

Published in final edited form as:

*Nature*. 2021 April 01; 592(7853): 277–282. doi:10.1038/s41586-021-03291-y.

## SARS-CoV-2 evolution during treatment of chronic infection

Steven A Kemp<sup>#1</sup>, Dami A Collier<sup>#1,2,3</sup>, Rawlings P Datir<sup>#2,3</sup>, Isabella ATM Ferreira<sup>2,3</sup>, Salma Gayed<sup>4</sup>, Aminu Jahun<sup>5</sup>, Myra Hosmillo<sup>5</sup>, Chloe Rees-Spear<sup>1</sup>, Petra Mlcochova<sup>2,3</sup>, Ines Ushiro Lumb<sup>6</sup>, David J Roberts<sup>6</sup>, Anita Chandra<sup>2,3</sup>, Nigel Temperton<sup>7</sup>, The CITIID-NIHR BioResource COVID-19 Collaboration

Stephen Baker<sup>2,3</sup> [Principal Investigators], Gordon Dougan<sup>2,3</sup> [Principal Investigators], Christoph Hess<sup>2,3,26,27</sup> [Principal Investigators], Nathalie Kingston<sup>20,12</sup> [Principal Investigators], Paul J. Lehner<sup>2,3</sup> [Principal Investigators], Paul A. Lyons<sup>2,3</sup> [Principal Investigators], Nicholas J. Matheson<sup>2,3</sup> [Principal Investigators], Willem H. Owehand<sup>20</sup> [Principal Investigators], Caroline Saunders<sup>19</sup> [Principal Investigators], Charlotte Summers<sup>3,24,25,28</sup> [Principal Investigators], James E.D. Thaventhiran<sup>2,3,22</sup> [Principal Investigators], Mark Toshner<sup>3,24,25</sup> [Principal Investigators], Michael P. Weekes<sup>2</sup> [Principal Investigators], Ashlea Bucke<sup>19</sup> [CRF and Volunteer Research Nurses], Jo Calder<sup>19</sup> [CRF and Volunteer Research Nurses], Laura Canna<sup>19</sup> [CRF and Volunteer Research Nurses], Jason Domingo<sup>19</sup> [CRF and Volunteer Research Nurses], Anne Elmer<sup>19</sup> [CRF and Volunteer Research Nurses], Stewart Fuller<sup>19</sup> [CRF and Volunteer Research Nurses], Julie Harris<sup>41</sup> [CRF and Volunteer Research Nurses], Sarah Hewitt<sup>19</sup> [CRF and Volunteer Research Nurses], Jane Kennet<sup>19</sup> [CRF and Volunteer Research Nurses], Sherly Jose<sup>19</sup> [CRF and Volunteer Research Nurses], Jenny Kourampa<sup>19</sup> [CRF and Volunteer Research Nurses], Anne Meadows<sup>19</sup> [CRF and Volunteer Research Nurses], Criona O'Brien<sup>41</sup> [CRF and Volunteer Research Nurses], Jane Price<sup>19</sup> [CRF and Volunteer Research Nurses], Cherry Publico<sup>19</sup> [CRF and Volunteer Research Nurses], Rebecca Rastall<sup>19</sup> [CRF and Volunteer Research Nurses], Carla Ribeiro<sup>19</sup> [CRF and Volunteer Research Nurses], Jane Rowlands<sup>19</sup> [CRF and Volunteer Research Nurses], Valentina Ruffolo<sup>19</sup> [CRF and Volunteer Research Nurses], Hugo Tordesillas<sup>19</sup> [CRF and Volunteer Research Nurses], Ben Bullman<sup>2</sup> [Sample Logistics], Benjamin J Dunmore<sup>3</sup> [Sample Logistics], Stuart Fawke<sup>30</sup> [Sample Logistics], Stefan Gräf<sup>3,12,20</sup> [Sample Logistics], Josh Hodgson<sup>3</sup> [Sample Logistics], Christopher Huang<sup>3</sup> [Sample Logistics], Kelvin Hunter<sup>2,3</sup> [Sample Logistics], Emma Jones<sup>29</sup> [Sample

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**Address for correspondence:** Ravindra K. Gupta, Cambridge Institute for Therapeutic Immunology and Infectious Diseases, Jeffrey Cheah Biomedical Centre, Puddicombe Wa, Cambridge CB2 0AW, UK, Tel: +44 1223 331491, rkg20@cam.ac.uk.

**Competing interests:** the authors declare no competing interests

### Ethics

The study was approved by the East of England – Cambridge Central Research Ethics Committee (17/EE/0025). Written informed consent was obtained from both the patient and family. Additional controls with COVID-19 were enrolled to the NIHR BioResource Centre Cambridge under ethics review board (17/EE/0025).

### Author contributions

Conceived study: RKG, SAK, DAC, AS, TG, EGK

Designed experiments: RKG, SAK, DAC, LEM, JAGB, EGK, AC, NT, AC, CS, RD, RG, DDP, YM

Performed experiments: SAK, DAC, LEM, RD, CRS, AJ, IATMF, KS, TG, CJRI, BB, JS, MJvG, LGC, GBM, LK

Interpreted data: RKG, SAK, DAC, PM, LEM, JAGB, PM, SG, KS, TG, JB, KGCS, IG, CJRI, JAGB, IUL, DR, JS, BB, RAG, DDP, RD, LCG, GBM

