOD/2, or LOD/$\sqrt{2}$. However, this substitution method has been shown to lead to bias in the estimates of mean associations and standard errors [15]. We fit the mixture model separately

to children with IgA < LOD and IgA ≥ LOD at the baseline visit, so that estimates of the association between baseline IgA and IgA response in both groups are unbiased [15]. We refer to the two groups as "baseline IgA-undetectable" and "baseline IgA-detectable" respectively.

2.4. Statistical analysis

We performed three analyses using the mixture model. We applied the model to examine the effect of vaccination on IgA response, including vaccination group as a covariate for both the probability of being a responder and the strength of IgA response among those who do respond. Then, we identified baseline variables that modified the association between vaccination and IgA response separately among the baseline IgA-detectable and IgA-undetectable groups. We added each baseline covariate and its interaction with vaccination to the response odds and mean response separately, and to both components in the same model. Finally, we identified baseline variables that were associated with IgA response independently of vaccination. To build this model, we performed a univariate analysis for each covariate by including it in the model in the IgA response odds component, in the IgA response mean component, and in both. We then chose covariates to be included in the multivariate model if the deviance information criterion (DIC) was < 2 greater than the DIC of the null model. We fit multivariate models including all combinations of chosen covariates, and used DIC to compare these models. The fit of the final models was assessed by comparing the predicted and observed values of the following two quantities: proportion of children who are below the LOD, and the mean log(IgA titre) among children whose titre is above the LOD.

To compare the results of the mixture model with standard approaches, we defined seroconversion as a 3-fold [16], 2-fold, or 4-fold rise in IgA from baseline to 18 weeks, or IgA ≥ 20 at 18 weeks for those with IgA < 20 at baseline. We performed univariate and multivariate logistic regression to assess the association between baseline covariates and seroconversion and compared the results with those of the mixture model.

We considered the following baseline variables: child serum IgA at baseline, child serum IgG at baseline, mother's breast milk IgA at baseline, administration of oral polio vaccine within 7 days of the baseline visit, child sex, mother's age (quartiles), and mother's MUAC (quartiles). We performed a complete case analysis, excluding any children with missing data for any of these variables.

As the model presented above involves several assumptions, we performed sensitivity analyses to address three of these assumptions: firstly, to allow more flexibility in the shape of the response distribution, we modelled the distribution of IgA response among responders with a lognormal and generalized gamma distribution. The gamma and lognormal distributions are special cases of the generalized gamma distribution [8]. Secondly, to assess the effect of dividing the population in IgA-detectable and IgA-undetectable, we combined the groups and imputed the value of baseline IgA below the LOD using maximum likelihood estimation [15]. Specifically, we assumed the log(IgA) at baseline was gamma-distributed, estimated the shape and rate of the distribution, and imputed the log(IgA) at baseline using a conditional expectation formula [17]. Finally, we fitted the same models to the data assuming that all children with IgA < 20 were seronegative, thus modelling the probability of having IgA ≥ 20 at 18 weeks, and the IgA among the group who had a seroresponse. IgA ≥ 20 has been cited previously as a protective threshold [18], so the aim of this sensitivity analysis was to explore whether defining "response" using a possibly more biologically relevant threshold would change the overall conclusions.

3. Results

The study population for the immunogenicity sub-study consisted of 1525 children enrolled from September 2015 through February 2017. 1398 children had complete information for all covariates considered in these models, and were thus included in the analysis population. Table 1 displays the baseline characteristics in the two groups.

Fig. 1 shows the distribution of log(IgA titre) for vaccinated (orange) and placebo (blue) children at baseline (left) and post-vaccination (right). 79% of children were IgA-undetectable at baseline. Among children that were IgA-undetectable at baseline, 50.9% had detectable IgA at post-vaccination, while among children that were IgA-detectable at baseline, 84% had detectable IgA post-vaccination.

