

Short communication

A log-odds system for waning and boosting of COVID-19 vaccine effectiveness

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ABSTRACT

Immunity to SARS-CoV-2 following vaccination wanes over time in a non-linear fashion, making modelling of likely population impacts of COVID-19 policy options challenging. We observed that it was possible to mathematize non-linear waning of vaccine effectiveness (VE) on the percentage scale as linear waning on the log-odds scale, and developed a random effects logistic regression equation based on UK Health Security Agency data to model VE against Omicron following two and three doses of a COVID-19 vaccine. VE on the odds scale reduced by 47% per month for symptomatic infection after two vaccine doses, lessening to 35% per month for hospitalisation. Waning on the odds scale after triple dose vaccines was 35% per month for symptomatic disease and 19% for hospitalisation. This log-odds system for estimating waning and boosting of COVID-19 VE provides a simple solution that may be used to parametrize SARS-CoV-2 immunity over time parsimoniously in epidemiological models.

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1. Introduction

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have repeatedly been shown to afford a high degree of protection from coronavirus disease 2019 (COVID-19) in the short term, particularly with regard to severe disease and death [1–3]. Vaccine effectiveness (VE), however, is known to peak soon after receipt of a full vaccination course and wanes thereafter, an effect that has been demonstrated across multiple SARS-CoV-2 variants [4–6]. This clearly poses significant obstacles to ongoing COVID-19 prevention and control efforts globally, but it also makes modelling of likely population impacts of COVID-19 policy options challenging.

There are now a plethora of published studies estimating VE over time following double and triple doses of multiple COVID-19 vaccines (e.g. [4,5,7]). In relation to the Omicron (B.1.1.529) SARS-CoV-2 variant, for example, protection against symptomatic disease following a primary course of the BNT162b2 (Comirnaty, Pfizer-BioNTech) vaccine has been shown to fall from 65.5% at 2–4 weeks following receipt of a second dose to 8.8% at ≥ 25 weeks [4]. After a booster dose of BNT162b2, protection increases to 67.2% at 2–4 weeks which then decreases to 45.7% by 10 weeks

[4]. Synthesising these observations for use within simulation models is not straightforward.

Whilst it is theoretically possible to have a VE less than 0% (e.g. chance, and perhaps if early protection makes one more susceptible at a future date), this is unusual. Assuming VE is bounded between 0% and 100%, a similarly bounded log-odds system may provide a parsimonious solution to modelling waning in VE. When plotted on a percentage scale, the gradient of vaccine-derived immunity waning often tends to be flatter soon after completion of a vaccine course and then steepens over time, before flattening out again as it asymptotes to 0%. This is consistent with linear decline in the log-odds when plotted back onto a percentage scale. A linear decrease in the log-odds is equivalent to a constant odds ratio (OR) applied to the VE odds every month. For example, consider an initial VE of 90%, which is 9 on the odds scale (90%/10%). Assuming an OR of waning over time of 0.6, the VE odds in months 2–6 would be $0.6 \times 9 = 5.40$; $0.6 \times 5.40 = 3.24$; 1.94; 1.17; and 0.7. Converted back to the percentage scale for months 1 to 6 this would be 90%; 84%; 76%; 66%; 54%; and 41%. Note the increasing monthly percentage point reduction, as observed in the many studies of VE over time. Note also that as VE falls below 50%, the steepening of the decline (on the percentage scale) begins to slow: extending the above series for months 7–10 gives VE on the percentage scale of 30%, 20%, 13% and 8%, respectively.

These properties, especially that we could mathematize non-linear waning on the percentage scale as simple linear waning on

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the log-odds scale, prompted us to test our schema on UK Health Security Agency (UKHSA) data for VE against Omicron for symptomatic illness and hospitalization [8].

2. Methods

Point estimates of VE against symptomatic disease and hospitalisation from infection with the Omicron variant on the percentage scale, and their corresponding upper and lower confidence limits, were extracted from tables (at [4]) and visually from graphs for latest data (from [8]) for all available ‘sub-studies’ (each different combination of vaccine course and outcome). The log-odds for all data points were then calculated, as well as the inverse variance of each observation. Variance was calculated as the difference between the 97.5th and 2.5th percentile limits on the log odds scale, divided by 3.92 (assuming a 95% confidence interval 3.92 standard errors wide), then squared.

