Towards the development of a SARS-CoV-2 variant risk assessment tool: expert consultation on the assessment of scientific evidence on emerging variants

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A systematic approach is required for the development of an evidence-based risk assessment tool to robustly estimate the risks and implications of SARS-CoV-2 variants. We conducted a survey among experts involved in technical advisory roles for WHO to capture their assessment of the robustness of different study types that provide evidence for potential changes in transmissibility, antigenicity, virulence, treatability, and detectability of SARS-CoV-2 variants. The views of 62 experts indicated that studies could be grouped on the basis of robustness and reliability for the different risk indicators mentioned. Several study types that experts scored as providing reliable evidence and that can be performed in a timely manner were identified. Although experts from different technical areas had varying responses, there was agreement on the highest and lowest scoring study types. These findings can help to prioritise, harmonise, and optimise study designs for the further development of a systematic, evidence-based, SARS-CoV-2 variant risk assessment tool.

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Introduction

Throughout the COVID-19 pandemic, genome sequencing has become embedded within SARS-CoV-2 surveillance and due to the massive sequencing efforts, viral variants can now be identified and tracked rapidly. A community of practice has developed in which viral genomes are shared rapidly in public databases such as the Global Initiative on Sharing All Influenza Data (GISAID)[1] and the International Nucleotide Sequence Database Collaboration (INSDC), which enables the scientific community, including the WHO Technical Advisory Group on SARS-CoV-2 Virus Evolution, to study the virus at molecular level in almost real time.

The global dispersal and high levels of circulation of SARS-CoV-2 over the past 3 years have allowed substantial genetic diversity to develop. Genomic data have been incorporated into surveillance and initially were used in outbreak investigations to study transmission pathways in hospitals[2] and nursing homes.[3] Such data have also been used to study transmission between humans and animals, including white-tailed deer, cats, dogs, hamsters, and mink.[4] The expansion of genomic sequencing during the COVID-19 pandemic and the extensive coverage of SARS-CoV-2 genomic surveillance in some countries or regions enabled rapid detection of viral variants with remarkable mutations, mainly located in the spike gene. Since the start of the global dispersal of SARS-CoV-2, the emergence of viral variants has shaped the course of the pandemic. WHO designated variants identified as being a potential risk to global health as variants of interest (VOIs) and variants of concern (VOCs), with VOCs showing the ability to spread rapidly around the globe and replace earlier circulating variants due to a selective advantage.[5]

The first VOC named by WHO was the alpha (B.1.1.7) variant, which was first noted around mid-November, 2020, and became the most prevalent variant in many countries worldwide just a few weeks later.[6] Additional VOCs were observed that attained regional dominance, such as the beta[7] (B.1.351) and the gamma (P.1) variants.[8] The delta (B.1.617.2) variant was a globally dispersed VOC reaching predominance by July, 2021, until it was replaced by the omicron (B.1.1.529) variant that became dominant in most countries at the start of 2022.[9] All five VOCs have genetic mutations that could potentially enhance infectivity or confer resistance to neutralising antibodies resulting in immune escape potential. In addition, differences in disease severity and host range have been observed between VOCs.[10–12] The exact mechanisms that confer fitness advantages also differ between the various VOCs. For instance, for the alpha and delta variants, increased fitness has been mostly attributed to increased viral loads in the upper airways,[13,14] whereas for omicron, immune escape seems likely to be a key driver.[15]

Each time a new variant emerges it is important to understand whether particular properties of the virus have changed that affect how quickly a variant spreads, disease severity, the performance of vaccines, therapeutics, and diagnostics, and other public health and social measures.[16] The rapid and robust assessment of variants is important to establish whether public health responses and advice from WHO need to be altered. Ideally, whether a variant affects one of the above indicators should be ascertained in the period between variant detection and dominance, which is a matter of weeks. In-silico or deep mutational scanning studies that predict the strength of antibody binding to SARS-CoV-2 variants or identify individual mutations that escape antibody binding can provide insights.[17] However, with the current state of knowledge, their findings should always be substantiated with follow-up experimental and epidemiological studies.[17] The full assessment of these characteristics and translating genotypes into phenotypes requires thoroughly designed

