OPEN LETTER

# Southeast Asia initiative to combat SARS-CoV-2 variants (SEACOVARIANTS) consortium [version 1; peer review: 2 approved, 1 approved with reservations]

Le Nguyen Truc Nhu[1], Mary Chambers[1,2], Narisara Chantratita[3], Phaik Yeong Cheah[2,4], Nicholas P.J. Day[2,4], Wanwisa Dejnirattisai[5], Susanna J. Dunachie[6], Alba Grifoni[7], Raph L. Hamers[2,8], Jennifer Hill[6], E. Yvonne Jones[6], Paul Klenerman[6], Juthathip Mongkolsapaya[3,9,10], Gavin Screaton[9,10], Alessandro Sette[7], David I. Stuart[6], Chee Wah Tan[11], Guy Thwaites[1,2], Vu Duy Thanh[1], Lin-Fa Wang[11], Le Van Tan[1], SEACOVARIANTS Consortium

[1]Oxford University Clinical Research Unit, Ho Chi Minh city, Vietnam
[2]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, England, UK
[3]Department of Microbiology and Immunology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[4]Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand
[5]Division of Emerging Infectious Disease, Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[6]Division of Structural Biology, Nuffield Department of Medicine, University of Oxford, Oxford, England, UK
[7]La Jolla Institute for Immunology, San Diego, California, USA
[8]Oxford University Clinical Research Unit Indonesia, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
[9]Chinese Academy of Medical Science (CAMS) Oxford Institute (COI), University of Oxford, Oxford, England, UK
[10]Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, England, UK
[11]Programme in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore, Singapore

**v1** **First published:** 11 Apr 2024, **9**:181
https://doi.org/10.12688/wellcomeopenres.20742.1
**Latest published:** 11 Apr 2024, **9**:181
https://doi.org/10.12688/wellcomeopenres.20742.1

## Abstract

A strong and effective COVID-19 and future pandemic responses rely on global efforts to carry out surveillance of infections and emerging SARS-CoV-2 variants and to act accordingly in real time. Many countries in Southeast Asia lack capacity to determine the potential threat of new variants, or other emerging infections. Funded by Wellcome, the Southeast Asia initiative to combat SARS-CoV-2 variants (SEACOVARIANTS) consortium aims to develop and apply a multidisciplinary research platform in Southeast Asia (SEA) for rapid assessment of the biological significance of SARS-CoV-2 variants, thereby informing coordinated local, regional and global responses to

**Open Peer Review**

**Approval Status** ? ✓ ✓

| | 1 | 2 | 3 |
|---|---|---|---|
| **version 1** 11 Apr 2024 | ? view | ✓ view | ✓ view |

1. **Sonika Bhatnagar**, Netaji Subhas University of Technology, Dwarka, New Delhi,, India
**Shubhangi Gupta**, Netaji Subhas University of Technology, New Delhi, India

the COVID-19 pandemic. Our proposal is delivered by the Vietnam and Thailand Wellcome Africa Asia Programmes, bringing together a multidisciplinary team in Indonesia, Thailand and Vietnam with partners in Singapore, the UK and the USA. Herein we outline five work packages to deliver strengthened regional scientific capacity that can be rapidly deployed for future outbreak responses.

## Plain language summary

Our project strengthens local scientific capacity in South East Asia (SEA) and therefore enables the rapid assessment of SARS-CoV-2 variants as they emerge within the region. While COVID-19 remains a global pandemic, future emerging infections caused by a novel virus is an inevitable event, with SEA being a global hot-spot for pathogen emergence. Consequently, the research capacity built, the scientists trained and the research network formed as part of this project will lay the foundation for future locally-led outbreak responses. Our project will demonstrate that novel research platforms can be set up in other low and middle income countries to address the unprecedented challenges presented by emerging infections.

## Keywords

SARS-CoV-2 variants, pandemic responses

**Corresponding author:** Le Van Tan (tanlv@oucru.org)

**Author roles: Nhu LNT**: Writing – Original Draft Preparation; **Chambers M**: Writing – Review & Editing; **Chantratita N**: Writing – Review & Editing; **Cheah PY**: Writing – Review & Editing; **Day NPJ**: Writing – Review & Editing; **Dejnirattisai W**: Writing – Review & Editing; **Dunachie SJ**: Writing – Review & Editing; **Grifoni A**: Methodology; **Hamers RL**: Writing – Review & Editing; **Hill J**: Writing – Review & Editing; **Jones EY**: Writing – Review & Editing; **Klenerman P**: Methodology; **Mongkolsapaya J**: Writing – Review & Editing; **Screaton G**: Writing – Review & Editing; **Sette A**: Writing – Review & Editing; **Stuart DI**: Writing – Review & Editing; **Tan CW**: Writing – Review & Editing; **Thwaites G**: Writing – Review & Editing; **Thanh VD**: Writing – Review & Editing; **Wang LF**: Writing – Review & Editing; **Tan LV**: Writing – Review & Editing;

**Competing interests:** L.V.T. received a consulting fee from MIMS Pte. Ltd. G.R.S. is in the GSK Vaccines Scientific Advisory Board, consults for AstraZeneca and is a founder member of RQ Biotechnology. No other competing interests were disclosed.

**Grant information:** This work was supported by Wellcome [226120].



**How to cite this article:** Nhu LNT, Chambers M, Chantratita N *et al.* **Southeast Asia initiative to combat SARS-CoV-2 variants (SEACOVARIANTS) consortium [version 1; peer review: 2 approved, 1 approved with reservations]** Wellcome Open Research 2024, **9**:181 https://doi.org/10.12688/wellcomeopenres.20742.1

**First published:** 11 Apr 2024, **9**:181 https://doi.org/10.12688/wellcomeopenres.20742.1

2. **Pushpamali De Silva**, Harvard Medical School,, Boston, MA, USA

3. **Takamasa Ueno**, Kumamoto University, Kumamoto, Japan

**Isaac Ngare**, Kumamoto University, Kumamoto, Japan

Any reports and responses or comments on the article can be found at the end of the article.

## Disclaimer

The views expressed in this article are those of the authors. Publication in Wellcome Open Research does not imply endorsement by Wellcome.

## Introduction

### Background

Tracking the evolution of new variants of SARS-CoV-2 and understanding their impact on disease phenotype has been one of the major challenges of the COVID-19 pandemic[1]. With SARS-CoV-2 continuing to circulate around the world, new variants with structural changes in the spike protein that can evade existing infection or vaccine-derived immunity will almost certainly continue to emerge. The rapid assessment of the impact of new SARS-CoV-2 variants on existing population immunity induced by vaccination and/or infection[2–5] and their clinical consequences of infection is critical to public health responses. However, there is limited capacity in the low- and middle-income countries (LMICs) of Southeast Asia (SEA) to make such assessments. Building on existing expertise and laboratory capacities within the Wellcome Africa Asia Programmes (AAPs) situated in Thailand, Vietnam and Indonesia, we are developing a new platform that will enable the rapid biological assessment of SARS-CoV-2 variants within SEA. Our platform utilises a multi-disciplinary research approach, encompassing structural biology, and antibody and T cell response analyses to generate timely data on the potential threat of new SARS-CoV-2 variants. These research activities are supported by policy-maker and public engagement components that will bring research results into practice, and will utilize engagement activities to inform the design of laboratory-based research.

