



# BMJ Open COVID-19 vaccine effectiveness and variants in Nepal: study protocol for a test-negative case-control study with SARS-CoV-2 genetic sequencing

Sanjeev M Bijukchhe <sup>1,2</sup>, Peter J O'Reilly,<sup>1</sup> Katherine Theiss-Nyland,<sup>1</sup> Meeru Gurung,<sup>2</sup> Bhishma Pokhrel,<sup>2</sup> Sarah Kelly,<sup>1</sup> Samita Acharya,<sup>2</sup> Shreekrishna Maharjan,<sup>2</sup> Ashis Shrestha,<sup>2</sup> Bimal Pandey,<sup>2</sup> Mipsang Lama,<sup>2</sup> Ira Shrestha,<sup>2</sup> Merryn Voysey,<sup>1,3</sup> Agnes Eordogh,<sup>1</sup> Sonu Shrestha,<sup>1</sup> Elaine Shuo Feng,<sup>1</sup> Grace Li,<sup>1</sup> Ganesh Shah,<sup>2</sup> Andrew J Pollard <sup>1,3</sup>, Shrijana Shrestha<sup>2</sup>

**To cite:** Bijukchhe SM, O'Reilly PJ, Theiss-Nyland K, *et al.* COVID-19 vaccine effectiveness and variants in Nepal: study protocol for a test-negative case-control study with SARS-CoV-2 genetic sequencing. *BMJ Open* 2023;**13**:e068334. doi:10.1136/bmjopen-2022-068334

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2022-068334>).

SMB, PJO and KT-N contributed equally.

SMB, PJO and KT-N are joint first authors.

Received 14 September 2022  
Accepted 30 March 2023



© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Sanjeev M Bijukchhe;  
sanjeev.bijukchhe@st-hildas.ox.ac.uk

## ABSTRACT

**Introduction** Inactivated, viral vector and mRNA vaccines have been used in the Nepali COVID-19 vaccination programme but there is little evidence on the effectiveness of these vaccines in this setting. The aim of this study is to describe COVID-19 vaccine effectiveness in Nepal and provide information on infections with SARS-CoV-2 variants.

**Methods and analysis** This is a hospital-based, prospective test-negative case-control study conducted at Patan Hospital, Kathmandu. All patients >18 years of age presenting to Patan Hospital with COVID-19-like symptoms who have received a COVID-19 antigen/PCR test are eligible for inclusion. The primary outcome is vaccine effectiveness of licensed COVID-19 vaccines against laboratory-confirmed COVID-19 disease.

After enrolment, information will be collected on vaccine status, date of vaccination, type of vaccine, demographics and other medical comorbidities. The primary outcome of interest is laboratory-confirmed SARS-CoV-2 infection. Cases (positive for SARS-CoV-2) and controls (negative for SARS-CoV-2) will be enrolled in a 1:4 ratio. Vaccine effectiveness against COVID-19 disease will be analysed by comparing vaccination status with SARS-CoV-2 test results. Positive SARS-CoV-2 samples will be sequenced to identify circulating variants and estimate vaccine effectiveness against common variants.

Measuring vaccine effectiveness and identifying SARS-CoV-2 variants in Nepal will help to inform public health efforts. Describing disease severity in relation to specific SARS-CoV-2 variants and vaccine status will also inform future prevention and care efforts.

**Ethics and dissemination** Ethical approval was obtained from the University of Oxford Tropical Ethics Committee (OxTREC) (ref: 561-21) and the Patan Academy of Health Sciences Institutional Review Board (ref: drs2111121578). The protocol and supporting study documents were approved for use by the Nepal Health Research Council (NHRC 550-2021). Results will be disseminated in peer-reviewed journals and to the public health authorities in Nepal.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Test-negative case-control design is a low-cost technique, which has been used successfully in other vaccine effectiveness studies.
- ⇒ There are several COVID-19 vaccines currently being distributed to the Nepali population, which makes comparisons between vaccines possible.
- ⇒ Genetic sequencing of SARS-CoV-2 positive samples will provide information on vaccine effectiveness against different circulating SARS-CoV-2 strains.
- ⇒ Certain groups, for example, healthcare workers, were more likely to receive one vaccine over another which will make vaccine comparisons more complex.