3.1. Vaccine immunogenicity

The mixture model estimated the effect of vaccination on probability of response and the level of IgA response among responders. Among children with undetectable IgA at baseline, vaccination was associated with a 5.16-fold (95% credible interval (CrI) 3.67, 8.25) change in the odds of being a responder compared to placebo, and a 0.93-log decrease (95% CrI 0.59, 1.28) in mean log IgA among those who did respond compared to placebo responders. In the baseline IgA-detectable group, vaccination was associated with a 1.63-fold (95% CrI 0.86, 3.16) change in the odds of being a responder compared to placebo, and a 0.53-log decrease (95% CrI 0.41, 0.65) in mean log IgA among those who did respond compared to placebo responders. This implies that the serological profile of IgA-detectable vaccinees is similar post-vaccination to that of IgA-detectable non-vaccinees at the same time.

3.2. Modifiers of vaccine immunogenicity

We tested interaction terms between vaccination status and a number of baseline covariates to identify factors that could modify the ability of the vaccine to generate an IgA response. In both groups there was a negative interaction between vaccination status and baseline IgG. Specifically, the negative association between IgG and seroresponse was stronger among vaccinated children (Table 2). In addition, the negative association between breast milk IgA and probability of a seroresponse was stronger among vaccinated children in the baseline IgA-undetectable group.

3.3. Independent predictors of seroresponse

In Table 3 we show the results of the best-fitting models, separately for the baseline IgA-undetectable and IgA-detectable groups,

Table 1
Baseline characteristics of the study population by vaccine group, compared to characteristics in the primary analysis cohort.

Characteristic	Immunogenicity study	
	BRV-PV	Placebo
N	731	667
Age - weeks		
At dose 1	6.5 ± 0.6	6.5 ± 0.6
At 28 days post-dose 3	18.7 ± 0.7	18.6 ± 0.7
Male sex - n(%)	358 (49.0)	345 (51.7)
Child serum IgA at baseline (log)	1.9 (1.4)	1.9 (1.4)
Child serum IgG at baseline (log)	5.7 (0.9)	5.7 (0.9)
Mother's breastmilk IgA at baseline (log)	3.5 (1.2)	3.5 (1.2)
Oral polio vaccine administered within 7 days of baseline visit	239 (32.7)	222 (33.3)

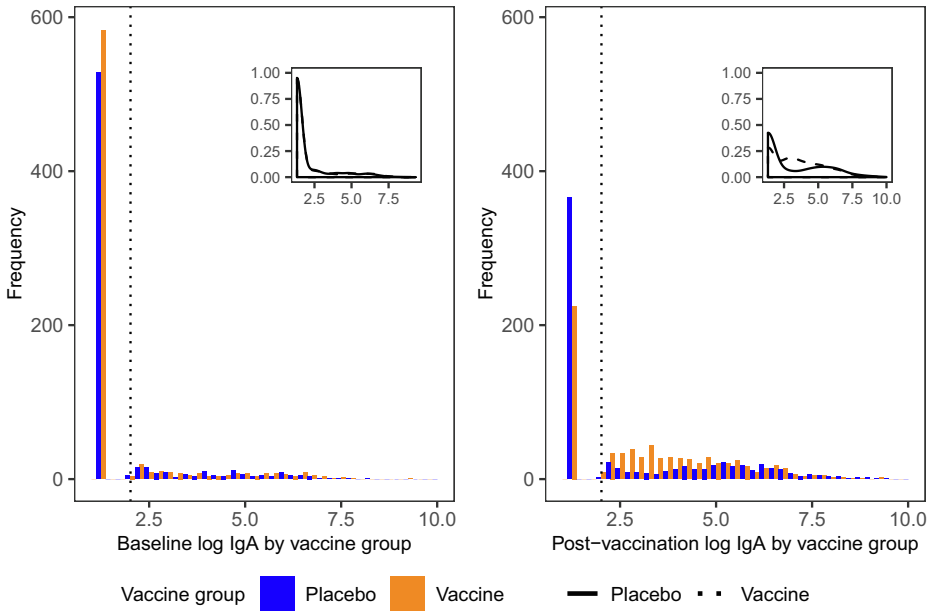

Fig. 1. Distribution of log IgA titre pre-vaccination (left) and post-vaccination (right) for placebo (blue) and vaccinated (orange) children. The vertical line represents the LOD. Density of log IgA titre distribution at each time point is shown in the inset graphs, for placebo (solid) and vaccinated (dotted) children.

