**SUPPLEMENTARY MATERIAL**

Table S1 Hospitalisations (WHO score >=4) by SARS-CoV-2 lineage and age

|  | ***ChAdOx1 nCoV-19*** | ***Control*** |
| --- | --- | --- |
| ***18-55 years*** | ***56 years +*** | ***18-55 years*** | ***56 years +*** |
| *Secondary cases**(> 21 days after dose 1, < 15 days after dose 2)* | *Undetermined/no swab* | 0 | 0 | 2 | 2 |
| *B.1.1.33* | 0 | 0 | 0 | 1 |
| *P.1* | 0 | 0 | 1 | 0 |
| *Primary cases**>= 15 days after dose 2* | *Undetermined/no swab* | 1 | 0 | 10 | 1 |
| *B.1.1.28* | 0 | 0 | 2 | 2 |
| *P.1* | 0 | 0 | 1 | 0 |
| *P.2* | 0 | 0 | 2 | 0 |

Table S2 Viral load from swabs (IU/mL)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Lineage | N  | Median | Lower Quartile | Upper Quartile | Minimum | Maximum |
| All swabs |
| B.1.1.28 | 78 | 10421194 | 3076815 | 134118446 | 45720 | 3719734679 |
| P.2 | 234 | 17495255 | 1129066 | 201985761 | 0 | 6030847082 |
| P.1 | 178 | 80814649 | 5753668 | 526356323 | 480 | 18347259144 |
| B.1.1.33 | 15 | 1341412 | 332255 | 13548956 | 61164 | 1408401265 |
| Undetermined | 135 | 117320 | 1882 | 63948286 | 0 | 3921994942 |
| Cases included in efficacy analysis |
| B.1.1.28 | 49 | 13565118 | 3433272 | 239472398 | 45720 | 3719734679 |
| P.2 | 153 | 16383823 | 1129066 | 208670379 | 0 | 6030847082 |
| P.1 | 18 | 28082673 | 1018799 | 371165029 | 98181 | 1988535214 |
| B.1.1.33 | 9 | 4209409 | 414335 | 11311270 | 332255 | 1408401265 |
| Undetermined | 71 | 2728762 | 2481 | 129539823 | 0 | 3921994942 |

Wilcoxon rank sum test comparing cases included in primary efficacy analysis with excluded cases, p=0.27.

Kruskal-Wallis test comparing viral load across lineages in all participants with swabs, p=0.0002.

Table S3 Days between illness onset and swabbing for NAAT testing

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Lineage** | **N** | **Median** | **Lower Quartile** | **Upper Quartile** |
| **Known lineage** |  |  |  |  |
|  **B.1.1.28** | 76 | 4 | 2.5 | 6 |
|  **B.1.1.33** | 15 | 4 | 2 | 6 |
|  **P.1** | 109 | 4 | 3 | 5 |
|  **P.2** | 238 | 4 | 3 | 6 |
| **Other B.1 lineage** | 19 | 3 | 2 | 6 |
| **Undetermined** | 49 | 8 | 6 | 12 |
| **Undetermined lineage – Not P.1 or P.2**  | 79 | 5 | 2 | 6 |

**RNA extraction and viral load quantification.**

For 96% of the sample set (650/676 samples, 516/518 of efficacy cohort), RNA was extracted from primary samples shipped at –80°C from participating sites in Brazil to the University of Oxford. The remaining samples were shipped as pre-extracted RNA. SARS-CoV-2 viral RNA was extracted from swab samples using the Quick-DNA/RNA Viral kit (Zymo Research): 200 µL of sample was mixed with 200 µL of DNA/RNA shield, before being extracted according to the manufacturer’s spin column protocol. RNA was eluted in 50 µL of DNAse/RNAse-free water and frozen at -80°C. SARS-CoV-2 RNA was quantified by real-time polymerase chain reaction (RT-PCR) using the CDC N1 oligonucleotide set (<https://www.cdc.gov/coronavirus/2019-ncov/lab/rt-pcr-panel-primer-probes.html>) and the Quantitect Probe RT-PCR kit (QIAGEN) in a 25 µL reaction volume containing 2 µL of extracted RNA. Oligonucleotides (ATDBio) were resuspended in ultrapure water. RT-PCR was performed on an Applied Biosystems StepOnePlus Real-Time PCR system (ThermoFisher Scientific) with the following settings: 50°C for 30 min (reverse transcription), 95°C for 10 min (hot-start polymerase activation), and 40 cycles of 94°C for 15 sec (denaturation) and 60°C for 1 min (combined annealing and extension). Intra-assay variation was controlled through use of a standard curve of synthetic RNA control 19/304 (NIBSC https://www.nibsc.org/products/brm\_product\_catalogue/detail\_page.aspx?CatId=19/304) serially diluted from 1,000 copies/reaction to 10 copies/reaction. RT-PCR Ct values were converted to copy number/reaction using the standard curve, and to international units/mL by the conversion rate provided by NIBSC for samples with known processing volumes.

