The “lickety-split” development of COVID-19 vaccines 326 days from when the SARS-COV-2 virus was first sequenced is indeed one of the public health successes of the 21st century. Particularly because an 18-month target was initially considered reasonable, and having achieved this success, a “moonshot” goal to ensure that a vaccine is available within 100 days after the next pandemic pathogen is recognized has been set [1].

The vaccine efficacy outcome in clinical trials is evaluated as the level of protection conferred on individuals against the target disease under “controlled conditions”, while vaccine effectiveness (VE) assesses vaccine performance in “real-world settings”. Given the contrasting epidemiology of COVID-19 especially in terms of health outcomes globally, it is essential to systematically collect and analyse VE data to provide evidence to guide context-specific policies for the COVID-19 response, including the vaccination programme. This is particularly relevant in engendering trust in many African countries such as Nigeria that were not included in the initial trials that established the efficacy of the COVID-19 vaccine (Figure 1).

In this commentary, we highlight the importance of undertaking locally designed COVID-19 VE studies in Nigeria, offer a review of current efforts to coordinate such studies and summarize the initial operational considerations in implementing these studies in Nigeria.
IMPLEMENTING THE COVID-19 VACCINE EFFECTIVENESS STUDY IN NIGERIA

As part of the national public health response to COVID-19, Nigeria began vaccine rollout in March 2021, about a year after the country reported its index case. Owing to the need for tailored evidence on VE in the country to guide policy and practice, the Nigeria Centre for Disease Control (NCDC) commenced plans to implement a study titled, “The Evaluation of COVID-19 Vaccine Effectiveness in Preventing Severe COVID-19 Disease among Adults in Nigeria” in February 2021. This NCDC-led study was designed as a multi-institutional collaboration with other governmental, non-governmental, and academic/research institutions, including the National Primary Health Care Development Agency, National Agency for Food and Drug Administration and Control, World Health Organisation (WHO), Joint United Nations Programme on HIV/AIDS, Africa Field Epidemiology Network, Nigeria COVID-19 Research Coalition (NCRC), and a network of tertiary health facilities managing COVID-19 cases as the study implementation sites.

The primary aim of this study is to evaluate the post-introduction effectiveness of a complete schedule of SARS-CoV-2 vaccines among adults in Nigeria against severe COVID-19, using a test-negative case-control (TNCC) design. The study will estimate VE in preventing severe COVID-19 disease by vaccine type, number of vaccine doses received, identifiable target cohorts (subgroups of comorbidity, history of previous COVID-19 infection, etc.), time since vaccination, and viral strain. The TNCC study design is commonly used in estimating the VE of Influenza vaccines, and it is now being increasingly used in COVID-19 VE studies [2-6].

Adaptation of global study protocols for health research is a common practice in Africa because it allows for standardisation and facilitates comparison of results/outcomes [7]. The development of this study protocol was guided by the WHO’s guideline on the evaluation of COVID-19 VE and the minimum sample size (890
This commentary highlights the importance of undertaking locally designed COVID-19 vaccine effectiveness studies in Nigeria, offers a review of current efforts to coordinate such studies, and summarizes the initial operational considerations.

A detailed exposition of the various COVID-19 VE strategies and research being conducted globally has been recently published by the WHO [10]. The TNCC was used in 142 out of the 1161 listed studies. So far, 6 studies have been conducted in sub-Saharan Africa, a third of them adopted the TNCC study design. For our study in Nigeria, recruitment of study participants began in September 2021 across 5 geopolitical zones, with a planned spread across all 6 geopolitical zones to ensure national representativeness (Figure 2).

IMPLEMENTATION REALITIES IN THE NIGERIAN CONTEXT: LESSONS FOR SCIENCE

Low COVID-19 mortality and morbidity

Nigeria has experienced relatively low morbidity and mortality of COVID-19, compared with the majority of countries in the world (particularly the global north) [10]. As of April 2022, Nigeria had reported about 255,500 cases of the disease, with a test positivity rate of about 5% and a mortality rate of less than 1.3% [11]. However, SARS-CoV-2 seroprevalence data indicate significantly higher exposure and transmission in parts of Nigeria in the first eight months of the COVID-19 epidemic in Nigeria with seroprevalence ranging from 9.3% (95% CI = 7.0–11.5) in Gombe in the north-east to 25.2% (95% CI = 21.8–28.6) in Enugu in the southeast. SARS-CoV-2 antibody prevalence suggests infections exceeded reported cases by 134:1 and 1211:1 in Gombe and Nasarawa, respectively [12]. This is in tandem with similar reports from across the world, i.e., COVID-19 cases numbers are underreported [13].
These realities have an impact on the implementation of VE studies in the country. Low testing rates and the consequent underreporting of cases reduce the pool of individuals who may be identified as eligible to participate in the study when using a TNCC study design. The ensuing challenge is that the minimum sample size may not be reached within the set timeline for the study, and lower sample size will negatively impact the statistical power of the study and/or precision of the measure of effect.