clinical, epidemiological, and experimental studies that can take considerable time. Due to the diversity of study types, variability in the performance of the individual studies, and timing of outcomes, assessing the available multidisciplinary evidence is not a straightforward process. One example is the comparative analysis of properties of the omicron variant: a study using human nasal epithelial cultures revealed more rapid replication for omicron than delta, similar to what was observed in an ex vivo culture model, which might support the hypothesis that the increased transmission potential of omicron is due to a higher concentration of virus particles in the upper respiratory tract.[12,18] However, hamster model experiments found lower infectious viral titres in the nose,[19] and a clinical study found similar infectious viral titres when comparing delta and omicron breakthrough infections in vaccinated individuals.[20] Given the challenge of interpreting such seemingly discrepant findings, WHO established the Technical Advisory Group on SARS-CoV-2 Virus Evolution to provide guidance on whether a given variant should be classified as a VOI or VOC according to WHO definitions.[16]

To provide a more systematic and structured way of assessing available evidence on virus properties, and to work towards a standardised risk assessment, an essential step is to examine what types of scientific evidence should be considered and possibly prioritised to estimate the risks posed by emerging SARS-CoV-2 variants. Here, we sought to capture emerging infectious disease experts' assessment of the robustness of study types that provide evidence of potential changes in transmissibility, antigenicity, virulence, treatability, and detectability of SARS-CoV-2 variants. To do so, we distributed a questionnaire to members of the WHO COVID-19 Secretariat (appendix pp 9–32). We show that study types can be grouped based on robustness and reliability for each of the identified risk indicators of relevance for public health, and that this information can be used for further development of a variant risk assessment.

See Online for appendix

	Explanation
Increased transmissibility or spread	Increased intrinsic transmissibility or increased spread observed in human populations, expanding host range
Increased disease severity	Increase in virulence or more severe clinical disease representation
Immune escape (vaccine-induced)	Potential to escape immunity acquired after vaccination; altered antigenicity
Immune escape (natural infection)	Potential to escape immunity acquired after infection; altered antigenicity
Effect on drugs and therapeutics	Potential to reduce the efficacy and effectiveness of available drugs and therapeutics
Effect on diagnostics	Reduced detection by molecular or antigen testing assays

Table: **Overview of the identified public health risk indicators of SARS-CoV-2 variants.**

Overall ranking of scientific evidence for different public health risk indicators

The questionnaire was divided into six different public health risk indicators (ie, increased transmissibility or spread, increased disease severity, immune escape [vaccine-induced], immune escape [natural infection], effects on drugs and therapeutics, and effect on diagnosis; table). Respondents were requested to indicate to what extent they were confident that a particular study provided reliable evidence for each of the six public health risk indicators. 62 (51%) of 121 invited individuals completed the questionnaire. The respondents were stratified into two distinct subgroups for analysis: laboratory experts (n=34) and epidemiology experts (n=9), as outlined in the appendix (p 3). If respondents indicated multiple disciplines that would result in an assignment to both sub-groups, they were not assigned a subgroup to avoid confounding. For all risk indicators, study types could be grouped based on robustness. A ranking order based on the proportion of confidence scores on the right side of the reference line set at a confidence score of 3 (including high [a score of 4] and very high [score of 5] confidence scores) was obtained (appendix p 5).

Top scoring studies per public health risk indicator and time assessment

The top five ranking study types for all indicators, including an arbitrary assessment of the time needed to perform the different studies, included epidemiological, clinical, animal, and in-vitro laboratory studies (figure). Most top scoring studies were epidemiological or clinical studies, some of which can be conducted reasonably quickly (within a few weeks) if protocols and permissions are in place (eg, household studies to assess transmissibility) and could provide information that is considered reliable and actionable. Other studies provide robust evidence but can take months—eg, prospective cohort studies to assess disease severity and randomised controlled trials (RCTs) to assess vaccine efficacy or vaccine-induced immune escape. Except for the disease severity risk indicator, all other risk indicators included a study type that could provide indicative results in a reasonably short timeframe, mostly within 1 month. These study types included in-vitro studies such as neutralisation assays with viral strains isolated from patients (for the immune escape risk indicators), virus inhibition studies in organoids (for the drugs and therapeutics risk indicator), and animal model studies (for the transmissibility or spread and drugs and therapeutics risk indicators).

