American Journal of Epidemiology, 2026, 195, 1108–1119
https://doi.org/10.1093/aje/kwaf254
Advance access publication date November 17, 2025
Practice of Epidemiology

Recommendations for estimating and reporting vaccine effectiveness by time since vaccination: a COVID-19 case study

Esther Kissling*[,1,2], Baltazar Nunes[1], Mariëtte Hooiveld[3], Iván Martínez-Baz[4,5], Susana Monge[5,6], Chris Robertson[7,8], Mirjam Knol[9], Noémie Sève[10], Ivan Mlinarić[11], Lisa Domegan[12], Ausenda Machado[13], Heather Whitaker[14], Mihaela Lazar[15], Adam Meijer[9], Theresa Enkirch[‡,16], Itziar Casado[4,5], Gloria Pérez-Gimeno[6], Naoma William[7], Vincent Enouf[17], Sanja Kurečić Filipović[11], Adele McKenna[12], Ana Paula Rodrigues[13], Simon de Lusignan[18,19], Olivia-Carmen Timnea[15], Neus Latorre-Margalef[16], Jesús Castilla[4,5], Francisco Pozo[5,20], Mark Hamilton[7], Shirley Masse[21], Maja Ilić[11], Luca Basile[5,22], Joan O'Donnell[§,12], Raquel Guiomar[23], Maximilian Riess[‡,16], Rodica-Manuela Popescu[24], Angela M. C. Rose[1], Nick Andrews[14], Sabrina Bacci[25], Lucia Pastore Celentano[25], Marta Valenciano[†,1], Alain Moren[§,1], Philippe Beutels[26], Niel Hens[26,27],
on behalf of I-MOVE-COVID-19 and ECDC primary care study teams

[1]Department of Epidemiology, Epiconcept, Paris, France
[2]Faculty of Medicine and Health Sciences, University of Antwerp, Antwerp, Belgium
[3]Nivel, Utrecht, Netherlands
[4]Instituto de Salud Pública de Navarra—IdiSNA, Pamplona, Spain
[5]CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain
[6]National Centre for Epidemiology, Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[7]Respiratory Team, Clinical and Protecting Health Directorate, Public Health Scotland, Glasgow, United Kingdom
[8]Department of Mathematics and Statistics, Strathclyde University, Glasgow, United Kingdom
[9]Centre for Infectious Diseases Control, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands
[10]Sorbonne Université, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP), F75012, Paris, France
[11]Division for Epidemiology of Communicable Diseases, Croatian Institute of Public Health, Zagreb, Croatia
[12]Health Service Executive-Health Protection Surveillance Centre, Dublin, Ireland
[13]Epidemiology Department, Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA), Lisbon, Portugal
[14]Statistics Unit, UK Health Security Agency, London, United Kingdom
[15]National Influenza Centre, "Cantacuzino" National Military Medical Institute for Research and Development, Bucharest, Romania
[16]Department of Microbiology, The Public Health Agency of Sweden (Folkhälsomyndigheten), Stockholm, Sweden
[17]Centre National de Référence Virus des Infections Respiratoire, M3P Unit, Institut Pasteur Université Paris Cité, Paris, France
[18]Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom
[19]Royal College of General Practitioners Research and Surveillance Centre, London, United Kingdom
[20]National Centre for Microbiology, Instituto de Salud Carlos III (ISCIII), Madrid, Spain
[21]Unite des Virus Emergents (UVE: Aix-Marseille Univ, Universita di Corsica, IRD 190, Inserm 1207, IRBA), Corsica, France
[22]Subdirección General de Vigilancia y Respuesta a Emergencias de Salud Pública, Agencia de Salud Pública, Catalunya, Spain
[23]Reference Laboratory for Influenza and Other Respiratory Virus, Instituto Nacional de Saúde Doutor Ricardo Jorge (INSA), Lisbon, Portugal
[24]National Institute of Public Health, National Centre for Communicable Diseases Surveillance and Control, Bucharest, Romania
[25]Vaccine Preventable Diseases and Immunisation, European Centre for Disease Prevention and Control, Stockholm, Sweden
[26]Centre for Health Economics Research and Modelling Infectious Diseases, Vaccine and Infectious Disease Institute, University of Antwerp, Antwerp, Belgium
[27]Data Science Institute, I-BioStat, Universiteit Hasselt, Hasselt, Belgium

*Corresponding author: Esther Kissling, Epidemiology Department, Epiconcept, 25 Rue Titon, 75011 Paris (e.kissling@epiconcept.fr)
†Present address: DG SANTE, European Commission, Brussels, Belgium.
‡Present address: European Centre for Disease Prevention and Control, Stockholm, Sweden.
§Retired.

Abstract

Estimating COVID-19 vaccine effectiveness (VE) by time since vaccination (TSV) is essential for understanding how protection may change over time and enables meaningful comparisons across studies. This is important for accurate comparisons of VE against different SARS-CoV-2 variants/sublineages, across age groups, during different periods post vaccination campaign, or by vaccine type/brand. We provide recommendations for case–control VE studies on estimating and reporting VE analyses by TSV, with the

Received: April 21, 2025. **Accepted:** November 2, 2025

aim of improving quality of these estimates. Our recommendations cover study design and pre-analysis considerations, descriptive analyses, choice of categories of TSV, categorical and continuous modeling approaches, and best practices for reporting VE by TSV. Using a real-life case–control study, we apply these recommendations and include accompanying statistical scripts in R and Stata. These recommendations will serve as a practical resource for researchers conducting VE analyses by TSV. We encourage ongoing refinement of them through input from other study groups.

Key words: vaccine effectiveness; COVID-19; time since vaccination; epidemiological methods; case–control study.

Introduction

Randomized controlled trials (RCTs) estimate vaccine efficacy: how well vaccines work under controlled experimental conditions and selected populations.[1,2] However, postauthorization observational studies are crucial to estimate vaccine effectiveness (VE) by time since vaccination (TSV), as real-world immunity may wane beyond RCT timeframes.

These observational studies estimate vaccine performance in the real-world context, although can be subject to bias. The two main types are case–control and cohort studies.[1] These have been used for estimating VE by TSV against several pathogens for both childhood and adult vaccinations (eg, cholera, pertussis, influenza).[3-6] For COVID-19, TSV is accepted as a key determinant of VE, with VE declining within weeks or months, depending on variant and outcome under investigation.[7,8]

COVID-19 VE estimates by TSV help us to understand how protection may change over time and allow meaningful comparisons across studies of VE against different SARS-CoV-2 variants/sublineages, across age groups, during periods post vaccination campaigns, or by vaccine type/brand. For instance, brand comparisons of COVID-19 VE are only meaningful when estimates are provided by TSV. Without accounting for TSV, differences in brand-specific VE may reflect vaccination or epidemic timing rather than true product differences. For example, during the 2023/24 winter season, the predominant SARS-CoV-2 sublineage shifted from XBB to JN.1 over time. Overall COVID-19 VE estimates—without accounting for TSV—reported lower VE against JN.1 than XBB. However, these estimates did not account for the longer TSV among those infected with JN.1, as it circulated later. To determine whether VE against JN.1 was truly lower, estimates by TSV were needed, as provided by several studies.[9-11]

This manuscript provides guidance for case–control VE studies on estimating and reporting descriptive and VE analyses by TSV, aiming to improve quality and comparability of such estimates. Recommendations are summarized, and applied using a real-life case–control study as an example, with R and Stata scripts in Appendix S1 and Appendix S2 of the Supplementary material.

TSV and descriptive analyses

Definitions

Key elements of case–control studies are definitions of study population, study period, relevant index date (eg, symptom onset date, swab date, hospital admission date), exposure (eg, vaccination ≥14 days before index date), and outcome (eg, laboratory-confirmed SARS-CoV-2 infection or hospitalization). These depend on the research question/study objectives, and form part of the protocol and statistical analysis plan (SAP).

Many countries now have seasonal COVID-19 vaccination campaigns. The study period start can be defined according to country-specific campaign start dates (eg, ≥14 days thereafter) and virus circulation.

