Check for updates

AUTHORS:
Nonhlanhla Yende-Zuma[1,2,3]
Tarylee Reddy[1,3]

AFFILIATIONS:
[1]Biostatistics Research Unit, South African Medical Research Council, Durban, South Africa
[2]Centre for the AIDS Programme of Research in South Africa (CAPRISA), Durban, South Africa
[3]School of Mathematics, Statistics and Computer Science, University of KwaZulu-Natal, Pietermaritzburg, South Africa

CORRESPONDENCE TO:
Nonhlanhla Yende-Zuma

EMAIL:
Nonhlanhla.yende-zuma@mrc.ac.za

DATES:
Received: 23 Sep. 2024
Revised: 14 May 2025
Accepted: 26 Aug. 2025
Published: 26 Nov. 2025

HOW TO CITE:
Yende-Zuma N, Reddy T. Challenges in assessing COVID-19 vaccine effectiveness in resource-limited settings: Experiences from South Africa. S Afr J Sci. 2025;121(11/12), Art. #19262. https://doi.org/10.17159/sajs.2025/19262

ARTICLE INCLUDES:
☒ Peer review
☐ Supplementary material

DATA AVAILABILITY:
☐ Open data set
☐ All data included
☐ On request from author(s)
☐ Not available
☒ Not applicable

EDITORS:
Pascal Bessong
Shane Redelinghuys

KEYWORDS:
COVID-19 vaccine, effectiveness, booster vaccines, study designs, statistical considerations

FUNDING:
South African National Treasury, South African National Department of Health, Solidarity Response Fund NPC, Michael and Susan Dell Foundation, Elma Vaccines and Immunization Foundation, Bill and Melinda Gates Foundation

© 2025. The Author(s). Published under a Creative Commons Attribution Licence.

Challenges in assessing COVID-19 vaccine effectiveness in resource-limited settings: Experiences from South Africa

Evaluating the real-world effectiveness of vaccines, including COVID-19 vaccines, and various biomedical interventions is crucial to address gaps in evidence from randomised controlled clinical trials and inform the national rollout of vaccinations. In the context of COVID-19, these gaps may include vaccine effectiveness against variants of concern and in high-risk subgroups such as people living with HIV. Designing vaccine effectiveness studies is more complex than designing randomised controlled clinical trials as it requires the availability of reliable, routinely collected data. Effectiveness studies in low- to middle-income countries (LMICs) are essential for tailoring vaccination strategies, addressing high-risk subgroups, ensuring equitable protection, and contributing valuable data to global health efforts. However, fewer COVID-19 vaccine effectiveness studies have been conducted in LMICs, including on the African continent, compared to high-income countries. Through our experience, it has become clear that national health data systems, resources and infrastructure, as well as adequate statistical capacity – which is crucial when conducting robust effectiveness studies – are lacking in LMICs. While each COVID-19 vaccine effectiveness study employed a specific study design and analytical approaches, none, to our knowledge, provided a rationale for their study design and statistical methods. Drawing from practical experiences, reflections and lessons learnt after designing a COVID-19 vaccine effectiveness study in a resource-limited setting, we present key considerations for data sources needed to run real-world effectiveness studies, for study designs, and for statistical modelling suitable for effectiveness studies. In the context of COVID-19, the study designs and statistical models are suitable for both prime and booster vaccines.

Significance:

- Substantially fewer COVID-19 vaccine effectiveness studies have been conducted in LMICs than in high-income countries.
- The lack of integrated national health data systems contributes to the lack of robust effectiveness studies in general and this was also observed during the COVID-19 pandemic.
- While each COVID-19 vaccine effectiveness study employed a specific study design and analytical approaches, none, to our knowledge, provided a rationale for their study design and statistical methods.
- Therefore, drawing from practical experiences, reflections and lessons learnt after designing a COVID-19 vaccine effectiveness study in a resource-limited setting, we present key considerations for study designs, data requirements and statistical modelling suitable for effectiveness studies.

Introduction

The COVID-19 pandemic started in December 2019 and affected millions of lives globally.[1] In March 2020, the first phase 1 trials of COVID-19 vaccines commenced.[2] By December 2020, there were several COVID-19 vaccine candidates being tested in large phase 3 randomised clinical trials.[3-5] Vaccine efficacy levels from randomised clinical trials ranged from 66% to 95%, depending on the endpoint of interest.[4-7] From December 2020, countries started rolling out vaccines, necessitating evaluation of vaccines outside randomised controlled trial settings.[8] Vaccine effectiveness studies in low- and middle-income countries (LMICs) are essential for tailoring vaccination strategies, addressing high-risk subgroups, ensuring equitable protection, and contributing valuable data to global health efforts. Moreover, these studies have the advantage of allowing for the detection of less frequent adverse effects.[9]

Regardless of the disease or condition, effectiveness studies are generally challenging to design, analyse and interpret due to their susceptibility to biases and methodological complexities.[10,11] This difficulty is due to the lack of random assignment of individuals, which reduces selection bias and systematic variations between, for example, vaccinated and unvaccinated individuals. Moreover, making probabilistic statements about the likely similarities between vaccinated and unvaccinated individuals concerning the outcome(s) and drawing causal inferences becomes challenging.

As a result, the World Health Organization (WHO) provided interim guidance on the evaluation of COVID-19 vaccine effectiveness[12], primarily aimed at evaluations undertaken in LMICs, to address study design, sample size, biases and data collection on potential covariates and confounders. Despite the WHO's guidance, only a few COVID-19 vaccine effectiveness studies have been conducted in the WHO's African region and most countries in the Global South.[13] According to the International Vaccines Access Center (IVAC)[13], and a systematic review of vaccines administered in Africa[14], as of May 2024, only seven COVID-19 vaccine effectiveness studies were reported in the WHO's African region[15-21]. In contrast, 257 studies were reported in the region of the Americas, 214 in the European region, 53 in the Western Pacific region, 30 in the eastern Mediterranean and 10 in the Southeast Asian region (Figure 1). The lack of contribution of the African region to vaccine effectiveness estimates is despite the commendable implementation of strategic, operational and tactical coordination mechanisms by the WHO AFRO