The following random effects logistic regression (with separate class for each ‘sub-study’, i.e. various combinations of vaccine type as primary and booster courses and clinical outcome) was fitted, excluding observations within 2 weeks since last vaccine dose (given peak immunity would still have been developing), weighted by the inverse variance:

$$\text{logistic}(VE) = \alpha + \beta_1 \cdot hosp + \beta_2 \cdot triple + \beta_3 \cdot month + \beta_4 \cdot hosp * month + \beta_5 \cdot triple * month$$

where *hosp* is a dummy variable for hospitalisation versus symptomatic illness; *triple* is a dummy variable for triple versus double vaccine course; *month* represents months since last vaccine dose minus 0.5 (i.e. ‘centered’ on two weeks post the last vaccine dose to aid interpreting model coefficients); *hosp*month* is an interaction term of hospitalisation and month; and *triple*month* is an interaction of triple and month.

3. Results

The coefficients from the final random effects logistic regression model are shown in Table 1. For models including interaction terms of *hosp*triple*month* and *triple*hosp* these coefficients had non-significant p values, and the differences in deviance statistics between these models and that without the interaction terms were trivial and non-significant. Similarly (when restricting to the outcome of symptomatic infection) p values for a term representing ChAdOx1 (Vaxzevria, AstraZeneca) as the primary vaccination course and for the interaction of this term and month were both > 0.15. As such none of these additional terms were retained in the final model.

Converting the intercept to the percentage scale gives a VE of 67.7% (95% confidence interval [CI] 62.1% to 72.8%) for the reference case of VE against symptomatic Omicron infection, two weeks post second dose. The OR for VE against hospitalisation compared to VE against symptomatic disease is 3.11 (95% CI 1.87 to 5.16), and for triple compared to double dose is 1.10 (95% CI 0.83 to 1.45). VE waning has an OR of 0.53 per month for symptomatic infection

after two doses, or a 47% reduction in the VE odds per month. For hospitalisation the VE odds reduces by 35% per month (i.e. 1 minus the OR of 0.65, where 0.65 = 0.53 × 1.24). After triple dose vaccination, the VE odds for symptomatic disease also decreases by 35% per month (1 minus 0.53 × 1.23), and the VE odds for hospitalisation decreases by 19% per month (1 minus 0.53 × 1.24 × 1.23).

Fig. 1 presents the predicted VE from the regression model converted to the percentage scale with the data points used to develop the regressions overlaid.

4. Discussion

Waning of immunity following COVID-19 vaccination presents a challenge when attempting to model likely population impacts of COVID-19 policy options. As more has been learnt about the nature of immunity to SARS-CoV-2, it has been necessary for models to move away from assuming constant VE to incorporating some type of waning function. These functions can vary in complexity from step functions to linear declines or more explicit relationships between neutralizing antibodies and protection against infection, symptomatic disease, hospitalisation, and death. Our analysis shows that a single simplifying assumption that waning immunity takes a log-odds functional form can explain reasonably well the observed profiles of protection across doses and outcomes, which may considerably assist in the parametrization of epidemiological COVID-19 models. Overlaying the data points used to develop the regression model onto the predicted VE provides a reasonable fit.

Predictive models of vaccine-derived immunity from COVID-19 have previously been published, notably a model by Khoury et al. which links in vitro neutralising antibody titers with observed protection from SARS-CoV-2 infection and severe disease to predict immunity waning [9]. In contrast, our model does not rely on the assumption that antibody neutralisation is the primary mechanism of protection over time (which may be important given the hypothesised role of cell-mediated immunity in protection against severe disease) [10] or that waning is uniformly dependent upon decay in neutralisation titer across clinical outcomes (for example, symptomatic disease and hospitalisation). Conceptualising VE as a simple logistic function of time based on real-world VE data also has the advantage of accessibility to a wide range of researchers. It does, however, have the disadvantage of not including a serological correlate of protection and as such relies on epidemiological VE studies (which may be delayed compared to serological studies) to inform updates to the model in the face of emerging SARS-CoV-2 variants.

Importantly, the log-odds system we have developed can be easily extended. First, it can be expanded to include more observations from the UKHSA data series as they are generated. Second, data from additional studies in other settings could be included. For example, data from Brazil could be incorporated into the model [11], noting that in countries with a less effective primary course vaccine, the VE boost with a third dose mRNA vaccine (i.e. the OR of a triple compared with a double dose) may be larger

Table 1
Logistic regression coefficients and odds ratios for vaccine efficacy against the Omicron SARS-CoV-2 variant.