Many viruses, including SARS-CoV-2, undergo frequent change, due to a high rate of amino acid substitutions,[12,13] which can lead to immune escape, for example, due to structural changes near/at the receptor binding sites.[13,14] To assess whether decline in VE reflects waning of vaccine-induced immunity, VE estimates against the same (sub)variant are needed, for example, against viruses similar in terms of immune escape. This can be done in (sub)variant/case definition (eg, using sequencing information to restrict the cases to specific variants/sublineages/genetic variants of SARS-CoV-2) or in the context of swift replacement (eg, Delta replacing Alpha, or JN.1 replacing XBB sublineages) by restricting the study period to times of specific virus circulation.

Calculating TSV

In case–control studies, TSV is calculated by subtracting the date of vaccination of interest from the relevant index date. For cases, this is often date of symptom onset, for controls, date of recruitment into the study. In test-negative design (TND) studies—a type of case–control study—patients presenting to healthcare (eg, hospitals or primary care) are enrolled and swabbed using a shared case definition. Cases are those who test positive and controls are those who test negative. Here, the index date is often symptom onset date for both cases and controls.

The reference group, usually study participants not vaccinated in the vaccination campaign of interest, or with the dose of interest, will not have a vaccination date for the vaccination of interest and can be coded as having 0 days since vaccination. These participants may have received other doses, and are not necessarily "never-vaccinated."

Vaccination and index dates of high completeness and quality are critical, as the VE by TSV could otherwise be imprecise—hampering inferences around the results—or be overestimated/underestimated. While missing data methods may have their use, complete data is preferable. Reporting should describe ascertainment of vaccination variables and any missing data techniques used.

Describing TSV by case status

Plotting the number of vaccinated cases and controls by day of TSV helps guide VE modeling choices and provide insights for interpreting VE by TSV.

Modeling VE by TSV: different approaches

Methods for modeling VE by TSV can vary in case–control studies, but there are two overarching approaches: (1) modeling VE by TSV categories and (2) modeling VE by TSV as a continuous variable. The choice depends on the research questions/objectives and the audience/readership; specific examples follow.

In case–control studies, VE is estimated as [1-odds ratio (OR) of vaccination among cases and controls]∗100 typically using logistic regression or conditional logistic regression (matched studies).

Modeling VE by categories of TSV

COVID-19 VE is most often presented by TSV categories.[7,8] This provides easily communicated public health messages, for

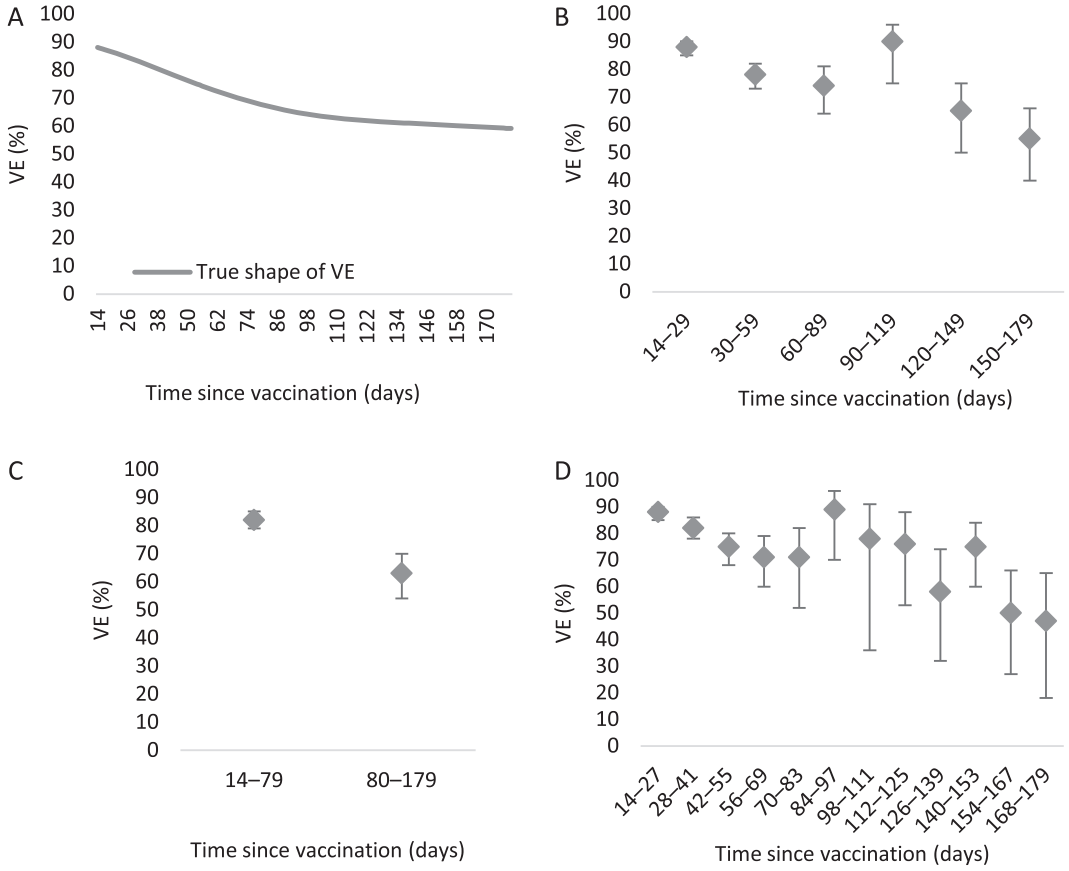

Figure 1. Fictitious example of the shape of COVID-19 vaccine effectiveness by days since vaccination (panel A), using monthly categories (panel B) and the effects of potentially too wide (C) and too narrow (D) categories of TSV. Panel A: VE by days since vaccination (true shape of the VE); Panel B: VE at 30-day intervals (suggested interval; diamonds with 95% CIs); Panel C: VE at 14-79 days since vaccination and VE at 80-179 days since vaccination (diamonds with 95% CIs); Panel D: VE every 14 days since vaccination (diamonds with 95% CIs). TSV, time since vaccination; VE, vaccine effectiveness.

example, VE is 70% within 1 month since vaccination, or at 3-4 months since from vaccination, VE declines to 50%.

Determining TSV categories can be challenging. The choice should balance ease of public health communication, the shape/functional form of VE by TSV, and sample size, which includes numbers vaccinated overall and by case status for each category of TSV, to ensure adequate precision (see also sections on "Minimum sample size and sparse data considerations").

Useful categories for public health messages and the shape of VE by TSV

COVID-19 VE may decline within a few months,[7,15,16] making months an effective and easily communicable unit for public health messaging around COVID-19 VE. Vaccine effectiveness by partial months (eg, 6 weeks, or 10 weeks) may not provide easy public health messages. However, particularly early after vaccination campaigns, units of weeks or days may be useful additional estimates in specific contexts, alongside monthly ones.[11,15] Longer intervals (eg, years) may be more appropriate for diseases with slower waning, notably pertussis or polio.[17]

The number of months per TSV category will depend on the form and rate of decline of the VE by TSV and also the distribution and sample size of cases and controls, and number of vaccinated patients in each group. Using too wide categories (eg, 0-6 months, or even 0-3 months) can mask the shape of VE by TSV (see example of this in Figure 1C). Too narrow categories may yield imprecise estimates (Figure 1D) or introduce sparse data bias—a bias that can occur if the data do not have adequate numbers of cases and controls in the selected categories.[18]

In the literature, VE estimates by TSV in months are presented in different ways, for example, 1-2 months, 30-59 days, or 31-60 days.[19] While these subtleties are unlikely to impact VE estimates, for harmonization, we recommend using multiples of 30 days, excluding the upper boundary, starting from the exposure definition (here ≥14 days after vaccination): 14-29, 30-59, 60-89, 90-119, 120-149, 150-179, 180-209, 210-239 days, etc.

Using equal TSV intervals facilitates comparison. However, if data are sparse with more TSV and little change in VE, combining tail-end categories may be appropriate. The final category should explicitly state the last day of TSV, for example, 150-199 days, rather than an open-ended range (≥150 days) to aid interpretation.

