International Journal of Epidemiology, 2025, **54(4)**, dyaf086
https://doi.org/10.1093/ije/dyaf086
Original article

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Original article

The potential bias introduced into COVID-19 vaccine effectiveness studies at primary care level due to the availability of SARS-CoV-2 tests in the general population

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Abstract

Background: With SARS-CoV-2 self-tests, persons with acute respiratory infections (ARI) can know their COVID-19 status. This may alter their decision to consult a general practitioner (GP), potentially biasing COVID-19 vaccine effectiveness (VE) studies. We explore bias mechanisms, simulate magnitude, and verify control methods.

Methods: We used directed acyclic graphs (DAGs) to illustrate the bias mechanisms. Based on the European primary care VEBIS multicentre test-negative design (TND) study, we simulated populations with varying true VE (20%–60%), proportions of persons with ARI self-testing (10%–30%), effect of COVID-19 vaccination on self-testing (1.5–2.5), and effect of self-test result on GP consultation (0.5–2). We performed 5000 runs per scenario, estimating VE among those consulting a GP. We calculated bias as true VE minus mean simulated VE, unadjusted and adjusted for self-testing, using logistic regression.

Results: DAGs suggested collider stratification bias if vaccination had an effect on self-testing and if self-test results affected GP consultation. Bias was −12% to 18% at 20% true VE, with the most extreme associations and 30% self-testing. With 60% true VE and 10%–20% self-

Received: 25 November 2024; **Editorial Decision:** 4 May 2025; **Accepted:** 21 May 2025
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testing, bias was lower. Bias was higher (−18% to 45%) if both positive and negative self-test results affected GP consultation. Adjusting for self-testing removed the bias.

Conclusions: Self-testing may bias COVID-19 VE TND studies in primary care if self-testing is high, particularly with low VE. We recommend primary care TND VE studies collect self-testing information to eliminate potential bias. Observational studies are needed to understand the relationship between vaccination, self-testing, and GP consultation, in these studies' source population.

Keywords: COVID-19; SARS-CoV-2; self-testing; vaccine effectiveness; bias; primary health care.

Key Messages

- We investigated how the use of SARS-CoV-2 tests in the general population could bias COVID-19 vaccine effectiveness studies at the primary care level, and how to mitigate this bias.
- Using directed acyclic graphs and data simulations, we showed that COVID-19 vaccine effectiveness could be biased due to self-test use, and that adjusting for self-testing removed this bias.
- Our findings have major implications for the validity of test-negative, case–control vaccine effectiveness studies and suggest that straightforward analytical techniques can be used to correct for bias of a potentially large magnitude.

Introduction

SARS-CoV-2 tests are readily available for purchase worldwide, especially in high- and middle-income countries. These can be self-administered or administered by a third party in pharmacies, using either rapid antigen tests or polymerase chain reaction (PCR) tests. Thus, an individual with respiratory infection symptoms can know their COVID-19 status before deciding to see their general practitioner (GP). Herewith, we refer to all SARS-CoV-2 tests carried out outside of a primary care/hospital environment as 'self-tests'. Little is known about the proportion of people with respiratory infection symptoms who self-test. It was estimated that 12%–21% of the general population in France and 73% of persons with respiratory symptoms in the Netherlands used self-tests in 2022 [1, 2].

Population-wide rollout of COVID-19 vaccines began in late 2020, and currently, many countries recommend COVID-19 vaccination to patients at risk of severe disease. Post-marketing COVID-19 vaccine effectiveness (VE) studies are key to evaluate these vaccination campaigns. COVID-19 VE against medically attended symptomatic SARS-CoV-2 infection can be evaluated in primary care. The test-negative design (TND) is used to estimate influenza VE [3–7], and most recently, COVID-19 VE at the primary care level [8–10]. Briefly, GPs systematically select patients consulting for an acute respiratory infection (ARI). The GPs swab patients meeting a common clinical case definition for ARI and collect clinical, demographic, and vaccination information. Biological specimens are tested by PCR for SARS-CoV-2. Cases and controls are patients testing positive and negative, respectively. To estimate VE, we compare the odds of vaccination among cases and controls.

Persons using self-tests may differ from those who do not, according to characteristics including COVID-19 vaccination [11]. The result of a self-test may influence GP consultation behaviour. Without self-testing, patients were blinded to their COVID-19 status before GP consultation. Now with self-testing, knowledge of COVID-19 status may alter the study population consulting the GP, potentially biasing COVID-19 VE TND studies at the primary care level, if vaccination also has an effect on self-testing. We outline our hypothesis around the mechanism of a potential bias in the COVID-19 VE estimates obtained from primary care TND studies and encode this using directed acyclic graphs (DAGs). We present simulations to help understand the magnitude and direction of potential bias and suggest analytical solutions to eliminate this bias.

