**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 |

Chart, scatter chart

Description automatically generated

**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.

Chart, scatter chart

Description automatically generated**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.

Map

Description automatically generated

**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 |

**Supplementary Material: Oxford Vaccine Trial Group**

|  |  |
| --- | --- |
| Lygia Accioly Tinoco | Hospital São Rafael e ID’OR, Brazil |
| Karla Cristina Marques Afonso Ferreira | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Cenusa Almeida | Hospital São Rafael e ID’OR, Brazil |
| Brian Angus | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Beatriz Arns | Hospital de Clinicas de Porto Alegre, Brazil |
| Laiana Arruda | Hospital São Rafael e ID’OR, Brazil |
| Renato De Ávila Kfouri | Universidade Federal de Sao Paulo, Brazil |
| Lucas Henrique Azevedo da Silva | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Matheus José Barbosa Moreira | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Brenda Vasconcelos Barbosa Paiva | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Louise Bates | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Nancy Bellei | Universidade Federal de Sao Paulo, Brazil |
| Bruno Boettger | Universidade Federal de Sao Paulo, Brazil |
| Leandro Bonecker Lora | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Nina Amanda Borges de Araújo | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Chrystiane do Nascimento Brito de Oliveira | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Charlie Brown-O'Sullivan | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Daniel Calich Luz | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Joao Renato Cardoso Mourão | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Caroline Scherer Carvalho | Hospital Universitário de Santa Maria, Santa Maria, Brazil |
| Paola Cicconi | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Ana Gibertoni Cruz | Nuffield Department of Population Health, University of Oxford, UK |
| Debora Cunha | Hospital de Clinicas de Porto Alegre, Brazil |
| Daniel Marinho Da Costa | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Isabela Garrido Da Silva Gonzalez | Universidade Federal de Sao Paulo, Brazil |
| Priscila de Arruda Trindade | Department of Clinical and Toxicological Analysis- Universidade Federal de Santa Maria, Santa Maria, Brazil |
| Bruno Solano de Freitas Souza | Monte Tabor Centro Ítalo Brasileiro de Promoção Sanitária, Fiocruz-BA e I’DOR, Brazil |
| Sergio Carlos Assis De Jesus Junior | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Maria Isabel de Moraes Pinto | Universidade Federal de Sao Paulo, Brazil |
| Karolyne Porto De Mores | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Maristela Miyamoto de Nobrega | Universidade Federal de Sao Paulo, Brazil |
| Milla Dias Sampaio | Hospital São Rafael e ID’OR, Brazil |
| Janaína Keyla Dionísio dos Santos | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Alexander D. Douglas | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Suzete Nascimento Farias da Guarda | Universidade Federal da Bahia, Brazil e Hospital São Rafael, Brazil e ID’OR, Brazil |
| Mujtaba Ghulam Farooq | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Elaine Shuo Feng | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Marcel Catão Ferreira dos Santos | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Marília Miranda Franco | Rede D’OR, Brazil |
| Marianne Garcia de Oliveira | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Fernanda Garcia Spina | Universidade Federal de SaoPaulo, Brazil |
| Tannyth Gomes dos Santos | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Alvaro Henrique Goyanna | IDOR, RIO DE JANEIRO; Hospital Quinta D'OR, Brazil |
| Rosana Esteves Haddad | Vaxtrials, F&F Tower, Calle 50, Panamá, Panama |
| Adrian V. S. Hill | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Mimi M. Hou | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Bruna Junqueira | Hospital São Rafael e ID’OR, Brazil |
| Bruna Somavilla Kelling | Universidade Federal de Santa Maria, Santa Maria, Brazil |
| Baktash Khozoee | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Renan Gustavo Kunst | Hospital Universitário de Santa Maria, Santa Maria, Brazil |
| Jonathan Kwok | Nuffield Department of Medicine, University of Oxford, UK |
| Meera Madhavan | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| José Antônio Mainardi de Carvalho | Department of Clinical and Toxicological Analysis-Universidade Federal de Santa Maria, Brazil |
| Olga Mazur | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Angela M. Minassian | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Leonardo Motta Ramos | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Celia Hatsuko Myasaki | Universidade Federal de Sao Paulo, Brazil |
| Helena Carolina Noal | Programa de Pós Graduação em Enfermagem- PPGENF-Universidade Federal de Santa Maria, Brazil |
| Natália Nóbrega de Lima | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Rabiullah Noristani | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Ana Luiza Perez | Hospital de Clinicas de Porto Alegre, Brazil |
| Jéssica Morgana Gediel Pinheiro | Hospital de Clinicas de Porto Alegre, Brazil |
| Priscila Pinheiro | Hospital São Rafael e ID’OR, Brazil |
| Marie Marcelle Prestes Camara | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Isabella Queiroz | Hospital São Rafael e ID’OR e UNIME, Brazil |
| Alessandra Ramos Souza | Universidade Federal de Sao Paulo, Brazil |
| Thais Regina Y Castro | Postgraduate Programme in Pharmaceutical Sciences- Universidade Federal de Santa Maria, Brazil |
| Hannah Robinson | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Marianna Rocha Jorge | Hospital São Rafael e ID’OR, Brazil |
| Talita Rochetti | Universidade Federal de Sao Paulo, Brazil |
| Mariana Bernadi S. Saba | Universidade Federal de Sao Paulo, Brazil |
| Natalia Zerbinatti Salvador | IDOR, RIO DE JANEIRO; Hospital Quinta D'OR, Brazil |
| Thaina G Santos | Hospital de Clinicas de Porto Alegre, Brazil |
| Fernanda Caldeira Veloso Santos | Hospital Universitário de Santa Maria, Santa Maria, Brazil |
| Mayara Fraga Santos Guerra | IDOR, Rio De Janeiro; Hospital Quinta D'OR, Brazil |
| Samiullah Seddiqi | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Roberta Senger | Hospital Universitário de Santa Maria, Santa Maria, Brazil |
| Robert Shaw | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Airanuedida Silva Soares | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Rinn Song | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Guilherme G Sorio | Hospital de Clinicas de Porto Alegre, Brazil |
| Ricardo Stein | Hospital de Clinicas de Porto Alegre, Brazil e Universidade Federal do Rio Grande do Sul, Brazil |
| Arabella V. S. Stuart | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Tais Tasqueto Tassinari | Programa de Pós Graduação em Enfermagem- PPGENF-Universidade Federal de Santa Maria, Brazil |
| Cheryl Turner | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Tarsila Vieceli | Hospital de Clinicas de Porto Alegre, Brazil |
| Taiane A Vieira | Hospital de Clinicas de Porto Alegre, Brazil |
| João Gabriel Villar Cavalcanti | Centro de Estudos e Pesquisas em Moléstias Infecciosas, Brazil |
| Marion E. E. Watson | Jenner Institute, Nuffield Department of Medicine, University of Oxford, UK |
| Andy Yao | Oxford Vaccine Group, Department of Paediatrics, University of Oxford, UK |
| Rafael Zimmer | Hospital de Clinicas de Porto Alegre, Brazil |