Shape of VE by TSV and the distribution of vaccinated cases and controls during the study period

The distribution of vaccinated individuals can vary across TSV in the study period, due to vaccination campaigns timings, vaccine uptake, and incidence of respiratory virus pathogens. This can even lead to different distributions within the same TSV category (eg, 30-59 days) across studies or between different study periods within the same study. For example, an early-season analysis might estimate VE at 30-59 days based on more individuals closer to 30 than 59 days (Figure 2: study A), whereas a later-season analysis might estimate VE based on

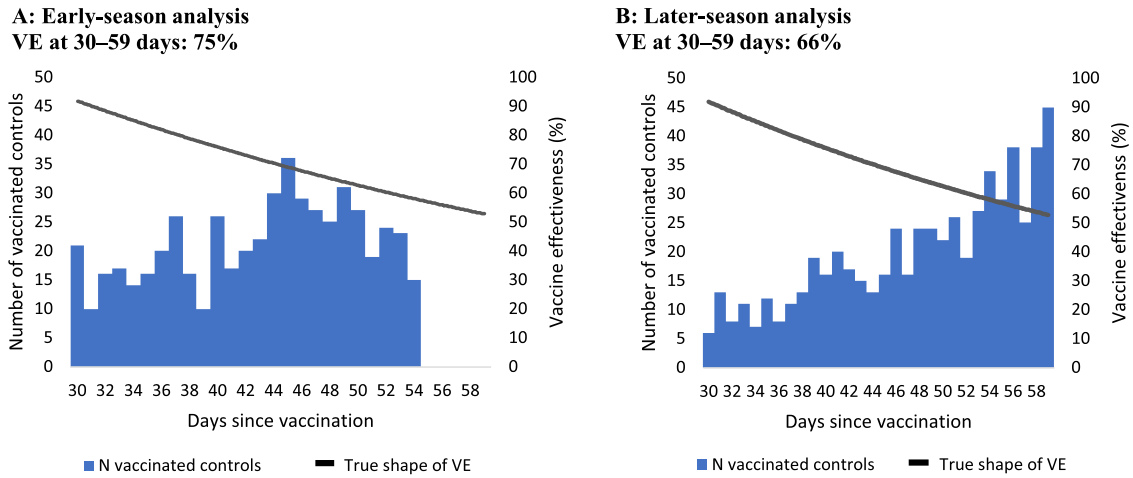

Figure 2. Vaccine effectiveness (VE) by days since vaccination (curve) and number of patients by days since vaccination (bars) in an early (A) and later season analysis (B), showing how different distributions of study participants can lead to different VE estimates at 30-59 days, using fictitious case–control study data.

individuals more heavily concentrated towards 59 days (study B). If true VE changes within 30-59 day interval, then the early-season and later-season estimates of VE may differ, despite using the same category of 30-59 days (Figure 2). If baseline rates of infection vary between studies, we can also observe this phenomenon of different distributions within the same TSV category.[20]

Therefore, studies should report the median TSV and interquartile range for cases and controls for each TSV category, to help interpret differences in the same categories of TSV (Table 1).

Considerations around minimum sample size and related bias

Underpowered studies provide imprecise VE estimates by TSV. We recommend performing sample size analyses, based on precision around expected VE (eg, ≤20% from CI's lower boundary to the point estimate) for each category before conducting the study/analysis. Powering studies to detect statistically significant differences between categories of TSV depends on the extent of the decline. Because of this, we recommend sizing studies to ensure adequate precision for each estimate.

With small sample size, few events in TSV categories, or few vaccinated, estimates may be biased, often known as "sparse data bias."[18] This includes "finite sample bias", which can occur with maximum likelihood estimation, for example, logistic regression in a case–control VE study, leading to a bias away from the null (more extreme estimates).[21-23] Criteria to avoid this bias should be prespecified in the protocol/SAP. To our knowledge no widely accepted thresholds/criteria for avoiding sparse data/finite sample bias exist for VE studies or even for case–control studies in general, although some solutions have been presented.[18]

Elements to consider:

- Events per variable ratio (EPV): Define a minimum EPV for the analysis, which is the number of cases (or controls, whichever is fewer) divided by the number of model parameters.[24] A common minimum EPV is 10, though values such as 5 or 15 may be used.[25,26]
- Minimum vaccinated sample size per TSV category: for example, ≥20 vaccinated patients.
- Minimum overall cases: for example, 50, although this is closely linked to the EPV criterium. Report the number of cases and controls per TSV category for transparency around sample size.[18]

In the SAP, specify actions if these criteria are violated, such as applying penalization, exact, bootstrapping, or other bias-reducing methods,[18,23,27,28] or abandoning the analysis entirely.

The points above are suggestions and can be adapted. Other approaches include calculating the expected number of vaccinated cases if VE were 0% (minimum requirement: 5 cases), or use of CI rules, for example, excluding estimates with CI both above AND below certain limits (eg, both above 80% AND below −50%). Avoid excluding VE estimates based on CI width, for example, ≥100%, as mathematically lower VE estimates yield wider CI (due to log OR transformation), making lower estimates more likely to be excluded, introducing bias.

Depending on vaccination campaign timing and study period, some categories of VE by TSV may lack sufficient sample size for

Table 1. Example table of how to report VE by TSV with descriptive information for each category that guides interpretation.

TSV categories	Cases (*N*)	Median TSV in days among cases (IQR) in days	Controls (*N*)	Median TSV among controls (IQR) in days	VE (95% CI)
Unvaccinated		NA		NA	Ref
14-29 days					
30-59 days					
60-89 days					

Abbreviations: IQR, interquartile range; NA, not applicable, as not vaccinated; Ref, reference group; TSV, time since vaccination; VE, vaccine effectiveness.

Table 2. Summary of recommendations for estimating and reporting VE by TSV.

Study design and prior to analysis

- Define clearly the study questions of the analysis.
- Ensure that the VE analyses are carried out against the same outcome. If several genetic variants are circulating, with different levels of immune escape, decline of VE by TSV cannot be disentangled from a decline associated with circulation of a variant against which the vaccine protects less well.
- Ensure high quality and completeness of vaccination dates and index dates, to avoid bias and loss of precision in VE by TSV analysis.
- Provide information on vaccination and vaccination date ascertainment and any imputation used.
- Carry out power analyses, based on desired precision around expected VE, before embarking on the study/analysis.
- Provide sparse data guidelines prior to analysis, for example, in the statistical analysis plan (SAP). These may differ according to analysis objectives and the epidemiological situation.
- If modeling VE by TSV as a continuous variable, ensure you have a good understanding of statistical interaction, and understand how you can use the resulting coefficients to obtain the interaction effects.
- State model selection techniques for VE by TSV in advance (eg, in the SAP), for example, the use of an information criterion.
- Keep accounting for calendar time in the analysis, even when estimating VE by TSV.

Descriptive analysis

- Plot the number of vaccinated cases and controls by TSV (eg, by days since vaccination).

Choice of categories for VE by time since vaccination

- The unit chosen for estimating VE by TSV in categories depends on the shape and rate of decline of VE by TSV and sample size. Modeling VE by TSV by month (eg, in 30-day intervals) or multiples thereof may provide a useful framework for within and between-study comparisons, if sample size allows. In the current context of COVID-19 VE, with rapid waning, we recommend VE by TSV by month as a primary analysis and VE by 2-month period as a secondary analysis, if precision allows.
- Depending on the study period start in relation to the vaccination campaign start, early or later months since vaccination may not be estimable (eg, VE estimates start at 60-89 days since vaccination, those < 60 days are not estimated).
- If the VE is more constant over time, wider bands of TSV could be considered.
- In general, equal intervals of TSV may be most useful for comparison purposes, although if there is sparse data with more TSV, with little change in VE, combining categories at the end could be considered (eg, 3-5 months since vaccination).
- For harmonization purposes, use multiples of 30, excluding the upper boundary: 14-29, 30-59, 60-89, 90-119, 120-149, 150-179, 180-209, 210-239 days, etc. With smaller numbers and with less waning (eg, influenza) these categories can be collapsed, although inclusion of VE by these finer categories in supplementary material is useful.
- Be specific with the end of the last category, for example, 180-199 days, rather than $\geq$180 days, in order to aid interpretation.