Methods

Hypothesis around bias mechanisms

COVID-19 vaccination status may impact self-testing behaviours, e.g. if vaccinated persons are more likely to self-test [11], and knowing the self-test result may affect GP consultation behaviour.

This effect may occur through a person testing negative being more likely to consult the GP, or a person testing positive being more likely to consult the GP.

In the context of a TND study, the combination of these two effects could introduce bias (see a numerical example in Supplementary Tables S1–S3). Importantly, healthcare-seeking behaviour, defined as one's propensity to seek care, is a determinant of vaccination, GP consultation, and self-testing [7]. In TND studies, it is generally assumed that healthcare-seeking behaviour is (at least partially) controlled for by design [7].

This study focuses on bias emerging from an effect of vaccination on self-testing that is independent from healthcare-seeking behaviour. These mechanisms are depicted below using DAGs.

Directed acyclic graphs

DAGs are used in epidemiology to graphically represent causal links between variables using directed arrows. An arrow going from one variable to another illustrates a causal effect of the first variable on the second. A box around a variable indicates that we either restrict based on this variable (e.g. we select participants with a certain value of this variable) or condition on this variable (e.g. we include this variable in an adjusted model at the analysis stage) [12]. A descendant of a variable is a variable positioned 'downstream' on a causal pathway.

Building on the existing literature [7, 12–14], we first depicted a TND study estimating COVID-19 VE at the primary care level, in the absence of self-testing. We then added variables measuring self-testing constructs. Based on our hypotheses about plausible biological and behavioural mechanisms, as well as emerging literature [1, 11], we represented the causal relationships between these self-testing variables and the other variables.

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With the updated DAG, we described the potential mechanisms introduced by self-testing that could bias COVID-19 VE in primary care, TND studies. We also explored ways to mitigate this bias.

Simulation

We conducted a simulation study to understand the potential magnitude and direction of the bias introduced by self-testing. All input parameters are presented in Table 1, and many originated from the 2022/23 season ECDC-funded VEBIS primary care TND multicentre study [15, 16].

Data generation process

For each simulation scenario, we generated 5000 random datasets of a source population comprising 60 000 people with ARI symptoms who were part of a target group for COVID-19 vaccination. The ratio of COVID-19 cases to SARS-CoV-2 negative controls was 1:5, with a 45% COVID-19 vaccination coverage among controls [15]. The vaccine coverage among cases depended on the COVID-19 VE among this source population of 60 000 people, further referred to as 'true VE'. We separately modelled scenarios of true VE of 20%, 40%, and 60% [8, 15]. We assumed that 10% of people not self-testing see their GP when developing ARI symptoms [17]. We also incorporated the sensitivity and specificity of SARS-CoV-2 self-tests (Table 1).

We considered one scenario for each possible combination of the following varying parameters: the true VE; the proportion self-testing for the current illness episode among the unvaccinated; the probability of self-testing among the vaccinated compared to the unvaccinated and the probabilities of GP consultation after a positive or negative self-test result compared to GP consultation among those not self-testing (Table 1).

Statistical analyses

Within each dataset of each scenario, we selected people consulting the GP to mimic recruitment into a primary care, TND study. Among this group, we calculated the log odds ratio of vaccination among cases and controls using logistic regression. To compute the estimated VE ($\widehat{VE}$) for each scenario, we calculated (1−exponential(mean(log odds ratio))) *100. We then estimated the bias as the absolute difference between the true VE and $\widehat{VE}$. We used the standard error of the mean log odds ratio to obtain the 95% confidence interval around the bias estimate. We assumed no other bias. We assumed that potential confounders of VE were held constant across simulations. We conducted the analyses using Stata version 16 (StataCorp, College Station, TX, USA). Scripts are available in the Supplementary Material. We consider any mean bias difference of ≥10% as large.

Results

Directed acyclic graphs

We represented in Fig. 1 hypothesized causal relationships between key variables in a TND study estimating COVID-19 VE against medically attended, symptomatic SARS-CoV-2 infection, in the absence of self-tests. As mentioned above, healthcare-seeking behaviour is a confounder of COVID-19 vaccination and SARS-CoV-2 infection and can also impact one's probability of consulting the GP when ill [7]. We assumed that the TND controls for confounding by healthcare-seeking behaviour by design, by only selecting into the study people who sought medical care. This is indicated by the box around this variable. For simplicity, we did not represent other recognized confounders that are implicitly adjusted for such as age, sex, calendar time, or chronic conditions [7, 18].