Assessing increased transmissibility or spread

The top five studies that yielded the highest scores for assessing increased transmissibility or spread in the human population belonged to the categories of epidemiological, clinical, and animal model studies

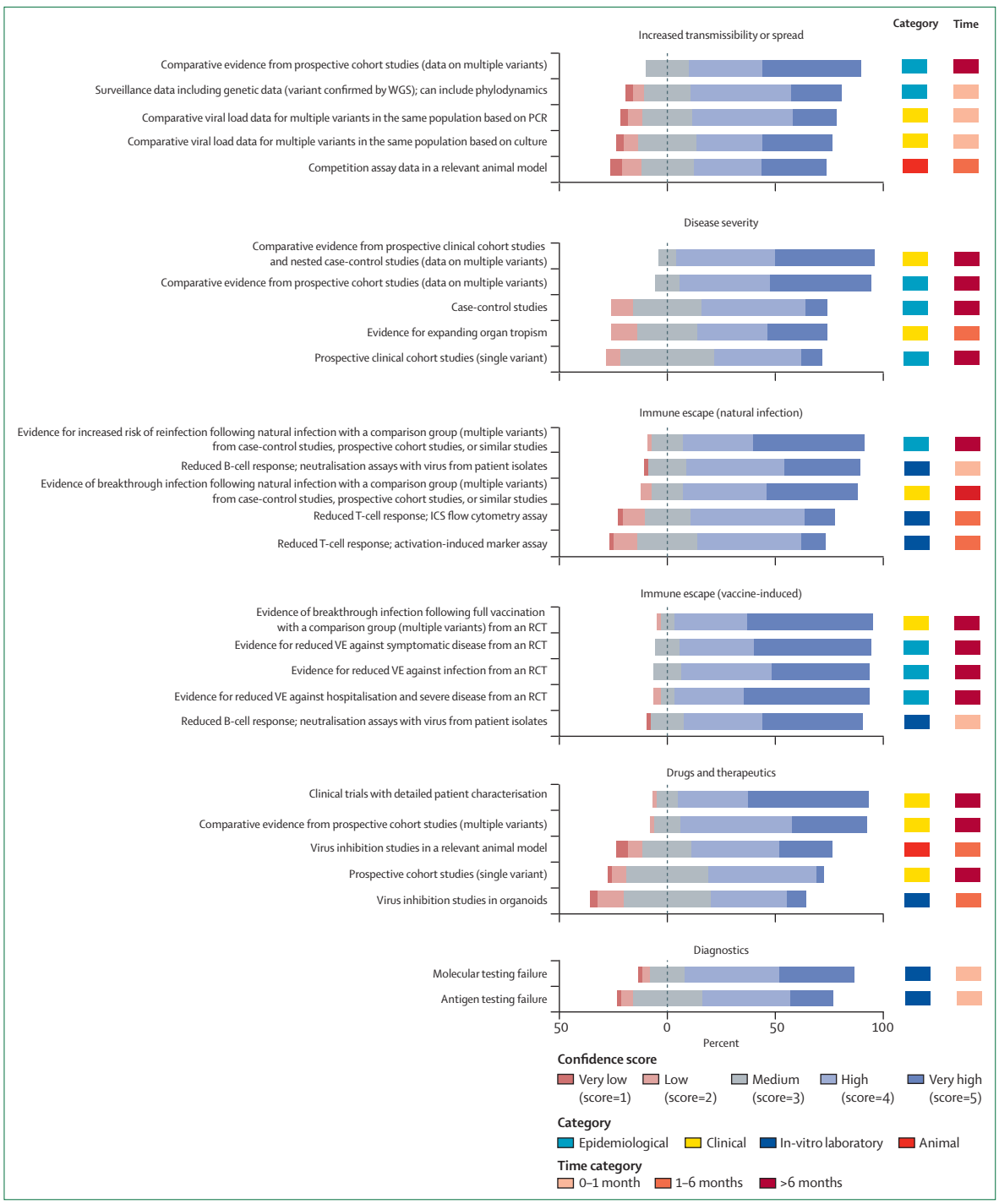

Figure: **The distribution of confidence scores for the top five scoring types of evidence related to six public health risk indicators**
The six risk indicators were: transmissibility or spread, disease severity, immune escape (natural infection), immune escape (vaccine-induced), drugs and therapeutics, and diagnostics. The different types of evidence are grouped by study category and estimated time needed to complete the study. The risk indicator diagnostics contained two study types in total. ICS=intracellular cytokine staining. RCT=randomised controlled trial. VE=vaccine efficacy. WGS=whole-genome sequencing.

(figure). The best scoring study type, according to the respondents, was prospective cohort studies assessing multiple variants (median confidence score of 4 [IQR 4–5]). When the results were stratified by expertise (laboratory experts and epidemiology experts), there was no difference in the ranking position, suggesting consensus among both groups on the high level of confidence this study type provides (appendix p 6). Other

study types considered to provide reliable evidence were studies obtaining observational surveillance data (including whole-genome sequencing [WGS]) and comparative viral load data (multiple variants) based on RT-PCR and virus culture in the same population; these studies can be performed within 1 month, with proper preparation. In addition, competition assays in a relevant animal model were among the top five ranking studies that can be performed within 6 months.

There was consensus among the respondents about the low level of confidence in surveillance data when the variant type was not confirmed by WGS, which has the lowest ranking position in both subgroups of experts (median confidence score of 2 [IQR 2–3]; appendix p 6).

Assessing increased disease severity

According to most respondents, possible increased virulence or a more severe clinical disease presentation could be most reliably assessed by clinical or epidemiological prospective cohort studies, or (nested) case-control studies that assess multiple variants at the same time (median confidence score of 4 [IQR 4–5]; figure; appendix p6). Furthermore, clinical evidence for expanding organ tropism and prospective cohort studies that assess a single