Structural biology is integrated into SARS-CoV-2 genomic surveillance within the UK and has been successfully used to accurately predict impacts of variants of concern (VOCs) on vaccines and therapeutics[3]. By integrating all known antibody binding/therapeutic target data with structural insight, it is possible to identify mutations/residues most likely to have a significant escape impact, informing subsequent *in vitro* assessment. Coupling structural biology analysis with laboratory assays will help generate timely data on the potential biological significance of SARS-CoV-2 variants emerging in SEA relevant to local settings, key to supporting policy makers with evidence-based decisions.

Although neutralising antibodies correlate with protection against COVID-19[6–9], T-cells are a vital component of antiviral defence, especially against severe disease. For example, the Omicron variant evades pre-existing antibody neutralisation[3] but T-cell responses are preserved in 70-80%[4,10–15], likely playing a major role in the low rates of hospitalization and death in vaccinated populations and contrasting with Omicron's high mortality in under-vaccinated people[16].

Several countries in SEA border mainland China, where SARS-CoV-1 (responsible for the 2003 outbreak)[17] and SARS-CoV-2 first emerged[18]. In this region, numerous SARS-CoV-1/2 related viruses of the subgenus *Sarbecovirus* have been discovered in a wide range of animal species, including bats and pangolins[19–23]. In rural SEA, people are regularly in close contacts with animals[24]. Therefore, these populations may have a different immune landscape compared to those in other geographic regions due to differences in past pathogen exposure[25] and/or human leukocyte antigens (HLA) repertoire. Therefore, findings from high-income countries, currently dominating the scientific literature, might not translate into the SEA setting.

Besides pathogen exposure and population genetics, vaccination is a major factor generating regional differences in immune landscape. High-income countries have predominantly deployed mRNA and viral vector vaccines. In SEA, more diverse vaccine products have been used, including mRNA (BNT162b2 and mRNA-1273), adenoviral vector (Oxford-AstraZeneca), whole-inactivated virus (Sinovac, SinoPharm) and protein subunit (Abdala, from Cuba) vaccines[26–28]. Relatively little is known about the immunogenicity of some of these vaccine candidates (e.g., Abdala[29]), and the T-cell responses to whole-killed virus vaccines[30]. The heterogeneity in vaccine products used, coupled with the potential differences in the pre-existing immune landscape and diverse HLA repertoires, make SEA a unique setting for studies characterising immune responses and clinical consequences of infection with VOCs.

The Thailand and Vietnam AAPs have more than four decades' experience of engaging with the public and policy makers. The scale of COVID-19 required an adjustment in priorities and new approaches to engagement. It has opened new partnerships and built a wider community of local engagement avenues. The AAPs have developed new models of on-line public engagement and training and identified those marginalised and made most vulnerable by the pandemic. On-line communications have strengthened collaborations and activities across SEA and form the basis for the new framework to be created by the SEACOVARIANTS consortium with funding from Wellcome to communicate and engage concerning virus variants and their threat to public health. In Vietnam, an Outbreak Advisory Board (OAB) was established with representatives from the Ministry of Health and major national and international institutes, including the WHO. The OAB provides a live interface between national policy makers and AAP researchers, enabling bidirectional flow of information. In SEACOVARIANTS we aim to extend the model to Indonesia to ensure our research findings translate rapidly into practice. In Indonesia, the AAP has advised and collaborated with MOH and local Health Offices to assist in laboratory diagnosis, genomic surveillance and advanced data analysis. The Thailand AAP facilitates and routinely consults various public and young persons' advisory groups; such as the decade-old Tak Province Community Ethics Advisory Board founded[31]; on their research and public health programmes including on COVID-19 research.

## Aims

Our overarching aim is to develop and apply a multidisciplinary research platform in SEA for rapid assessment of the biological significance of SARS-CoV-2 variants, thereby informing coordinated local, regional and global responses to the COVID-19 pandemic. Our specific aims are:

1. Establish a new SEA research platform that supports locally led investigations evaluating the biology of emerging SARS-CoV-2 variants.
2. Employ state-of-the art structural biology to provide rapid prediction of the ability of new variants to evade host immunity and drugs.
3. Evaluate the impact of VOCs on antibody and T-cell responses in SEA populations, and the clinical consequences of infection.
4. Create a framework for effective communication and engagement with policy makers and the public concerning new virus variants and their potential to threaten public health.

## Research approaches

Our approaches to data generation and public health impact are outlined in Figure 1. Our objectives are delivered through five work packages (WPs), with work under aim 3 subdivided into WP3 (antibody responses) and WP4 (T-cell responses) (Figure 2). The core laboratory research activities are described under WP3&4, supported by WP1, 2 & 5. More specifically, WP1 will establish a foundation for the delivery of the laboratory-based analysis (WP3&4), while WP2 will inform key analysis undertaken under WP3 & 4. Finally, WP5 aims are to bring research results