Logistics], Ekaterina Legchenko<sup>3</sup> [Sample Logistics], Cecilia Matara<sup>3</sup> [Sample Logistics], Jennifer Martin<sup>3</sup> [Sample Logistics], Federica Mescia<sup>2,3</sup> [Sample Logistics], Ciara O'Donnell<sup>3</sup> [Sample Logistics], Linda Pointon<sup>3</sup> [Sample Logistics], Nicole Pond<sup>2,3</sup> [Sample Logistics], Joy Shih<sup>3</sup> [Sample Logistics], Rachel Sutcliffe<sup>3</sup> [Sample Logistics], Tobias Tilly<sup>3</sup> [Sample Logistics], Carmen Treacy<sup>3</sup> [Sample Logistics], Zhen Tong<sup>3</sup> [Sample Logistics], Jennifer Wood<sup>3</sup> [Sample Logistics], Marta Wylot<sup>36</sup> [Sample Logistics], Laura Bergamaschi<sup>2,3</sup> [Sample Processing and Data Acquisition], Ariana Betancourt<sup>2,3</sup> [Sample Processing and Data Acquisition], Georgie Bower<sup>2,3</sup> [Sample Processing and Data Acquisition], Chiara Cossetti<sup>2,3</sup> [Sample Processing and Data Acquisition], Aloka De Sa<sup>3</sup> [Sample Processing and Data Acquisition], Madeline Epping<sup>2,3</sup> [Sample Processing and Data Acquisition], Stuart Fawke<sup>32</sup> [Sample Processing and Data Acquisition], Nick Gleadall<sup>20</sup> [Sample Processing and Data Acquisition], Richard Grenfell<sup>31</sup> [Sample Processing and Data Acquisition], Andrew Hinch<sup>2,3</sup> [Sample Processing and Data Acquisition], Oisin Huhn<sup>32</sup> [Sample Processing and Data Acquisition], Sarah Jackson<sup>3</sup> [Sample Processing and Data Acquisition], Isobel Jarvis<sup>3</sup> [Sample Processing and Data Acquisition], Daniel Lewis<sup>3</sup> [Sample Processing and Data Acquisition], Joe Marsden<sup>3</sup> [Sample Processing and Data Acquisition], Francesca Nice<sup>39</sup> [Sample Processing and Data Acquisition], Georgina Okecha<sup>3</sup> [Sample Processing and Data Acquisition], Ommar Omarjee<sup>3</sup> [Sample Processing and Data Acquisition], Marianne Perera<sup>3</sup> [Sample Processing and Data Acquisition], Nathan Richoz<sup>3</sup> [Sample Processing and Data Acquisition], Veronika Romashova<sup>2,3</sup> [Sample Processing and Data Acquisition], Natalia Savinykh Yarkoni<sup>3</sup> [Sample Processing and Data Acquisition], Rahul Sharma<sup>3</sup> [Sample Processing and Data Acquisition], Luca Stefanucci<sup>20</sup> [Sample Processing and Data Acquisition], Jonathan Stephens<sup>20</sup> [Sample Processing and Data Acquisition], Mateusz Strezlecki<sup>31</sup> [Sample Processing and Data Acquisition], Lori Turner<sup>2,3</sup> [Sample Processing and Data Acquisition], Eckart M.D.D. De Bie<sup>3</sup> [Clinical Data Collection], Katherine Bunclark<sup>3</sup> [Clinical Data Collection], Masa Josipovic<sup>40</sup> [Clinical Data Collection], Michael Mackay<sup>3</sup> [Clinical Data Collection], Federica Mescia<sup>2,3</sup> [Clinical Data Collection], Alice Michael<sup>25</sup> [Clinical Data Collection], Sabrina Rossi<sup>35</sup> [Clinical Data Collection], Mayurun Selvan<sup>3</sup> [Clinical Data Collection], Sarah Spencer<sup>15</sup> [Clinical Data Collection], Cissy Yong<sup>35</sup> [Clinical Data Collection], Ali Ansaripour<sup>25</sup> [Royal Papworth Hospital ICU], Alice Michael<sup>25</sup> [Royal Papworth Hospital ICU], Lucy Mwaura<sup>25</sup> [Royal Papworth Hospital ICU], Caroline Patterson<sup>25</sup> [Royal Papworth Hospital ICU], Gary Polwarth<sup>25</sup> [Royal Papworth Hospital ICU], Petra Polgarova<sup>28</sup> [Addenbrooke's Hospital ICU], Giovanni di Stefano<sup>28</sup> [Addenbrooke's Hospital ICU], Codie Fahey<sup>34</sup> [Cambridge and Peterborough Foundation Trust], Rachel Michel<sup>34</sup> [Cambridge and Peterborough Foundation Trust], Sze-How Bong<sup>21</sup> [ANPC and Centre for Molecular Medicine and Innovative Therapeutics], Jerome D. Coudert<sup>33</sup> [ANPC and Centre for Molecular Medicine and Innovative Therapeutics], Elaine Holmes<sup>37</sup> [ANPC and Centre for Molecular Medicine and Innovative Therapeutics], John Allison<sup>20,12</sup> [NIHR BioResource], Helen Butcher<sup>12,38</sup> [NIHR BioResource], Daniela Caputo<sup>12,38</sup> [NIHR BioResource], Debbie Clapham-Riley<sup>12,38</sup> [NIHR BioResource], Eleanor Dewhurst<sup>12,38</sup> [NIHR BioResource], Anita Furlong<sup>12,38</sup> [NIHR BioResource], Barbara Graves<sup>12,38</sup> [NIHR BioResource], Jennifer Gray<sup>12,38</sup> [NIHR BioResource], Tasmin Ivers<sup>12,38</sup> [NIHR BioResource], Mary Kasanicki<sup>12,28</sup> [NIHR BioResource], Emma Le Gresley<sup>12,38</sup> [NIHR BioResource], Rachel Linger<sup>12,38</sup> [NIHR BioResource], Sarah Meloy<sup>12,38</sup> [NIHR

BioResource], Francesca Muldoon<sup>12,38</sup> [NIHR BioResource], Nigel Ovington<sup>12,20</sup> [NIHR BioResource], Sofia Papadia<sup>12,38</sup> [NIHR BioResource], Isabel Phelan<sup>12,38</sup> [NIHR BioResource], Hannah Stark<sup>12,38</sup> [NIHR BioResource], Kathleen E Stirrups<sup>12,20</sup> [NIHR BioResource], Paul Townsend<sup>12,20</sup> [NIHR BioResource], Neil Walker<sup>12,20</sup> [NIHR BioResource], Jennifer Webster<sup>12,38</sup> [NIHR BioResource]