Analysis of VE by time since vaccination in categories

- Set out in advance whether a categorical or partitioned analysis will be used. Consider a comparison analysis, to understand if results differ. If results differ, a partitioned analysis may be preferred.

Modeling VE by time since vaccination with a continuous variable

- When modeling VE by TSV, consider comparing models using a variety of functional forms, including polynomials, transformations and splines.
- As with any regression model, it is important to view the coefficients and standard errors to identify any issues in the model. These could include excessively big or small coefficients, or when the standard error exceeds the coefficient.
- Beware of over- and underfitted models of VE by TSV. Information criteria can be used to select between models, along with inspection of the coefficients and standard errors of the model outputs. An alignment of the model to the study question and expert knowledge is important too.
- Ensure that when comparing AIC, BIC or other information criteria of models, you are using the same data.

Reporting VE by time since vaccination analyses

- Provide the number of cases and controls for each category of TSV for transparency around sample size. Doing so, even when modeling TSV as a continuous variable, helps the reader to better understand the data and sample sizes.
- Provide for each category of VE by TSV the median and interquartile range of TSV for cases and controls separately.
- When reporting VE by TSV, report the software and the statistical routines/commands used, as results may differ slightly according to the methods used.
- If modeling VE by TSV, provide estimates by category of TSV either alongside in a table, or alternatively super-imposed in a graph to better validate the results.
- Consider presenting candidate models in supplementary information of a report/manuscript.

estimation. For example, in analyses with study periods long after vaccination campaign start, VE estimates at 14-29 days and 30-59 days since vaccination may not be estimable.

Analysis of VE by TSV in categories

Estimating by TSV categories is an exposure–response analysis: unvaccinated individuals are unexposed (TSV = 0) and vaccinated individuals are grouped in categories of TSV "exposure." Two analysis approaches exist. First a categorical analysis that uses the whole dataset with TSV coded as 0, 1, 2, 3, etc., for as many categories of TSV as there are (categorical analysis), allowing statistical comparisons between TSV categories (eg, Wald test). A limitation can be that if there is an interaction effect of the adjustment covariates with TSV, it can be complicated to model. Second, a partitioned analysis, which analyses only one category of TSV at a time with the unexposed group, using separate datasets. This

reduces power, but avoids issues around differential confounding. For both approaches (categorical or partitioned) we estimate the adjusted OR for each category of TSV, with the unvaccinated (eg, those not vaccinated in the vaccination campaign of interest) as the reference.

Specify in advance whether a categorical or a partitioned analysis will be used. Consider applying both and comparing results. If results differ, a partitioned analysis may be preferred.

Modeling VE by TSV as a continuous variable

Analyzing VE by TSV categories can lead to information loss due to grouping and artificial step changes between categories. An alternative is modeling VE by TSV as a continuous variable, capturing the shape of decline. Having this knowledge of shape of decline provides insights to public health questions, such as optimal timing for booster campaigns.

A particular challenge when modeling VE by TSV as a continuous variable is avoiding an overfitted or underfitted model. We aim to provide a generalizable model, not a model including unnecessary fluctuations (an overfitted model), or a model simplifying important fluctuations (an underfitted model). Statistical criteria (see "Comparison between models" section) can guide selection, although alignment with study objectives and expert knowledge remain crucial.

Model validation can include comparing VE by TSV as a continuous variable with VE by TSV categories. Category estimates can be provided in a table, or super-imposed on a graph to assess consistency with the modeling. Large discrepancies should be explored by testing different continuous and categorical model specifications, and/or reflecting in-depth on data validity and study set up (including sample size).

Modeling VE by TSV: functional forms

VE by TSV can be modeled using various functional forms, such as a linear term on the log-odds scale, polynomials, transformations, or splines. Splines—piece-wise polynomial curves—offer greater flexibility than simple polynomials.[29] The choice of functional form depends on the complexity of the shape of the true VE by TSV and the analysis objectives.

For COVID-19, for example, modeling TSV from 14 days since vaccination (as time 0), when a person is considered "immunized," allows using both simple and complex functional forms. Including 1-13 days since vaccination may require a more complex form, as early observed VE can change rapidly due to immediate immune responses and biases.[30]

Vaccine effectiveness by TSV can be modeled by adding an interaction term between vaccination status (vaccinated/unvaccinated) and the TSV functional form, with unvaccinated individuals coded as having TSV = 0. A good understanding of statistical interaction, meaning of coefficients, and postestimation commands are important to model VE by TSV. Not all software routines/packages for interaction analysis are suitable here, as only one level of the interaction term varies (representing the vaccinated). The logistic regression formula, assuming for simplicity a linear functional form for TSV on the log-odds scale and no confounders, is as follows:

$$\ln(\text{odds of being a COVID-19 case}) = b0 + b1\text{covvacc} + b2\text{tsv} + b3\ \text{covvacc} \times \text{tsv},$$

where

- covvacc = 0 for unvaccinated and 1 for vaccinated;
- tsv = 0 among unvaccinated; a continuous variable for days since vaccination among vaccinated;
- *b0:* baseline log-odds among unvaccinated;
- *b1:* log-odds ratio of being a case on the day of vaccination compared to unvaccinated (not practically meaningful);
- *b2:* log-odds of change for each day since vaccination; and
- *b3:* not calculable, unvaccinated have no TSV

For easier interpretation of *b1*, the TSV variable can be shifted (eg, starting at 14 days postvaccination), though this requires careful calculation of VE, particularly with transformations.

b2 + *b3* represents the log-odds ratio for each additional day since vaccination. However, in commonly used statistical software such as R and Stata, the entire coefficient is assigned to *b2*, and *b3* is not estimated as unvaccinated individuals have no TSV.

The formula above is functionally equivalent to the following:

$$\ln(\text{odds of being a COVID-19 case}) = b0 + b1\text{covvacc} + b2\text{tsv}$$

as tsv here represents the interaction term among those with covvacc = 1.

To estimate VE at each day since vaccination, we can estimate the OR for vaccination (assuming the entire coefficient is assigned to *b2*):

$$\text{OR} = \left[\exp(b0 + b1 + b2\text{tsv})\right] / \left[\exp(b0)\right] = \exp(b1 + b2\text{tsv})$$

For example, VE at 60 days since vaccination, with VE estimated as one minus the OR for vaccination, expressed as a percentage, would be:

$$\text{VE} = (1 - \text{OR}_{60}) \times 100 = (1 - \exp(b1 + b2 \times (60))) \times 100.$$

Exploring multiple functional forms for the TSV analysis can help capture the true VE shape. In the example, we investigate: a linear term, log transformation, square root transformation, quadratic term, and splines. In this article, we focus only on two popular splines: restricted cubic splines (RCS) and P-splines. Excellent overviews of other types of splines exist elsewhere.[29]

Restricted cubic splines. Restricted cubic splines (natural splines) are a set of curves with a cubic function that vary between a predefined number of knots. The tails of the spline (the data either side of the boundary knots) are "restricted" to a linear term, for improved model fit. Analysts must choose the number and location of knots, with number of knots often more critical than exact location.[31] Knot location choice can be user-defined (eg, based on some known biological criteria), or data-driven, as recommended by Harrell.[31] In absence of knowledge of the true shape of VE by TSV, we recommend the latter. The "Comparison between models" section describes how to select the number of knots.

P-splines. P-splines are penalized splines, based on cubic splines, that incorporate more knots (often 10-40) spaced equidistantly, and contain an extra penalty term to smooth the curve without excessive degrees of freedom. Users can select penalty weights, though most statistical software provides automated options. Here, generalized additive models can be used to model this nonlinear relationship.