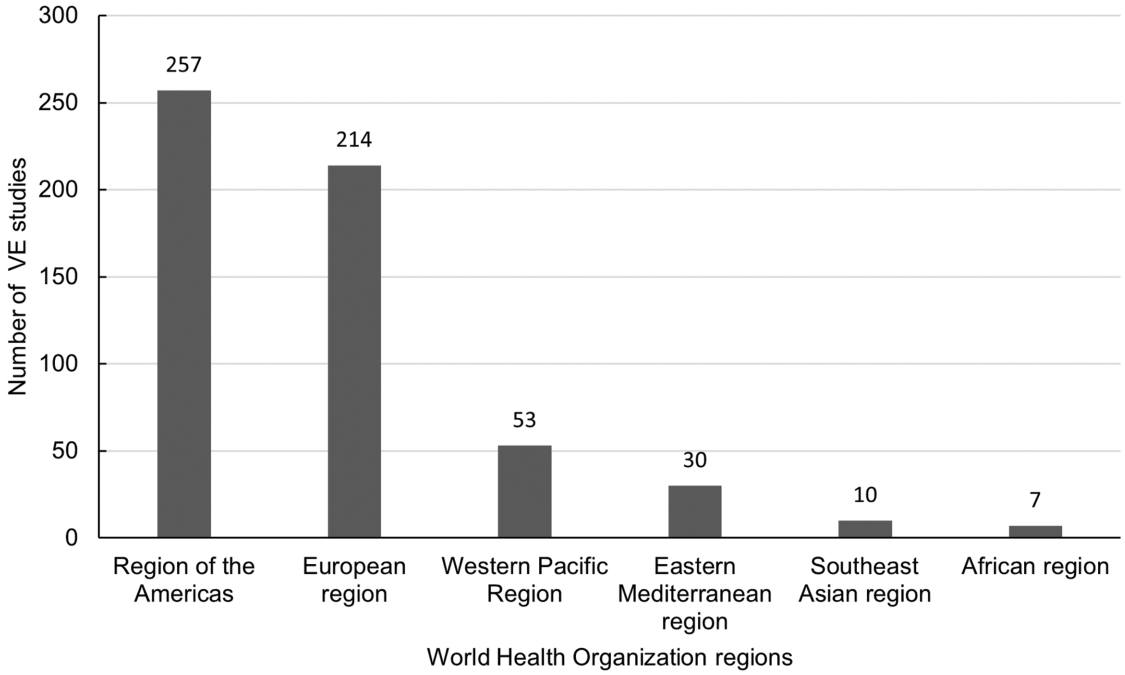


Figure 1: COVID-19 vaccine effectiveness (VE) studies conducted in the regions of the World Health Organization.

region in response to COVID-19.[22] This paucity of COVID-19 vaccine effectiveness studies highlights an urgent need to strengthen health and data systems, not only to produce timeous health reports to track pandemics and epidemics, carry out effectiveness studies for various interventions and keep the research community updated, but also to contribute to improving the welfare of the African population.[23]

While several articles that we sourced from Google Scholar, PubMed and other sources presented COVID-19 vaccine effectiveness estimates, to the best of our knowledge, none has provided a rationale and motivation behind the choice of the study design and statistical analysis approach. In this paper, we discuss key considerations for data sources needed to run real-world vaccine effectiveness studies for prime and booster vaccines, for study designs and for statistical modelling suitable for vaccine effectiveness studies, reflecting on lessons from the Sisonke Phase 3b trial implementation study[15] which was conducted in South Africa. These considerations are not exclusive to vaccines but also applicable to most biomedical interventions evaluated in clinical trials.

Study designs used in assessing vaccine effectiveness

The WHO recommended five study designs to measure COVID-19 vaccine effectiveness: test-negative case-control, cohort, case-control, screening method and regression discontinuity design.[12]

It is important to note that each of the aforementioned designs has strengths, weaknesses and biases that should be mitigated. To date, the most commonly used study designs are cohort, test-negative case-control, and, to a lesser extent, case-control; these are the focus of the next section. It is important to outline these study designs because the challenges in conducting vaccine effectiveness studies are directly linked to the availability of data sources required for each study design. Moreover, this outline will be broadly applicable to other diseases for which effectiveness studies are crucial.

Test-negative case-control study

The test-negative case-control design, which is suitable for infectious diseases, was introduced in 2007[24], and has been widely used to estimate the effectiveness of influenza and rotavirus vaccines. This design has been used to assess vaccine effectiveness against symptomatic SARS-CoV-2 infection or severe COVID-19 in countries such as England[25], Brazil[26], Canada[27], Qatar[28], the USA[29], and South Africa[17-19].

In the test-negative case-control design, individuals seeking medical care for COVID-19-like or respiratory symptoms are tested for SARS-CoV-2. Those who test positive for the pathogen serve as cases and those who test negative serve as controls.

The most important strength of this design is that cases and controls have a similar symptom profile and are therefore likely to be similar in various respects, thereby reducing selection bias. The same selective forces that lead individuals to be tested should operate on both those who test positive and those who test negative, and this mechanism is expected to produce a valid vaccine effectiveness estimate. Symptomatic individuals can be recruited from the same health facility (inpatient or outpatient).

The WHO recommended test-negative case-control design as an efficient and accurate method in LMICs to assess vaccine effectiveness against severe and symptomatic COVID-19.[12] On paper, this design is easy to implement. At a minimum, a data set with the following variables is suitable for this design: Among individuals who present with COVID-19 symptoms (as inpatients or outpatients): (i) the symptoms that people present with to confirm eligibility; (ii) SARS-CoV-2 results from highly sensitive and specific diagnostic tests such as polymerase chain reaction (PCR) and specimen collection date; (iii) vaccination date, which should be captured at the time of specimen collection; and (iii) sociodemographic and clinical variables associated with vaccination and COVID-19.

The WHO recommended that, if necessary, cases and controls should be matched by time of enrolment to account for the evolving nature of the pandemic and circulating variants. This approach ensures that cases and controls are selected at a similar time period. Subsequently, multivariable logistic regression should be used to estimate the ratio of the odds of vaccination among cases compared with controls.