<sup>19</sup>Cambridge Clinical Research Centre, NIHR Clinical Research Facility, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>20</sup>Department of Haematology, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>21</sup>Australian National Phenome Centre, Murdoch University, Murdoch, Western Australia WA 6150, Australia <sup>22</sup>MRC Toxicology Unit, School of Biological Sciences, University of Cambridge, Cambridge CB2 1QR, UK <sup>23</sup>R&D Department, Hycult Biotech, 5405 PD Uden, The Netherlands <sup>24</sup>Heart and Lung Research Institute, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>25</sup>Royal Papworth Hospital NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>26</sup>Department of Biomedicine, University and University Hospital Basel, 4031 Basel, Switzerland <sup>27</sup>Botnar Research Centre for Child Health (BRCC) University Basel & ETH Zurich, 4058 Basel, Switzerland <sup>28</sup>Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>29</sup>Department of Veterinary Medicine, Madingley Road, Cambridge, CB3 0ES, UK <sup>30</sup>Cambridge Institute for Medical Research, Cambridge Biomedical Campus, Cambridge CB2 0XY, UK <sup>31</sup>Cancer Research UK, Cambridge Institute, University of Cambridge CB2 0RE, UK <sup>32</sup>Department of Obstetrics & Gynaecology, The Rosie Maternity Hospital, Robinson Way, Cambridge CB2 0SW, UK <sup>33</sup>Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute, Murdoch University, Perth, WA, Australia <sup>34</sup>Cambridge and Peterborough Foundation Trust, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EF, UK <sup>35</sup>Department of Surgery, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>36</sup>Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK <sup>37</sup>Centre of Computational and Systems Medicine, Health Futures Institute, Murdoch University, Harry Perkins Building, Perth, WA 6150, Australia <sup>38</sup>Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK <sup>39</sup>Cancer Molecular Diagnostics Laboratory, Department of Oncology, University of Cambridge, Cambridge CB2 0AH, UK <sup>40</sup>Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK <sup>41</sup>Department of Paediatrics, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK

, The COVID-19 Genomics UK (COG-UK) Consortium

Samuel C Robson<sup>54</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], Nicholas J Loman<sup>82</sup>, Thomas R Connor<sup>51,110</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Software and analysis tools], Tanya Golubchik<sup>46</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], Rocio T Martinez Nunez<sup>83</sup> [Funding acquisition, Metadata curation, Samples

and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], Catherine Ludden<sup>129</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Project administration, and Samples and logistics], Sally Corden<sup>110</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Ian Johnston<sup>140</sup>, David Bonsall<sup>46</sup> [Funding acquisition, Leadership and supervision, Project administration, Samples and logistics, and Sequencing and analysis], Colin P Smith<sup>128</sup>, Ali R Awan<sup>69</sup> [Funding acquisition, Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation], Giselda Bucca<sup>128</sup> [Funding acquisition, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], M. Estee Torok<sup>63,142</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Kordo Saeed<sup>122,151</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Visualisation], Jacqui A Prieto<sup>124,150</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Visualisation], David K Jackson<sup>140</sup> [Leadership and supervision, Metadata curation, Project administration, Sequencing and analysis, and Software and analysis tools], William L Hamilton<sup>63</sup> [Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Software and analysis tools], Luke B Snell<sup>52</sup> [Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Visualisation], Catherine Moore<sup>110</sup> [Funding acquisition, Leadership and supervision, Metadata curation, and Samples and logistics], Ewan M Harrison<sup>129,140</sup> [Funding acquisition, Leadership and supervision, Project administration, and Samples and logistics], Sonia Goncalves<sup>140</sup> [Leadership and supervision, Metadata curation, Project administration, and Samples and logistics], Derek J Fairley<sup>44,113</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Matthew W Loose<sup>59</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Joanne Watkins<sup>110</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Rich Livett<sup>140</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Software and analysis tools], Samuel Moses<sup>66,147</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Visualisation], Roberto Amato<sup>140</sup> [Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools], Sam Nicholls<sup>82</sup> [Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools], Matthew Bull<sup>110</sup> [Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools], Darren L Smith<sup>1,99,146</sup> [Leadership and supervision, Project administration, Samples and logistics, and Sequencing and analysis], Jeff Barrett<sup>140</sup> [Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation], David M Aanensen<sup>55</sup> [Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation], Martin D Curran<sup>106</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Surendra Parmar<sup>106</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Dinesh Aggarwal<sup>1,140,105</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], James G Shepherd<sup>89</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Matthew D Parker<sup>134</sup>

[Metadata curation, Project administration, Sequencing and analysis, and Software and analysis tools], Sharon Glaysher<sup>102</sup> [Metadata curation, Samples and logistics, Sequencing and analysis, and Visualisation], Matthew Bashton<sup>78,99</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Anthony P Underwood<sup>55</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Nicole Pacchiarini<sup>110</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Katie F Loveson<sup>118</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Alessandro M Carabelli<sup>129</sup> [Project administration, Sequencing and analysis, Software and analysis tools, and Visualisation], Kate E Templeton<sup>94,131</sup> [Funding acquisition, Leadership and supervision, and Metadata curation], Cordelia F Langford<sup>140</sup> [Funding acquisition, Leadership and supervision, and Project administration], John Sillitoe<sup>140</sup> [Funding acquisition, Leadership and supervision, and Project administration], Thushan I de Silva<sup>134</sup> [Funding acquisition, Leadership and supervision, and Project administration], Dennis Wang<sup>134</sup> [Funding acquisition, Leadership and supervision, and Project administration], Dominic Kwiatkowski<sup>140,148</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Andrew Rambaut<sup>131</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Justin O'Grady<sup>111,130</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Simon Cottrell<sup>110</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Matthew T.G. Holden<sup>109</sup> [Leadership and supervision, Metadata curation, and Sequencing and analysis], Emma C Thomson<sup>89</sup> [Leadership and supervision, Metadata curation, and Sequencing and analysis], Husam Osman<sup>77,105</sup> [Leadership and supervision, Project administration, and Samples and logistics], Monique Andersson<sup>100</sup> [Leadership and supervision, Project administration, and Samples and logistics], Anoop J Chauhan<sup>102</sup> [Leadership and supervision, Project administration, and Samples and logistics], Mohammed O Hassan-Ibrahim<sup>47</sup> [Leadership and supervision, Project administration, and Samples and logistics], Mara Lawniczak<sup>140</sup> [Leadership and supervision, Project administration, and Sequencing and analysis], Alex Alderton<sup>140</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Meera Chand<sup>107</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Chrystala Constantinidou<sup>135</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Meera Unnikrishnan<sup>135</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Alistair C Darby<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Julian A Hiscox<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Steve Paterson<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Inigo Martincorena<sup>140</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], David L Robertson<sup>89</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Erik M Volz<sup>80</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Andrew J Page<sup>111</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Oliver G Pybus<sup>64</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Andrew R Bassett<sup>140</sup> [Leadership and supervision, Sequencing and analysis, and Visualisation], Cristina V Ariani<sup>140</sup> [Metadata curation,