Infection with SARS-CoV-2 can lead to ARI symptoms, and we represented the selection of patients with ARI symptoms = yes into our study by the box around this variable. Similarly, the development of symptoms can lead to GP consultation. We select patients with GP consultation = yes. The GP would perform a SARS-CoV-2 PCR test, which would then lead to a PCR test result. Patients with SARS-CoV-2 have a much higher chance (proportional to test sensitivity) of testing positive, which is illustrated by the arrow going from SARS-CoV-2 infection to PCR test result.

According to Fig. 1, there are no non-causal paths open between COVID-19 vaccination and SARS-CoV-2 infection.

Table 1. Input parameter values for simulation to calculate the magnitude of potential bias in COVID-19 vaccine effectiveness related to self-testing

Parameter[a]	Simulation value(s)	References
Size of the source population (the population with acute respiratory infection)	60 000 people	VEBIS primary care study [13]
Ratio of cases to controls among the source population	1:5	VEBIS primary care study [13]
Vaccination coverage among controls of the source population[b]	45%	VEBIS primary care study [15]
Proportion of SARS-CoV-2-positive patients among the source population	16.7%	VEBIS primary care study [15]
True VE	20%, 40%, 60%	[8, 15]
Proportion of source population consulting their GP among those not self-testing	10%	[2]
Proportion of self-testing in unvaccinated source population	10%, 20%, 30%	[17]
Sensitivity of the self-test result	60%	[18]
Specificity of the self-test result	99%	[19]
Probability of self-testing among vaccinated compared to self-testing among unvaccinated	1, 1.5, 2, 2.5	[2, 20]
Probability of consulting the GP after a positive self-test result compared to consulting the GP among those not self-testing	0.5, 0.7, 1, 1.5, 2	[2]
Probability of consulting the GP after a negative self-test result compared to consulting the GP among those not self-testing	0.5, 0.7, 1, 1.5, 2	Assumption

[a] All parameter values apply to the source population of people with acute respiratory infection symptoms.
[b] Vaccination coverage among test-negative controls of the source population should be representative of that among the general population.

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The causal odds ratio, and hereafter unbiased VE, may thus be estimated.

In Fig. 2A, we added self-testing variables and represented the direct impacts of healthcare-seeking behaviour, COVID-19 vaccination and ARI symptoms on self-test use. The patients taking a self-test would know the self-test result (positive/negative), and their probability of consulting a GP could vary based on this knowledge. The true underlying SARS-CoV-2 infection status influences the self-test result, in proportion to the test sensitivity and specificity.

In Fig. 2A, the non-causal path COVID-19 vaccination → self-testing → self-test result ← SARS-CoV-2 infection (in bold) is open because, by design, we restrict based on GP consultation, which is a descendant of the collider variable self-test result [19].

Direction and magnitude of bias: results from the simulation study

Figure 3 presents the directions and magnitudes of bias when varying the following parameters: the true VE (20%, 40%, and 60%); the proportion self-testing among the unvaccinated (20% and 30%); the probability of self-testing among the vaccinated compared to the unvaccinated (1.5, 2, and 2.5); and the probabilities of GP consultation based on self-test results (compared to the probability of GP consultation among those not self-testing) (0.5, 0.7, 1, 1.5, and 2). Supplementary Figure S1 presents the same, but for 10% self-testing. Supplementary Figure S2 presents the directions and magnitude of bias when both positive and negative self-test results affect GP consultation concomitantly, at 20% VE, 30% self-testing among the unvaccinated and a probability

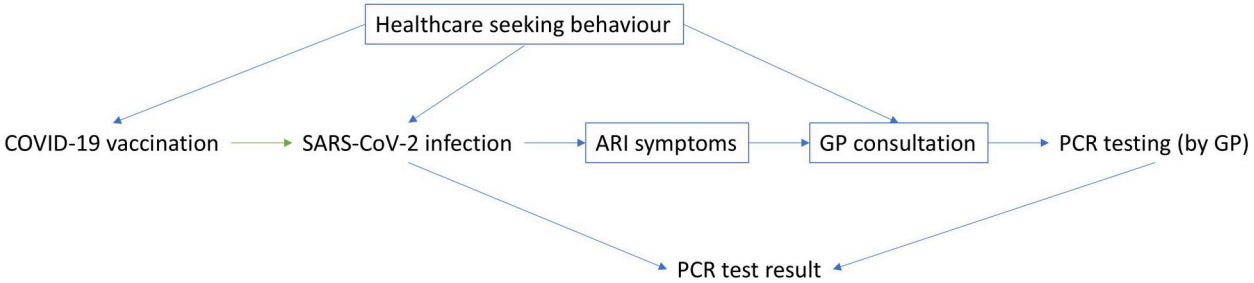

Figure 1. Directed acyclic graph representing hypothesized causal relationships between key variables in a test-negative design study of COVID-19 vaccine effectiveness at primary care level, in the absence of self-test use. The effect of interest is that of COVID-19 vaccination on SARS-CoV-2 infection.