Comparison between models

Model comparison is challenging, and statistical criteria and expert knowledge both play a role. Analysts can present multiple

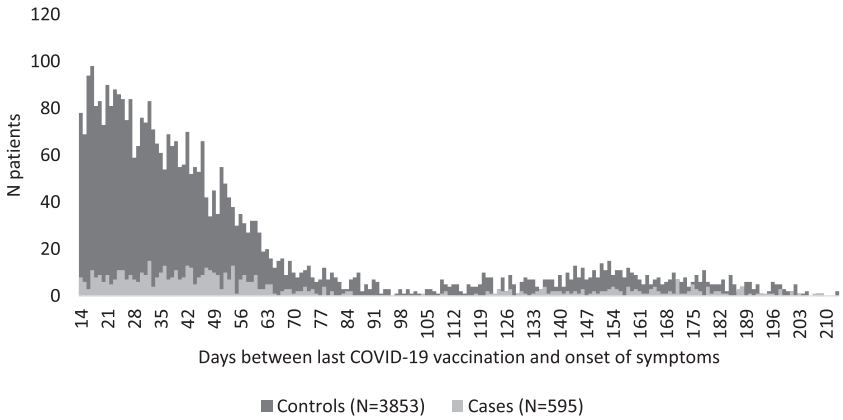

Figure 3. Number of cases and controls by days between the second dose of Comirnaty vaccine receipt and onset of symptoms, I-MOVE-COVID-19/ECDC data, Europe, July-August 2021.

Table 3. Number of cases and controls by days since the second dose of Comirnaty and onset of symptoms, I-MOVE-COVID-19/ECDC data, Europe, July-August 2021.

TSV categories	Cases (*N*)	Controls (*N*)
Never vaccinated	1045	1684
14-29 days	123	1287
30-59 days	261	1584
60-89 days	60	335
90-119 days	5	91
120-149 days	48	203
150-179 days	69	250
180-213 days	29	103

candidate models, for example, in a supplement, acknowledging model selection uncertainty.[32]

Standard logistic regression model selection techniques apply and should be described in advance (protocol/SAP). Here we select between models with the same variables and number of study participants, but with differences in functional forms for TSV (this includes the number of knots for RCS). In this scenario, model comparison using an information criterion is valid. With information criteria, lower values indicate better model fit, although models within 2 units from each other considered equivalent and models differing by more than 4 units considered distinct.[32] Only comparisons of information criterion on the same data are valid. In the example, we use the Akaike Information Criterion (AIC), and expert knowledge for model selection of models within 4 AIC points.

As with any regression model, review model coefficients and standard errors for issues such as excessively large/small coefficients, or when standard errors exceed coefficients.

Adjusting by calendar time

While TSV and calendar time can be similar in certain studies, for example, where vaccination is carried out in the study population very rapidly, they are not equivalent. We must still consider accounting for calendar time (through adjustment using categories or splines, or matching in matched studies) to avoid confounding. Often in VE studies the proportion of vaccinated increases with time and the ratio of cases and controls changes with time. Calendar time thus meets the criteria of being a confounder.[33,34]

Considerations around minimum sample size and related bias

Adequate sample size is crucial to ensure precise estimates and to avoid "sparse data bias" or "finite data bias." Sample size calculation for precision around a continuous exposure may be challenging, requiring generally simulation-based approaches. Descriptive analyses can identify TSV sections with very few cases (or controls), which can lead to low precision or bias. If such sections exist, consider excluding them or starting/stopping the TSV analysis at this section.

See the section on "Considerations around minimum sample size and related bias" subsection "Modelling VE by categories of time since vaccination" for guidance.

Statistical software and routines

Two popular statistical software programs for epidemiological analysis are Stata and R. Scripts for estimating VE by TSV are provided in R in Appendix S1 and in Stat in Appendix S2 of the Supplementary material. There can be underlying computational differences between the implementation of the methods in each software program, so results can differ slightly.

For modeling VE by TSV, we used the user-written mfpi routine in Stata,[35] and in R, the rms() package for RCS and the mgcv() package for P-splines.[36,37] Other R packages exist, but these are popular with over 3 and 10 million downloads, respectively.[38]

Example analysis: I-MOVE-COVID-19 and ECDC networks outpatient study

We used the European I-MOVE-COVID–19 and European Centre for Disease Prevention and Control (ECDC) networks outpatient study conducted during the SARS-CoV-2 Delta period, among patients aged 30-59 years with swab dates between 1 July and August 31, 2021, when Delta was predominant across all sites.[39] We aimed to estimate the effectiveness of two doses of Comirnaty COVID-19 original mRNA vaccine containing BNT162b2 variant spike protein against symptomatic SARS-CoV-2 infection by TSV to assess potential waning of the vaccine effect.

The I-MOVE-COVID-19/ECDC study was a test-negative design multicenter study. Details are provided elsewhere.[39-41] In this analysis, we compared those vaccinated with two doses of Comirnaty to the reference group of those never vaccinated. A person was defined as vaccinated 14 days after receiving their second

Table 4. COVID-19 vaccine effectiveness and 95% CIs by TSV, categorical analysis, I-MOVE-COVID-19/ECDC data, Europe, July-August 2021.

TSV categories	Cases (*N*)	Median TSV in days among cases (IQR)[a]	Controls (*N*)	Median TSV among controls (IQR)[a]	VE (95% CI)
Never vaccinated	1045	NA	1684	NA	Ref
14-29 days	123	22 (18-25)	1287	21 (17-25)	87 (84-90)
30-59 days	261	43 (36-50)	1584	41 (35-49)	76 (71-80)
60-89 days	60	68 (62.5-74.5)	335	69 (63-77)	70 (59-79)
90-119 days	5	110 (109-110)	91	109 (95-113)	89 (73-96)
120-149 days	48	135.5 (127-141.5)	203	137 (128-144)	64 (49-74)
150-179 days	69	165 (158-172)	250	161.5 (155-171)	60 (46-70)
180-213 days	29	190 (187-198)	103	190 (185-197)	60 (37-75)

Abbreviations: IQR, interquartile range; NA, not applicable, as not vaccinated; Ref, reference group; TSV, time since vaccination; VE, vaccine effectiveness.
[a]There can be some differences in how percentiles (for the IQR) and CIs are calculated between statistical software (eg, Stata and R).

dose, with those vaccinated 1-13 days before symptom onset or partially vaccinated were excluded.

The dataset included 1640 COVID-19 cases (595 vaccinated) and 5537 controls (3853 vaccinated). We used logistic regression and calculated VE as 1 minus the adjusted OR for vaccination expressed as a percentage.[42] We included study site, swab week, sex, presence of a chronic condition, and age (in 10-year age bands) as a priori covariates in all statistical models.

We carried out analyses both in R and Stata and provide the scripts in Appendix S1 and Appendix S2 of the Supplementary material.[43,44]

Example: TSV and descriptive analyses

We plotted the distribution of TSV by case status (Figure 3). The proportion of cases increased with longer TSV. Between 14 and 99 days since vaccination, 12% of patients were cases and 19% between 100 and 180 days. The median TSV for cases was 47 days (IQR: 31-73) and 38 (IQR: 25-57) for controls.

Sample size decreased after around 60 days since vaccination (3255 patients at 14-59 days and 1193 patients at 60-213 days), with few cases (7 of 595 vaccinated cases) at 85-120 days since vaccination, due to fewer vaccinations carried out in April/May 2021 among study participants. This data sparsity may impact the robustness of the VE estimates in that range.

Example: VE by categories of TSV

We categorized TSV into 30-day categories (Table 3).

There were few cases in the 90-119 days (3-4 month) category.

We estimated VE by TSV using a categorical analysis (Table 4). The differences between the categorical and partitioned analysis were ≤2% (Table 4 and Table S1 in the Supplementary material). We note a spuriously high VE in the 90-119 days (3-4 month) TSV category, which has lower numbers than other categories.

Example: VE by TSV as a continuous variable

We modeled VE by TSV as a continuous variable, using 8 functional forms: (1) linear; (2) logarithmic; (3) square root; (4) quadratic; (5-7) RCS with 3, 4, and 5 knots; and (8) P-splines. We based knot locations for RCS on Harrell's quantiles.[31] For P-splines, we used a generalized additive model using the default setting in the mgcv() R package. We compared models using the AIC, excluding models where standard errors exceeded coefficients.

All models showed declining VE by TSV (Figure 4). The P-spline and RCS model with 5 knots had lowest AICs (Table 5). However, the 5-knot RCS model was excluded due to large standard errors compared to coefficients.

The shape of the best models demonstrated an initial steeper decline within the first days since vaccination, followed by a slower decline.