Cohort study

This study design is broadly applicable to both infectious and non-infectious disease outcomes, and has been used to assess vaccine effectiveness against any documented SARS-CoV-2 infection, symptomatic SARS-CoV-2 infection, COVID-19 related hospital admissions and mortality in countries such as South Africa[15], Morocco[30], Israel[31] and the USA[32,33].

In a cohort study, vaccinated and unvaccinated individuals are prospectively followed up to ascertain an endpoint or disease occurrence. The WHO recommended that this design be used in settings with the capacity for

rigorous follow-up to determine vaccination status and disease status and collect accurate and complete covariates to adequately adjust for confounding. This design can also be conducted retrospectively; however, reliable vaccination status is difficult to ascertain in retrospective cohorts without good vaccination records. Under this design, stratified analyses can be undertaken based on subgroups and common variants of concern. To assess vaccine effectiveness under specific variants of concern, either the sequencing data or the availability of data showing when each variant was dominant in various countries is crucial. After extraction of these timepoints, the follow-up period of an individual is split accordingly, thereby allowing individuals to contribute person-time to each variant of concern during their period of observation.

A data set with a minimum of the following variables is suitable for this design: (i) vaccination date, which should be constantly updated during follow-up to avoid misclassification; (ii) date of endpoint/ diagnosis or date when endpoint(s) was measured; and (iii) sociodemographic and clinical variables associated with vaccination and COVID-19. Vaccinated and unvaccinated individuals can be matched on key characteristics, or they could be adjusted for in a multivariable model.

Thereafter, the rate of disease is estimated within each of the vaccinated and unvaccinated groups and compared using either multivariable Poisson regression, with exposure time as an offset, or multivariable Cox proportional hazards regression.

Case-control study

The case-control design, also suitable for infections and non-infectious diseases, was used to measure vaccine effectiveness against asymptomatic and symptomatic SARS-CoV-2 infection, severe illness, hospitalisation and death in Zambia[20], China[34] and the USA[35].

In a traditional case-control design, individuals diagnosed with COVID-19, irrespective of symptoms, are eligible to be considered as cases. Controls are individuals not diagnosed with COVID-19 but who had the same likelihood of being classified as cases if they had been infected with SARS-CoV-2. Controls should be drawn from the same setting or population from which cases were derived, e.g. community, hospital or prison. Drawing controls from each of these settings can be challenging[36], especially for community controls, as they would not have presented themselves to healthcare facilities for complete data collection, necessitating costly fieldwork to be carried out. Cases and controls can be matched on variables associated with vaccination and SARS-CoV-2 infection, including the calendar time of enrolment.

Like other designs, case-control studies are also susceptible to biases that could decrease or increase vaccine effectiveness estimates. Healthcare-seeking behaviour or access to care can bias vaccine effectiveness estimates towards the null because vaccinated individuals may be more likely to seek care if diagnosed with SARS-CoV-2 infection and thus defined as cases.[37] As indicated, test-negative case-control attempts to mitigate this bias, as both cases and controls seek care.

A data set with the following variables is suitable for this design: (i) SARS-CoV-2 results from highly sensitive and specific diagnostic tests and specimen collection date; (ii) vaccination date which should be captured at the time of specimen collection; and (iii) sociodemographic and clinical variables associated with vaccination and COVID-19. Similarly to test-negative case-control, multivariable logistic regression should be used to calculate the ratio of the odds of vaccination among cases compared with controls.

Lessons learnt from evaluating vaccine effectiveness in the Sisonke study

The Sisonke study was a single-arm, open-label, phase 3B implementation study that enrolled 477 102 healthcare workers aged 18 years and older.[15] The study participants received a single dose of Ad26.COV2.S vaccine between 17 February 2021 and 17 May 2021[15] and were eligible for a second dose of Ad26.COV2.S (via the Sisonke 2 trial) from 9 November 2021. Assessing vaccine effectiveness required a robust comparator group of unvaccinated individuals with exposure to SARS-CoV-2 comparable to that of healthcare workers.

When COVID-19 emerged in South Africa, the South African Department of Health and Public Health institutes such as the National Institute for Communicable Diseases (NICD) worked extremely hard to develop databases to collect vaccination data, SARS-CoV-2 test results and COVID-19 related admissions. The country had a well-established Civil Registration and Vital Statistics System (CRVS) with a high proportion of deaths being registered.

However, in 2021, linking all these databases to design a cohort study or test-negative case-control study within Sisonke posed challenges. One of these challenges was the inconsistent capturing of the unique identifier in the form of a South African identification number. This limitation was also observed in other epidemiological studies in the same setting.[38] Secondly, none of the databases collected data on COVID-19-related symptoms at the time of testing for SARS-CoV-2 – an important premise for a valid and robust test-negative case-control study.

In view of the many individuals being tested as a result of contact with confirmed or suspected COVID-19 cases, or prior to any hospitalszation (trauma events, elective surgeries, etc.), the available data from our setting would severely compromise the test-negative case-control design. While valuable, the routinely collected data on SARS-CoV-2 infection, COVID-19 hospitalisation and deaths for only the Sisonke participants were clearly not sufficient to evaluate vaccine effectiveness. The solution was to use data from two medical care organisations that provide health insurance in South Africa to design a vaccine effectiveness study. While these databases played a crucial role in vaccine effectiveness studies by providing complete and reliable data on demographics, comorbidities and endpoints, we acknowledge that the insured population may not be representative of the general population. Insured individuals tend to be older than the uninsured[39] or the general population[40]. Moreover, a larger proportion have a tertiary education, have a higher total monthly household income and greater access to healthcare services compared to the uninsured population.[39]

As already indicated, without symptoms linked to both cases and controls, the robustness of test-negative case-control becomes questionable. Consequently, in one South African study that utilised the test-negative case-control design, data on COVID-19-like symptoms were not available.[16] Still, a deduction was made on the basis that COVID-19 PCR tests were funded from medical scheme benefits on referral from a clinician. Hence, test results were most likely to be available for the symptomatic population.