## INTRODUCTION

Nepal detected its first COVID-19 case on 23 January 2020. On 4 April 2020, the first locally transmitted case was diagnosed.<sup>1,2</sup> Since then, the number of cases has increased dramatically, to hundreds of thousands of patients with over 11 000 deaths.<sup>3</sup> The Government of Nepal issued nationwide lockdowns in the first and second waves to reduce pressure on healthcare services. During the second wave, Nepal's Ministry of Health and Population reported B.1.617.2 to be the third variant found in the country after the B.1.1.7 variant and the original SARS-CoV-2 virus. The second wave resulted in much higher numbers of new cases and deaths, and the country faced a major health crisis with a shortage of oxygen and hospital beds.<sup>4</sup>

Despite difficulties in acquiring COVID-19 vaccines,<sup>5</sup> on 27 January, 2021, Nepal's government offered ChAdOx1 nCoV-19

vaccines to 438 000 people in high-risk groups—health workers, supporting staff at health facilities, community health volunteers, security personnel, sanitation workers, elderly people living in care homes and prisoners.<sup>6</sup> As of 9 May 2022, 12.5 million Covishield ChAdOx1 nCoV-19, 19.7 million Sinovac-Coronavac, 3.5 million Janssen Ad26.COV2.S, 0.6 million Pfizer BNT162b2, COVID-19 mRNA and 5.9 million Moderna mRNA-1273 vaccines have been administered in people aged >12 years of age.<sup>7</sup>

COVID-19 vaccines may perform differently in clinical trials versus real-world settings. There are several different reasons for this. Population genetics, underlying health conditions and general health may play a role in vaccine effectiveness (VE). Another important reason may be the emergence of new SARS-CoV-2 variants. In 2020, P.1, B.1.1.7, B.1.617.1 and B.1.351 variants were described. Each of those variants was distinctly different from the original SARS-CoV-2 strain.<sup>8</sup> Each new variant has the potential to cause more or less severe disease and to transmit more or less readily.

Likewise, COVID-19 vaccines may provide greater or lesser protection against each strain, both in terms of virus transmission and the severity of illness presenting. This has been noted with the ChAdOx1 nCoV-19 vaccine, for example, providing little protection against mild or moderate SARS-CoV-2 Beta strain, and with all vaccines providing limited protection against mild infection with omicron, but still providing high levels of protection against hospitalisation and death from this strain.<sup>9 10</sup> Likewise, vaccine protection from several vaccines is lower for the Delta-variant, as compared with protection against other circulating strains.<sup>11 12</sup>

In Nepal, VE has not been established and few data exist on SARS-CoV-2 genetic variants circulating in the country. Understanding the dominant variants in Nepal, as well as describing the changes in circulating variants over time, will help to inform public health efforts. Describing disease severity in relation to specific SARS-CoV-2 variants and vaccine status can also support prevention and care efforts as we move forward. Therefore, we will conduct a test-negative case-control study (TNCC) to study the VE and genetic variants in the country.

The TNCC design is more cost-effective than traditional cohort studies and is less affected by potential selection biases due to differential healthcare-seeking behaviour. The TNCC design is an important methodological tool used in the evaluation of VE. Recently, many VE studies, including COVID-19 vaccine studies, have used this design. A TNCC study from England in 2021 estimated the real-world effectiveness of the Pfizer-BioNTech BNT162b2 and Oxford-AstraZeneca ChAdOx1-S vaccines.<sup>9</sup> Likewise, a systematic review and meta-analysis on TNCC studies studying the effectiveness of influenza vaccines was published in 2017.<sup>13</sup>

Our study aims to compare SARS-CoV-2 positive individuals with SARS-CoV-2 negative controls to understand VE within Nepal. We will also identify SARS-CoV-2 variants in the SARS-CoV-2 positive cases to analyse and understand

vaccine protection against different circulating SARS-CoV-2 variants (table 1).