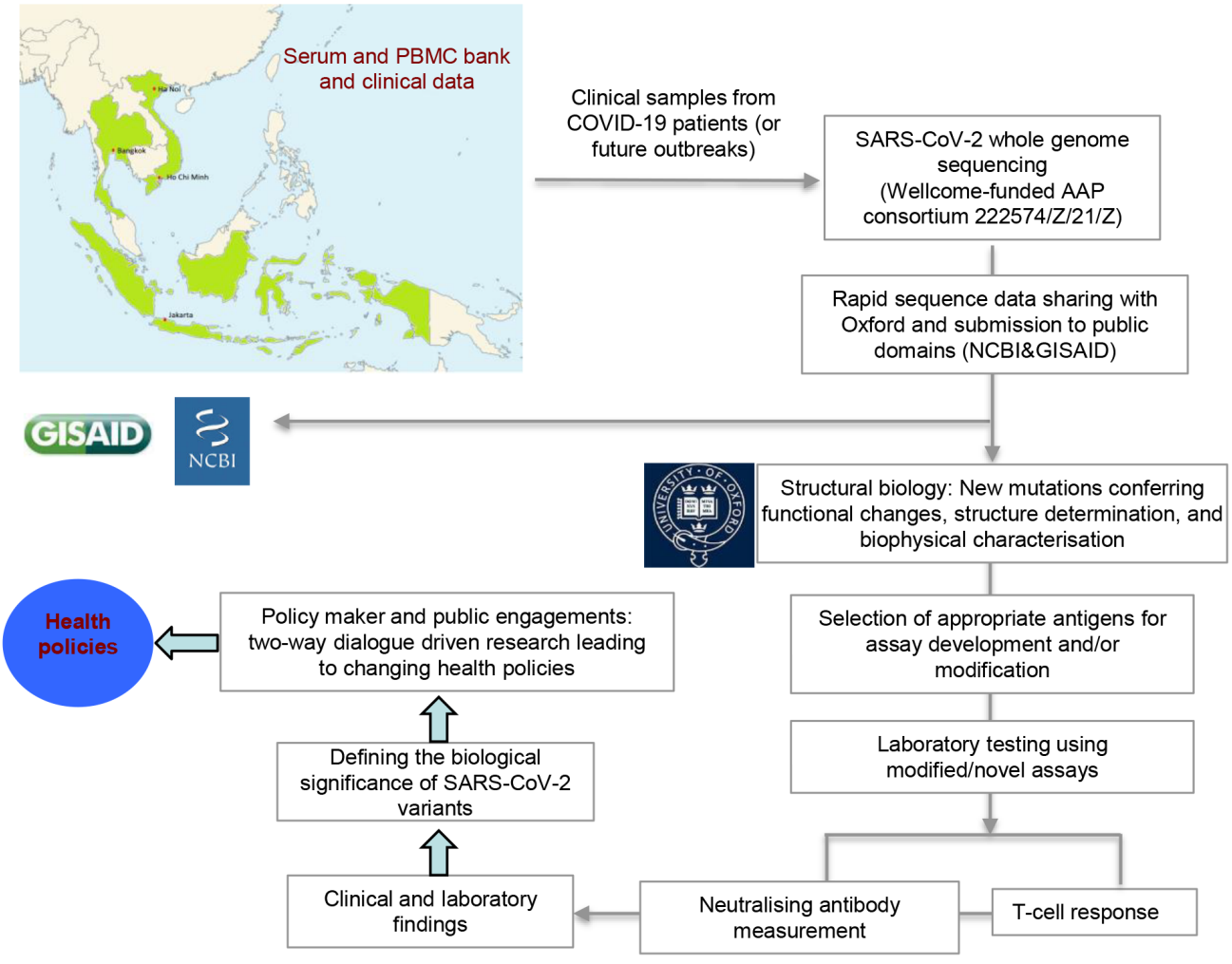


**Figure 1. An outline of our approaches from genetic characterization of variants of concern to generation of immunological data to inform public health response.** The platform that enables rapid biological assessment of SARS-CoV-2 variants within SEA is being built on existing expertise and laboratory capacities within Vietnam and Thailand Wellcome Africa Asia Programmes. This will allow a locally-led research response to the COVID-19 pandemic and future outbreaks.

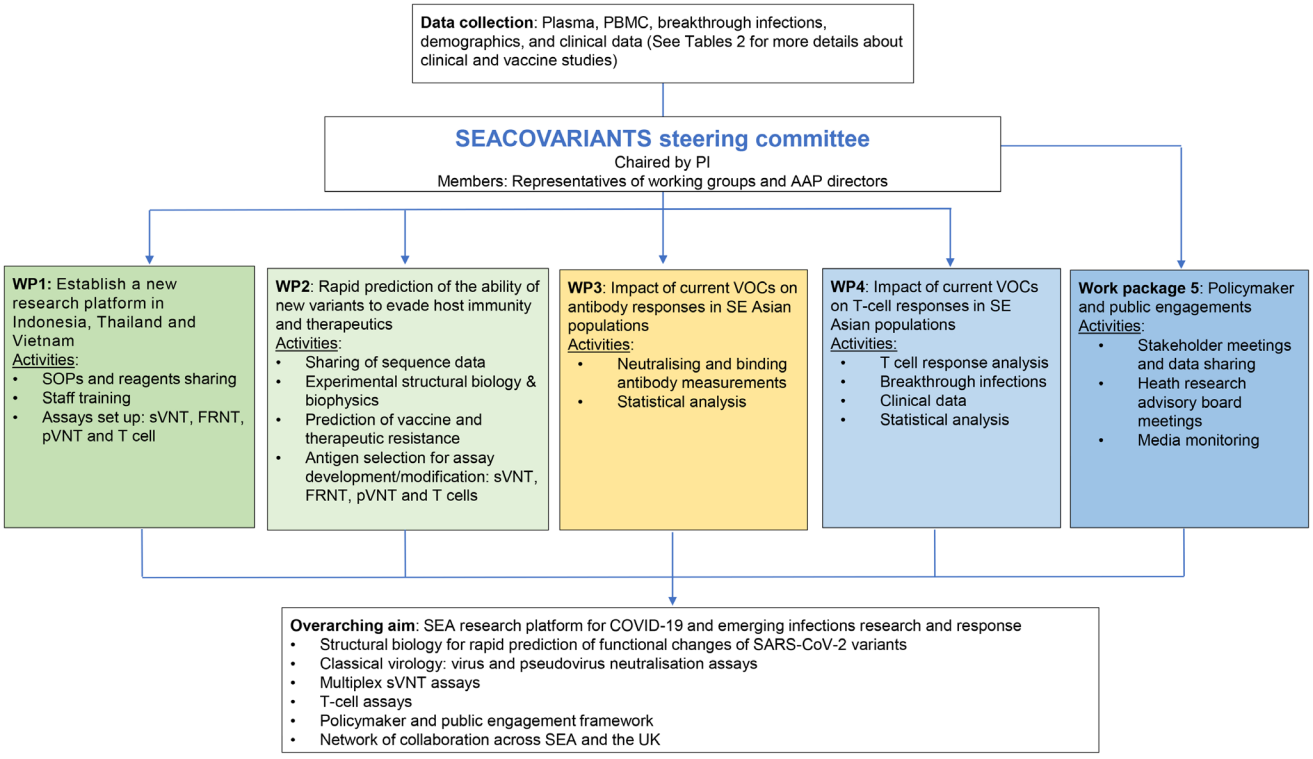


**Figure 2. SEACOVARIANTS work packages.** Our objectives are delivered through five Work Packages (WPs). The core laboratory research activities are described under WP3&4, supported by WP1, 2 & 5. WP1 will establish a foundation for the delivery of the laboratory-based analysis (WP3&4), while WP2 will inform key analysis undertaken under WP3 & 4. WP5 brings research results (WP3 & 4) into practice and utilizes engagement activities to inform the design of WP3 & 4.

(WP3 & 4) into practice and to utilize engagement activities to inform the design of WP3 & 4.

***WP1 (objective 1)**: Establish a new research platform in Indonesia, Thailand and Vietnam*

Laboratory capacity development will be accomplished through sharing of SOPs and reagents, and training of local laboratory staff during lab visits, and co-supervision of PhD students. Table 1 illustrates existing and laboratory capacity in Indonesia, Thailand and Vietnam as well as capacity to be developed through the work of the consortium.

***WP2 (objective 2):** Rapid prediction of the ability of new variants to evade host immunity and therapeutics*

Building on approaches implemented for UK surveillance structural analyses is used to assess the impact of mutations arising in SEA on responses from current vaccines and infection, as well as on therapeutics. These insights will inform the selection of appropriate antigens for pseudovirus, surrogate virus and focus reduction neutralization test (PVNT, sVNT and FRNT) and T-cell assay development/adjustment. Potentially significant mutations will be experimentally dissected by structural analysis (via cryo-EM or crystallography), pseudovirus analysis, and biophysical characterization of changes to binding to representative monoclonal antibodies, therapeutic antibodies and ACE2 receptor[3].

***WP3 (objective 3)**: Impact of current VOCs on antibody responses in SEA populations*

We focus on variants currently circulating in the region (including sublineages of Omicrons such as XBB.1.5 and XBB.1.16), and future VOCs arising during the timeframe of the award. Antibody responses will be assessed using a panel of sera collected from individuals with different infection and/or vaccination status (Table 2).