Infrastructure and national data systems

Ideally, vaccine effectiveness and effectiveness studies in general require national data systems similar to those from the medical insurance schemes in which vaccination data, sociodemographic data, clinical characteristics and outcomes can be found in the same database and are linked by a unique identifier. Although South Africa does not have a national health data system, the Western Cape Department of Health has a Provincial Health Data Centre, which consolidates all person-level health data (hospital, laboratory, pharmacy, primary care, disease management, mortality, etc.).[41] These data were valuable for generating valid vaccine effectiveness estimates despite being confined to only one of the nine provinces in South Africa[42]; routine data collected across all nine provinces would be beneficial for country-wide evidence-based decision-making. Availability of data is crucial for preventing, preparing for, and responding to future pandemics and endemic diseases.

As already stated, effectiveness studies are not limited to COVID-19 research. South Africa reported the highest number of new human immunodeficiency virus (HIV) infections globally in 2023.[43] Various pre-exposure prophylactics have been found to be effective for HIV, ranging from pills to long-acting formulations such as injectable cabotegravir and lenacapavir[44-46], although real-world implementation and effectiveness of such interventions across populations not represented in clinical trials are still needed[47]. However, this will not be possible in resource-limited countries in the Global South that do not have national health data systems

unless such interventions are conducted within research sites, using clinical trials infrastructure by teams already running clinical trials.

A common drawback of vaccine effectiveness studies is the lack of random assignment of individuals to vaccination, which exacerbates selection bias due to potential differential key characteristics between vaccinated and unvaccinated individuals and also between cases and controls. Therefore, complete data on these characteristics are necessary to enable robust (less biased) and near valid vaccine effectiveness estimates.

In the Sisonke study, self-reported HIV prevalence obtained from the electronic vaccination data system was 8.3%, compared with 16.3% obtained from medical insurance data – about a twofold difference.[15] Further considering the high burden of undiagnosed disease among men and women in LMICs[48], this indicates a large misclassification of participants due to potential underreporting of comorbidities. Medical insurance data allowed for complete adjustment for effect modifiers, confounders and stratification (sub-group) analyses at the expense of utilising half the Sisonke cohort.

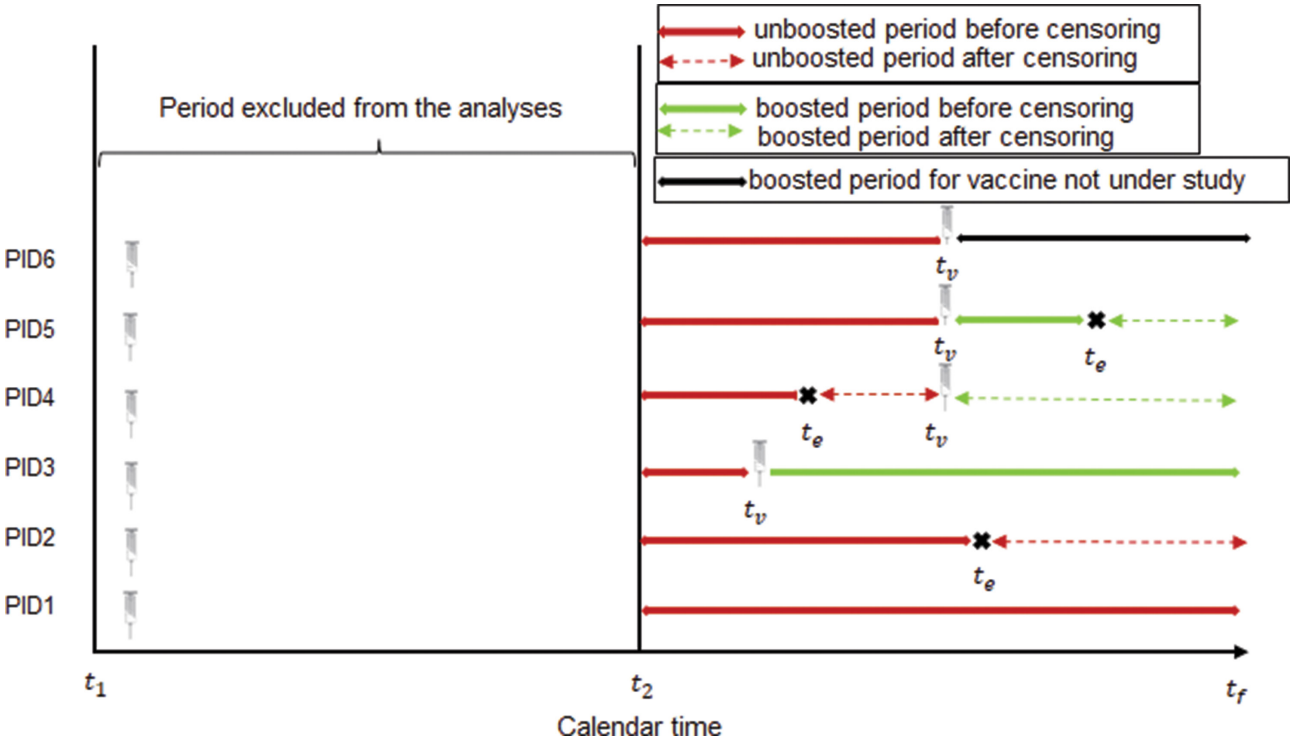
Despite recommendations from the WHO to conduct test-negative case-control studies in LMICs to assess vaccine effectiveness against severe and symptomatic COVID-19, this approach was not always feasible in our setting. In the Sisonke study, conducting a matched cohort study was the next viable approach. However, this approach was very resource intensive. The data set was extremely large with the total insured population in excess of two million, and tasks such as data manipulation, matching vaccinated and unvaccinated individuals, and creating bootstrap samples required advanced programming skills and high-performance computers. High-performance computers are essential because bootstrap sampling is computationally intensive; in our case, it took over 12 hours to complete.

It is worth mentioning that this type of sampling and analysis requires the services of well-trained biostatisticians, a specialised and scarce skill set that still needs capacity building in Africa.[49] While there are numerous initiatives to address the shortage and lack of local biostatistician capacity in the African setting[50], these initiatives need to be coupled with practical exposure or experience. Between 2010 and 2019, only 2% of clinical trials worldwide were set in sub-Saharan African countries.[51] The implications are clear: researchers in the African setting are not getting maximum exposure to groundbreaking research activities, including designing and analysing clinical trials.