Variable	Coefficient	Std Error	Odds	(95% CI)
Intercept (i.e. protection against symptomatic infection with double dose in first month)	0.740	0.125	2.10	(1.64–2.68)
			OR	(95% CI)
Months since last dose	−0.643	0.029	0.53	(0.50–0.56)
Hospitalisation (c.f. symptomatic infection)	1.134	0.258	3.11	(1.87–5.16)
Triple dose (c.f. double dose)	0.092	0.144	1.10	(0.83–1.45)
Interaction of Months and Hospitalisation	0.218	0.095	1.24	(1.03–1.50)
Interaction of Months and Triple	0.211	0.033	1.23	(1.16–1.32)

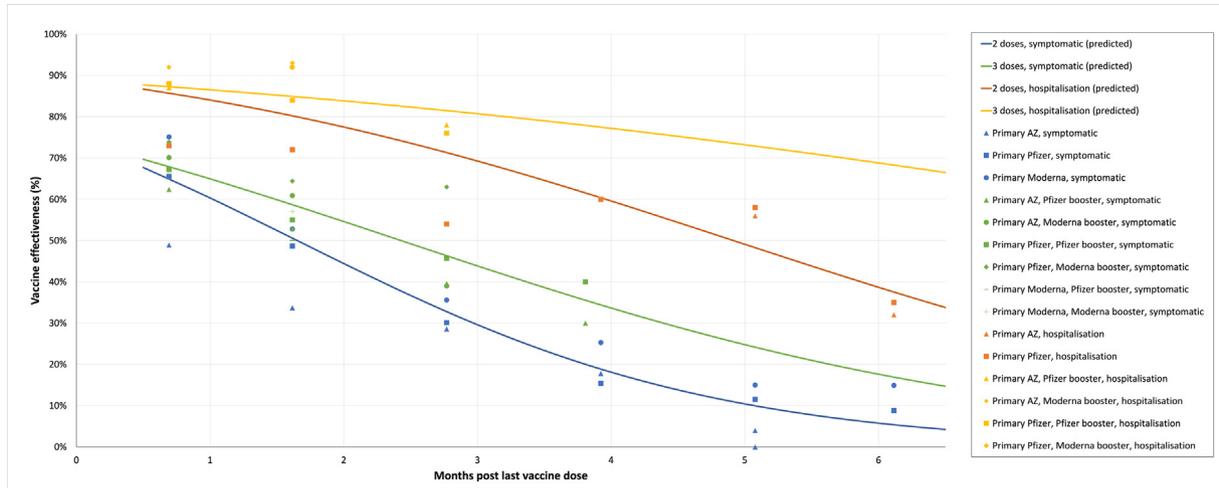


Fig. 1. Predicted vaccine effectiveness against the Omicron SARS-CoV-2 variant using a log-odds system, overlaid with observed data points used to fit model Confidence bands about the predictions are shown in the [Supplementary Figure](#).

than in the UK. It will be critical in future to add data from additional studies, settings and vaccine types to increase model validity and generalizability. This should be performed systematically (i.e. with careful inclusion and exclusion criteria) to avoid bias and was therefore considered to be outside the scope of this initial study.

Third, the system can be reconfigured to include additional covariates. For example, there is good evidence of lesser VE among older people following vaccination, particularly for symptomatic disease [5]. Even if age-related data are not available for the regression model (as was the case with the UKHSA data we used to develop our model), one can still ‘add’ an extra variable to separate VE estimates by age – ensuring the weighted average by age of VE still returns that obtained in the starting model (e.g. by adjusting the intercept).

Fourth, importantly for modelling, this mathematical system can be extended to include ‘known unknowns’. For example, there may be a desire in future to undertake scenario modelling of next-generation vaccines or new variants of concern. If plausible scenarios regarding the ‘boost’ in VE compared to triple dose of current-generation vaccines or relative immune escape are available, it is straightforward to extend these equations for use in simulation modelling of these scenarios.

Immunity developed from the combination of previous infection and vaccination is another important concept to consider. If directly added into a single logistic model with vaccines, this will require factoring in variants responsible for primary infection and re-exposure, the time interval between infection and vaccination as well as the time interval between these sensitising events and re-exposure, and the waning of infection-derived immunity in addition to waning of vaccine-derived immunity. This task is complex. An alternative and more parsimonious solution (and one we are pursuing elsewhere) is to build a parallel and separate logistic function for natural immunity protection, and combine the VE and natural infection protection after regression modelling, i.e. total percentage reduction in infection risk = $1 - (1 - VE)(1 - \text{nat ural infection protection})$.

Ultimately, for population-level mathematical models to be useful they need to include assumptions about the functional form of waning immunity, and how it differs by outcome (for example, symptomatic infection compared to hospitalisation) and the number of vaccine doses received. This log-odds system for estimating waning and boosting of COVID-19 VE provides a simple to apply solution that may be used to more accurately approximate

SARS-CoV-2 immunity over time when parametrizing epidemiological COVID-19 models.

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.2022.05.039>.

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