## METHODS AND ANALYSIS

### Study design

Hospital-based prospective TNCC study with genetic sequencing of SARS-CoV-2.

### Setting

Patan Hospital is a 640-bed autonomous, non-profit teaching hospital of Patan Academy of Health Sciences (PAHS) located in the Lalitpur district of Kathmandu valley, Nepal. It serves the people of the Kathmandu valley and is a major referral centre for people living outside the valley. Patan Hospital was the first public hospital dedicated to COVID-19 in Nepal and also played a significant role in the vaccination drive in the Kathmandu Valley.

### Study population

Adult patients presenting to Patan Hospital with COVID-19-like symptoms who have had a SARS-CoV-2 antigen/PCR test ordered as part of their routine clinical care. Patan Hospital serves the population of the Kathmandu Valley, but most patients are from the city of Lalitpur which has a population of about half a million people. Patan Hospital also acts as a tertiary referral centre so patients can be referred from anywhere in Nepal.

### Study period

The initial period of recruitment into this study is from November 2021 to July 2023 (figure 1).

### Inclusion criteria

All adults over 18 years of age presenting with COVID-19-like symptoms (fever  $\geq 37.8^{\circ}\text{C}$ , persistent cough (for more than an hour, or three or more coughing episodes in 24 hours), shortness of breath, loss of sense of taste, loss of sense of smell, altered consciousness, feverishness, abdominal pain, decreased feeding, fatigue, runny nose, sore throat, chest pain, muscle aches, joint aches, excess sputum, haemoptysis, headache, confusion, seizures, vomiting, nausea, diarrhoea, cyanosis/mottling, generally unwell, malaise or other symptoms which the clinical team suspect are related to COVID-19 disease) being screened for COVID-19 by PCR and/or antigen test.

### Exclusion criteria

Participants unwilling or unable to give informed consent for participation in the study.

### Outcome measures and definitions

Cases are defined as any 18 years old or above patients who present to Patan Hospital with symptoms suggestive of COVID-19 and subsequently having a positive SARS-CoV-2 PCR test. Controls are defined as any 18 years old or above patients who present to Patan Hospital with symptoms suggestive of COVID-19 and who subsequently have a negative SARS-CoV-2 PCR test.

**Table 1** Aim and objectives of the study

|                      |   |   |
|----------------------|---|---|
| General aim          | To study vaccine effectiveness in Nepal against COVID-19 disease and identify circulating SARS-CoV-2 variants in Nepal  |   |
|                      | Objectives  | Endpoints   |
| Primary objective    | To estimate vaccine effectiveness of licensed COVID-19 vaccines against laboratory-confirmed COVID-19 disease.  | Comparison of vaccination status between individuals with a positive or negative SARS-CoV-2 PCR result, in individuals presenting with symptoms consistent with COVID-19 disease to Patan Hospital. |
| Secondary objectives | To identify the circulating SARS-CoV-2 variants in Nepal.   | Genotyping of SARS-CoV-2 PCR-positive oropharyngeal/nasopharyngeal swabs.   |
|                      | To estimate vaccine effectiveness against specific SARS-CoV-2 variants identified.  | Vaccination status for individuals with specific SARS-CoV-2 variants compared with matched SARS-CoV-2-negative controls.  |
|                      | To estimate vaccine effectiveness against severe COVID-19 disease.  | Comparison of vaccination status between individuals with a positive or negative SARS-CoV-2 PCR result, in individuals presenting with severe COVID-19 disease.                                     |
|                      | To estimate the effectiveness of all licensed COVID-19 vaccines in use in Nepal (including ChAdOx1 nCoV-19, Sinovac-CoronaVac, Janssen Ad26.COV2.S, Pfizer's BNT162b2, COVID-19 mRNA and Moderna mRNA-1273 vaccines and any other licensed COVID-19 vaccine, which are introduced during the study in Nepal) against different SARS-CoV-2 variants and different COVID-19 disease severities. | Comparison of vaccination status of individuals with a positive or negative SARS-CoV-2 PCR result, stratified by disease severity and/or variant.   |
| Exploratory          | To evaluate disease severity due to different circulating SARS CoV-2 variants.  | Comparison of individuals with COVID-19 by disease severity, age and SARS-CoV-2 variant.  |
|                      | Estimate prevalence of symptoms of long COVID-19.   | Persistence of COVID-19-related symptoms at 4 weeks, 3 months and 6 months following enrolment.   |