Project administration, and Samples and logistics], Michael H Spencer Chapman<sup>129,140</sup> [Metadata curation, Project administration, and Samples and logistics], Kathy K Li<sup>89</sup> [Metadata curation, Project administration, and Samples and logistics], Rajiv N Shah<sup>89</sup> [Metadata curation, Project administration, and Samples and logistics], Natasha G Jesudason<sup>89</sup> [Metadata curation, Project administration, and Samples and logistics], Yusri Taha<sup>91</sup> [Metadata curation, Project administration, and Samples and logistics], Martin P McHugh<sup>94</sup> [Metadata curation, Project administration, and Sequencing and analysis], Rebecca Dewar<sup>94</sup> [Metadata curation, Project administration, and Sequencing and analysis], Aminu S Jahun<sup>65</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Claire McMurray<sup>82</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Sarojini Pandey<sup>125</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], James P McKenna<sup>44</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Andrew Nelson<sup>99,146</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Gregory R Young<sup>78,99</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Clare M McCann<sup>99,146</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Scott Elliott<sup>102</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Hannah Lowe<sup>66</sup> [Metadata curation, Samples and logistics, and Visualisation], Ben Temperton<sup>132</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Sunando Roy<sup>123</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Anna Price<sup>51</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Sara Rey<sup>110</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Matthew Wyles<sup>134</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Stefan Rooke<sup>131</sup> [Metadata curation, Sequencing and analysis, and Visualisation], Sharif Shaaban<sup>109</sup> [Metadata curation, Sequencing and analysis, and Visualisation], Mariateresa de Cesare<sup>139</sup> [Project administration, Samples and logistics, Sequencing and analysis], Laura Letchford<sup>140</sup> [Project administration, Samples and logistics, and Software and analysis tools], Siona Silveira<sup>122</sup> [Project administration, Samples and logistics, and Visualisation], Emanuela Pelosi<sup>122</sup> [Project administration, Samples and logistics, and Visualisation], Eleri Wilson-Davies<sup>122</sup> [Project administration, Samples and logistics, and Visualisation], Myra Hosmillo<sup>65</sup> [Samples and logistics, Sequencing and analysis, and Software and analysis tools], Áine O'Toole<sup>131</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Andrew R Hesketh<sup>128</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Richard Stark<sup>135</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Louis du Plessis<sup>64</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Chris Ruis<sup>129</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Helen Adams<sup>45</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Yann Bourgeois<sup>117</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Stephen L Michell<sup>132</sup> [Funding acquisition, and Leadership and supervision], Dimitris Gramatopoulos<sup>125,153</sup> [Funding acquisition, and Leadership and supervision], Jonathan Edgeworth<sup>53</sup> [Funding acquisition, and Leadership and supervision], Judith Breuer<sup>71,123</sup> [Funding acquisition, and Leadership and supervision], John A Todd<sup>139</sup> [Funding acquisition, and Leadership and supervision], Christophe Fraser<sup>46</sup> [Funding acquisition, and Leadership and supervision], David Buck<sup>139</sup> [Funding

acquisition, and Project administration], Michaela John<sup>50</sup> [Funding acquisition, and Project administration], Gemma L Kay<sup>111</sup> [Leadership and supervision, and Metadata curation], Steve Palmer<sup>140</sup> [Leadership and supervision, and Project administration], Sharon J Peacock<sup>129,105</sup> [Leadership and supervision, and Project administration], David Heyburn<sup>110</sup> [Leadership and supervision, and Project administration], Danni Weldon<sup>140</sup> [Leadership and supervision, and Samples and logistics], Esther Robinson<sup>105,77</sup> [Leadership and supervision, and Samples and logistics], Alan McNally<sup>82,127</sup> [Leadership and supervision, and Samples and logistics], Peter Muir<sup>105</sup> [Leadership and supervision, and Samples and logistics], Ian B Vipond<sup>105</sup> [Leadership and supervision, and Samples and logistics], John BoYes<sup>70</sup> [Leadership and supervision, and Samples and logistics], Venkat Sivaprakasam<sup>87</sup> [Leadership and supervision, and Samples and logistics], Tranprit Salluja<sup>116</sup> [Leadership and supervision, and Samples and logistics], Samir Dervisevic<sup>95</sup> [Leadership and supervision, and Samples and logistics], Emma J Meader<sup>95</sup> [Leadership and supervision, and Samples and logistics], Naomi R Park<sup>140</sup> [Leadership and supervision, and Sequencing and analysis], Karen Oliver<sup>140</sup> [Leadership and supervision, and Sequencing and analysis], Aaron R Jeffries<sup>132</sup> [Leadership and supervision, and Sequencing and analysis], Sascha Ott<sup>135</sup> [Leadership and supervision, and Sequencing and analysis], Ana da Silva Filipe<sup>89</sup> [Leadership and supervision, and Sequencing and analysis], David A Simpson<sup>113</sup> [Leadership and supervision, and Sequencing and analysis], Chris Williams<sup>110</sup> [Leadership and supervision, and Sequencing and analysis], Jane AH Masoli<sup>114,132</sup> [Leadership and supervision, and Visualisation], Bridget A Knight<sup>114,132</sup> [Metadata curation, and Samples and logistics], Christopher R Jones<sup>114,132</sup> [Metadata curation, and Samples and logistics], Cherian Koshy<sup>42</sup> [Metadata curation, and Samples and logistics], Amy Ash<sup>42</sup> [Metadata curation, and Samples and logistics], Anna Casey<sup>112</sup> [Metadata curation, and Samples and logistics], Andrew Bosworth<sup>105,77</sup> [Metadata curation, and Samples and logistics], Liz Ratcliffe<sup>112</sup> [Metadata curation, and Samples and logistics], Li Xu-McCrae<sup>77</sup> [Metadata curation, and Samples and logistics], Hannah M Pymont<sup>105</sup> [Metadata curation, and Samples and logistics], Stephanie Hutchings<sup>105</sup> [Metadata curation, and Samples and logistics], Lisa Berry<sup>125</sup> [Metadata curation, and Samples and logistics], Katie Jones<sup>125</sup> [Metadata curation, and Samples and logistics], Fenella Halstead<sup>87</sup> [Metadata curation, and Samples and logistics], Thomas Davis<sup>62</sup> [Metadata curation, and Samples and logistics], Christopher Holmes<sup>57</sup> [Metadata curation, and Samples and logistics], Miren Iturriza-Gomara<sup>133</sup> [Metadata curation, and Samples and logistics], Anita O Lucaci<sup>133</sup> [Metadata curation, and Samples and logistics], Paul Anthony Randell<sup>79,145</sup> [Metadata curation, and Samples and logistics], Alison Cox<sup>79,145</sup> [Metadata curation, and Samples and logistics], Pinglawathee Madona<sup>79,145</sup> [Metadata curation, and Samples and logistics], Kathryn Ann Harris<sup>71</sup> [Metadata curation, and Samples and logistics], Julianne Rose Brown<sup>71</sup> [Metadata curation, and Samples and logistics], Tabitha W Mahungu<sup>115</sup> [Metadata curation, and Samples and logistics], Dianne Irish-Tavares<sup>115</sup> [Metadata curation, and Samples and logistics], Tanzina Haque<sup>115</sup> [Metadata curation, and Samples and logistics], Jennifer Hart<sup>115</sup> [Metadata curation, and Samples and logistics], Eric Witele<sup>115</sup> [Metadata curation, and Samples and logistics], Melisa Louise Fenton<sup>116</sup> [Metadata curation, and Samples and logistics], Steven Liggett<sup>120</sup> [Metadata curation, and Samples and logistics], Clive Graham<sup>97</sup> [Metadata curation, and Samples and logistics], Emma Swindells<sup>98</sup> [Metadata curation, and Samples and logistics], Jennifer Collins<sup>91</sup>