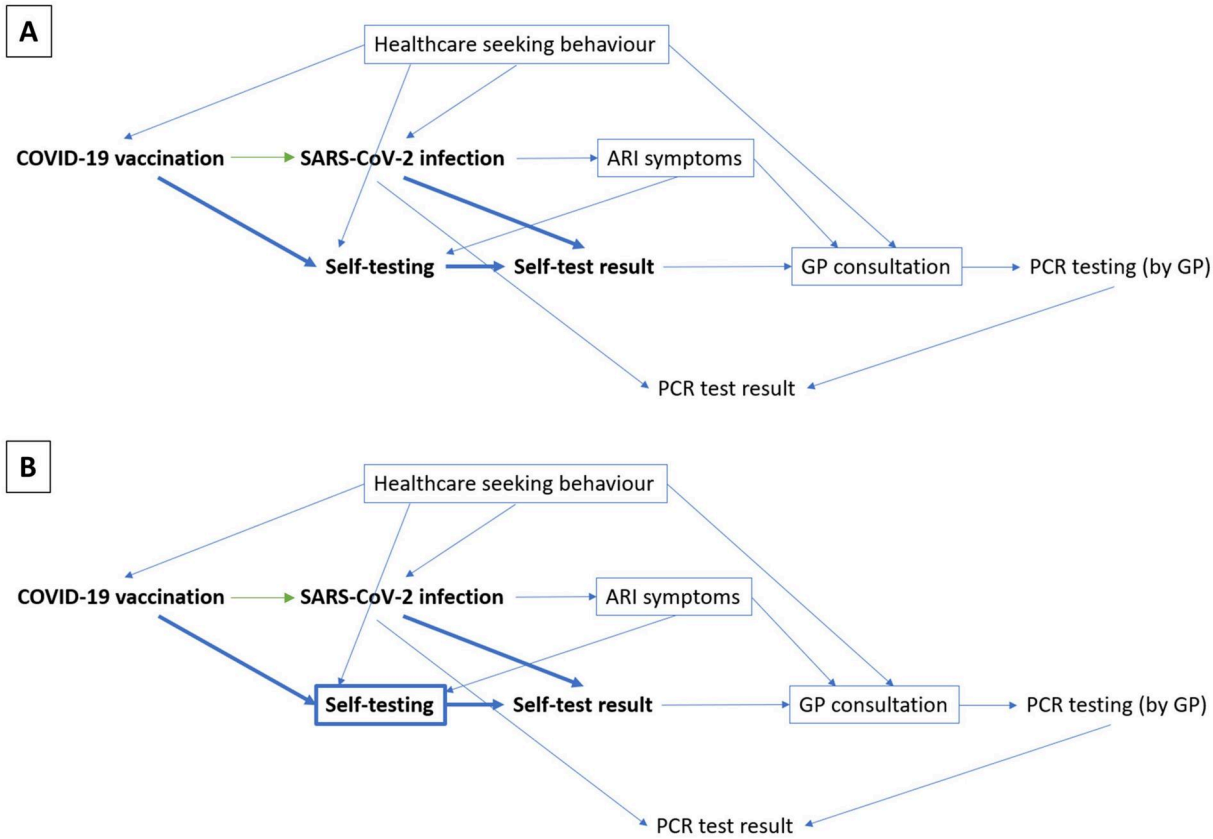

Figure 2. Directed acyclic graph representing hypothesized causal relationships between variables in a test-negative design study of COVID-19 vaccine effectiveness at primary care level, in the context of self-test use, (A) without adjustment for self-testing and (B) with adjustment for self-testing. The effect of interest is that of COVID-19 vaccination on SARS-CoV-2 infection.