Exposure is evaluated through the review of the participant's SARS-CoV-2 vaccination history. The primary outcome of interest is laboratory-confirmed COVID-19 disease, which is defined as laboratory-confirmed SARS-CoV-2 infection with symptoms suggestive of COVID-19 disease. Secondary outcomes include the variant of SARS-CoV-2 and the severity of the disease.

Exploratory outcomes include disease severity during periods with different circulating variants of SARS-CoV-2 and prevalence of symptoms of long COVID-19 (see table 1). Using the WHO definition, severe COVID-19 is defined by any of: oxygen saturation <90% on room air; severe pneumonia; signs of severe respiratory distress (in adults, accessory muscle use, inability to complete full sentences, respiratory rate >30 breaths per minute; and, in children, very severe chest wall in-drawing, grunting, central cyanosis or presence of any other general danger signs including inability to breastfeed or drink, lethargy, convulsions or reduced level of consciousness).<sup>14</sup>

### Vaccine effectiveness

VE against acute COVID-19 disease will be analysed by comparing vaccination status and SARS-CoV-2 PCR test results.

Long COVID as defined by the National Institute for Health and Clinical Excellence, the Scottish Intercollegiate Guidelines Network and the Royal College of General Practitioners includes two conditions within the

umbrella of long COVID (ongoing symptomatic COVID-19: signs and symptoms of COVID-19 from 4 to 12 weeks, and post-COVID-19 syndrome: signs and symptoms that develop during or after an infection consistent with COVID-19, continue for more than 12 weeks and are not explained by an alternative diagnosis).<sup>15</sup>

Symptoms are highly variable including generalised pain, fatigue, shortness of breath, chest pain, muscle aches, rash, loss of smell, persistent cough, diarrhoea, abdominal pain, palpitations, persisting high temperature, cognitive dysfunction, headache and tinnitus.<sup>9</sup>