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Southgate<sup>51,110</sup> [Sequencing and analysis, and Software and analysis tools], Benjamin B Lindsey<sup>134</sup> [Sequencing and analysis, and Software and analysis tools], Timothy M Freeman<sup>134</sup> [Sequencing and analysis, and Software and analysis tools], Jon-Paul Keatley<sup>140</sup> [Software and analysis tools, and Visualisation], Joshua B Singer<sup>140</sup> [Software and analysis tools, and Visualisation], Leonardo de Oliveira Martins<sup>140</sup> [Software and analysis tools, and Visualisation], Corin A Yeats<sup>55</sup> [Software and analysis tools, and Visualisation], Khalil Abudahab<sup>140,140</sup> [Software and analysis tools, and Visualisation], Ben EW Taylor<sup>140</sup> [Software and analysis tools, and Visualisation], Mirko Menegazzo<sup>55</sup> [Software and analysis tools, and Visualisation], John Danesh<sup>140</sup> [Leadership and supervision], Wendy Hogsden<sup>87</sup> [Leadership and supervision], Sahar Eldirdiri<sup>62</sup> [Leadership and supervision], Anita Kenyon<sup>62</sup> [Leadership and supervision], Jenifer Mason<sup>140</sup> [Leadership and supervision], Trevor I Robinson<sup>84</sup> [Leadership and supervision], Alison Holmes<sup>140,144</sup> [Leadership and supervision], James Price<sup>140,140</sup> [Leadership and supervision], John A Hartley<sup>123</sup> [Leadership and supervision], Tanya Curran<sup>140</sup> [Leadership and supervision], Alison E Mather<sup>111</sup> [Leadership and supervision], Giri Shankar<sup>110</sup> [Leadership and supervision], Rachel Jones<sup>110</sup> [Leadership and supervision], Robin Howe<sup>110</sup> [Leadership and supervision], Sian Morgan<sup>50</sup> [Leadership and supervision], Elizabeth Wastenge<sup>140</sup> [Metadata curation], Michael R Chapman<sup>1,129,140</sup> [Metadata curation], Siddharth Mookerjee<sup>79,144</sup> [Metadata curation], Rachael Stanley<sup>95</sup> [Metadata curation], Wendy Smith<sup>56</sup> [Metadata curation], Timothy Peto<sup>100</sup> [Metadata curation], David Eyre<sup>100</sup> [Metadata curation], Derrick Crook<sup>100</sup> [Metadata curation], Gabrielle Vernet<sup>74</sup> [Metadata curation], Christine Kitchen<sup>51</sup> [Metadata curation], Huw Gulliver<sup>51</sup> [Metadata curation], Ian Merrick<sup>51</sup> [Metadata curation], Martyn Guest<sup>51</sup> [Metadata curation], Robert Munn<sup>140</sup> [Metadata curation], Declan T Bradley<sup>140,113</sup> [Metadata curation], Tim Wyatt<sup>104</sup> [Metadata curation], Charlotte Beaver<sup>140</sup> [Project administration], Luke Foulser<sup>140</sup> [Project administration], Sophie Palmer<sup>140</sup> [Project administration], Carol M Churcher<sup>129</sup> [Project administration], Ellena Brooks<sup>140</sup> [Project administration], Kim S Smith<sup>129</sup> [Project administration], Katerina Galai<sup>140</sup> [Project administration], Georgina M McManus<sup>129</sup> [Project administration], Frances Bolt<sup>79,144</sup> [Project administration], Francesc Coll<sup>60</sup> [Project administration], Lizzie Meadows<sup>140</sup> [Project administration], Stephen W Attwood<sup>64</sup> [Project administration], Alisha Davies<sup>140</sup> [Project administration], Elen De Lacy<sup>110</sup> [Project administration], Fatima Downing<sup>110</sup> [Project administration], Sue Edwards<sup>140</sup> [Project administration], Garry P Scarlett<sup>117</sup> [Project administration], Sarah Jeremiah<sup>124</sup> [Project administration], Nikki Smith<sup>134</sup> [Project administration], Danielle Leek<sup>129</sup> [Samples and logistics], Sushmita Sridhar<sup>140,140</sup> [Samples and logistics], Sally Forrest<sup>129</sup> [Samples and logistics], Claire Cormie<sup>140</sup> [Samples and logistics], Harmeet K Gill<sup>129</sup> [Samples and logistics], Joana Dias<sup>140</sup> [Samples and logistics], Ellen E Higginson<sup>129</sup> [Samples and logistics], Mailis Maes<sup>129</sup> [Samples and logistics], Jamie Young<sup>129</sup> [Samples and logistics], Michelle Wantoch<sup>140</sup> [Samples and logistics], Sanger Covid Team<sup>140</sup> [Samples and logistics], Dorota Jamrozy<sup>140</sup> [Samples and logistics], Stephanie Lo<sup>140</sup> [Samples and logistics], Minal Patel<sup>140</sup> [Samples and logistics], Verity Hill<sup>140</sup> [Samples and logistics], Claire M Bewshea<sup>132</sup> [Samples and logistics], Sian Ellard<sup>114,132</sup> [Samples and logistics], Cressida Auckland<sup>114</sup> [Samples and logistics], Ian Harrison<sup>107</sup> [Samples and logistics], Chloe Bishop<sup>107</sup> [Samples and logistics], Vicki Chalker<sup>107</sup> [Samples and logistics], Alex Richter<sup>126</sup> [Samples and logistics], Andrew