Low vaccination coverage
According to the initial vaccination plan, 40% of Nigerians would have been vaccinated by the end of 2021 [14]. As of April 2022, however, 17.3% and 11.5% of the eligible population have received at least one and two doses respectively of the COVID-19 vaccine [15]. Ideally, VE studies should be implemented soon as vaccination is rolled out. Despite obtaining ethical approval to begin the study in February 2021, study implementation (participant recruitment) did not begin until September 2021 due to the limited availability of vaccines in the country and the consequent low vaccination coverage. Poor vaccination coverage reduces the feasibility of conducting VE evaluations of infection and transmission and may be overcome by the use of adaptive designs in evaluating VE in settings [9].

Mixing of vaccine brands and introduction of vaccine booster doses
In the face of an evolving understanding of the immunogenicity of COVID-19 vaccines, Nigeria introduced booster doses in December 2021 with a schedule that inevitably implies the mixing of vaccine brands. This inadvertently limits our ability to infer attribution of VE to a single brand but rather to the omnibus of available vaccines. More detailed analytical designs such as pre-and-post immunological studies would otherwise be required to isolate individual benefits of vaccine brands.

Building bridges across silos in the conduct of COVID-19 vaccine effectiveness studies
Disparate groups are conducting COVID-19 VE and safety studies in the country. Considering the resource-intensive nature of these studies, this approach may result in duplicated efforts and inefficiency. Under good leadership and coordination, building bridges to link silos in this research subject could lead to improved effectiveness and efficiency in the conduct of COVID-19 VE research in the country.

Consequently, the NCDC is supporting the NCRC in mapping COVID-19 Vaccine Safety and Effectiveness studies being planned or ongoing in the country, to form a national research coordinating team for COVID-19 VE studies in Nigeria. A consultative meeting was held in the latter half of 2021. The meeting had in attendance representatives from key governmental agencies, researchers from more than 20 institutions, and potential local and international funders. Over the next few months, the national research coordinating team plans to facilitate the harmonization of indigenous study protocols, develop a master protocol for research conduct, and actively seek opportunities to fund nationally representative research.

CONCLUSION
Studying the effectiveness of COVID-19 vaccination in Nigeria presents an essential, but substantial and complex research undertaking. The low COVID-19 hospitalisation and mortality rates, despite the low vaccine coverage rate and resource limitations in the country, raise questions on the value of assessing VE in this setting. However, we find value in assessing VE in Nigeria, particularly in this scenario where COVID-19 vaccine trials were not conducted in-country. The results will contribute to demand creation, and further guide policy and programming around COVID-19 in Nigeria, particularly in addressing the increasing threat of vaccine hesitancy to vaccination uptake. Thus, we recommend the development of unified/master study protocols based on the realities in the continent and the implementation of research priorities in a country with limited resources.

Several studies have shown the effectiveness of COVID-19 vaccines in reducing morbidity and mortality from the disease [16,17]. Routinely reported case data from COVID-19 surveillance in Nigeria also suggests this. Scientific evidence has also demonstrated the cost-saving and cost-effectiveness of COVID-19 vaccination compared with no vaccination across diverse contextual settings [18-20]. Plagued with recurrent outbreaks of infectious diseases and an increasing burden of non-communicable diseases, Nigeria grapples with competing health research needs that require significant resource allocation. Thus, implementing low-cost routine passive surveillance activities that assess the effectiveness of COVID-19 vaccination beyond one-off analytical
investigations may be a better option. Finally, we call on the NCDC to use its convening role to create coalitions among currently disparate groups conducting COVID-19 vaccine safety and effectiveness research in the country, for broader national relevance and efficient use of scarce resources.

Acknowledgements: We appreciate all the local and international partners who contributed to the development and implementation of this study protocol, specifically the Nigeria country offices of the WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS). We specially appreciate the former Director General of the NCDC, Dr Chikwe Ihekweazu who initiated and supported the conceptualisation of the NCDC-led study. We acknowledge the significant contribution of members of the implementation team at all study sites and members of the Epidemiology Studies Working Group of the Nigeria COVID-19 Research Coalition. In addition, we are grateful to colleagues who provided technical and administrative support for the implementation of this study.

Funding: This paper was not funded by any institution or department.

Authorship contributions: EUI conceived the idea for the paper. OWA wrote the first draft of the manuscript. EUI, CLO and IMA played supervisory roles. All authors critically reviewed, revised, and approved the final draft of the manuscript.

Disclosure of interest: The authors completed the ICMJE Disclosure of Interest Form (available upon request from the corresponding author) and declare no conflicts of interest.