**Sequencing.** Samples with Ct<31 were taken forward for veSEQ sequencing as previously described,1 using 30 µl RNA per sample as input volume and performing target capture on batches of 90 samples, alongside a series of quantification standards and positive and controls. Samples were demultiplexed using unique dual indexes (UDI), and read output was validated against Ct values to confirm sample integrity. Genomes were assembled from sequencing reads using the ShiverCovid pipeline v1.8 (https://github.com/BDI-pathogens/ShiverCovid) with variant frequencies calculated using shiver (tools/AnalysePileup.py),2 using default settings of no base alignment quality and maximum pileup depth of 1000000. Lineages were assigned by Pangolin version 2.4.2 (lineages version 2021–04–28) combined with phylogenetic placement within the relevant clade, using the determined consensus genome for each sequenced sample. For incomplete genomes, lineages were assigned based on presence of lineage-defining mutations for P.1 and P.2 in the sequencing reads ( <https://github.com/phe-genomics/variant_definitions/blob/main/variant_yaml/> ) and by genotyping as described below.

**Phylogenetic reconstruction.** Consensus sequences were aligned using MAFFT version 7.402.3 Phylogenetic reconstruction was performed on the alignment consisting of consensus sequences rooted with the Wuhan-Hu-1 reference sequence (RefSeq NC\_045512), using IQ-TREE version 1.6.12,4 with the generalised time reversible + FreeRate model and 1000 bootstrap replicates.

**Genotyping.** Samples for which genome sequencing did not give a clear lineage classification, or which showed evidence of RNA degradation (as identified by unexpectedly low read yield and library fragment sizes <200b; typical median fragment size 380b), were genotyped using allele specific PCR (ASP)-based assays.5 Custom P.1 and P.2 ASP assays were designed to identify lineage-specific and highly sensitive single-nucleotide polymorphisms (SNPs) S:K417T (P.1) and ORF1a:L3468V (P.2). The ASP utilizes two dye-labelled probes that differ only in the SNP location, and leverages differential binding affinities of each probe due to primer-target mismatches to genotype the SNP with a higher sensitivity than sequencing. The assays were validated using sequence-confirmed P.1 and P.2 samples from the present dataset, with samples from other non-P.1/P.2 lineages as controls (supp. Figures 1 and 2). ASP was performed using the Quantitect Probe RT-PCR kit (QIAGEN) in a 25 µL reaction volume containing 5 µL of extracted RNA and performed on the Applied Biosystems StepOnePlus Real-Time PCR system using a genotyping program. P.1 and P.2 oligonucleotide sequences and reaction concentrations are listed in table X. The P.1 ASP was performed with the following settings: 50°C for 30 min, 60°C for 30 seconds (pre-amplification read), 95°C for 10 min, 45 cycles of 95°C for 15 sec, 58°C for 20 seconds, and 60°C for 45 seconds, and 60°C for 30 seconds (post-amplification read). The P.2 ASP was performed with the following settings: 50°C for 30 min, 66.5°C for 30 seconds (pre-amplification read), 95°C for 10 min, 50 cycles of 95°C for 15 sec and 66.5°C for 1 minute, and 66.5°C for 30 seconds (post-amplification read). cDNA of sequence-confirmed samples was generated using the SuperScript III First-Strand Synthesis System (ThermoFisher Scientific) according to the manufacturer’s instructions for gene-specific primers, except reverse transcription of the P.2 cDNA controls was performed at 50°C. Serially diluted cDNA aliquots of sequence-confirmed P.1, P.2, and non-P.1/P.2 samples were used as discrimination controls and ultrapure water served as no-template controls (NTCs). The change in fluorescent signal between pre-amplification and post-amplification reads for both dye-labelled probes was plotted on a cartesian plane. SNPs were designated based on their clustering with discrimination controls. Samples that failed to achieve a change in signal in either probe greater than those of the NTCs or lacked evidence of amplification were designated “undetermined.” Samples that were genotyped as non-P.1/P.2 by ASP and had no sequence data were classified as “Other lineage (non-P.1/P.2)”. Samples that could not be assigned a lineage by either sequencing or genotyping were classified as "Undetermined”.