Neutralising antibodies are measured using a combination of live virus focus reduction neutralisation tests, high throughput Luminex multiplex surrogate viral neutralisation tests (sVNT) and/or pseudovirus neutralisation tests (PVNT)[3]. Although live virus neutralisation assays remain the gold standard, these assays are limited in throughput compared with alternatives, and require live viruses and BSL3 facilities. The Luminex sVNT accommodates >20 antigens (sufficient to cover all VOCs and a wide range of sarbecoviruses, including SARS-CoV-1) in one reaction tube and can be carried

**Table 1. Existing and required laboratory capacity in three research sites.**

| | BSL3 facility | N and S protein binding antibody | Multiplex sVNT | FRNT | Pseudovirus | Ex vivo IFN-γ ELISpot | Intracellular staining | CellTrace Violet proliferation |
|---|---|---|---|---|---|---|---|---|
| Indonesia | ● | ● | ● | ● | ● | ● | ● | ● |
| Thailand | ● | ● | ● | ● | ● | ● | ● | ● |
| Vietnam | ● | ● | ● | ● | ● | ● | ● | ● |

**Note to Table 1**: Blue circles: existing capacities for SARS-CoV-2, red circles: required capacities, purple circles: capacities available for other viral pathogens, and deployable for SARS-CoV-2. BSL = BioSafety Level, sVNT = surrogate Viral Neutralisation Test, FRNT = Focus Reduction Neutralisation Test, ELISpot = Enzyme-Linked Immunosorbent Spot.

**Table 2. Available cohorts for analysis.** Antibody responses will be assessed using a panel of sera collected from individuals with different infection and/or vaccination status from different study cohorts in Indonesia, Thailand and Vietnam.

| Site | Cohort | Primary doses | Booster | Population |
|---|---|---|---|---|
| **Vietnam** | Vaccine | ChAdOx1-S | BNT162b2 | HCW |
| | | Abdala | Abdala or BNT162b2 | General population |
| | SARS survivors | Pending | Pending | General population |
| | Natural Infection | | | General population |
| **Indonesia** | Vaccine cohort | CoronaVac | mRNA-1273 | HCW, general population and pregnant women |
| | Natural Infection | | | General population |
| **Thailand** | Vaccine cohort | CoronaVac | B162b2 or ChAdOx1-S | General population |
| | Natural Infection | | | General population |

out at BSL2[32]. The FRNT, sVNT and PVNT assays generate complementary data and will allow a broad assessment of cross reactivity between VOCs and sarbecoviruses.

***WP4 (objective 3):*** *Impact of current VOCs on T-cell responses in SEA populations*

The impact of VOCs on T cell responses is assessed using three complementary assays: *ex vivo* interferon gamma (IFN-γ) ELISpot assay, intracellular staining (ICS), and the CellTrace™ Violet (CTV) proliferation assay[33]. The ELISpot assay measures the effector T-cell response to peptides spanning SARS-CoV-2, and can be adapted to analyse T-cell responses to mutated regions of SARS-CoV-2 using custom-made peptide sets to look for T-cell escape[34–36]. The ELISpot protocol implemented has been optimized to be highly sensitive and specific[33] delivering consistent results across UK laboratories[35–37]. ICS gives key information about the character of the T-cell response, including the helper CD4 or cytotoxic CD8 composition and memory phenotype[33,35,37]. The CTV proliferation assay measures the central memory CD4 and CD8 response[33,38], and therefore can also identify cross-reactivity between VOCs and previous exposure with other sarbecoviruses, and/or common cold coronaviruses. There will be opportunity to evaluate the impact of baseline T-cell responses to the "common cold" coronaviruses (229E, NL63, OC43, HKU-1) on the T-cell response to ancestral strains and VOCs after vaccination through co-ordination with current research in Oxford. The platform will benefit from collaboration with La Jolla Institute for Immunology. La Jolla lab was able to rapidly support investigation of the T-cell response to Omicron by shipping peptides to five global labs within 2 weeks of release of viral sequence, and will collaborate to supply SARS-CoV-2 peptides and expertise for this study[15,39].

The T-cell response to circulating VOCs will be compared between cohorts of individuals with COVID-19, between recipients of different primary vaccine courses and between populations (Table 2), to define protection of populations against current and emerging VOCs.

Through clinical studies, we have been collecting meta clinical data during hospitalization and samples from COVID-19 patients admitted to our collaborating hospitals[40,41].

This has enabled us to start assessing the severity associated with respective SARS-CoV-2 variants, and will allow us to relate immune responses to individual variants with severity profiles.

***WP5 (objective 4):*** *Policymaker and public engagements*
SEACOVARIANTS will synthesizes data about immune/vaccine/therapeutic escape potential of SARS-CoV-2 variants allied with clinical data and provide critical information for policy makers as the pandemic progresses in SEA. Over decades, we have established strong connections with health policy makers (including Ministry of Health (MOH)) in our respective countries. We have been able to rapidly disseminate our COVID-19 research findings to in-country local policy makers using various approaches; 1) OAB meetings organized every quarter, 2) regular written reports, 3) oral presentations, 4) personal communication, 5) consultation meetings, and 6) press releases. In response to the Omicron emergence, Vietnam AAP Director Prof Guy Thwaites and lead consortium PI Tan were invited to attend informal consultation meetings with the Director of Health Service and the Party Committee Secretary of HCMC in November 2021. On 22nd April 2022, lead applicant Tan presented findings from our on-going Wellcome-funded genomic surveillance project at an MOH meeting. In Indonesia, the team has catalysed high throughput genomics assays and monthly bulletins with recommendations for the MOH.

In many LMICs the public, and in particular young people, have little opportunity to contribute to public health decision making. Adults strongly influence the decisions made for children. SEACOVARIANTS is creating platforms for public involvement in this project, providing valuable feedback on public perceptions about SARS-CoV-2 variants. Youth-led engagement and adult involvement from the outset will inform researchers and stakeholders and support public health measures preventing and controlling new outbreaks. The partnership with young people through media and digital engagement will increase public awareness of the benefits of research.

Engagement activities are led by senior engagement practitioners imbedded in the AAPs with decades of experience in LMICs, including:

**Health Research Advisory Groups**: existing public adult groups in Vietnam and Thailand give feedback on study design, science findings and their wider implications. They will offer insights into wider public perceptions about variants, surveillance etc.

**Youth Working Groups**: local groups of young people aged 18–24 have been established through our existing youth networks. They are ambassadors for the project and bring youth voices to researchers and stakeholders around new variants, and collaborate with the research teams to develop and lead engagement activities relevant to their communities.

**Media monitoring**: Tracking misinformation and public concerns regarding VOCs in social media informs the content of engagement activities to be relevant to local populations. We have a successful track record of monitoring COVID-19 related media across SEA to inform social media and public health messaging content.

Public and youth engagement are raising the profile of the research, create opportunities for public voices in the process, build our understanding of public priorities regarding pandemics, and support the case when research is presented to policymakers. The partnerships and engagement models developed in each site will build capacity for ongoing engagement for the researchers, and within the research centres.