Assessing relative effectiveness of boosters

As new information regarding the durability of vaccines emerged, booster vaccines were widely recommended, and the need to assess the relative effectiveness of booster vaccines emerged.

Robust measurement of the relative effectiveness of boosters in South Africa after the booster vaccine rollout at the end of 2021 was challenging due to the fewer number of patients admitted to hospital, less clinically severe illness, and a lower case-fatality ratio compared to the first three COVID-19 waves between May 2020 and September 2021.[52,53] This directly impacts the precision in booster vaccine effectiveness, which is a function of the number of events. Crucially, assessing booster effectiveness requires accurate and complete documentation of vaccine records, allowing endpoints and supporting data to be linked to the correct vaccination episode. This complexity makes it challenging to design cohort or test-negative case-control studies.



t_1, date of primary dose receipt; t_2, earliest date of the booster dose (i.e. date when individuals were eligible to get a booster dose); t_f, end of study follow-up; t_v, booster vaccine administration date; t_e, endpoint date

PID1: An unboosted individual who did not experience an event during follow-up. Unboosted person-time begins from the date when individuals were eligible to receive the booster (t_2) to the end of follow-up (t_f).

PID2: An unboosted individual who experienced an event. Unboosted person-time begins from t_2 to event date (t_e).

PID3: A boosted individual who did not experience an event. Person-time will be separated into (i) unboosted from t_2 to booster dose receipt date (t_v) and (ii) boosted from t_v +14 days to t_f.

PID4: A boosted individual who experienced an event before boosting. Unboosted person-time begins from t_2 to t_e. Exposure time after boosting will be excluded from the analyses.

PID5: A boosted individual who experienced an event after boosting. Person-time will be separated into (i) unboosted from t_2 to t_v and (ii) boosted from t_v+14 days to t_e.

PID6: An individual who received a booster not under study. Unboosted person-time begins from t_2 to t_v.

Note: The period between t_1 and t_2 is excluded from the analyses.

Figure 2: Illustration of exposure time and the timing of events before and after boosting using pseudo individual identifiers (PID).

As a result, an alternative statistical approach that allows for vaccination status per individual to vary over time has been used to assess COVID-19 booster vaccine effectiveness.[54-61] This approach enables studying multiple boosters, whether they are homologous or heterologous. This approach is achieved by modelling the time-varying vaccination status as an exposure variable while adjusting for potential confounders in a Cox proportional hazards regression model (Equation 1). Time-varying exposures are common in survival analyses, making this valid approach easy to implement in standard software packages.

The hazard function is given by:

$$h\left(t \mid Z_i(t), PV, X_{i.}\ M_i(t),\right) = h_0(t)\ \exp\left(\beta_1 Z_i(t) + \beta_2 PV_i + \beta_3 X_i^T + \beta_4 M_i^T(t)\right) \quad \text{Equation 1}$$

for $i = 1, \ldots, n$ individuals. $Z_i(t)$ represents the boost indicator, which is a time-varying covariate which takes a value of 0 before the boost and a value of 1 or 2 when the time is 14 or more days after the first or second boost, respectively. Here, heterologous and homologous boosting can be assessed together. X_i represents a vector of time-fixed covariates and $M_i(t)$ represents a vector of time-varying covariates. PV is the standardised time since prime vaccination (i.e. first or primary dose of any vaccine) defined as *P- min (P)*, where *min(P)* is the time since the prime dose for someone who had the shortest time since the primary dose.

For ease of illustration, see Figure 2, where individuals start from the unboosted period and cross over to the booster period provided they receive a booster that is under study. Figure 2 is based on a vaccine regime where an individual is considered fully vaccinated after receiving one dose (e.g. Ad26.COV2.S vaccine).

Calendar time is used instead of time to event scale where exposure time is calculated from the official date when individuals are eligible to receive boosters (i.e. time t_2). This is intuitive for analyses of vaccines for some infectious diseases, as risk can vary substantially over time. This phenomenon was observed between 2020 and 2022 when COVID-19 epidemic waves resulted in high rates of SARS-CoV-2 infection and hospital admissions, and this varied across different variants of concerns.[52,53] Through a simulation study, it was shown that using calendar time yielded less-biased estimates when compared with analyses using time to event scale.[62] Again, this type of analysis requires the services of well-trained biostatisticians with expertise in advanced survival analysis. It is worth noting that this model can be applied to any type of effectiveness study in which the exposure varies over time, either by design or due to factors such as non-adherence, non-compliance or treatment switches.

Conclusion

Evaluating the effectiveness of biomedical interventions in resource-limited countries is challenging due to the lack of integrated national healthcare data systems, limited biostatistics capacity and availability of high-performance computing resources.

The consequences of this are clearly evident from the fewer COVID-19 vaccine effectiveness studies for both prime and booster vaccines conducted in the African region and countries in the Global South.

Despite the WHO AFRO region's implementation of a multilayered coordination mechanism to manage the COVID-19 pandemic, challenges remain. In the absence of national health data systems, it will be difficult to monitor future pandemics or generate data-driven evidence on their impact. Most importantly, epidemiology, statistics, data science, mathematical modelling and data management capacity should continuously be strengthened to ensure that advanced and novel analytical tools are readily available, not only for pandemics, but also for enhancing everyday research endeavours in Africa.

Acknowledgements

We thank the healthcare workers who participated in the Sisonke study, the clinical research site investigators and the study staff. We also acknowledge the Sisonke study principal investigators, co-investigators and all the researchers and collaborators who were part of the Sisonke project. We thank the data and analytical teams at different medical aid schemes for supporting our endeavours when we were designing the Sisonke study.

Funding

The Sisonke study was funded by the National Treasury of South Africa, the National Department of Health, Solidarity Response Fund NPC, The Michael & Susan Dell Foundation, The Elma Vaccines and Immunization Foundation, and the Bill and Melinda Gates Foundation.

Data availability

There are no data pertaining to this article.

Declarations

We have no competing interests to declare. We have no AI or LLM use to declare.

Authors' contributions

N.Y-Z.: Conceptualisation, methodology, writing – original draft, writing – review and editing. T.R.: Conceptualisation, methodology, writing – review and editing. Both authors read and approved the final manuscript.