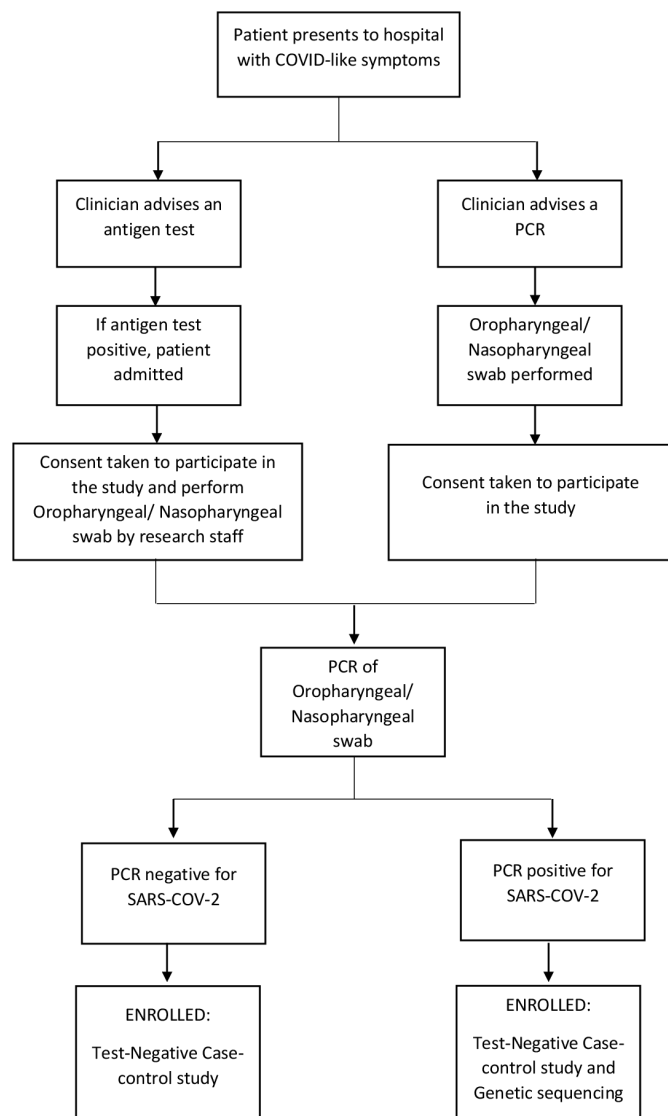
### Data sources

Data sources include nasopharyngeal and/or oropharyngeal swabs tested for SARS-CoV-2 infection, medical record review, self-reported demographic information and medical history (online supplemental table 2).

### Recruitment

Participants will be recruited from the emergency department and outpatients clinics. Fully trained clinical research fellows recruit the participants after taking written informed consent before or soon after the participant has their SARS-CoV-2 test. Participants will be recruited before the result of their SARS-CoV-2 test is available. We will collect the same baseline data on cases and controls in the study; this will include data on demographics, medical history, health presentation,





**Figure 1** Participant enrolment flow diagram. Participants may be enrolled after oropharyngeal/nasopharyngeal swab is performed as long as the swab result is not available to the study team. Participants may be enrolled following an antigen test result only if they refuse a further swab for PCR, this group will be analysed separately if numbers allow.

results of SARS CoV-2 test, hospital records, area of residence, occupation, comorbidities and other possible confounding factors (online supplemental tables 1 and 2). If the participant is illiterate, then a third party may act as an independent representative for the participant to attest that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the participant and that informed consent was freely given by the participant. Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study if the investigator considers the participant is no longer eligible for the study. If the

participant is withdrawn from the study, data collected up to the point of withdrawal will be retained.

### Sample collection

Research fellows will work with the clinical staff to coordinate research activities with routine clinical care. Nasopharyngeal and/or oropharyngeal swabs are taken for SARS-CoV-2 PCR testing as part of routine clinical care conducted at Patan Hospital when a SARS-CoV-2 infection is suspected. However, in rare cases, the clinical team may advise that an antigen test is sufficient for diagnosis prior to admission. In these cases, a research fellow approaches the participant and asks if an additional swab can be taken as part of the research study so that this can be tested using PCR at a later point. If the participant consents, then a swab is taken but participants can be enrolled in the study based on their antigen result alone if they refuse an additional swab.

### Definition of end of study

The 'end of the study' is the date when the processing of the study's samples is completed.

### Laboratory methods and microbiology

All nasopharyngeal swabs are stored and transported in viral transport media (VTM). The swabs are tested for SARS-CoV-2 DNA using qPCR at Patan Hospital. Positive swabs will be frozen at  $-80^{\circ}\text{C}$  and stored at Patan Hospital—and later sent to the Centre for Clinical Vaccinology and Tropical Medicine, Oxford, UK, for further analysis (including genetic sequencing). Either an aliquot of the VTM or the extracted RNA will be sent depending on the volume and quality of the extracted RNA sample available. Extracted RNA may degrade with storage and transport, so aliquots of VTM may provide more robust sequencing data.

### Safety reporting

We do not anticipate any adverse events due to swabs for PCR tests. The research activities are limited to obtaining consent, collecting clinical data and a nasopharyngeal swab, reviewing medical records and sequencing swabs which are positive for SARS-CoV-2 by PCR.

### Power calculation and sample size

The power for sample size calculation was calculated using the following assumptions:

- ▶ Sixteen per cent vaccine coverage within the population (this was the estimated COVID-19 vaccination coverage in Nepal at the time of protocol development).
- ▶ Two vaccines (or multiple vaccines analysed as two groups).
- ▶ Two circulating variants.
- ▶ Cases will be matched with controls in a 1:4 ratio.

With these assumptions, we had a 90% power with a 0.01 level of significance to detect 70% VE with a minimum of 1125 cases and 4500 matched controls, for a total sample size of 5625.