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logistics], Emma Wise<sup>140,152</sup> [Samples and logistics], Nathan Moore<sup>140,152</sup> [Samples and logistics], Matilde Mori<sup>140,140,152</sup> [Samples and logistics], Nick Cortes<sup>140,152</sup> [Samples and logistics], Stephen Kidd<sup>140,152</sup> [Samples and logistics], Rebecca Williams<sup>74</sup> [Samples and logistics], Laura Gifford<sup>110</sup> [Samples and logistics], Kelly Bicknell<sup>102</sup> [Samples and logistics], Sarah Wyllie<sup>102</sup> [Samples and logistics], Allyson Lloyd<sup>102</sup> [Samples and logistics], Robert Impey<sup>140</sup> [Samples and logistics], Cassandra S Malone<sup>140</sup> [Samples and logistics], Benjamin J Cogger<sup>47</sup> [Samples and logistics], Nick Levene<sup>103</sup> [Samples and logistics], Lynn Monaghan<sup>140</sup> [Samples and logistics], Alexander J Keeley<sup>140</sup> [Samples and logistics], David G Partridge<sup>140,134</sup> [Samples and logistics], Mohammad Raza<sup>119,134</sup> [Samples and logistics], Cariad Evans<sup>140,134</sup> [Samples and logistics], Kate Johnson<sup>119,134</sup> [Samples and logistics], Emma Betteridge<sup>140</sup> [Sequencing and analysis], Ben W Farr<sup>140</sup> [Sequencing and analysis], Scott Goodwin<sup>140</sup> [Sequencing and analysis], Michael A Quail<sup>140</sup> [Sequencing and analysis], Carol Scott<sup>140</sup> [Sequencing and analysis], Lesley Shirley<sup>140</sup> [Sequencing and analysis], Scott AJ Thurston<sup>140</sup> [Sequencing and analysis], Diana Rajan<sup>140</sup> [Sequencing and analysis], Iraad F Bronner<sup>140</sup> [Sequencing and analysis], Louise Aigrain<sup>140</sup> [Sequencing and analysis], Nicholas M Redshaw<sup>140</sup> [Sequencing and analysis], Stefanie V Lensing<sup>140</sup> [Sequencing and analysis], Shane McCarthy<sup>140</sup> [Sequencing and analysis], Alex Makunin<sup>140</sup> [Sequencing and analysis], Carlos E Balcazar<sup>140</sup> [Sequencing and analysis], Michael D Gallagher<sup>140</sup> [Sequencing and analysis], Kathleen A Williamson<sup>140</sup> [Sequencing and analysis], Thomas D Stanton<sup>140</sup> [Sequencing and analysis], Michelle L Michelsen<sup>140</sup> [Sequencing and analysis], Joanna Warwick-Dugdale<sup>132</sup> [Sequencing and analysis], Robin Manley<sup>132</sup> [Sequencing and analysis], Audrey Farbos<sup>140</sup> [Sequencing and analysis], James W Harrison<sup>140</sup> [Sequencing and analysis], Christine M Sambles<sup>140</sup> [Sequencing and analysis], David J Studholme<sup>132</sup> [Sequencing and analysis], Angie Lackenby<sup>107</sup> [Sequencing and analysis], Tamyo Mbisa<sup>107</sup> [Sequencing and analysis], Steven Platt<sup>107</sup> [Sequencing and analysis], Shahjahan Miah<sup>107</sup> [Sequencing and analysis], David Bibby<sup>107</sup> [Sequencing and analysis], Carmen Manso<sup>107</sup> [Sequencing and analysis], Jonathan Hubb<sup>107</sup> [Sequencing and analysis], Gavin Dabrera<sup>107</sup> [Sequencing and analysis], Mary Ramsay<sup>107</sup> [Sequencing and analysis], Daniel Bradshaw<sup>107</sup> [Sequencing and analysis], Ulf Schaefer<sup>107</sup> [Sequencing and analysis], Natalie Groves<sup>107</sup> [Sequencing and analysis], Eileen Gallagher<sup>107</sup> [Sequencing and analysis], David Lee<sup>107</sup> [Sequencing and analysis], David Williams<sup>107</sup> [Sequencing and analysis], Nicholas Ellaby<sup>107</sup> [Sequencing and analysis], Hassan Hartman<sup>107</sup> [Sequencing and analysis], Nikos Manesis<sup>107</sup> [Sequencing and analysis], Vineet Patel<sup>107</sup> [Sequencing and analysis], Juan Ledesma<sup>140</sup> [Sequencing and analysis], Katherine A Twohig<sup>108</sup> [Sequencing and analysis], Elias Allara<sup>140,129</sup> [Sequencing and analysis], Clare Pearson<sup>140,140</sup> [Sequencing and analysis], Jeffrey K. J. Cheng<sup>135</sup> [Sequencing and analysis], Hannah E Bridgewater<sup>135</sup> [Sequencing and analysis], Lucy R Frost<sup>140</sup> [Sequencing and analysis], Grace Taylor-Joyce<sup>140</sup> [Sequencing and analysis], Paul E Brown<sup>135</sup> [Sequencing and analysis], Lily Tong<sup>89</sup> [Sequencing and analysis], Alice Broos<sup>89</sup> [Sequencing and analysis], Daniel Mair<sup>89</sup> [Sequencing and analysis], Jenna Nichols<sup>140</sup> [Sequencing and analysis], Stephen N Carmichael<sup>140</sup> [Sequencing and analysis], Katherine L Smollett<sup>81</sup> [Sequencing and analysis], Kyriaki Nomikou<sup>140</sup> [Sequencing and analysis], Elihu Aranday-Cortes<sup>89</sup> [Sequencing and analysis], Natasha Johnson<sup>89</sup> [Sequencing and analysis], Seema Nickbakhsh<sup>140,140</sup> [Sequencing and analysis], Edith E Vamos<sup>133</sup>