References

1. Cucinotta D, Vanelli M. WHO declares COVID-19 a pandemic. Acta Biomed. 2020;91(1):157–160. https://doi.org/10.23750/abm.v91i1.9397
2. Anderson EJ, Rouphael NG, Widge AT, Jackson LA, Roberts PC, Makhene M, et al. Safety and immunogenicity of SARS-CoV-2 mRNA-1273 vaccine in older adults. N Engl J Med. 2020;383(25):2427–2438. https://doi.org/10.1056/NEJMoa2028436
3. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: An interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. Lancet. 2021;397(10269):99–111. https://doi.org/10.1016/s0140-6736(20)32661-1
4. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. N Engl J Med. 2020;383(27):2603–2615. https://doi.org/10.1056/NEJMoa2034577
5. Sadoff J, Gray G, Vandebosch A, Cardenas V, Shukarev G, Grinsztejn B, et al. Safety and efficacy of single-dose Ad26.COV2.S vaccine against Covid-19. N Engl J Med. 2021;384(23):2187–2201. https://doi.org/10.1056/NEJMoa2101544
6. Sadoff J, Gray G, Vandebosch A, Cárdenas V, Shukarev G, Grinsztejn B, et al. Final analysis of efficacy and safety of single-dose Ad26.COV2.S. N Engl J Med. 2022;386(9):847–860. https://doi.org/10.1056/NEJMoa2117608
7. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. N Engl J Med. 2021;384(5):403–416. https://doi.org/10.1056/NEJMoa2035389
8. World Health Organization (WHO). WHO SAGE values framework for the allocation and prioritization of COVID-19 vaccination, 14 September 2020. Geneva: WHO; 2020. https://apps.who.int/iris/handle/10665/334299
9. Faksova K, Walsh D, Jiang Y, Griffin J, Phillips A, Gentile A, et al. COVID-19 vaccines and adverse events of special interest: A multinational Global Vaccine Data Network (GVDN) cohort study of 99 million vaccinated individuals. Vaccine. 2024;42(9):2200–2211. https://doi.org/10.1016/j.vaccine.2024.01.100
10. Griffith GJ, Morris TT, Tudball MJ, Herbert A, Mancano G, Pike L, et al. Collider bias undermines our understanding of COVID-19 disease risk and severity. Nat Commun. 2020;11(1), Art. #5749. https://doi.org/10.1038/s41467-020-19478-2
11. Hernán MA, Hernández-Díaz S, Robins JM. A structural approach to selection bias. Epidemiology. 2004;15(5):615–625. https://doi.org/10.1097/01.ede.0000135174.63482.43
12. World Health Organization (WHO). Evaluation of COVID-19 vaccine effectiveness: Interim guidance, 17 March 2021. Geneva: WHO; 2021. https://apps.who.int/iris/handle/10665/340301
13. International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub [homepage on the Internet]. No date [cited 2022 Sep 11]. Available from: www.view-hub.org

14. Raji T, Fallah MP, Dereje N, Kakooza F, Ndembi N, Abdulaziz M, et al. Efficacy and effectiveness of COVID-19 vaccines in Africa: A systematic review. PLoS One. 2024;19(6), e0306309. https://doi.org/10.1371/journal.pone.0306309

15. Bekker LG, Garrett N, Goga A, Fairall L, Reddy T, Yende-Zuma N, et al. Effectiveness of the Ad26.COV2.S vaccine in health-care workers in South Africa (the Sisonke study): Results from a single-arm, open-label, phase 3B, implementation study. Lancet. 2022;399(10330):1141–1153. https://doi.org/10.1016/S0140-6736(22)00007-1

16. Gray G, Collie S, Goga A, Garrett N, Champion J, Seocharan I, et al. Effectiveness of Ad26.COV2.S and BNT162b2 vaccines against Omicron variant in South Africa. N Engl J Med. 2022;386(23):2243–2245. https://doi.org/10.1056/NEJMc2202061

17. Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 vaccine against Omicron variant in South Africa. N Engl J Med. 2022;386(5):494–496. https://doi.org/10.1056/NEJMc2119270

18. Collie S, Nayager J, Bamford L, Bekker LG, Zylstra M, Gray G. Effectiveness and durability of the BNT162b2 vaccine against Omicron sublineages in South Africa. N Engl J Med. 2022;387(14):1332–1333. https://doi.org/10.1056/NEJMc2210093

19. Collie S, Saggers RT, Bandini R, Steenkamp L, Champion J, Gray G, et al. Association between regular physical activity and the protective effect of vaccination against SARS-CoV-2 in a South African case–control study. Br J Sports Med. 2023;57(4):205–211. https://doi.org/10.1136/bjsports-2022-105734

20. Simwanza J, Hines JZ, Sinyange D, Sinyange N, Mulenga C, Hanyinza S, et al. COVID-19 vaccine effectiveness during a prison outbreak when Omicron was the dominant circulating variant – Zambia, December 2021. Am J Trop Med Hyg. 2022;107(5):1055–1059. https://doi.org/10.4269/ajtmh.22-0368

21. Chanda D, Hines JZ, Itoh M, Fwoloshi S, Minchella PA, Zyambo KD, et al. COVID-19 vaccine effectiveness against progression to in-hospital mortality in Zambia, 2021–2022. Open Forum Infect Dis. 2022;9(9), Art. #ofac469. https://doi.org/10.1093/ofid/ofac469

22. Ngoy N, Oyugi B, Ouma PO, Conteh IN, Woldetsadik SF, Nanyunja M, et al. Coordination mechanisms for COVID-19 in the WHO Regional office for Africa. BMC Health Serv Res. 2022;22(1), Art. #711. https://doi.org/10.1186/s12913-022-08035-w

23. Malakoane B, Heunis JC, Chikobvu P, Kigozi NG, Kruger WH. Public health system challenges in the Free State, South Africa: A situation appraisal to inform health system strengthening. BMC Health Serv Res. 2020;20(1), Art. #58. https://doi.org/10.1186/s12913-019-4862-y