### Collaborative approach

From many years of collaborative experience, from our perspective a key lesson learnt is that export of pathogen and human samples to high-income countries for analysis can be slow or even impossible. Pandemic and outbreak investigation require rapid access to sophisticated laboratory techniques. Our platform is therefore designed to enable the bulk of the work to be completed locally, by establishing a network of support between labs, including in Oxford. Experimental structural biology, biophysics and monoclonal antibody testing will be performed in Oxford due to the need for specialist infrastructure (e.g., synchrotron radiation source, cryoEM), however, provision of tools to visualise, and expertise to assess, the likely impact of mutations will be developed, to underpin informed decision making across all partners.

Allocation of resources and training is based on the need from each project partner to ensure all participating sites have sufficient resources and capacity to deliver the project at the highest standard. The data will be made available at the time of publication. Contributing individuals are acknowledged and/or named as authors in scientific publications, according to the authorship criteria.

The project is overseen by the consortium Steering Committee, chaired by the lead applicant with members including co-investigators, public health stakeholders in respective countries and AAP directors (Figure 2). The committee meets virtually at least every six months to discuss the overall strategic direction of the project and progress. Additionally, working groups ensure specific WPs are delivered as scheduled.

## Conclusion

Emerging viruses pose a significant threat to healthcare systems worldwide, as exemplified by the COVID-19 pandemic. Yet, another new pathogen, causing ‘disease X’, will almost certainly emerge within the next decades. Pandemic preparedness is one of the top priorities of the WHO. Asia is home to more than 50% of the world’s population.

The population in Indonesia, Thailand and Vietnam combined accounts for over 65% of the >655 million people living in SEA. Fragile health systems, dense populations with people and animals living close together, rapid urbanization and economic development, yet with stark health inequalities make the region highly susceptible to emerging pathogens[42].

A critical component of pandemic preparedness and response is to establish essential capacities that enable rapid and robust scientific laboratory, epidemiological, clinical and social research within the most relevant settings and structures. Alongside the development of laboratory capacity in the region, the SEACOVARIANTS consortium will graduate a cohort of local scientists, including post-doctoral researchers, PhDs and research assistants with expertise in structural analysis, classical virology, advanced T-cell immunity and serology in SEA. The project helps strengthen our long-standing networks with policy makers and key stakeholders in respective countries, bring our research into practice, and further establish a scientific relationship between SEA and the UK. Collectively, the SEACOVARIANTS will provide proof-of-principle that such advanced laboratory tools can be applied effectively in LMICs and thereby help SEA and the world to better prepare for future pandemics.

## Data availability

### Underlying data

No data are associated with this article.

### Acknowledgements

**SEACOVARIANTS consortium members**

Priyanka Abraham[1], Kanpong Boonthaworn[2], Cao Thu Thuy[3], Mary Chambers[3], Warangkana Chantima[4], Narisara Chantratita[5], Phaik-Yeong Cheah[2,6], Raksha Das[7], Nicholas PJ Day[2,6], Wanwisa Dejnirattisai[8], Ragil Dien[9], Aiete Dijokaite-Guraliuc[7], Adul Dulsuk[5], Susanna J Dunachie[1,10], Alba Grifoni[11], Winahyu Handayani[9], Raph L Hamers[6,9], Jennifer Hill[1], Sophon Iamsirithaworn[12], E Yvonne Jones[1], Paul Klenerman[1,10], Barbara Kronsteiner-Dobramysl[1], Lam Anh Nguyet[3], Lam Minh Yen[3], Le Nguyen Truc Nhu[3], Le Van Tan[3], Le Kim Thanh[3], Lim Beng Lee[13], Chang Liu[7], Juthathip Mongkolsapaya[2,7,14], Nghiem My Ngoc[3], Nguyen To Anh[3], Nguyen Thi Thu Hong[3], Nguyen Thi Han Ny[3], Nguyen Thi Thao[3], Pham Tieu Kieu[3], Prapassorn Poolchanuan[5], Tassawan Poomchaichote[2], Jingshan Ren[1], Gavin Screaton[7,14], Muneeswaran Selvaraj[7], Alessandro Sette[11], Anuraj Shankar[9], Eva Simarmata[9], David I Stuart[1], Piyada Supasa[7], Suwarti[9], Chee-Wah Tan[13], Yanie Tayipto[9], Guy Thwaites[3,6], Louise Thwaites[3,6], Vichapon Tiacharoen[5], Tran Tan Thanh[3], Tran Ba Thien[3], Truong Hoang Chau Truc[3], H.Rogier van Doorn[15], Vo Tan Hoang[3], Vu Thi Ty Hang[3], Vu Duy Thanh[3], Lin-Fa Wang[13], Wee-Chee Yap[13], Sabighoh Zanjabila[9] and Martha Zewdie[1].

(*Names are alphabetically listed)

[1]Division of Structural Biology, Nuffield Department of Medicine, University of Oxford, Oxford, UK

[2]Mahidol Oxford Tropical Medicine Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

[3]Oxford University Clinical Research Unit, Ho Chi Minh City, Vietnam

[4]Siriraj Center of Research Excellence in Dengue and Emerging Pathogens, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[5]Department of Microbiology and Immunology, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand

[6]Centre for Tropical Medicine and Global Health, Nuffield Department of Medicine, University of Oxford, Oxford, UK

[7]Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, UK

[8]Division of Emerging Infectious Disease, Research Department, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[9]Oxford University Clinical Research Unit Indonesia, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia

[10]Oxford University Hospitals NHS Foundation Trust, Oxford, UK

[11]La Jolla Institute for Immunology, CA, USA

[12]Department of Disease Control, Ministry of Public Health, Thailand

[13]Programme in Emerging Infectious Diseases, Duke-NUS Medical School, Singapore

[14]Chinese Academy of Medical Science (CAMS) Oxford Institute (COI), University of Oxford, Oxford, UK

[15]Oxford University Clinical Research Unit, Ha Noi, Vietnam

## References

1. WHO: **Global genomic surveillance strategy 2022-2032.** 2021.
Reference Source

2. Planas D, Veyer D, Baidaliuk A, *et al.*: **Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization.** *Nature.* 2021; **596**(7871): 276–280.
PubMed Abstract | Publisher Full Text

3. Dejnirattisai W, Huo J, Zhou D, *et al.*: **SARS-CoV-2 omicron-B.1.1.529 leads to widespread escape from neutralizing antibody responses.** *Cell.* 2022; **185**(3): 467–484.e15.
PubMed Abstract | Publisher Full Text | Free Full Text

4. Gao Y, Cai C, Grifoni A, *et al.*: **Ancestral SARS-CoV-2-specific T cells**

**cross-recognize the omicron variant.** *Nat Med.* 2022; **28**(3): 472–476.
PubMed Abstract | Publisher Full Text | Free Full Text

5. Rössler A, Riepler L, Bante D, *et al.*: **SARS-CoV-2 omicron variant neutralization in serum from vaccinated and convalescent persons.** *N Engl J Med.* 2022; **386**(7): 698–700.
PubMed Abstract | Publisher Full Text | Free Full Text