For the secondary objectives, estimating VE of specific vaccines against COVID-19 disease and VE against circulating variants, the sample size calculated above would need to be multiplied by the number of vaccines and variants present in the population.

Given the realities of vaccine coverage to date, and the lack of knowledge about currently circulating variants, this study will continue to enrol participants for the study period (approximately 18 months) to increase the power to describe the VE of each vaccine against the most common circulating variants.

The participants to be recruited and outcomes/endpoints for this observational epidemiological study are described below.

### Case-control ratio

The study aims to enrol four controls for each case. Case and controls will be matched temporally by week of SARS-CoV-2 test to ensure cases and controls are captured within the same 'wave' of the COVID-19 epidemic. Depending on vaccine coverage over time, and vaccine eligibility, as defined by the government vaccination programme, cases and controls may also be matched by age (in bands).

### Exposure categories

The exposure of interest is SARS-CoV-2 vaccination history. Vaccination status is defined as:

- ▶ Unvaccinated—having never received a COVID-19 vaccine.
- ▶ Partial-first-dose—enrolled in the study 0–13 days after receiving the first dose of a COVID-19 vaccine.
- ▶ Full first dose—enrolled in the study 14 days after the first dose or up to 13 days after the second dose of a COVID-19 vaccine, if a second dose has been received.
- ▶ Fully vaccinated—enrolled in study 14 or more days after the second dose of a COVID-19 vaccine; (or 14 days after a single dose of the Janssen Ad26.COV2.S vaccine).

Further exposure categories may be added based on the real-life use of COVID-19 vaccines (These could include a variation on the window period between doses, or additional doses beyond 2, eg). Vaccine type, date of vaccination, type of vaccination facility and location of vaccination will also be recorded for use in the analysis.

### Potential confounders

Potential confounders and effect modifiers are recorded for possible use in the final analysis. Participant information known to impact risk of COVID-19 disease including age, sex, medical comorbidities and occupation will be recorded. See online supplemental table 2 for a full list of potential confounders.

### Statistical analysis plan

A logistic regression model will be used to calculate the adjusted OR ( $OR_{adj}$ ). The  $OR_{adj}$  will be used to produce a covariate-adjusted point estimate of VE, calculated as  $VE = (1 - OR_{adj}) \times 100\%$ . Cases will be matched temporally and by age at the time of inclusion in the model. Age

may also be investigated as an effect modifier if enough cases across age categories are presented to stratify. The model will be adjusted for sex, medical comorbidities, prior infection and high-risk occupations as *a priori* potential confounders. Descriptive analysis will be presented with numbers, and percentages for each factor included.  $\chi^2$  tests of significance will be used and 95% CIs will be calculated for each VE estimate. We will use up-to-date reporting guidelines when reporting VE, such as the 'Evaluation of postintroduction COVID-19 VE: Summary of interim guidance of the WHO.'<sup>16</sup> Two-sided 5% significance will be used to identify statistical differences between cases and controls. The data will be stratified by severity of disease, age, sex, etc, to understand variations in VE within this population if the statistical power allows.

As secondary analyses, for each vaccine available and each SARS-CoV-2 variant with a substantial number of cases present, a separate VE will be calculated to estimate the effectiveness of each vaccine in preventing each prevalent variant. The same confounder adjustments will be used for each subanalysis, as described above.

The method will be repeated to investigate other objectives, such as the relationship between the SARS-CoV-2 variant and severity of disease. We will analyse the duration of protection by looking at the time between completion of primary vaccination series and presentation to hospital. We will also examine the duration of protection in high-risk groups, as this will be important when deciding on booster doses. A separate analysis with only PCR tested individuals will be conducted.

Individuals can contribute more than one positive or negative result (be a case or control more than once) if the test results are at least 6 weeks apart. The first positive result will be used where any results are within 6 weeks (eg, if positive-positive, positive-negative or negative-positive). The first negative result will be used if it occurs within 6 weeks of a subsequent negative test result (negative-negative).