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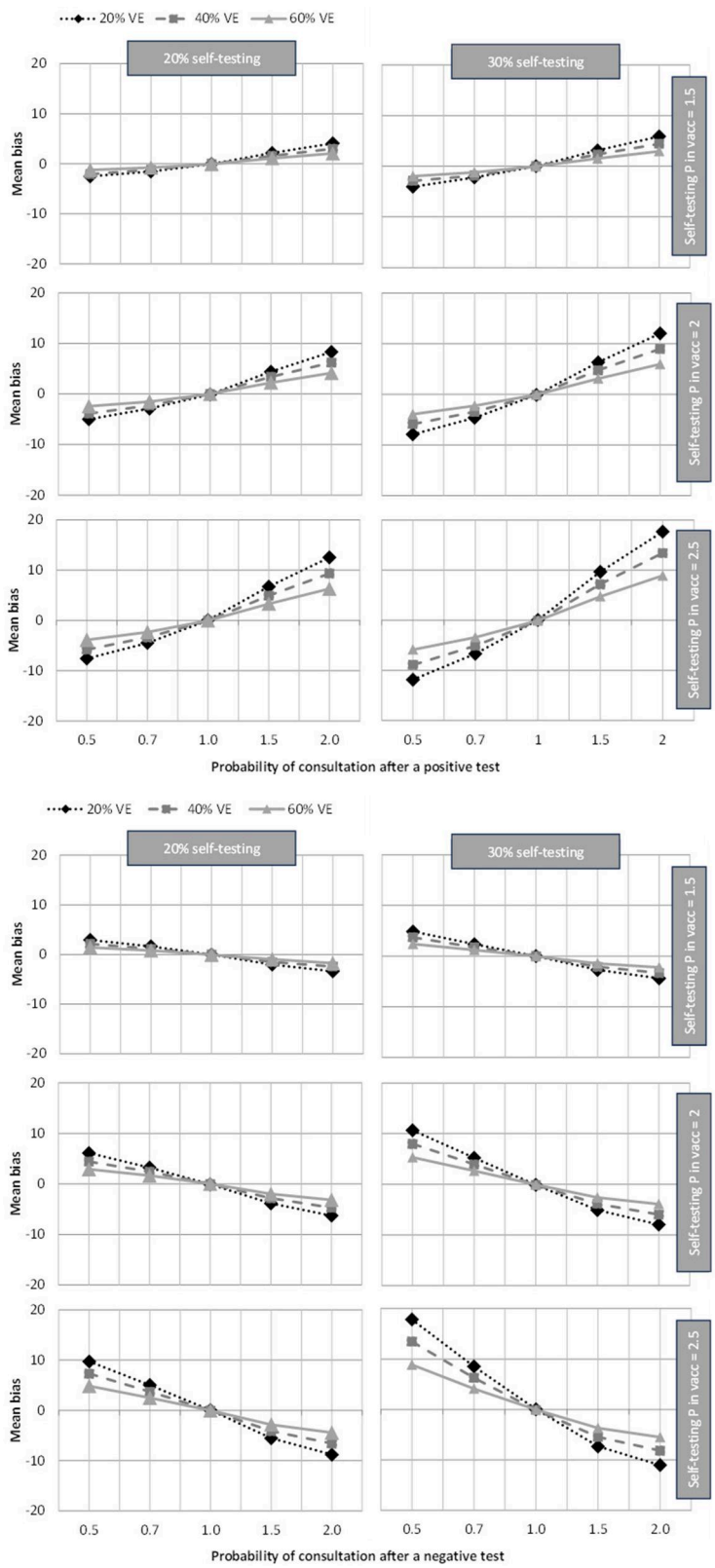

Figure 3. Difference between the estimated VE and the true VE (mean bias), in a simulated primary care-based test-negative design study, under different scenarios defined by key parameters, in the context of self-test use, without adjustment for self-testing. The first set of plots presents results of simulations varying the probability of GP consultation after a positive self-test result (expressed relatively to that among those not self-testing). The second set of plots presents results of simulations varying the probability of GP consultation after a negative self-test result (expressed relatively to that among those not self-testing). The probability of self-testing among the vaccinated is expressed relatively to that among the unvaccinated. 10% self-testing in the unvaccinated population equates to 17% overall, 20% self-testing to 34% overall, and 30% self-testing to 50% overall, under the assumption of a 2.5 probability ratio for self-testing among the vaccinated population. P, probability; Vacc, vaccinated.

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of self-testing 2.5 times higher among the vaccinated. All results are presented in Supplementary Table S4.

In all scenarios where the probability of GP consultation after a positive *or* negative self-test result (but not both) varied from 1, we observed a greater bias with lower true VE (−12% to 18% for a 20% VE versus −6% to 9% for a 60% VE), with higher proportions of self-testing (−12% to 18% with 30% self-testing, versus −5% to 7% with 10% self-testing), and with a greater effect of vaccination on self-testing (−12% to 18% for a probability ratio of 2.5 versus −4% to 6% for an probability ratio of 1.5) (Fig. 3, Supplementary Fig. S1 and Table S4). Mean bias differences ranged from −12% to 18% with an effect of positive self-test results on GP consultation, and from −11% to 18% with an effect of negative self-test results on GP consultation. More extreme bias occurred when the probability of GP consultation differed from 1 after *both* a positive and negative self-test. The most extreme bias of 45% occurred with a 20% VE, 30% self-testing among the unvaccinated and 2.5 times higher self-testing among the vaccinated, and the largest difference between GP consultation behaviours after a positive or negative self-test result (i.e. consultation probability ratio of 2 after a positive self-test, combined with consultation probability ratio of 0.5 after a negative self-test, or vice versa) (Supplementary Fig. S2 and Table S4). With equal probability ratios of consultation after negative and positive self-tests, VE was not biased.