6. Feng S, Phillips DJ, White T, *et al.*: **Correlates of protection against symptomatic and asymptomatic SARS-CoV-2 infection.** *Nat Med.* 2021; **27**(11): 2032–2040.
PubMed Abstract | Publisher Full Text | Free Full Text

7. Khoury DS, Cromer D, Reynaldi A, *et al.*: **Neutralizing antibody levels are highly predictive of immune protection from symptomatic SARS-CoV-2 infection.** *Nat Med.* 2021; **27**(7): 1205–1211.
PubMed Abstract | Publisher Full Text

8. Addetia A, Crawford KHD, Dingens A, *et al.*: **Neutralizing antibodies correlate with protection from SARS-CoV-2 in humans during a fishery vessel outbreak with a high attack rate.** *J Clin Microbiol.* 2020; **58**(11): e02107–20.
PubMed Abstract | Publisher Full Text | Free Full Text

9. Moore PL, Moyo-Gwete T, Hermanus T, *et al.*: **Neutralizing antibodies elicited by the Ad26.COV2.S COVID-19 vaccine show reduced activity against 501Y.V2 (B.1.351), despite protection against severe disease by this variant.** *BioRxiv.* 2021; **01**: 1–23.
Publisher Full Text

10. Keeton R, Tincho MB, Ngomti A, *et al.*: **T cell responses to SARS-CoV-2 spike cross-recognize omicron.** *Nature.* 2022; **603**(7901): 488–492.
PubMed Abstract | Publisher Full Text | Free Full Text

11. GeurtsvanKessel CH, Geers D, Schmitz KS, *et al.*: **Divergent SARS-CoV-2 omicron-reactive T and B cell responses in COVID-19 vaccine recipients.** *Sci Immunol.* 2022; **7**(69): eabo2202.
PubMed Abstract | Publisher Full Text | Free Full Text

12. Madelon N, Heikkilä N, Royo IS, *et al.*: **Omicron-specific cytotoxic T-Cell responses after a third dose of mRNA COVID-19 vaccine among patients with multiple sclerosis treated with ocrelizumab.** *JAMA Neurol.* 2022; **79**(4): 399–404.
PubMed Abstract | Publisher Full Text | Free Full Text

13. Fabrizio C, Capone A, Sabatini A, *et al.*: **Preserved T cell reactivity to the SARS-CoV-2 omicron variant indicates continued protection in vaccinated individuals.** *BioRxiv.* 2021.
Publisher Full Text

14. Liu J, Chandrashekar A, Sellers D, *et al.*: **Vaccines elicit highly conserved cellular immunity to SARS-CoV-2 omicron.** *Nature.* 2022; **603**(7901): 493–496.
PubMed Abstract | Publisher Full Text | Free Full Text

15. Tarke A, Coelho CH, Zhang Z, *et al.*: **SARS-CoV-2 vaccination induces immunological T cell memory able to cross-recognize variants from alpha to omicron.** *Cell.* 2022; **185**(5): 847–859.e11.
PubMed Abstract | Publisher Full Text | Free Full Text

16. Mefsin Y, Chen D, Bond HS, *et al.*: **Epidemiology of infections with SARS-CoV-2 omicron BA.2 variant in hongkong.** *MedRxiv.* 2022; **28**(9): 2022.04.07.22273595.
Publisher Full Text

17. Drosten C, Günther S, Preiser W, *et al.*: **Identification of a novel coronavirus in patients with severe acute respiratory syndrome.** *N Engl J Med.* 2003; **348**(20): 1967–1976.
PubMed Abstract | Publisher Full Text

18. Zhu N, Zhang D, Wang W, *et al.*: **A novel coronavirus from patients with pneumonia in China, 2019.** *N Engl J Med.* 2020; **382**(8): 727–733.
PubMed Abstract | Publisher Full Text | Free Full Text

19. Li W, Shi Z, Yu M, *et al.*: **Bats are natural reservoirs of SARS-like coronaviruses.** *Science.* 2005; **310**(5748): 676–679.
PubMed Abstract | Publisher Full Text

20. Lau SKP, Woo PCY, Li KSM, *et al.*: **Severe Acute Respiratory Syndrome CoronaVirus-like virus in Chinese horseshoe bats.** *Proc Natl Acad Sci U S A.* 2005; **102**(39): 14040–14045.
PubMed Abstract | Publisher Full Text | Free Full Text

21. Wacharapluesadee S, Tan CW, Maneeorn P, *et al.*: **Evidence for SARS-CoV-2 related coronaviruses circulating in bats and pangolins in southeast asia.** *Nat Commun.* 2021; **12**(1): 972.
PubMed Abstract | Publisher Full Text | Free Full Text

22. Nga NTT, Latinne A, Thuy HB, *et al.*: **Evidence of SARS-CoV-2 related coronaviruses circulating in sunda pangolins (*manis javanica*) confiscated from the illegal wildlife trade in viet nam.** *Front Public Health.* 2022; **10**: 826116.
PubMed Abstract | Publisher Full Text | Free Full Text

23. Delaune D, Hul V, Karlsson EA, *et al.*: **A novel SARS-CoV-2 related Coronavirus in bats from Cambodia.** *Nat Commun.* 2021; **12**(1): 6563.
PubMed Abstract | Publisher Full Text | Free Full Text

24. Tu NTK, Tue NT, Vapalahti O, *et al.*: **Occupational animal contact in southern and central vietnam.** *EcoHealth.* 2019; **16**(4): 759–771.
PubMed Abstract | Publisher Full Text | Free Full Text

25. Tan CW, Chia WN, Young BE, *et al.*: **Pan-sarbecovirus neutralizing antibodies in BNT162b2-immunized SARS-CoV-1 survivors.** *N Engl J Med.* 2021; **385**(15): 1401–1406.
PubMed Abstract | Publisher Full Text | Free Full Text

26. Chau NVV, Nguyet LA, Truong NT, *et al.*: **Immunogenicity of Oxford-AstraZeneca COVID-19 vaccine in vietnamese health-care workers.** *Am J Trop Med Hyg.* 2022; **106**(2): 556–561.
PubMed Abstract | Publisher Full Text | Free Full Text

27. Sinto R, Utomo D, Nelwan EJ, *et al.*: **Serum anti-Spike antibody titers before and after heterologous booster with mRNA-1273 SARS-CoV-2 vaccine following two doses of inactivated whole-virus CoronaVac vaccine.** *MedRxiv.* 2021; **021**: 1–23.
Publisher Full Text

28. Assawakosri S, Kanokudom S, Suntronwong N, *et al.*: **Neutralizing activities against the omicron variant after a heterologous booster in healthy adults receiving two doses of CoronaVac vaccination.** *J Infect Dis.* 2022; **226**(8): 1372–1381.
PubMed Abstract | Publisher Full Text

29. Hernández-Bernal F, Ricardo-Cobas MC, Martín-Bauta Y, *et al.*: **Safety, tolerability, and immunogenicity of a SARS-CoV-2 recombinant spike protein vaccine: a randomised, double-blind, placebo-controlled, phase 1-2 clinical trial (ABDALA Study).** *MedRxiv.* 2021.
Publisher Full Text