While the P-splines model had the lowest AIC, CIs were wide. The next best model was the RCS model with 4 knots (3 AIC points higher).

As defined prior to analysis, selecting among models within 4 AIC points of each other, and using expert knowledge, we selected the model using RCS with 4 knots as the primary model. The P-spline results were retained as supplementary, providing additional information to the report or article.

To validate the results, we superimposed the VE estimates by TSV categories with those by days since vaccination (Figure 5).

Other considerations

In this manuscript, we assume the decline in VE is due to waning of immunity induced by the vaccine in the individual. However, other factors may contribute. These include if the "case" definition covers several SARS-CoV-2 genetic variants/(sub)lineages or strains that are antigenically different (have different VE), and that are circulating differently over time (see "Definitions").

Additionally, spurious decline in VE by TSV may arise, linked to mode of action of vaccine (ie, leaky or all-or-nothing vaccines) and the study design used, which has been extensively discussed in the literature.[45-48] In case–control studies, individuals with short- or medium-term immunity due to prior infection often cannot be excluded from the population at risk—this information is typically unavailable. We can then observe spurious waning, a phenomenon often associated with the term "depletion of susceptibles," which can occur in other VE study designs too.[45,49] Evidence suggests this "depletion of susceptibles" effect is modest in TND VE studies of influenza and COVID-19 VE,[50,51] although it is dependent on the epidemiological situation.[52]

Other approaches to modeling VE by TSV include restricting to vaccinated individuals only and estimating relative VE. However, this may be more difficult to compare between studies, as its interpretation depends on the underlying absolute VE.[53] The self-controlled case series design is another method that can be used to estimate VE by TSV, using just case data.[54,55] More recently, quantifying vaccine waning as a challenge effect has been proposed.[56]

Discussion

This article offers step-by-step guidance for estimating and reporting VE by TSV, focusing on COVID-19 VE case–control studies. Understanding VE by TSV helps support choices for

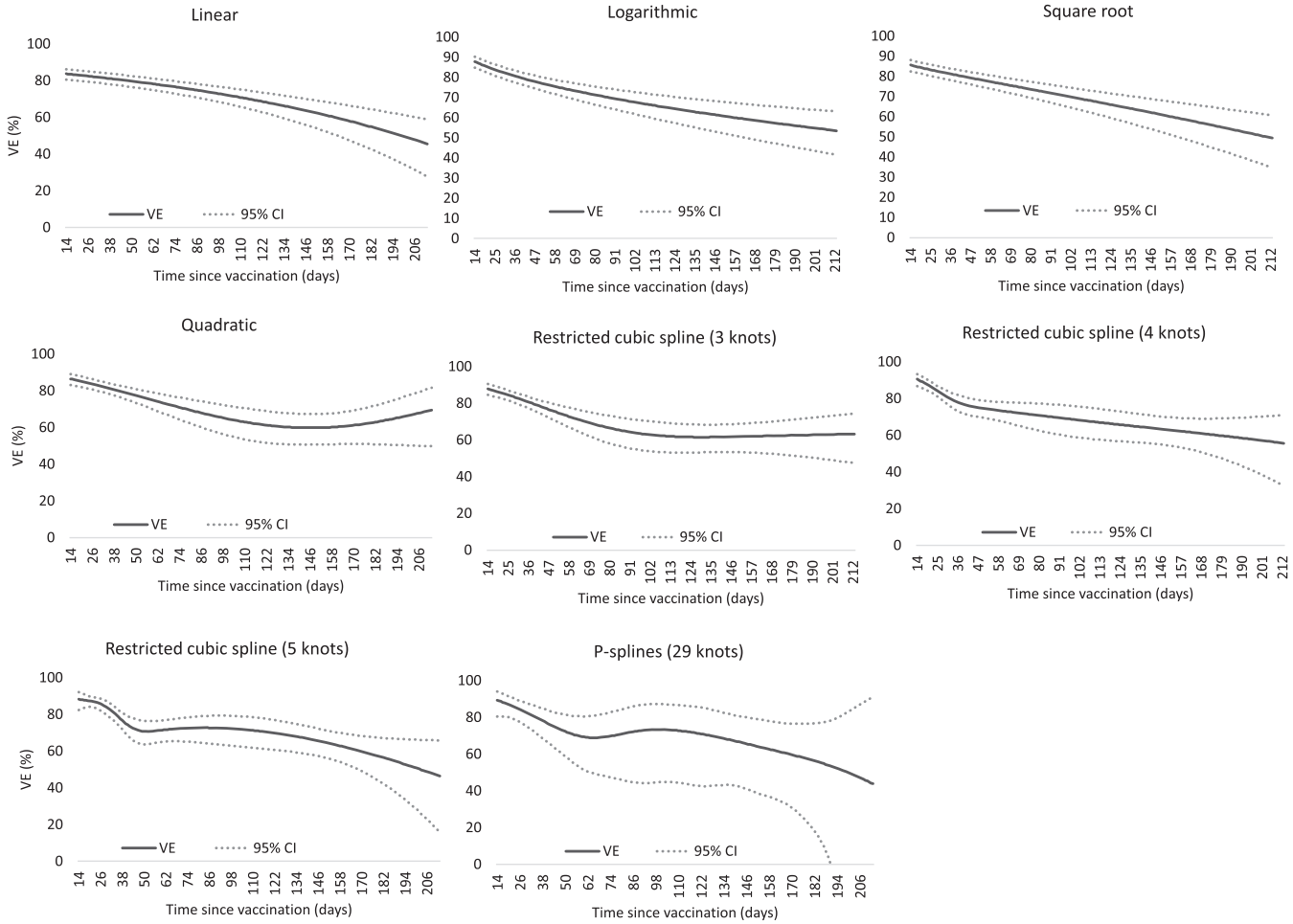

Figure 4. COVID-19 VE by TSV, modeled as different functional forms, I-MOVE-COVID-19/ECDC data, Europe, July–August 2021. TSV, time since vaccination; VE, vaccine effectiveness.

Table 5. Akaike information criterion according to functional form of modeling VE by TSV, I-MOVE-COVID-19/ECDC data, Europe, July-August 2021.

Functional form of TSV	AIC
Linear	6662.9
Logarithmic	6650.3
Square root	6656.4
Quadratic	6656.7
RCS (3 knots)	6651.5
RCS (4 knots)	6649.6
RCS (5 knots)	6646.7
P-spline	6646.6

Abbreviations: AIC, Akaike information criterion; RCS, restricted cubic splines; TSV, time since vaccination.

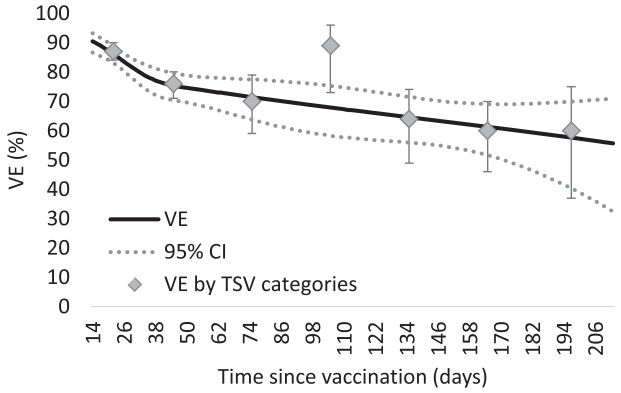

Figure 5. COVID-19 VE by TSV, modeled as an RCS with 4 knots, with VE by TSV in categories superimposed, I-MOVE-COVID-19/ECDC data, Europe, July-August 2021. RCS, restricted cubic splines; TSV, time since vaccination; VE, vaccine effectiveness.

optimal vaccination campaigns timings, and our aim is to help researchers improve quality and comparability of these estimates. We provide accompanying scripts in two widely used statistical software in epidemiology, Stata and R, to support this aim. The emphasis is on reporting and statistical methods, rather than explaining the causes of time-varying VE, as detailed discussion of reasons for VE decline is outside the scope of this article.