### Procedure for accounting for missing, unused and spurious data

The reason for missing data (eg, consent withdrawn or unable to obtain any laboratory results) will be indicated. For missing potential confounders, records will be dropped in an analysis where the exposure or outcome of interest is missing.

### Procedures for reporting any deviations from the original statistical plan

Any additional analysis or deviation from the analysis plan will be documented and updated according to the statistical standard operating procedure.

### Inclusion in analysis

The main analysis will be conducted on all patients matched as cases and controls, as far as is practically possible, given any missing data. All data will be included

up until the time that a participant is withdrawn from the study.

## Data management

### Access to data

Direct access is granted to authorised representatives from the sponsor or host institution for monitoring and/or audit of the study to ensure compliance with regulations.

### Data recording and record-keeping

Source documents include but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the case report form), clinical and office charts, laboratory and pharmacy records, diaries, radiographs and correspondence.

Wherever possible, data are collected via direct data entry. All study files with demographic and clinical details on the participants are kept in a locked research office within the paediatric ward at Patan Hospital. The study details are entered onto an electronic database protected by a password. All results of hospital investigations are identified by a study number only and have no personal identifiers.

The participants are identified only by a study-specific number and/or code in any database. Participant names and any other identifying details are not included in any study data electronic file.

## Patient and public involvement

Patients and the public were not involved in any way in the production of the research.

## ETHICS AND DISSEMINATION

All efforts will be made to conduct the research in a way that is sensitive to the Nepali culture and social values. Nepali research fellows will be present at all times during the consent process, and the information sheet will be printed in both Nepali and English.

Only anonymised samples and data will be sent outside of the research site. At the end of the study, any remaining sample will be destroyed or returned to Nepal for storage at Patan Hospital under the oversight of PAHS. Storage of these samples may also allow important future research to be done without needing to take new samples.

Ethical approval was obtained from the University of Oxford Tropical Ethics Committee (OxTREC) (ref: 561-21) and the Patan Academy of Health Sciences Institutional Review Board (ref: drs2111121578). The protocol and supporting study documents were approved for use by the Nepal Health Research Council (NHRC 550-2021).

Samples used in this study will be collected and stored for the purposes of research and improved public health knowledge related to combating the COVID-19 pandemic. This work will feed into the government efforts to understand the SARS-CoV-2 epidemic in Nepal, and all findings will be shared with local authorities. Results will be

disseminated in peer-reviewed journals and to the public health authorities in Nepal.

## DISCUSSION

This study is the first SARS-CoV-2 TNCC study in Nepal. Our TNCC design will ensure cases and controls are enrolled from the population of interest, allowing us to investigate VE in a relevant real-world setting.

Our study has some important limitations. Nepal has obtained vaccines from different sources at different times so high-risk groups will be more likely to have received the first vaccines to become available, and lower-risk groups will have received subsequent vaccines; we will need to account for this in the analysis. Different SARS-CoV-2 variants are likely to circulate in Nepal throughout the study; VE against currently circulating variants will be the most important for public health officials. Ideally, sequencing of samples should be done in a timely manner to provide up-to-date research, which can be used to help with future vaccine policy decisions.

COVID-19 research is taking place within a rapidly changing environment. The decisions made while writing this protocol were based on the best available information at the time. For any future updates to this protocol, we would have to take into account new developments. We would have to consider several issues including the definition of 'fully vaccinated' in the setting of booster vaccination programmes, updated definitions for post-COVID-19 condition (long COVID) and Nepal's increasing vaccination rates.

The study will provide new insights into the protection provided by different COVID-19 vaccines against different variants of SARS-CoV-2 among the Nepalese population. This study will also provide information on VE against severe COVID-19 disease and hospitalisation. Thus, the findings from this study could provide useful information to public health officials in formulating national guidelines for the management of COVID-19 disease.

Recruitment to this study has commenced, and initial results will be reported as soon as enrolment allows.