variant were in the top five ranking for robustness (median confidence score of 4 [IQR 3–5]; figure). All top-ranking study designs to assess disease severity typically take weeks to perform, and most studies would require more than six months to complete (except, potentially, for studies in countries with high levels of genomic surveillance in parallel in the community and hospitals). The overall lowest ranking study type for the assessment of disease severity is the collection of surveillance data excluding genetic data (variant not confirmed by WGS; median confidence score of 2 [IQR 2–3]; appendix p 5).

Assessing immune escape (vaccine-induced and natural infection)

The five highest ranked studies providing reliable and robust evidence for the assessment of variants that might result in potential escape from vaccine-induced immunity were RCTs of vaccines that obtained evidence for breakthrough infection or reduced vaccine efficacy against different outcomes (>6 months to perform) and in-vitro neutralisation assays using live virus (0–1 month to perform; all with median confidence scores ≥4 [IQR 4–5]; figure; appendix p 6). The highest-ranking studies differed between laboratory and epidemiology experts. Laboratory experts considered neutralisation assays with live virus as the best way to assess vaccine-induced immune escape, whereas epidemiology experts considered evidence for breakthrough infections from RCTs as the most robust study and ranked neutralisation assays in the eighth position (appendix p 6). However, both groups agree that RCTs provide robust results. Evidence for breakthrough infections after being fully vaccinated without a comparison group from case reports, outbreak reports, postmarketing studies, or other similar studies were assessed as the least reliable study design in the overall ranking (median confidence score of 3 [IQR 2–3]; appendix p 5) by both laboratory and epidemiology experts (appendix p6).

Study types designed to assess the potential of a variant to escape immunity after natural infection are similar to those used to investigate variant immune escape after vaccination, with the exception of vaccine efficacy and effectiveness studies. Studies using the intracellular cytokine staining flow cytometry assay or the activation-induced marker assay to measure T-cell responses were among the top five highest ranked studies (median confidence score of 4 [IQR 3–4]; figure). The other results for naturally acquired immune escape reflect those seen in the vaccine-induced risk indicator group (appendix p 7).