Table 2
Interaction terms between vaccination status and baseline covariates.

Baseline IgA status	Variable	Model	Effect estimate among placebo (95% CrI)	Effect estimate among vaccinated (95% CrI)
IgA <7.5	log(serum IgG)	Response odds	−0.22 (−0.01, −0.41)	−0.51 (−0.24, −0.80)
	log(breast milk IgA)	Response odds	−0.23 (−0.07, −0.41)	−0.60 (−0.35, −0.92)
IgA ≥ 7.5	log(serum IgG)	Response mean	0.01 (−0.29, 0.29)	−0.48 (−0.74, −0.20)

Table 3
Predictors of IgA response at 18 weeks among children by IgA status pre-vaccination.

Model	Variable	Estimate (95% CrI Interval)	
		IgA <7.5 pre-vaccination n = 1,086	IgA ≥7.5 pre-vaccination n = 282
Response odds	Group (vaccine vs placebo)	1.72 (1.35, 2.24)	0.56 (−0.11, 1.28)
	IgA at baseline	–	0.38 (0.15, 0.63)
	Breast milk IgA at baseline	−0.22 (−0.38, −0.05)	–
Response mean	Group (vaccine vs placebo)	−0.91 (−1.27, −0.58)	−0.33 (−0.71, 0.04)
	IgA at baseline	–	−0.5 (−0.62, −0.37)
	IgG at baseline	−0.37 (−0.53, -0.20)	−0.23 (−0.46, −0.005)
	Breast milk IgA at baseline	−0.25 (−0.41, −0.08)	−0.18 (−0.36, 0.003)
	Female sex	–	0.51 (0.14, 0.89)

that included vaccination as a covariate for response odds and response mean. Effect estimates presented are log odds ratios for the response odds model, and change in log titre for the response mean model.

In the baseline IgA-undetectable group, IgG and breast milk IgA at baseline were negatively associated with mean response among those who responded, and breast milk IgA was negatively associated with probability of being a responder. For this model, the estimated proportion of children with undetectable IgA was 0.489, compared with an observed value of 0.487, while the estimated vs. observed mean log(IgA) among children with detectable IgA was 4.30 vs. 4.26.

In the baseline IgA-detectable group, IgA at baseline was positively associated with probability of being a responder but also negatively associated with mean change in IgA from baseline. Finally, IgG and mother's breast milk IgA were both negatively associated with mean IgA among those who responded, and girls had a stronger response than boys. For this model, the estimated proportion of children with undetectable IgA was 0.165, compared with an observed value of 0.163, while the estimated vs. observed mean log(IgA) among children with detectable IgA was 5.09 vs. 5.16.

3.4. Sensitivity analyses

The final model using the gamma distribution had lower DIC than the final models using the lognormal and generalized gamma distribution, and the predictors of IgA response were broadly the same across models (see Supplementary Material), implying that results were robust to the choice of distribution and that the gamma distribution was the best choice of distribution out of the three.

Results for models assuming that children with IgA < 20 were seronegative, and imputing the IgA for those with undetectable IgA, are shown in the Supplementary Material.

3.5. Comparison with logistic regression for seroconversion

We performed univariate and multivariate logistic regression for seroresponse as defined by a 3-fold rise in IgA from baseline to post-vaccination. In the univariate analysis, vaccination was associated with a 3.28-fold (95% confidence interval 2.56, 4.20) change in the odds of seroresponse compared to placebo in the

baseline IgA-undetectable group, and a 0.83-fold (95% confidence interval 0.48, 1.41) change in the odds of seroresponse compared to placebo in the baseline IgA-detectable group. As independent predictors of IgA response, the logistic regression estimated a negative association between baseline IgG and breast milk IgA and odds of seroresponse (see Supplementary Material). In the baseline IgA-detectable group, IgA was significantly associated with decreased odds of seroresponse, and IgG was marginally associated with decreased odds of seroresponse. There was no significant association between seroresponse and breast milk IgA or sex, and results defining seroresponse as a 2-fold or 4-fold rise in IgA, or as IgA $\geq$ 20 post-vaccination among those with IgA < 20 pre-vaccination were qualitatively similar (see Supplementary Material).