24. Skowronski DM, Masaro C, Kwindt TL, Mak A, Petric M, Li Y, et al. Estimating vaccine effectiveness against laboratory-confirmed influenza using a sentinel physician network: Results from the 2005–2006 season of dual A and B vaccine mismatch in Canada. Vaccine. 2007;25(15):2842–2851. https://doi.org/10.1016/j.vaccine.2006.10.002

25. Lopez Bernal J, Andrews N, Gower C, Robertson C, Stowe J, Tessier E, et al. Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on covid-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. BMJ. 2021;373, Art. #n1088. https://doi.org/10.1136/bmj.n1088

26. Hitchings MDT, Ranzani OT, Torres MSS, de Oliveira SB, Almiron M, Said R, et al. Effectiveness of CoronaVac among healthcare workers in the setting of high SARS-CoV-2 Gamma variant transmission in Manaus, Brazil: A test-negative case-control study. Lancet Reg Health Am. 2021;1, Art. #100025. https://doi.org/10.1016/j.lana.2021.100025

27. Chung H, He S, Nasreen S, Sundaram ME, Buchan SA, Wilson SE, et al. Effectiveness of BNT162b2 and mRNA-1273 covid-19 vaccines against symptomatic SARS-CoV-2 infection and severe covid-19 outcomes in Ontario, Canada: Test negative design study. BMJ. 2021;374, Art. #n1943. https://doi.org/10.1136/bmj.n1943

28. Abu-Raddad LJ, Chemaitelly H, Butt AA. Effectiveness of the BNT162b2 Covid-19 vaccine against the B.1.1.7 and B.1.351 variants. N Engl J Med. 2021;385(2):187–189. https://doi.org/10.1056/NEJMc2104974

29. Thompson MG, Stenehjem E, Grannis S, Ball SW, Naleway AL, Ong TC, et al. Effectiveness of Covid-19 vaccines in ambulatory and inpatient care settings. N Engl J Med. 2021;385(15):1355–1371. https://doi.org/10.1056/NEJMoa2110362

30. Zhang Y, Belayachi J, Yang Y, Fu Q, Rodewald L, Li H, et al. Real-world study of the effectiveness of BBIBP-CorV (Sinopharm) COVID-19 vaccine in the Kingdom of Morocco. BMC Public Health. 2022;22(1), Art. #1584. https://doi.org/10.1186/s12889-022-14016-9

31. Dagan N, Barda N, Biron-Shental T, Makov-Assif M, Key C, Kohane IS, et al. Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy. Nat Med. 2021;27(10):1693–1695. https://doi.org/10.1038/s41591-021-01490-8

32. Polinski JM, Weckstein AR, Batech M, Kabelac C, Kamath T, Harvey R, et al. Durability of the single-dose Ad26.COV2.S vaccine in the prevention of COVID-19 infections and hospitalizations in the US before and during the Delta variant surge. JAMA Netw Open. 2022;5(3), e222959. https://doi.org/10.1001/jamanetworkopen.2022.2959

33. Thompson MG, Burgess JL, Naleway AL, Tyner H, Yoon SK, Meece J, et al. Prevention and attenuation of Covid-19 with the BNT162b2 and mRNA-1273 vaccines. N Engl J Med. 2021;385(4):320–329. https://doi.org/10.1056/NEJMoa2107058

34. Huang Z, Xu S, Liu J, Wu L, Qiu J, Wang N, et al. Effectiveness of inactivated and Ad5-nCoV COVID-19 vaccines against SARS-CoV-2 Omicron BA.2 variant infection, severe illness, and death. BMC Med. 2022;20(1):400. https://doi.org/10.1186/s12916-022-02606-8

35. Eick-Cost AA, Ying S, Wells N. Effectiveness of mRNA-1273, BNT162b2, and JNJ-78436735 COVID-19 vaccines among US military personnel before and during the predominance of the Delta variant. JAMA Netw Open. 2022;5(4), e228071. https://doi.org/10.1001/jamanetworkopen.2022.8071

36. Verani JR, Baqui AH, Broome CV, Cherian T, Cohen C, Farrar JL, et al. Case-control vaccine effectiveness studies: Preparation, design, and enrollment of cases and controls. Vaccine. 2017;35(25):3295–3302. https://doi.org/10.1016/j.vaccine.2017.04.037

37. Lewnard JA, Patel MM, Jewell NP, Verani JR, Kobayashi M, Tenforde MW, et al. Theoretical framework for retrospective studies of the effectiveness of SARS-CoV-2 vaccines. Epidemiology. 2021;32(4):508–517. https://doi.org/10.1097/ede.0000000000001366

38. Wolter N, Jassat W, Walaza S, Welch R, Moultrie H, Groome M, et al. Early assessment of the clinical severity of the SARS-CoV-2 Omicron variant in South Africa: A data linkage study. Lancet. 2022;399(10323):437–446. https://doi.org/10.1016/s0140-6736(22)00017-4

39. Goudge J, Alaba OA, Govender V, Harris B, Nxumalo N, Chersich MF. Social health insurance contributes to universal coverage in South Africa, but generates inequities: Survey among members of a government employee insurance scheme. Int J Equity Health. 2018;17(1), Art. #1. https://doi.org/10.1186/s12939-017-0710-z

40. Mannie C, Kharrazi H. Assessing the geographical distribution of comorbidity among commercially insured individuals in South Africa. BMC Public Health. 2020;20(1), Art. #1709. https://doi.org/10.1186/s12889-020-09771-6

41. Boulle A, Heekes A, Tiffin N, Smith M, Mutemaringa T, Zinyakatira N, et al. Data centre profile: The Provincial Health Data Centre of the Western Cape Province, South Africa. Int J Popul Data Sci. 2019;4(2), Art. #1143. https://doi.org/10.23889/ijpds.v4i2.1143

42. Kassanjee R, Davies MA, Heekes A, Mahomed H, Hawkridge AJ, Morden E, et al. COVID-19 vaccine uptake and effectiveness by time since vaccination in the Western Cape Province, South Africa: An observational cohort study during 2020–2022. Vaccines. 2024;12(6), Art. #628. https://doi.org/10.3390/vaccines12060628

43. World Health Organization (WHO). Global Health Observatory data [webpage on the Internet]. No date [cited 2025 May 10]. Available from: https://www.who.int/data/gho/data/indicators/indicator-details/GHO/number-of-new-hiv-infections