A strength is use of the real-world example: I-MOVE-COVID-19/ECDC primary care study data during the SARS-CoV-2 Delta variant predominant period. These recommendations can also be extended to other pathogens with in-season waning of VE, such as influenza or maternal RSV vaccine. For influenza, researchers might use broader TSV intervals (eg, multiples of months), given its slower decline, particularly for influenza A(H1N1)pdm09 and B.[57] The recommendations may also apply to vaccines against pathogens displaying immunological decline over longer timescales, such as cholera or typhoid, provided the units for

analysis are adjusted. Many of these principles extend to other study designs, such as cohort studies. Careful model selection is important to avoid over- and underfitted models, which may provide spurious results. We emphasize the importance of good quality studies, large sample sizes, power analyses in advance of the study and expert opinion.

Limitations include the exclusion of certain estimation methods (eg, analyses restricted to vaccinated patients) and certain functional forms (eg, other types of splines or fractional polynomials).

Conclusions

These recommendations serve as a resource for researchers estimating VE by TSV. They are not intended to replace expert statistical guidance. We encourage ongoing refinement of these guidelines through input from other study groups.

Acknowledgments

We would like to acknowledge all former colleagues involved in I-MOVE-COVID-19 and ECDC primary care study teams for worked performed, including Tessa Jansen (Nivel, Netherlands); Aitziber Echeverria, Camino Trobajo-Sanmartín, and Guillermo Ezpeleta (Instituto de Salud Pública de Navarra, Spain); Ana Navascués and Carmen Ezpeleta (Hospital Universitario de Navarra, Spain); Bernard Kaić, Ivana Ferenčak, Katica Čusek Adamić, Mirjana Lana Kosanović Ličina, Danijela Lakošeljac, Ivana Mihin Huskić, and Diana Nonković (Croatian I-MOVE-COVID-19 primary care study team); Adrian Jidovu, Catalina Pascu, Alina Ivanciuc, Iulia Bistriceanu, Sorin Dinu, Mihaela Oprea, and Maria Elena Mihai (Cantacuzino National Military–Medical Institute for Research and Development, Bucharest, Romania). We would like to acknowledge Mia Brytting (Public Health Agency of Sweden), who is deeply missed.

Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

Funding

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement no 101003673. This project received funding from the European Centre for Disease Prevention and Control (ECDC) under the contract ECD.11486.

Conflict of interest

Professor de Lusignan has received grants not directly relating to this work, from AstraZeneca, GSK, Sanofi, Seqirus, and Takeda for vaccine-related research and has been a member of advisory boards for AstraZeneca, Sanofi, and Seqirus.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Crowcroft NS, Klein NP. A framework for research on vaccine effectiveness. *Vaccine*. 2018;36(48):7286-7293. https://doi.org/10.1016/j.vaccine.2018.04.016
2. Halloran ME, Haber M, Longini IM, et al. Direct and indirect effects in vaccine efficacy and effectiveness. *Am J Epidemiol*. 1991;133(4):323-331. https://doi.org/10.1093/oxfordjournals.aje.a115884
3. Klein NP, Bartlett J, Rowhani-Rahbar A, et al. Waning protection after fifth dose of acellular pertussis vaccine in children. *N Engl J Med*. 2012;367(11):1012-1019. https://doi.org/10.1056/NEJMoa1200850
4. Durham LK, Longini IM, Halloran ME, et al. Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines. *Am J Epidemiol*. 1998;147(10):948-959. https://doi.org/10.1093/oxfordjournals.aje.a009385
5. Pebody RG, Andrews N, McMenamin J, et al. Vaccine effectiveness of 2011/12 trivalent seasonal influenza vaccine in preventing laboratory-confirmed influenza in primary care in the United Kingdom: evidence of waning intra-seasonal protection. *Euro Surveill*. 2013;18(5):20389. https://doi.org/10.2807/ese.18.05.20389-en
6. Kissling E, Valenciano M, Larrauri A, et al. Low and decreasing vaccine effectiveness against influenza A(H3) in 2011/12 among vaccination target groups in Europe: results from the I-MOVE multicentre case-control study. *Euro Surveill*. 2013;18(5):20390. https://doi.org/10.2807/ese.18.05.20390-en
7. Feikin DR, Higdon MM, Abu-Raddad LJ, et al. Duration of effectiveness of vaccines against SARS-CoV-2 infection and COVID-19 disease: results of a systematic review and meta-regression. *Lancet*. 2022;399(10328):924-944. https://doi.org/10.1016/S0140-6736(22)00152-0
8. Menegale F, Manica M, Zardini A, et al. Evaluation of waning of SARS-CoV-2 vaccine–induced immunity. *JAMA Netw Open*. 2023;6(5):e2310650. https://doi.org/10.1001/jamanetworkopen.2023.10650
9. Tartof SY, Slezak JM, Puzniak L, et al. Effectiveness of BNT162b2 XBB vaccine against XBB and JN.1 sublineages. *Open Forum Infect Dis*. 2024;11(7):ofae370. https://doi.org/10.1093/ofid/ofae370
10. Carazo S, Skowronski DM, Brousseau N, et al. Monovalent mRNA XBB.1.5 vaccine effectiveness against COVID-19 hospitalization in Quebec, Canada: impact of variant replacement and waning protection during 10-month follow-up. *PloS One*. 2025;20(6):e0325269. https://doi.org/10.1371/journal.pone.0325269
11. Kirsebom FCM, Stowe J, Lopez Bernal J, et al. Effectiveness of autumn 2023 COVID-19 vaccination and residual protection of prior doses against hospitalisation in England, estimated using a test-negative case-control study. *J Infect*. 2024;89(1):106177. https://doi.org/10.1016/j.jinf.2024.106177
12. Shih ACC, Hsiao TC, Ho MS, et al. Simultaneous amino acid substitutions at antigenic sites drive influenza A hemagglutinin evolution. *Proc Natl Acad Sci U S A*. 2007;104(15):6283-6288. https://doi.org/10.1073/pnas.0701396104
13. Harvey WT, Carabelli AM, Jackson B, et al. SARS-CoV-2 variants, spike mutations and immune escape. *Nat Rev Microbiol*. 2021;19(7):409-424. https://doi.org/10.1038/s41579-021-00573-0
14. Koel BF, Burke DF, Bestebroer TM, et al. Substitutions near the receptor binding site determine major antigenic change during influenza virus evolution. *Science*. 2013;342(6161):976-979. https://doi.org/10.1126/science.1244730
15. Laniece Delaunay C, Melo A, Maurel M, et al. Effectiveness of COVID-19 vaccines administered in the 2023 autumnal