4. Discussion

We present a novel statistical method for analysing immunogenicity data, applied to a Phase III randomized trial for a rotavirus vaccine in Niger. Using a mixture model approach, we found that the vaccine was effective in generating an IgA response and estimate the magnitude of the effect among children with detectable IgA after vaccination. Logistic regression, which does not account for the full distribution of the titre, showed increased odds of seroconversion associated with vaccination but was unable to make inferences about the average change in IgA among seroresponders. In contrast, the mixture model, by jointly modelling the probability of having detectable IgA and the level of IgA among responders, showed that being vaccinated was associated with increased odds of having detectable IgA following vaccination, but decreased IgA among those who did respond. This result implies that the IgA response induced by vaccination is weaker than that induced by natural exposure to rotavirus. This may explain why the odds ratio for seroresponse in the mixture model is higher than that for the traditional logistic regression for seroconversion. In smaller studies, this phenomenon could limit the ability of a traditional approach to detect the effect of vaccination on immune response.

In addition, we identified modifiers and predictors of the immunogenic effect of the vaccine. In particular, the vaccine appeared to be more immunogenic among children with undetectable IgA pre-vaccination, and it was not clear that vaccinated children detectable IgA pre-vaccination had higher IgA post-vaccination than placebo children. Maternal antibodies were generally associated with lower odds of IgA response at 18 weeks, and lower level of response among those who responded. For IgG, this effect appeared to be stronger among vaccinated children, suggesting that IgG interferes with vaccine-induced IgA response more than IgA response induced by natural exposure.

These findings are in line with those from previous immunogenicity studies in low-income settings. Lee et al [19] found that children with high levels of serum IgG had lower rates of seroconversion. Several other studies have demonstrated evidence for interference of maternal antibodies on vaccine response: transplacental IgG inhibited IgA response among vaccinees but not placebos [20]; higher titres of breast milk IgA was associated with lower rate of seroconversion following vaccination in mother-child pairs in Lusaka [21]; and pre-vaccination IgA and IgG were negatively associated with IgA seroconversion among vaccinated children in Soweto, South Africa [22]. To add to these studies, we have demonstrated that the effect of IgG on seroconversion is stronger among vaccinated children, suggesting that IgG interferes with vaccine response more than response to natural exposures.

Weaker immune response among vaccinees with detectable IgA after vaccination has been observed for influenza [23,24]. The implications of this finding depend on the relationship between serum IgA and protection from infection. IgA has generally been accepted as a non-mechanistic correlate of protection (i.e. an immune marker that is correlated with but does not cause protection from infection) [16,25,26]. Recent results from lower-income settings have showed low correlation between changes in IgA following vaccination and vaccine efficacy [19,27]. If the value of IgA titre is important beyond whether it crosses a certain threshold, the weaker IgA response among vaccinated responders is indicative of weaker immunogenicity of the vaccine compared to natural infection. This could explain the reduced vaccine efficacy seen in the second year of life in lower-income settings: while the vaccine provides protection against infection relative to children with no previous infections, once placebo children have acquired protection from natural infection the difference in hazard between the two groups is small.

There are several limitations to the study. The vaccine group is receiving a combination of vaccine-derived and natural exposures to rotavirus. This suggests that any interaction terms between the two groups underestimate the true interaction between vaccine and natural exposures. Therefore, we may have missed some other interactions. Small sample size of children with detectable IgA at baseline may have affected our ability to discern associations between baseline covariates and IgA response in this group. In addition, our statistical model does not account for the possibility of false positives, assuming instead that all samples with IgA $\geq$ 7.5 truly had an IgA response. However, the results of the sensitivity analysis in which we considered IgA $\geq$ 20 as the cut-off for seroresponse were similar, implying that our results were robust to measurement error in true non-responders.

In summary, we have introduced a flexible and powerful statistical method that can be used to approach other analyses of immune response following vaccination.

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.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2020.10.079.

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