REFERENCES

1. The Global Pandemic Preparedness Summit. On the road to 100-Day vaccines. Available: https://cepi.net/news_cepi/the-global-pandemic-preparedness-summit-on-the-road-to-100-day-vaccines/. Accessed: 6 April 2022.
2. Yildirim I, Kao CM, Tippett A, Suntarattiwong P, Munye M, Yi J, et al. A Retrospective Test-Negative Case-Control Study to Evaluate Influenza Vaccine Effectiveness in Preventing Hospitalizations in Children. Clin Infect Dis. 2021;73:1759-67. Medline:3410341 doi:10.1093/cid/cab709
3. Shi M, An Q, Ainslie KEC, Haber M, Orenstein WA. A comparison of the test-negative and the traditional case-control study designs for estimation of influenza vaccine effectiveness under nonrandom vaccination. BMC Infect Dis. 2017;17:757. Medline:34496195 doi:10.1056/NEJMe2113151
4. Dean NE, Hogan JW, Schnitzer ME. Covid-19 Vaccine Effectiveness and the Test-Negative Design. N Engl J Med. 2021;385:1431-3. Medline:34496195 doi:10.1056/NEJMe2113151
5. 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;385:1355-71. Medline:34496195 doi:10.1056/NEJMe2113151
6. Hyams C, Marlow R, Maseko Z, King J, Ward L, Fox K, et al. Effectiveness of BNT162b2 and ChAdOx1 nCoV-19 COVID-19 vaccination at preventing hospitalisations in people aged at least 80 years: a test-negative, case-control study. Lancet Infect Dis. 2021;21:1539-48. Medline:34174190 doi:10.1016/S1473-3099(21)00330-3
7. Vischer N, Pfeiffer C, Kealy J, Burri C. Increasing protocol suitability for clinical trials in sub-Saharan Africa: a mixed methods study. Glob Health Res Policy. 2017;2:11. Medline:29202079 doi:10.1186/s41256-017-0033-1
8. O’Neill RT. On sample sizes to estimate the protective efficacy of a vaccine. Stat Med. 1988;7:1279-88. Medline:3231951 doi:10.1002/sm.1478071208
9. World Health Organization. Evaluation of COVID-19 vaccine effectiveness: Interim Guidance. 17 Mar 2021. Available: https://www.who.int/publications-detail-redirect/WHO-2019-nCoV-vaccine_effectiveness-measurement-2021.1. Accessed: 30 January 2022.
10. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Available: https://covid19.who.int. Accessed: 14 April 2022.
11. Nigeria Centre for Disease Control. COVID-19 Nigeria. 2022. Available: https://covid19.ncdc.gov.ng/. Accessed: 14 April 2022.
12. Nigeria Centre for Disease Control. NCDC and NIMR Release Findings of COVID-19 Household Seroprevalence Surveys in Four States of Nigeria. Available: https://ncdc.gov.ng/news/213/ncdc-and-nimr-release-findings-of-covid-19-household-seroprevalence-surveys-in-four-states-of-nigeria. Accessed: 14 April 2022.
13. Albani V, Loria J, Massad E, Zubelli J. COVID-19 underreporting and its impact on vaccination strategies. BMC Infect Dis. 2021;21:1111. Medline:34771190 doi:10.1186/s12879-021-06780-7
14. Osae-Brown A, Cranny M. Africa News: Nigeria Plans Covid-19 Vaccination For 40% of Population in 2021. Available: https://www.bloomberg.com/news/articles/2021-01-14/nigeria-plans-covid-19-vaccination-for-40-of-population-in-2021. Accessed: 14 April 2022.
15. National Primary Health Care Development Agency. COVID-19 Vaccination Update. Available: https://nphcda.gov.ng/. Accessed: 14 April 2022.
16. Tang P, Hasan MR, Chemaitelly H, Yassine HM, Benslimane FM, Al Khatib HA, et al. BNT162b2 and mRNA-1273 COVID-19 vaccine effectiveness against the SARS-CoV-2 Delta variant in Qatar. Nat Med. 2021;27:2136-43. Medline:34728831 doi:10.1038/s41591-021-01383-4
17. Public Health England. Direct and indirect impact of the vaccination programme on COVID-19 infections and mortality. Available: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/997493/Impact_of_COVID-19_vaccine_on_infection_and_mortality.pdf. Accessed: 14 April 2022.
Pearson CAB, Bozzani F, Procter SR, Davies NG, Huda M, Jensen HT, et al. COVID-19 vaccination in Sindh Province, Pakistan: A modelling study of health impact and cost-effectiveness. PLoS Med. 2021;18:e1003815. Medline:34606520 doi:10.1371/journal.pmed.1003815

Debrabant K, Grønbæk L, Kronborg C. The Cost-Effectiveness of a COVID-19 Vaccine in a Danish Context. Clin Drug Investig. 2021;41:975-88. Medline:34623627 doi:10.1007/s40261-021-01085-8

Kohli M, Maschio M, Becker D, Weinstein MC. The potential public health and economic value of a hypothetical COVID-19 vaccine in the United States: Use of cost-effectiveness modeling to inform vaccination prioritization. Vaccine. 2021;39:1157-64. Medline:33483216 doi:10.1016/j.vaccine.2020.12.078

Correspondence to:
Oluwatosin Wuraola Akande MBBS, MPH, FMCPH
Department of Prevention Programmes and Knowledge Management
Nigeria Centre for Disease Control
Plot 801 Ebitu Ukiwe Street
Jabi
Abuja
Nigeria
akande.wuraola@gmail.com