campaigns in Europe: results from the VEBIS primary care test-negative design study, September 2023–January 2024. *Vaccine*. 2024;42(19):3931-3937. https://doi.org/10.1016/j.vaccine.2024.05.067
16. Antunes L, Mazagatos C, Martínez-Baz I, et al. Early COVID-19 XBB.1.5 vaccine effectiveness against hospitalisation among adults targeted for vaccination, VEBIS hospital network, Europe, October 2023–January 2024. *Influenza Resp Viruses*. 2024;18(8):e13360. https://doi.org/10.1111/irv.13360
17. Gao H, Lau EHY, Cowling BJ. Waning immunity after receipt of pertussis, diphtheria, tetanus, and polio-related vaccines: a systematic review and meta-analysis. *J Infect Dis*. 2022;225(4):557-566. https://doi.org/10.1093/infdis/jiab480
18. Greenland S, Mansournia MA, Altman DG. Sparse data bias: a problem hiding in plain sight. *BMJ*. 2016;352:i1981. https://doi.org/10.1136/bmj.i1981
19. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. Accessed November 12, 2024. https://view-hub.org/vaccine/covid/
20. Kennedy-Shaffer L, Kahn R, Lipsitch M. Estimating vaccine efficacy against transmission via effect on viral load. *Epidemiology*. 2021;32(6):820-828. https://doi.org/10.1097/EDE.0000000000001415
21. Sterne JAC, Gavaghan D, Egger M. Publication and related bias in meta-analysis. *J Clin Epidemiol*. 2000;53(11):1119-1129. https://doi.org/10.1016/S0895-4356(00)00242-0
22. Nemes S, Jonasson JM, Genell A, et al. Bias in odds ratios by logistic regression modelling and sample size. *BMC Med Res Methodol*. 2009;9(1):56. https://doi.org/10.1186/1471-2288-9-56
23. Firth D. Bias reduction of maximum likelihood estimates. *Biometrika*. 1993;80(1):27-38. https://doi.org/10.1093/biomet/80.1.27
24. Peduzzi P, Concato J, Kemper E, et al. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. 1996;49(12):1373-1379. https://doi.org/10.1016/S0895-4356(96)00236-3
25. Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. *Am J Epidemiol*. 2007;165(6):710-718. https://doi.org/10.1093/aje/kwk052
26. Courvoisier DS, Combescure C, Agoritsas T, et al. Performance of logistic regression modeling: beyond the number of events per variable, the role of data structure. *J Clin Epidemiol*. 2011;64(9):993-1000. https://doi.org/10.1016/j.jclinepi.2010.11.012
27. Stolte M, Herbrandt S, Ligges U. A comprehensive review of bias reduction methods for logistic regression. *Statist Surv*. 2024;18(none):139-162. https://doi.org/10.1214/24-SS148
28. Xu L, Gotwalt C, Hong Y, et al. Applications of the fractional-random-weight bootstrap. *Am Stat*. 2020;74(4):345-358. https://doi.org/10.1080/00031305.2020.1731599
29. Perperoglou A, Sauerbrei W, Abrahamowicz M, et al. A review of spline function procedures in R. *BMC Med Res Methodol*. 2019;19(1):46. https://doi.org/10.1186/s12874-019-0666-3
30. Ostropolets A, Hripcsak G. COVID-19 vaccination effectiveness rates by week and sources of bias: a retrospective cohort study. *BMJ Open*. 2022;12(8):e061126. https://doi.org/10.1136/bmjopen-2022-061126
31. Harrell FE. *Regression Modeling Strategies: With Applications to Linear Models, Logistic Regression, and Survival Analysis*. *Springer*; 2001:568.
32. Burnham KP, Anderson DR. *Model Selection and Multimodel Inference: A Practical Information-Theoretic Approach*. 2nd ed. Springer; 2010:488.
33. Varma A, Andrews NJ, Carazo S, et al. Analytical approaches and examples of addressing time-varying factors in COVID-19 vaccine effectiveness studies: report from a meeting of the World Health Organization. *Vaccine*. 2025;62:127567. https://doi.org/10.1016/j.vaccine.2025.127567
34. Dean NE, Halloran ME, Longini IM Jr. Temporal confounding in the test-negative design. *Am J Epidemiol*. 2020;189(11):1402-1407. https://doi.org/10.1093/aje/kwaa084
35. Royston P, Sauerbrei W. Two techniques for investigating interactions between treatment and continuous covariates in clinical trials. *Stata J*. 2009;9(2):230-251. https://doi.org/10.1177/1536867X0900900204
36. Jr FEH. rms: Regression Modeling Strategies. 2024. Accessed November 11, 2025. https://CRAN.R-project.org/package=rms
37. Wood SN. *Generalized Additive Models: An Isntroduction with R*. 2nd ed. CRC Press/Taylor & Francis Group; 2017:476.
38. DataScienceMeta. *CRAN R Packages by Number of Downloads*. Accessed October 3, 2024. https://www.datasciencemeta.com/rpackages
39. Kissling E, Hooiveld M, Martínez-Baz I, et al. Effectiveness of complete primary vaccination against COVID-19 at primary care and community level during predominant Delta circulation in Europe: multicentre analysis, I-MOVE-COVID-19 and ECDC networks, July to August 2021. *Eurosurveillance*. 2022;27(21):2101104. https://doi.org/10.2807/1560-7917.ES.2022.27.21.2101104
40. Epiconcept. COVID-19 vaccine effectiveness at primary care level in Europe: I-MOVE-COVID-19 generic protocol. 2021. Accessed July 20, 2024. https://www.imoveflu.org/wp-content/uploads/2021/05/I-MOVE-COVID-19-primary-care-COVID-19-vaccine-effectiveness-protocol-v2.3.pdf
41. Kissling E, Hooiveld M, Sandonis Martín V, et al. Vaccine effectiveness against symptomatic SARS-CoV-2 infection in adults aged 65 years and older in primary care: I-MOVE-COVID-19 project, Europe, December 2020 to May 2021. *Eurosurveillance*. 2021;26(29):2100670. https://doi.org/10.2807/1560-7917.ES.2021.26.29.2100670
42. Rodrigues LC, Smith PG. Use of the case-control approach in vaccine evaluation: efficacy and adverse effects. *Epidemiol Rev*. 1999;21(1):56-72. https://doi.org/10.1093/oxfordjournals.epirev.a017988
43. R core team. *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing. https://www.R-project.org/
44. StataCorp. *Stata Statistical Software*. StataCorp LLC.
45. Halloran ME, Longini IM, Struchiner CJ. *Design and Analysis of Vaccine Studies*. Springer; 2010:387.
46. Kanaan MN, Farrington CP. Estimation of waning vaccine efficacy. *J Am Stat Assoc*. 2002;97(458):389-397. https://doi.org/10.1198/016214502760046943
47. Lewnard JA, Tedijanto C, Cowling BJ, et al. Measurement of vaccine direct effects under the test-negative design. *Am J Epidemiol*. 2018;187(12):2686-2697. https://doi.org/10.1093/aje/kwy163
48. Hahné S, Bollaerts K, Farrington P. *Vaccination Programmes: Epidemiology, Monitoring, Evaluation*. 1st ed. Routledge; 2021.
49. O'Hagan JJ, Hernán MA, Walensky RP, et al. Apparent declining efficacy in randomized trials: examples of the Thai RV144 HIV vaccine and South African CAPRISA 004 microbicide trials. *AIDS*. 2012;26(2):123-126. https://doi.org/10.1097/QAD.0b013e32834e1ce7
50. Andrejko KL, Pry JM, Myers JF, et al. Waning of 2-dose BNT162b2 and mRNA-1273 vaccine effectiveness against symptomatic

SARS-CoV-2 infection accounting for depletion-of-susceptibles bias. *Am J Epidemiol*. 2023;192(6):895-907. https://doi.org/10.1093/aje/kwad017

51. Tokars JI, Patel MM, Foppa IM, et al. Waning of measured influenza vaccine effectiveness over time: the potential contribution of leaky vaccine effect. *Clin Infect Dis*. 2020;71(10):e633-e641. https://doi.org/10.1093/cid/ciaa340
52. Kahn R, Feikin DR, Wiegand RE, et al. Examining bias from differential depletion of susceptibles in vaccine effectiveness estimates in settings of waning. *Am J Epidemiol*. 2024;193(1):232-234. https://doi.org/10.1093/aje/kwad191
53. Lewis NM, Murray N, Adams K, et al. Absolute and relative vaccine effectiveness of primary and booster series of COVID-19 vaccines (mRNA and adenovirus vector) against COVID-19 hospitalizations in the United States, December 2021-April 2022. *Open Forum Infect Dis*. 2023;10(1):ofac698. https://doi.org/10.1093/ofid/ofac698s
54. Whitaker HJ, Farrington CP, Spiessens B, et al. Tutorial in biostatistics: the self-controlled case series method. *Stat Med*. 2006;25(10):1768-1797. https://doi.org/10.1002/sim.2302
55. Ray GT, Lewis N, Klein NP, et al. Intraseason waning of influenza vaccine effectiveness. *Clin Infect Dis*. 2019;68(10):1623-1630. https://doi.org/10.1093/cid/ciy770
56. Janvin M, Stensrud MJ. Quantification of vaccine waning as a challenge effect. *J Am Stat Assoc*. 2025;120(549):96-106. https://doi.org/10.1080/01621459.2024.2408776
57. Young B, Sadarangani S, Jiang L, et al. Duration of influenza vaccine effectiveness: a systematic review, meta-analysis, and meta-regression of test-negative design case-control studies. *J Infect Dis*. 2018;217(5):731-741. https://doi.org/10.1093/infdis/jix632

American Journal of Epidemiology, 2026, **195**, 1108–1119
https://doi.org/10.1093/aje/kwaf254
Practice of Epidemiology