44. Bekker LG, Das M, Abdool Karim Q, Ahmed K, Batting J, Brumskine W, et al. Twice-yearly lenacapavir or daily F/TAF for HIV prevention in cisgender women. N Engl J Med. 2024;391(13):1179–1192. https://doi.org/10.1056/NEJMoa2407001

45. Delany-Moretlwe S, Hughes JP, Bock P, Ouma SG, Hunidzarira P, Kalonji D, et al. Cabotegravir for the prevention of HIV-1 in women: Results from HPTN 084, a phase 3, randomised clinical trial. Lancet. 2022;399(10337):1779–1789. https://doi.org/10.1016/S0140-6736(22)00538-4

46. Landovitz RJ, Donnell D, Clement ME, Hanscom B, Cottle L, Coelho L, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med. 2021;385(7):595–608. https://doi.org/10.1056/NEJMoa2101016

47. Fonner VA, Ridgeway K, van der Straten A, Lorenzetti L, Dinh N, Rodolph M, et al. Safety and efficacy of long-acting injectable cabotegravir as preexposure prophylaxis to prevent HIV acquisition. AIDS. 2023;37(6):957–966. https://doi.org/10.1097/qad.0000000000003494

48. Wong EB, Olivier S, Gunda R, Koole O, Surujdeen A, Gareta D, et al. Convergence of infectious and non-communicable disease epidemics in rural South Africa: A cross-sectional, population-based multimorbidity study. Lancet Glob Health. 2021;9(7):e967–e976. https://doi.org/10.1016/S2214-109X(21)00176-5

49. Machekano R, Young T, Rusakaniko S, Musonda P, Sartorius B, Todd J, et al. The Africa Center for Biostatistical Excellence: A proposal for enhancing biostatistics capacity for sub-Saharan Africa. Stat Med. 2015;34(27):3481–3489. https://doi.org/10.1002/sim.6572

50. Chirwa TF, Matsena Zingoni Z, Munyewende P, Manda SO, Mwambi H, Kandala NB, et al. Developing excellence in biostatistics leadership, training and science in Africa: How the Sub-Saharan Africa Consortium for Advanced Biostatistics (SSACAB) training unites expertise to deliver excellence. AAS Open Res. 2020;3, Art. #51. https://doi.org/10.12688/aasopenres.13144.2

51. Park JJH, Grais RF, Taljaard M, Nakimuli-Mpungu E, Jehan F, Nachega JB, et al. Urgently seeking efficiency and sustainability of clinical trials in global health. Lancet Glob Health. 2021;9(5):e681–e690. https://doi.org/10.1016/S2214-109X(20)30539-8

52. Jassat W, Abdool Karim SS, Mudara C, Welch R, Ozougwu L, Groome MJ, et al. Clinical severity of COVID-19 in patients admitted to hospital during the omicron wave in South Africa: A retrospective observational study. Lancet Glob Health. 2022;10(7):e961–e969. https://doi.org/10.1016/S2214-109X(22)00114-0

53. Jassat W, Abdool Karim SS, Ozougwu L, Welch R, Mudara C, Masha M, et al. Trends in cases, hospitalizations, and mortality related to the Omicron BA.4/BA.5 subvariants in South Africa. Clin Infect Dis. 2023;76(8):1468–1475. https://doi.org/10.1093/cid/ciac921

54. Fintzi J, Follmann D. Assessing vaccine durability in randomized trials following placebo crossover. Stat Med. 2021;40(27):5983–6007. https://doi.org/10.1002/sim.9001

55. Berec L, Šmíd M, Přibylová L, Májek O, Pavlík T, Jarkovský J, et al. Protection provided by vaccination, booster doses and previous infection against covid-19 infection, hospitalisation or death over time in Czechia. PLoS One. 2022;17(7), e0270801. https://doi.org/10.1371/journal.pone.0270801

56. Šmíd M, Berec L, Přibylová L, Májek O, Pavlík T, Jarkovský J, et al. Protection by vaccines and previous infection against the Omicron variant of severe acute respiratory syndrome coronavirus 2. J Infect Dis. 2022;226(8):1385–1390. https://doi.org/10.1093/infdis/jiac161

57. Bar-On YM, Goldberg Y, Mandel M, Bodenheimer O, Freedman L, Kalkstein N, et al. Protection of BNT162b2 vaccine booster against Covid-19 in Israel. New Engl J Med. 2021;385(15):1393–1400. https://doi.org/10.1056/NEJMoa2114255

58. Jara A, Cuadrado C, Undurraga EA, García C, Nájera M, Bertoglia MP, et al. Effectiveness of the second COVID-19 booster against Omicron: A large-scale cohort study in Chile. Nat Commun. 2023;14(1), Art. #6836. https://doi.org/10.1038/s41467-023-41942-y

59. Jara A, Undurraga EA, González C, Paredes F, Fontecilla T, Jara G, et al. Effectiveness of an inactivated SARS-CoV-2 vaccine in Chile. N Engl J Med. 2021;385(10):875–884. https://doi.org/10.1056/NEJMoa2107715

60. Santos CVBD, Valiati NCM, Noronha TG, Porto VBG, Pacheco AG, Freitas LP, et al. The effectiveness of COVID-19 vaccines against severe cases and deaths in Brazil from 2021 to 2022: A registry-based study. Lancet Reg Health Am. 2023;20, Art. #100465. https://doi.org/10.1016/j.lana.2023.100465

61. Garrett N, Reddy T, Yende-Zuma N, Takalani A, Woeber K, Bodenstein A, et al. Safety, effectiveness and immunogenicity of heterologous mRNA-1273 boost after prime with Ad26.COV2.S among healthcare workers in South Africa: The single-arm, open-label, phase 3 SHERPA study. PLOS Glob Public Health. 2024;4(12), e0003260. https://doi.org/10.1371/journal.pgph.0003260

62. Lund LC, Støvring H, Pottegård A, Andersen M, Hallas J. Cox regression using a calendar time scale was unbiased in simulations of COVID-19 vaccine effectiveness & safety. J Clin Epidemiol. 2023;156:127–136. https://doi.org/10.1016/j.jclinepi.2023.02.012