30. Melo-González F, Soto JA, González LA, *et al.*: **Recognition of variants of concern by antibodies and T cells induced by a SARS-CoV-2 inactivated vaccine.** *Front Immunol.* 2021; **12**: 747830.
PubMed Abstract | Publisher Full Text | Free Full Text

31. Maung Lwin K, Cheah PY, Cheah PK, *et al.*: **Motivations and perceptions of community advisory boards in the ethics of medical research: the case of the Thai-Myanmar border.** *BMC Med Ethics.* 2014; **15**(1): 12.
PubMed Abstract | Publisher Full Text | Free Full Text

32. Wang LF, Tan CW, Chia WN, *et al.*: **Differential escape of neutralizing antibodies by SARS-CoV-2 omicron and pre-emergent sarbecoviruses.** *Res Sq.* 2022; rs.3.rs-1362541.
PubMed Abstract | Publisher Full Text | Free Full Text

33. Ogbe A, Kronsteiner B, Skelly DT, *et al.*: **T cell assays differentiate clinical and subclinical SARS-CoV-2 infections from cross-reactive antiviral responses.** *Nat Commun.* 2021; **12**(1): 2055.
PubMed Abstract | Publisher Full Text | Free Full Text

34. Skelly DT, Harding AC, Gilbert-Jaramillo J, *et al.*: **Two doses of SARS-CoV-2 vaccination induce robust immune responses to emerging SARS-CoV-2 variants of concern.** *Nat Commun.* 2021; **12**(1): 5061.
PubMed Abstract | Publisher Full Text | Free Full Text

35. Payne RP, Longet S, Austin JA, *et al.*: **Immunogenicity of standard and extended dosing intervals of BNT162b2 mRNA vaccine.** *Cell.* 2021; **184**(23): 5699–5714.e11.
PubMed Abstract | Publisher Full Text | Free Full Text

36. de Silva TI, Liu G, Lindsey BB, *et al.*: **The impact of viral mutations on recognition by SARS-CoV-2 specific T cells.** *iScience.* 2021; **24**(11): 103353.
PubMed Abstract | Publisher Full Text | Free Full Text

37. Angyal A, Longet S, Moore SC, *et al.*: **T-cell and antibody responses to first BNT162b2 vaccine dose in previously infected and SARS-CoV-2-naive UK health-care workers: a multicentre prospective cohort study.** *Lancet Microbe.* 2022; **3**(1): e21–e31.
PubMed Abstract | Publisher Full Text | Free Full Text

38. Tomic A, Skelly DT, Ogbe A, *et al.*: **Divergent trajectories of antiviral memory after SARS-CoV-2 infection.** *Nat Commun.* 2022; **13**(1): 1251.
PubMed Abstract | Publisher Full Text | Free Full Text

39. Tarke A, Sidney J, Methot N, *et al.*: **Impact of SARS-CoV-2 variants on the total $CD4^+$ and $CD8^+$ T cell reactivity in infected or vaccinated individuals.** *Cell Rep Med.* 2021; **2**(7): 100355.
PubMed Abstract | Publisher Full Text | Free Full Text

40. Surendra H, Elyazar IR, Djaafara BA, *et al.*: **Clinical characteristics and mortality associated with COVID-19 in Jakarta, Indonesia: A hospital-based retrospective cohort study.** *Lancet Reg Health West Pac.* 2021; **9**: 100108.
PubMed Abstract | Publisher Full Text | Free Full Text

41. Chau NVV, Lam VT, Dung NT, *et al.*: **The natural history and transmission potential of asymptomatic Severe Acute Respiratory Syndrome Coronavirus 2 infection.** *Clin Infect Dis.* 2020; **71**(10): 2679–2687.
PubMed Abstract | Publisher Full Text | Free Full Text

42. Coker RJ, Hunter BM, Rudge JW, *et al.*: **Emerging infectious diseases in Southeast Asia: regional challenges to control.** *Lancet.* 2011; **377**(9765): 599–609.
PubMed Abstract | Publisher Full Text | Free Full Text

# Open Peer Review

## Current Peer Review Status: ? ✓ ✓

**Version 1**

Reviewer Report 16 July 2024

https://doi.org/10.21956/wellcomeopenres.22953.r87710



✓ **Takamasa Ueno**
Kumamoto University, Kumamoto, Japan
**Isaac Ngare**
Joint Research Center for Human Retrovirus Infection, Kumamoto University, Kumamoto, Kumamoto Prefecture, Japan

The original version of this report was made by a PhD student (currently under evaluation for PhD), Isaac Ngare in my lab, and then I edited and approved it.

Le Nguyen Truc Nhu et al, provide a detailed plan of the Wellcome-funded southeast Asia initiative to combat SARS-CoV-2 variants (SEACOVARIANTS) activities in the southeast Asia region where SARS-CoV-2 surveillance is underdeveloped and the majority of rural populations are in close contact with animals making them susceptible to zoonotic spillovers. The manuscript is clearly written and provides a detailed and elaborate step-by-step account of the consortium's plan to combat the emergence of new SARS-CoV-2 variants of concern. There are however a few concerns that need to be addressed to improve the clarity of the manuscript.

1. The tone of the manuscript appears to be set in the middle of the COVID-19 pandemic while in many parts of the world, COVID-19 has been downgraded to the public health threat level of seasonal flus. This distinction is especially important because it has implications in the testing and detection of COVID-19 infections in public hospitals. As of 2024, many countries in Africa, and maybe high income countries, had stopped mass testing for COVID-19 unless requested by the client at their own cost. How is the situation SEA currently? If there are no government/insurance-funded tests, will this initiative carter the costs of COVID-19 tests for all the cases presenting with flu-like symptoms before sampling the positive cases? I believe this may have significant cost implications and the authors could clarify it.
2. Another concern is how the findings from antibody and T cell responses will be converted to policy. Although antibody and T cell response are correlates of protection, the threshold below which protection is lost has been elusive and could vary across assays in WP3 and WP4. If for instance responses against a new variant are 2-fold lower than the prevalent variant, is this difference biologically significant to justify changes in policy? Also, the magnitude of antibody and

T cell responses to new variants will significantly be influenced by the duration since vaccination or exposure to preceding variants. A clarification on how these factors will accounted for before inclusion in policy could be informative to the reader.

**Is the rationale for the Open Letter provided in sufficient detail?**
Yes

**Does the article adequately reference differing views and opinions?**
Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**
Yes

**Is the Open Letter written in accessible language?**
Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**
Yes

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** immunology, virology, HIV/AIDS, SARS-CoV-2, a member of Gene-to-Phenotypes in Japan for COVID-19

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 26 June 2024

https://doi.org/10.21956/wellcomeopenres.22953.r81748



**Pushpamali De Silva**
Harvard Medical School,, Boston, MA, USA

The SEACOVARIANTS initiative outlines a comprehensive multidisciplinary research platform aimed at rapidly assessing the biological significance of SARS-CoV-2 variants in SEA. The overarching goal is to inform coordinated local, regional, and global responses to the COVID-19 pandemic. This manuscript reports the clarity, feasibility, and potential impact of the aims, research approaches, and collaborative strategies proposed by SEACOVARIANTS.