|  |
| --- |
| **AMPHEUS Project** |
| **Oxford Viral Sequencing Group, Wellcome Centre for Human Genetics, University of Oxford, UK** |
| David Buck |
| Angie Green |
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| --- |
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| George Bouliotis |
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| Elizabeth Bukusi |
| Cornelia Dekker |
| Robert Heyderman |
| Gregory Hussey |
| Paul Kaye |
| Bernhards Ogutu |
| Walter Orenstein |
| Sonia Ramos |
| Manish Sadarangani |
| **Department of Paediatrics, University of Oxford** |
| Georg A. Holländer |
| **Endpoint Evaluation Committee** |
| Jeremy Carr |
| Steve Chambers |
| Kim Davis |
| Simon Drysdale |
| Malick Gibani |
| Elizabeth Hammershaimb |
| Michael Harrington |
| Celina Jin |
| Seilesh Kadambari |
| Rama Kandasamy |
| Toby Maher |
| Jamilah Meghji |
| Claire Munro |
| David Pace |
| Rekha Rapaka |
| Robindra Basu Roy |
| Daniel Silman |
| Gemma Sinclair |
| Jing Wang |
| **Jenner Institute, University of Oxford** |
| Iona Tarbet |
| **Nuffield Department of Medicine, University of Oxford** |
| Richard Cornall |
| Richard Liwicki |
| Denis Murphy |
| Elizabeth Salter |
| Katherine Skinner |
| Philip Taylor |
| Oto Velicka |
| **Oxford Research Services (Contracts)** |
| Carly Banner |
| Sally Pelling-Deeves |
| Gary Priest |
| **Oxford University Hospitals Trust** |
| Bruno Holthof |
| **Public Affairs Directorate and Divisional Communication Team** |
| Alison Brindle |
| Alexander Buxton |
| James Colman |
| Chris McIntyre |
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