Assessing effect on drugs and therapeutics

The most reliable study type for establishing the effect of a SARS-CoV-2 variant on drugs and therapeutics was found to be clinical trials with detailed patient characterisation, which can take more than 6 months to complete (median confidence score of 5 [IQR 4–5]; figure). Both laboratory and epidemiology experts agreed on the reliability of clinical trials but had different ranking orders (appendix p 7). The laboratory experts ranked clinical trials with detailed patient characterisation second (after prospective cohort studies assessing multiple variants), whereas the epidemiology experts ranked this study type as the highest. Other reliable study types in the top five overall ranking were virus inhibition studies in a relevant animal model, which take less than 6 months to complete. The laboratory experts assigned higher median scores to this study type than the epidemiology experts did (Δmedian=1). Virus inhibition studies in organoids also ranked in the top five for assessing the effect of a SARS-CoV-2 variant on available drugs and therapeutics (figure). The least reliable study type in the overall ranking was the case report (median confidence score of 2 [IQR 2–3]; appendix p 5) and both laboratory and epidemiology experts exhibited agreement on this study type (appendix p 7).

Assessing effect on diagnostics

Respondents assigned high scores to studies evaluating both the failure of molecular tests and antigen tests (the only two study types considered for this risk indicator; median confidence score of 4 [IQR 4–5]; figure) with no difference in ranking order between the laboratory and epidemiology experts (appendix p 7). A slightly higher proportion of high scores was assigned to evidence from molecular testing failure than antigen testing failure.

Prioritisation and standardisation of study types is needed for timely and reliable assessment of emerging SARS-CoV-2 variants

The speed at which emerging SARS-CoV-2 variants spread is surpassing our current ability to quickly and

thoroughly assess potential changes in their phenotype. Several organisations including WHO, the European Centre for Disease Prevention and Control, UK Health Security Agency, and the US Centers for Disease Control and Prevention implement frameworks for assessing SARS-CoV-2 variants, and all require that multidisciplinary evidence be considered. This Personal View provides an overview of the expert opinion on the reliability of studies to assess phenotypical traits of SARS-CoV-2 variants to provide evidence for public health and clinical decision making.

The identification of new SARS-CoV-2 variants involves analysing genomic sequences and metadata available on public databases such as GISAID and INSDC. To prioritise these variants for further study, their genetic diversity compared with previous circulating variants needs to be mapped, with a focus on mutations in crucial regions (eg, the receptor-binding domain and T-cell epitopes that are known to reduce the effectiveness of currently available vaccines or therapeutics or enable diagnostic escape). Follow-up research is warranted when variants display increased growth advantage across multiple countries or regions. By assessing the risk indicators and their consequences on the basis of the robustness of the study and replication of results across different countries and regions with differing immune landscapes, an overall risk score can be calculated.

The degree of urgency for characterising a new variant is dependent on the potential consequences of its emergence and differs for the categories mentioned. For instance, the assessment of susceptibility of new variants to existing diagnostic assays and drugs and therapeutics (eg, monoclonal antibodies) is urgently needed as it might affect case-finding activities and treatment of risk groups. For the indicator drugs and therapeutics, in-vitro organoid and animal model studies that can be performed within 6 months are included in the shortlist of reliable studies.

A second time-sensitive variable is the effect of variant emergence on vaccine effectiveness, which could inform vaccination strategies. A rapidly executable study that should be prioritised to assess immune escape from vaccination is the in-vitro neutralisation assay (using live virus). With the emergence of the omicron variant and its numerous sublineages, neutralisation studies using postvaccination serum samples and either pseudo or live viruses quickly showed drastic reductions in cross-neutralising capacity against omicron BA.1 and sublineages compared with the ancestral virus or previous VOCs.[21,22] Indications of a change in transmissibility could rapidly be highlighted by epidemiological studies using surveillance data or clinical studies assessing comparative viral load data. We identified no studies that could provide evidence for changes in disease severity within a short timeframe. Since evidence for expanding organ tropism as provided by clinical studies was considered reliable, a potential rapid alternative laboratory study could be to use organoid studies. Organoid research has allowed insight into SARS-CoV-2 cellular tropism and host responses,[23–25] and has shown value for the rapid screening and evaluations of multiple antiviral drugs.[26,27]