Mitigation of potential bias

This bias in COVID-19 VE can be mitigated by adjusting the logistic regression model by self-test use (yes/no), if this information is collected within the study without misclassification. Figure 4 provides one example, and results for other parameter values are available in Supplementary Table S4. For a numerical example, see Supplementary Equation S1. While a selection bias is introduced into the study, it can be mitigated with techniques used to adjust for confounding, such as regression modelling [20, 21].

This mitigation can also be derived using DAGs. In Fig. 2A, the non-causal path COVID-19 vaccination → self-testing → self-test result ← SARS-CoV-2 infection is open. However, we can block this path by adjusting for self-testing at the analysis stage (this is represented by a box around the self-testing variable in Fig. 2B), provided that information is collected on self-test use prior to GP consultation.

Discussion

Our results confirm that COVID-19 VE studies conducted at the primary care level may be biased when the probability of self-testing varies by vaccination status independently of healthcare-seeking behaviour and when self-test results influence the probability of GP consultation. These bias mechanisms can lead to under- or over-estimating VE by more than 10%, and up to 45%, depending on the direction of the assumed effects. Bias increased with lower true VE, higher proportions of self-testing, greater effect of vaccination on self-testing, greater effect of self-test result on GP consultation, and when positive and negative self-test results affected consultation in opposite directions. If present, these effects could jeopardise the validity of COVID-19 VE studies at the primary care level.

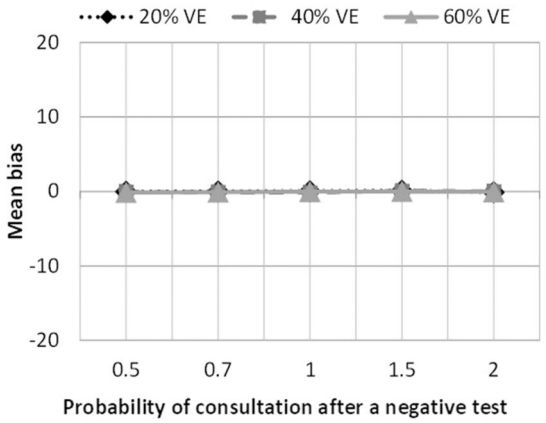

Figure 4. Difference between the estimated VE and the true VE (mean bias), in a simulated primary care-based test-negative design study, with a probability ratio of self-testing of 2.5 among the vaccinated, 30% self-testing in the unvaccinated, and no effect of positive result on GP consultation, in the context of self-test use, with adjustment for self-testing. The probability of consultation after a negative self-test result is expressed relatively to that among those not self-testing.

We demonstrated that researchers can mitigate the selection bias introduced by self-testing by simply adjusting for self-testing at the analysis stage, provided that information is collected on self-testing (yes/no) for the illness episode for which the patient is consulting the GP. Indeed, adjusting for self-testing closes a non-causal path opened by conditioning on the descendant (GP consultation) of a collider (self-test result). Importantly, self-testing is not a confounder in this study.

Strengths of our approach include the joint use of two methods for understanding and mitigating potential biases. Simulation and causal inference results are in line. In addition to improving robustness, this joint approach allows us to establish a dialogue with investigators coming from diverse backgrounds. Our findings have implications for numerous VE studies, and potential threats to validity should be further investigated. Parameter values for the simulations were extracted from well-established, empirical VE studies, and our investigations can be replicated using data from another setting/period (Stata scripts are available in the Supplementary Material). Finally, our recommendation to collect self-reported information on self-testing and self-test results is relatively easy to implement in existing studies. We recommend estimating VE both adjusted (as a main analysis) and unadjusted for self-testing, to understand its effects.

A limitation is that we assumed no additional sources of bias beyond those related to the impact of COVID-19 vaccination status on self-testing, and of self-testing results on GP consultation. Some potential biases can threaten the validity of any TND study: we assumed that healthcare-seeking behaviour was adequately adjusted for, and this assumption is difficult to check [7, 13]. We also assumed no measurement error in SARS-CoV-2 infection status with PCR tests, as the sensitivity and specificity of these tests are high and considered as gold standard [22]. Further, in the context of self-testing, vaccinated patients with a positive self-test result may have a different GP consultation behaviour than unvaccinated patients with a positive self-test result. Conversely, vaccinated patients with a negative self-test result may have a different GP consultation behaviour than unvaccinated patients with a negative self-test result, or both. Differential

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GP consultation behaviour by vaccination status could lead to selection bias. In that case, only adding the GP consultation probabilities for each combination of vaccination status and self-test result as weights within the VE analysis would allow for this bias to be mitigated. These selection probabilities would require specific additional studies in the source population for the TND. This selection bias can even be present in the absence of an effect of vaccination on self-testing.