### Author affiliations

<sup>1</sup>Department of Paediatrics, University of Oxford, Oxford, UK

<sup>2</sup>Department of Paediatrics, Patan Academy of Health Sciences, Lalitpur, Nepal

<sup>3</sup>NIHR Oxford Biomedical Research Centre, Oxford, UK

**Contributors** SMB, PJO'R and KT-N designed the study, and wrote and revised the manuscript. MG, BhP, SK, SA, SM, AS, BiP, ML, IS, MV, AE, SoS, ESF, GL, GS, AJP and ShS designed the study and revised the manuscript. SMB, PJO'R and KTN contributed equally as the first authors to this paper. All coauthors contributed to the reviewing and approving the final version of the manuscript for submission.

**Funding** This research was funded by AstraZeneca. For the purpose of Open Access, the author has applied a CC BY public copyright licence to any author accepted manuscript (AAM) version arising from this submission.

**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Sanjeev M Bijukchhe <http://orcid.org/0000-0002-6436-6859>

Andrew J Pollard <http://orcid.org/0000-0001-7361-719X>

#### REFERENCES

- 1 Bastola A, Sah R, Rodriguez-Morales AJ, *et al*. The first 2019 novel coronavirus case in nepal. *Lancet Infect Dis* 2020;20:279–80.
- 2 Shrestha R, Shrestha S, Khanal P, *et al*. Nepal's first case of COVID-19 and public health response. *J Travel Med* 2020;27:taaa024.
- 3 Worldometer. Wordometer - nepal coronavirus update. 2021. Available: <https://www.worldometers.info/coronavirus/country/nepal/> [Accessed 19 May 2021].
- 4 India To. Nepal confirms presence of third and new variant of coronavirus. 2021. Available: <https://timesofindia.indiatimes.com/world/south-asia/nepal-confirms-presence-of-third-and-new-variant-of-coronavirus/articleshow/82761558.cms> [Accessed 19 May 2021].
- 5 Pandey A, Belbase P, Parajuli A. COVID-19 vaccine development to vaccination. *J Nepal Health Res Counc* 2021;18:807–9.
- 6 POst TK. Nepal's vaccination status. 2021. Available: <https://kathmandupost.com/health/2021/05/12/nepal-s-vaccination-status> [Accessed 20 May 2021].
- 7 MOHP N. COVID-19 update 2022. 2022. Available: <https://covid19.mohp.gov.np/> [Accessed 10 May 2022].
- 8 WHO. Tracking SARS-cov-2 variants. 2022. Available: <https://www.who.int/activities/tracking-SARS-CoV-2-variants> [Accessed 10 May 2022].
- 9 Bernal JL, Andrews N, Gower C, *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. 2021;373.
- 10 Andrews N, Stowe J, Kirsebom F, *et al*. Covid-19 vaccine effectiveness against the omicron (B. 1.1. 529) variant. 2022;386:1532–46.
- 11 Bernal JL, Andrews N, Gower C, *et al*. Effectiveness of covid-19 vaccines against the B.1.617.2 variant. *Epidemiology* [Preprint] 2021.
- 12 Nanduri S, Pilishvili T, Derado G, *et al*. Effectiveness of pfizer-biontech and moderna vaccines in preventing SARS-cov-2 infection among nursing home residents before and during widespread circulation of the SARS-cov-2 B.1.617.2 (delta) variant - national healthcare safety network, march 1-august 1, 2021. *MMWR Morb Mortal Wkly Rep* 2021;70:1163–6.
- 13 Rondy M, El Omeiri N, Thompson MG, *et al*. Effectiveness of influenza vaccines in preventing severe influenza illness among adults: a systematic review and meta-analysis of test-negative design case-control studies. *J Infect* 2017;75:381–94.
- 14 WHO. Clinical management of COVID-19: living guideline. 2023. Available: <https://www.who.int/publications/i/item/WHO-2019-nCoV-clinical-2023.1> [Accessed 15 Jan 2023].
- 15 Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med* 2021;9:129.
- 16 Patel MK, Bergeri I, Bresee JS, *et al*. Evaluation of post-introduction COVID-19 vaccine effectiveness: summary of interim guidance of the world health organization. *Vaccine* 2021;39:4013–24.