In addition to the rapidly executable studies, we identified studies that are reliable but take longer to perform, such as observational (prospective) cohort studies and RCTs that assess multiple variants at the same time. The challenges of conducting studies such as RCTs for SARS-CoV-2 3 years after its first introduction include difficulties with finding eligible participants due to high levels of exposure and immunity, controlling for earlier interventions, and finding comparison groups, making observational studies a more realistic option.[28,29]

The results of this survey should be interpreted with caution. Although the response rate of 51% is acceptable, the number of responses is small. We invited to fill in the questionnaire experts involved in technical advisory roles for WHO representing a diverse range of areas of expertise and different WHO regions. Although a considerable proportion of the respondents were virologists and some study types were prioritised differently by technical discipline, there was a consensus on the top three highest and lowest scoring studies in each group among all respondents. Arbitrary time estimates for conducting a study were made, assuming facilities, expertise, protocols, and permissions are available, but it is important to realise that, for example, for some epidemiological study designs, speed is also dependent on sequencing coverage and well established operational preparation procedures. Another limitation of this study is that new methods continue to be developed, and therefore we might not have included all possible assays or study types in the questionnaire when we developed it in 2021. Respondents mentioned several additional studies that could be considered and potentially integrated into a risk assessment tool (appendix p 8). Nonetheless, the insights of this study provide a foundation for the development of a SARS-CoV-2 risk assessment tool. First, incoming data and existing literature on SARS-CoV-2, which has rapidly expanded in the past 3 years, can be placed in this framework, and could be assigned a weight score based on the level of confidence it provides, which can be used to assign a risk score to newly emerging SARS-CoV-2 variants. Second, the ranking of the studies can be used to decide which studies should be prioritised for genotype-to-phenotype characterisation.

The evolution of SARS-CoV-2 has been astonishing and as more SARS-CoV-2 variants will emerge in the coming years, a global, balanced, and proportionate surveillance system is needed to track, monitor, and assess emerging variants to continue to provide evidence for public health response measures. Complicating factors are the global differences in background population immunity; access to, availability, and use of vaccines; and national vaccination strategies. Therefore, further efforts on

standardisation and harmonisation of the prioritised study types are essential, and these efforts should include the availability of protocols and essential assays in reference centres in each WHO region. Although efforts on standardisation are made (such as collecting sets of reference strain and serum samples that can be shared through a BioHub[16]), assay and protocol standardisation are key, including building an international collaborative network of experts with agreements in place for rapid risk assessment studies and working towards comparability of data through targeted studies. Although the focus of this study was to show which studies provide robust evidence, reducing time barriers to obtain results is also an important aspect. A possible way of accelerating some studies is to leverage existing data sources, such as registries or administrative databases, to reduce the need for primary data collection. Moreover, collaboration between researchers and institutions to pool resources and data is crucial and should be stimulated to accelerate the pace of studies.

The global assessment system that has been established for SARS-CoV-2 will be modified as we learn more about this virus as the pandemic progresses, and by learning from other processes established for influenza by the WHO Global Influenza Surveillance and Response System and Tool for Influenza Pandemic Risk Assessment. As a systematic collaborative multidisciplinary approach for the phenotypic characterisation of future SARS-CoV-2 variants is further developed by WHO, this study provides advice on study types that provide reliable evidence for the assessment of SARS-CoV-2 variants that can be done in a timely manner.

Contributors

NW, LS BBOM, and MPGK contributed to study conception and design. NW, LS, MDP, MDVK, BBOM, and MPGK contributed to data collection. NW, LS, JvB, and BBOM contributed to data analysis and interpretation of results. NW produced the figure. NW, BBOM, and MPGK contributed to the preparation of the original draft. LS, MDP, MDVK, AA, MC, and JvB critically read and contributed to the manuscript. NW, BBOM, LS, and JvB verified the raw data. All authors were permitted access to the raw data. All authors accepted responsibility to submit this manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymised individual-level data collected from the questionnaire are available upon request to the corresponding author. The questionnaire is provided in the appendix (pp 9–32) for reference.

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