Other limitations include the fact that behaviour of GPs was not taken into account. Indeed, if a patient consults the GP and presents a positive self-test result, swabbing behaviour and selection by the GP into the study may be affected. However, in our protocols, we emphasize systematic selection of patients meeting the case definition, regardless of other patient attributes. In addition, we base parameter values on specific studies and articles, and they may not hold in other settings or periods, such as the 45% vaccination coverage or the 60% sensitivity of self-tests compared to PCR tests.

Additionally, through a potential correlation between COVID-19 and influenza vaccination behaviour, SARS-CoV-2 self-testing may indirectly introduce a potential bias in influenza VE studies [23]. Further research into this is warranted. We also note that self-testing may bias COVID-19 VE studies in primary care using an alternative study design to the TND. However, the bias within the TND is likely to be greater, as ARI patients are also recruited as the control population. Of note that if self-testing is not prevalent within a population (e.g. it is only 10%), the magnitude of bias is likely to be low. In order to better understand the proportion of self-testing within a population and differences by population groups (e.g. by age group), as well as the effects of vaccination on self-testing and of self-test results on GP consultation, we recommend carrying out population-representative studies within the source population for TND studies at the primary care level. This source population is those registered with a sentinel GP and part of a target group for COVID-19 vaccination. Here, a prospective or retrospective cohort study could be carried out to obtain this important information. As a new cohort study requires a lot of resources, this study could be nested within already existing cohorts, collecting information on ARI, COVID-19 vaccination, and GP consultation behaviour, such as the participatory surveillance Influenzanet, other existing cohorts, or within regularly carried out health information surveys [24–26].

Results from these surveys would provide more accurate parameters for our simulation, so we could better understand the potential bias within TND studies. Using these data, we could identify if vaccination is associated with self-testing independently of GP consultation. Additionally, if there is indeed selection bias due to differential GP consultation behaviour by vaccination status, the studies could be used to obtain the selection probabilities to be added as weights within the VE analysis.

To conclude, the possibility of ARI patients knowing their COVID-19 status through self-tests prior to GP consultation can influence their decision whether or not to consult the GP. If this is combined with an effect of vaccination on self-testing, the validity of COVID-19 VE TND studies at the primary care level is jeopardised. Under certain circumstances, the bias introduced by self-testing can be mitigated at the analysis stage. Yet, studies within the source population for COVID-19 VE studies are needed to better understand the proportion of patients self-testing, the effects of vaccination on self-testing, and of self-test results on GP consultation, as well as potential selection bias due to third factors within these associations.

Acknowledgements

We acknowledge the contribution by the VEBIS Primary Care Vaccine Effectiveness Group: Croatia—Ivana Ferenčak, Bernard Kaić, Maja Ilić, Vesna Višekruna Vučina, Croatian Institute of Public Health, Zagreb; Katica Čusek Adamić, Institute of Public Health, Varaždin County, Varaždin; Mirjana Lana Kosanović Ličina, 'Dr Andrija Štampar' Teaching Institute of Public Health, Zagreb; Danijela Lakošeljac, Teaching Institute of Public Health, Primorje-Gorski kotar County, Rijeka; Ivana Mihin Huskić, Teaching Institute of Public Health, Osijek-Baranja County, Osijek; Diana Nonković, Teaching Institute for Public Health, Split-Dalmatia County, Split. France—Thierry Blanchon, Caroline Guerrisi, Titouan Launay, Aubane Renard, Sorbonne Université, INSERM, Institut Pierre Louis d'épidémiologie et de Santé Publique (IPLESP UMRS 1136); Marie Chazelle, Alessandra Falchi, Shirley Masse, Laboratoire de Virologie, Université de Corse-Inserm; Vincent Enouf, Sylvie van der Werf, Centre National de Référence Virus des Infections Respiratoire (CNR VIR), Institut Pasteur. Germany—Luise Goerlitz, Silke Buda, Ute Preuss, Kristin Tolksdorf, Carolin Hackmann, Department for Infectious Disease Epidemiology, Respiratory Infections Unit, Robert Koch Institute; Barbara Biere, Djin-Ye Oh, Janine Reiche, Marianne Wedde, National Reference Centre for Influenza, Robert Koch Institute. Hungary—Judit Krisztina Horváth, Krisztina Mucsányiné Juhász, Katalin Krisztalovics, Csaba Luca, National Laboratory for Health Security, Epidemiology and Surveillance Centre, Semmelweis University, Budapest; Katalin Kristóf, Institute of Laboratory Medicine, Semmelweis University, Budapest. The Hungarian study team works as part of the National Laboratory for Health Security Hungary (RRF-2.3.1-21-2022-00006) supported by the National Research, Development and Innovation Office (NKFIH). Ireland—Joan O'Donnell, HSE Health Protection Surveillance Centre, Dublin; Jeff Connell, National Virus Reference Laboratory, Dublin; Michael Joyce, Olga Levis and the Irish sentinel GP network, Irish College of General Practitioners, Dublin; The Netherlands Lynn Aarts, Mariam Bagheri, Danytza Berry, Sanne Bos, Sharon van den Brink, Dirk Eggink, Rianne van Gageldonk-Lafeber, Gabriel Goderski, Liz Jenniskens, Femke Jongenotter, Adam Meijer, Tara Sprong, Anne Teirlinck, molecular pool technicians, National Institute for Public Health and the Environment (RIVM), Bilthoven; Nivel Primary Care Database—Sentinel Practices team, Ruud van den Broek, Safira Wortel, Ruben van der Burgh, Cathrien Kager, Mayra Klinkhamer, Bart Knottnerus, Marloes Riethof, Nienke Veldhuijzen, participating general practices and their patients, Nivel, Utrecht. Portugal—Vitor Borges, Licínia Gomes, Camila Henriques, Ana Paula Rodrigues, Daniela Dias, Débora Pereira, Pais de Lacerda, Susana Maia Silva, Paula Pinto, Cristina Bárbara, Epidemiology Department, Instituto Nacional de Saúde Doutor Ricardo Jorge, Lisbon. Romania—Maria Elena Mihai, Alina Ivanciuc, Catalina Pascu, Iulia Bistriceanu, Sorin Dinu, Mihaela Oprea, Olivia Timnea, Adrian Jidovu, 'Cantacuzino' National Military-