**Table S4: Oligonucleotide sequences used in this study.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Sequence Name | Target | Purpose | 5’>3’ sequence | Reaction conc. |
| 2019\_nCoV\_N1\_F | N gene | Quantification | GACCCCAAAATCAGCGAAAT | 500 nM |
| 2019\_nCoV\_N1\_R | TCTGGTTACTGCCAGTTGAATCTG | 500 nM |
| 2019\_nCoV\_N1\_P | FAM-ACCCCGCATTACGTTTGGTGGACC-BHQ1 | 125 nM |
| K417T\_FW | S:417 | Genotyping | GAGGTGATGAAGTCAGACAAATCGC | 600 nM |
| K417T\_RV | GATTGTTAGAATTCCAAGCTATAACGCAGC | 600 nM |
| K417T\_P\_WT | HEX-TCAGCAATMTTTCCAGTTTGCCCTGG-BHQ1 | 150 nM |
| K417T\_P\_P1 | FAM-TCAGCAATMGTTCCAGTTTGCCCTGG-BHQ1 | 150 nM |
| L3468V\_FW | Orf1a:3468 | Genotyping | CACAAGCAGCTGGTACGGACACA | 500 nM |
| L3468V\_RV | GCAGAAAGAGGTCCTAGTATGTCAACATGG | 500 nM |
| L3468V\_P\_WT | HEX-TTAATGTTTTAGCTTGGTTGTACGCTGCTG-BHQ1 | 125 nM |
| L3468V\_P\_P2 | FAM-TTAATGTTGTAGCTTGGTTGTACGCTGCTG-BHQ1 | 125 nM |



**Supplementary Figure 1: Validation of P.1 ASP.** Allelic discrimination of the P.1 assay was validated using 49 sequenced-confirmed samples (10 P.1, 39 non-P.1). Assay was performed as described in *methods*; cartesian plot visualizations change in signal for both probes from pre- and post-amplification reads. One P.1 sample and two non-P.1 samples failed to amplify and are located near the origin of the plot.

**Supplementary Figure 2: Validation of P.2 ASP.** Allelic discrimination of the P.2 assay was validated using 47 sequenced-confirmed samples (25 P.2, 22 non-P.2). Assay was performed as described in Methods; cartesian plot visualizations change in signal for both probes from pre- and post-amplification reads. Two non-P.2 samples failed to amplify and are located near the origin of the plot.



**Supplementary Figure 3. Map of Brazil showing trial sites collecting samples in the present study.**

**Table S5 List of NAAT assays used in COV003 by study site**

|  |  |
| --- | --- |
| **Location** | **Assays** |
| Salvador | 1. Seegene Allplex multiplex 2. Thermofisher Taqpath multiplex |
| Porto Alegre | 1. US-CDC protocol 2. Xpert Xpress SARS-Cov-2, GeneXPert |
| Rio de Janeiro | 1. Allplex, Seegene SARS CoV-2 RT PCR 2. Xpert Xpress SARS-Cov-2 GeneXPert 3. BioFire Respiratory Panel 2.1 - including SARS-CoV-2, BioMérieux |
| São Paulo | 1. XGEN MASTER COVID-19 kit, Mobius Life Science |
| Natal |  1. Xgen Master COVID-19 Mobius Life  2. Norgen Biotek (2019-nCoV TaqMan RT-PCR) |
| Santa Maria | 1. In house assay based on Charite protocol https://www.who.int/docs/default-source/coronaviruse/protocol-v2-1.pdf?sfvrsn=a9ef618c\_2 2. Bio-Manguinhos (FIOCRUZ) kit, also based on Charite protocol |

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