**Strengths:**

- The aims of SEACOVARIANTS are well-defined and aligned with addressing critical gaps in understanding SARS-CoV-2 variants. Each aim contributes uniquely to the overall objective of enhancing pandemic preparedness through local capacity building, structural biology predictions, immune response evaluations, and effective communication strategies.
- The initiative employs a structured approach with five work packages (WPs) that integrate laboratory-based investigations (WP3&4) with foundational activities (WP1), structural biology predictions (WP2), and translation into policy and practice (WP5). This structured approach ensures robust data generation and impactful public health outcomes.
- A commendable aspect of SEACOVARIANTS is its emphasis on establishing and enhancing local research capacities across Indonesia, Thailand, and Vietnam. This includes laboratory infrastructure development, training of local personnel, and collaborative efforts with international partners to ensure sustainability beyond the project duration.
- The initiative leverages expertise across structural biology, virology, immunology, and public health, facilitated through a collaborative framework involving academic institutions, public health stakeholders, and policy makers. This approach fosters knowledge exchange and strengthens scientific relationships between SEA and the UK.
- SEACOVARIANTS incorporates robust public engagement strategies aimed at informing and involving policy makers and the public about virus variants and associated public health risks. These efforts are critical for fostering trust, addressing misinformation, and enhancing community participation in pandemic response efforts.

**Areas for Consideration:**

- While the initiative outlines ambitious goals, there should be careful consideration of operational challenges such as logistical coordination across multiple countries, ensuring uniformity in data collection protocols, and navigating regulatory landscapes for research involving human subjects and pathogens.
- Sustainability beyond the project period is crucial. SEACOVARIANTS should outline plans for continued funding, institutional support, and capacity building to ensure that local research capacities are maintained and expanded beyond the immediate scope of the initiative.
- While the initiative primarily focuses on biological and clinical aspects, integrating social sciences could provide deeper insights into community perceptions, vaccine acceptance, and behavioral responses to variants. This holistic approach would enhance the effectiveness of public health interventions.
- Given the global significance of variant surveillance, ensuring timely data sharing and accessibility is essential. SEACOVARIANTS should establish clear protocols for data management, sharing agreements, and open-access publication of findings to facilitate broader scientific collaboration and policy impact.
- Incorporating robust mechanisms for monitoring and evaluating the impact of SEACOVARIANTS on local health systems, policy development, and public awareness is vital. This will enable continuous improvement and evidence-based advocacy for sustaining and expanding similar initiatives.

Overall, SEACOVARIANTS represents a commendable collaborative effort that aligns with global health priorities and demonstrates a proactive approach to pandemic preparedness in the region.

**Is the rationale for the Open Letter provided in sufficient detail?**

Yes

**Does the article adequately reference differing views and opinions?**
Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**
Partly

**Is the Open Letter written in accessible language?**
Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**
Yes

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** Immunology, Biology

**I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Reviewer Report 29 May 2024

https://doi.org/10.21956/wellcomeopenres.22953.r81753



?

**Sonika Bhatnagar**
Netaji Subhas University of Technology, Dwarka, New Delhi,, India
**Shubhangi Gupta**
Computational and Structural Biology laboratory, Department of Biological Sciences and Engineering, Netaji Subhas University of Technology, New Delhi, Delhi, India

In the article, the authors have discussed about the Southeast Asia initiative to combat SARS-CoV-2 variants (SEACOVARIANTS) consortium funded by Wellcome. This represents a well-planned effort to develop a multidisciplinary research platform in Southeast Asia for the rapid assessment of the biological significance of SARS-CoV-2 variants. Authors have emphasized on the importance of pandemic preparedness and the need for developing robust laboratory, epidemiological, clinical, and social research infrastructure in Southeast Asia.
The consortium aims to strengthen local scientific capacity in Southeast Asia to enable the fast evaluation of emerging SARS-CoV-2 variants that could pose a potential threat to public health. The project seeks to build research capacity, train scientists, and establish a research network to

lay the foundation for locally-led outbreak responses. This initiative would further lead to establishment of a new research platform, rapid prediction of the ability of new variants to evade host immunity, evaluation of the impact of variants on antibody and T-cell responses, as well as the creation of a framework for effective communication and engagement with the public and policymakers.
The research approaches presented in the form of work packages are detailed, including the structural biology analysis of the potential SARS-CoV-2 variants, their assessment of antibody and T-cell responses along with engagement activities with policymakers and the public.

Comments:

1. I am particularly impressed with the arguments in favor of starting the SEA SARS-CoV-2 consortium, including population density, close contact with animals, diversity of vaccine strategies, etc. The biology and thus the clinical profile of new and emerging variants is going to keep changing – and will need to be investigated. Therefore, apart from genomics, basic biology correlated with clinical findings will be key to monitoring the effects of new SARS-CoV-2 variants. This will also have considerable impact on capacity building and pandemic preparedness for the SEA countries. I am also happy with the plans for public engagement, particularly the youth, who can particularly help with contact within the community. This research could also help further evaluation of the differences in immune responses among individuals with different infections/vaccination status/HLA repertoires.
2. The authors state that “With SARS-CoV-2 continuing to circulate around the world, new variants with structural changes in the spike protein that can evade existing infection or vaccine-derived immunity will almost certainly continue to emerge.” It is my understanding that such variants that evade infection/vaccine derived immunity may emerge due to a large number of mechanisms, not just due to structural changes in the Spike protein. Are there plans underway for structural elucidation of other proteins/complexes apart from Spike?
3. The variants that have posed most health complications in the South East Asian countries could be mentioned.
4. HLA repertoire differences can occur not only because of being in close contact with animals but also because of the different climatic/ environmental conditions. What are the major differences in the HLA repertoires of the individuals in South East Asian countries in comparison with others?
5. Can healthy individuals who have been affected by after-effects of the vaccine also be included in the cohort?
6. The SEA consortium must network well with neighboring SA and other countries, as once any advantageous mutations are gained, the variant will spread rapidly and become the dominant form.
7. While statistical validation is a very intrinsic and necessary part of the whole endeavor, completely new integrative ways of looking at and analyzing the data will be required in view of the diverse data types gathered from this kind of a project.
8. A focused effort will be required to frame key biological questions and to collect the key parameters related to variant biology, clinical outcomes, long-Covid and breakthrough infections. Once such information is available, it would be beneficial to harness AI/ML techniques.
9. While all the named components of the project are very important, the computational genomics has not been sufficiently outlined in my opinion.
10. I wish the investigators and all involved a brilliant scientific journey ahead.

**Is the rationale for the Open Letter provided in sufficient detail?**
Yes

**Does the article adequately reference differing views and opinions?**
Yes

**Are all factual statements correct, and are statements and arguments made adequately supported by citations?**
Yes

**Is the Open Letter written in accessible language?**
Yes

**Where applicable, are recommendations and next steps explained clearly for others to follow?**
Yes

***Competing Interests:*** No competing interests were disclosed.

***Reviewer Expertise:*** SARS CoV-2, Structural Biology, Computational Biology, Infectious disease, Cardiovascular disease

**We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however we have significant reservations, as outlined above.**