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Medical Institute for Research and Development, Bucharest; Rodica Popescu, National Institute of Public Health, Bucharest. Spain, national—SiVIRA surveillance and vaccine effectiveness group. Spain, Navarre—Itziar Casado, Aitziber Echeverria, Camino Trobajo-Sanmartín, Manuel García Cenoz, Guillermo Ezpeleta, Instituto de Salud Pública de Navarra—IdiSNA, CIBERESP, Pamplona; Ana Navascués, Miguel Fernández-Huerta, Carmen Ezpeleta, Hospital Universitario de Navarra—IdiSNA, Pamplona. Sweden—Annasara Carnahan (epidemiology team), Emmi Andersson, Eva Hansson-Pihlainen, Elin Arvesen, Nora Nid, Anna-Lena Hansen and Lena Dillner (influenza virus surveillance team) and the NGS platform, Public Health Agency of Sweden, Stockholm, Sweden. All study teams are very grateful to all patients, general practitioners, paediatricians, laboratory teams, and regional epidemiologists who have contributed to the studies. We would like to acknowledge Gilles Desvé for his contribution to and validation of the simulation study methods and programming, and Ruoran Li for her contribution to the development of directed acyclic graphs.

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Charlotte Lanièce Delaunay: conceptualization, formal analysis, methodology, validation, visualization, writing—original draft preparation, writing—review and editing. Baltazar Nunes: methodology, validation, writing—review and editing. Susana Monge: conceptualization, methodology, validation, writing—review and editing. Marit de Lange, Gergő Túri, Ausenda Machado, Neus Latorre-Margalef, Ivan Mlinarić, Mihaela Lazar, Paloma Botella Rocamora, Annika Erdwiens, Noémie Sève, Lisa Domegan, Iván Martínez-Baz, Mariëtte Hooiveld, Beatrix Oroszi, Raquel Guiomar, Maike Sperk, Sanja Kurečić Filipović, Catalina Pascu, Juan Antonio Linares Dopido, Ralf Dürrwald, Marie-Anne Rameix-Welti, Adele McKenna, Jesús Castilla: writing—review and editing. Cheyenne van Hagen, Mirjam Knol: methodology, writing—review and editing. Esther Kissling: conceptualization, formal analysis, funding acquisition, methodology, project administration, supervision, validation, visualization, writing—original draft preparation, writing—review and editing. Esther Kissling is the guarantor.

Supplementary data

Supplementary data is available at *IJE* online.

Conflict of interest: None declared.

Funding

This study received funding from the European Centre for Disease Prevention and Control (ECDC), through the framework contract Vaccine Effectiveness, Burden and Impact Studies (VEBIS) of COVID-19 and Influenza ECDC/2021/019.

Data availability

Stata scripts for generation of simulated data available in the Supplementary Material as well as in the following publicly available GitHub repository: https://github.com/epi-gde/STATA-SIMUL

Use of artificial intelligence tools

No artificial intelligence tools were used in this manuscript.

Ethics approval

Ethics approval was not needed as simulated data were used for this study.

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International Journal of Epidemiology, 2025, 54, 1–9
https://doi.org/10.1093/ije/dyaf086
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