[Sequencing and analysis], Margaret Hughes<sup>133</sup> [Sequencing and analysis], Lucille Rainbow<sup>133</sup> [Sequencing and analysis], Richard Eccles<sup>133</sup> [Sequencing and analysis], Charlotte Nelson<sup>133</sup> [Sequencing and analysis], Mark Whitehead<sup>133</sup> [Sequencing and analysis], Richard Gregory<sup>133</sup> [Sequencing and analysis], Matthew Gemmell<sup>133</sup> [Sequencing and analysis], Claudia Wierzbicki<sup>140</sup> [Sequencing and analysis], Hermione J Webster<sup>140</sup> [Sequencing and analysis], Chloe L Fisher<sup>140</sup> [Sequencing and analysis], Adrian W Signell<sup>61</sup> [Sequencing and analysis], Gilberto Betancor<sup>140</sup> [Sequencing and analysis], Harry D Wilson<sup>61</sup> [Sequencing and analysis], Gaia Nebbia<sup>53</sup> [Sequencing and analysis], Flavia Flaviani<sup>140</sup> [Sequencing and analysis], Alberto C Cerda<sup>140</sup> [Sequencing and analysis], Tammy V Merrill<sup>140</sup> [Sequencing and analysis], Rebekah E Wilson<sup>137</sup> [Sequencing and analysis], Marius Cotic<sup>123</sup> [Sequencing and analysis], Nadua Bayzid<sup>123</sup> [Sequencing and analysis], Thomas Thompson<sup>113</sup> [Sequencing and analysis], Erwan Acheson<sup>113</sup> [Sequencing and analysis], Steven Rushton<sup>140</sup> [Sequencing and analysis], Sarah O'Brien<sup>140</sup> [Sequencing and analysis], David J Baker<sup>111</sup> [Sequencing and analysis], Steven Rudder<sup>111</sup> [Sequencing and analysis], Alp Aydin<sup>111</sup> [Sequencing and analysis], Fei Sang<sup>59</sup> [Sequencing and analysis], Johnny Debebe<sup>59</sup> [Sequencing and analysis], Sarah Francois<sup>140</sup> [Sequencing and analysis], Tetyana I Vasylyeva<sup>140</sup> [Sequencing and analysis], Marina Escalera Zamudio<sup>64</sup> [Sequencing and analysis], Bernardo Gutierrez<sup>64</sup> [Sequencing and analysis], Angela Marchbank<sup>51</sup> [Sequencing and analysis], Joshua Maksimovic<sup>50</sup> [Sequencing and analysis], Karla Spellman<sup>50</sup> [Sequencing and analysis], Kathryn McCluggage<sup>50</sup> [Sequencing and analysis], Mari Morgan<sup>110</sup> [Sequencing and analysis], Robert Beer<sup>50</sup> [Sequencing and analysis], Safiah Afifi<sup>50</sup> [Sequencing and analysis], Trudy Workman<sup>51</sup> [Sequencing and analysis], William Fuller<sup>51</sup> [Sequencing and analysis], Catherine Bresner<sup>51</sup> [Sequencing and analysis], Adrienn Angyal<sup>140</sup> [Sequencing and analysis], Luke R Green<sup>140</sup> [Sequencing and analysis], Paul J Parsons<sup>140</sup> [Sequencing and analysis], Rachel M Tucker<sup>134</sup> [Sequencing and analysis], Rebecca Brown<sup>134</sup> [Sequencing and analysis], Max Whiteley<sup>134</sup> [Sequencing and analysis], James Bonfield<sup>140</sup> [Software and analysis tools], Christoph Puethel<sup>140</sup> [Software and analysis tools], Andrew Whitwham<sup>140</sup> [Software and analysis tools], Jennifer Liddle<sup>140</sup> [Software and analysis tools], Will Rowe<sup>82</sup> [Software and analysis tools], Igor Siveroni<sup>140</sup> [Software and analysis tools], Thanh Le-Viet<sup>140</sup> [Software and analysis tools], Amy Gaskin<sup>110</sup> [Software and analysis tools], Rob Johnson<sup>80</sup> [Visualisation]

<sup>42</sup>Barking, Havering and Redbridge University Hospitals NHS Trust, Barking, United Kingdom <sup>43</sup>Basingstoke Hospital, Basingstoke, United Kingdom <sup>44</sup>Belfast Health & Social Care Trust, Belfast, United Kingdom <sup>45</sup>Betsi Cadwaladr University Health Board, Betsi Cadwaladr, United Kingdom <sup>46</sup>Big Data Institute, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom <sup>47</sup>Brighton and Sussex University Hospitals NHS Trust, Brighton & Sussex, United Kingdom <sup>48</sup>Cambridge Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom <sup>49</sup>Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom <sup>50</sup>Cardiff and Vale University Health Board, Cardiff, United Kingdom <sup>51</sup>Cardiff University, Cardiff, United Kingdom <sup>52</sup>Centre for Clinical Infection & Diagnostics Research, St. Thomas' Hospital and Kings College London, London, United Kingdom <sup>53</sup>Centre for Clinical Infection and Diagnostics Research, Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation

Trust, London, United Kingdom <sup>54</sup>Centre for Enzyme Innovation, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>55</sup>Centre for Genomic Pathogen Surveillance, University of Oxford, Oxford, United Kingdom <sup>56</sup>Clinical Microbiology Department, Queens Medical Centre, Nottingham, United Kingdom <sup>57</sup>Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom <sup>58</sup>County Durham and Darlington NHS Foundation Trust, Durham, United Kingdom <sup>59</sup>Deep Seq, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, United Kingdom <sup>60</sup>Department of Infection Biology, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom <sup>61</sup>Department of Infectious Diseases, King's College London, London, United Kingdom <sup>62</sup>Department of Microbiology, Kettering General Hospital, Kettering, United Kingdom <sup>63</sup>Departments of Infectious Diseases and Microbiology, Cambridge University Hospitals NHS Foundation Trust; Cambridge, UK, Cambridge, United Kingdom <sup>64</sup>Department of Zoology, University of Oxford, Oxford, United Kingdom <sup>65</sup>Division of Virology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom <sup>66</sup>East Kent Hospitals University NHS Foundation Trust, Kent, United Kingdom <sup>67</sup>East Suffolk and North Essex NHS Foundation Trust, Suffolk, United Kingdom <sup>68</sup>Gateshead Health NHS Foundation Trust, Gateshead, United Kingdom <sup>69</sup>Genomics Innovation Unit, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom <sup>70</sup>Gloucestershire Hospitals NHS Foundation Trust, Gloucester, United Kingdom <sup>71</sup>Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom <sup>72</sup>Guy's and St. Thomas' BRC, London, United Kingdom <sup>73</sup>Guy's and St. Thomas' Hospitals, London, United Kingdom <sup>74</sup>Hampshire Hospitals NHS Foundation Trust, Hampshire, United Kingdom <sup>75</sup>Health Data Research UK Cambridge, Cambridge, United Kingdom <sup>76</sup>Health Services Laboratories, London, United Kingdom <sup>77</sup>Heartlands Hospital, Birmingham, Birmingham, United Kingdom <sup>78</sup>Hub for Biotechnology in the Built Environment, Northumbria University, Northumbria, United Kingdom <sup>79</sup>Imperial College Hospitals NHS Trust, London, United Kingdom <sup>80</sup>Imperial College London, London, United Kingdom <sup>81</sup>Institute of Biodiversity, Animal Health & Comparative Medicine, Glasgow, United Kingdom <sup>82</sup>Institute of Microbiology and Infection, University of Birmingham, Birmingham, United Kingdom <sup>83</sup>King's College London, London, United Kingdom <sup>84</sup>Liverpool Clinical Laboratories, Liverpool, United Kingdom <sup>85</sup>Maidstone and Tunbridge Wells NHS Trust, Maidstone, United Kingdom <sup>86</sup>Manchester University NHS Foundation Trust, Manchester, United Kingdom <sup>87</sup>Microbiology Department, Wye Valley NHS Trust, Hereford, United Kingdom <sup>88</sup>MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom <sup>89</sup>MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom <sup>90</sup>National Infection Service, PHE and Leeds Teaching Hospitals Trust, Leeds, United Kingdom <sup>91</sup>Newcastle Hospitals NHS Foundation Trust, Newcastle, United Kingdom <sup>92</sup>Newcastle University, Newcastle, United Kingdom <sup>93</sup>NHS Greater Glasgow and Clyde, Glasgow, United Kingdom <sup>94</sup>NHS Lothian, Edinburgh, United Kingdom <sup>95</sup>Norfolk and Norwich University Hospital, Norfolk, United Kingdom <sup>96</sup>Norfolk County Council, Norfolk, United Kingdom <sup>97</sup>North Cumbria Integrated Care NHS Foundation Trust, Carlisle, United Kingdom <sup>98</sup>North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees, United Kingdom <sup>99</sup>Northumbria University, Northumbria, United Kingdom <sup>100</sup>Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom <sup>101</sup>PathLinks, Northern

Lincolnshire & Goole NHS Foundation Trust, Lincolnshire, United Kingdom <sup>102</sup>Portsmouth Hospitals University NHS Trust, Portsmouth, United Kingdom <sup>103</sup>Princess Alexandra Hospital Microbiology Dept., Harlow, United Kingdom <sup>104</sup>Public Health Agency, London, United Kingdom <sup>105</sup>Public Health England, London, United Kingdom <sup>106</sup>Public Health England, Clinical Microbiology and Public Health Laboratory, Cambridge, United Kingdom <sup>107</sup>Public Health England, Colindale, London, United Kingdom <sup>108</sup>Public Health England, Colindale, London, United Kingdom <sup>109</sup>Public Health Scotland, Glasgow, United Kingdom <sup>110</sup>Public Health Wales NHS Trust, Cardiff, United Kingdom <sup>111</sup>Quadram Institute Bioscience, Norwich, United Kingdom <sup>112</sup>Queen Elizabeth Hospital, Birmingham, United Kingdom <sup>113</sup>Queen's University Belfast, Belfast, United Kingdom <sup>114</sup>Royal Devon and Exeter NHS Foundation Trust, Devon, United Kingdom <sup>115</sup>Royal Free NHS Trust, London, United Kingdom <sup>116</sup>Sandwell and West Birmingham NHS Trust, Sandwell, United Kingdom <sup>117</sup>School of Biological Sciences, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>118</sup>School of Pharmacy and Biomedical Sciences, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>119</sup>Sheffield Teaching Hospitals, Sheffield, United Kingdom <sup>120</sup>South Tees Hospitals NHS Foundation Trust, Newcastle, United Kingdom <sup>121</sup>Swansea University, Swansea, United Kingdom <sup>122</sup>University Hospitals Southampton NHS Foundation Trust, Southampton, United Kingdom <sup>123</sup>University College London, London, United Kingdom <sup>124</sup>University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom <sup>125</sup>University Hospitals Coventry and Warwickshire, Coventry, United Kingdom <sup>126</sup>University of Birmingham, Birmingham, United Kingdom <sup>127</sup>University of Birmingham Turnkey Laboratory, Birmingham, United Kingdom <sup>128</sup>University of Brighton, Brighton, United Kingdom <sup>129</sup>University of Cambridge, Cambridge, United Kingdom <sup>130</sup>University of East Anglia, East Anglia, United Kingdom <sup>131</sup>University of Edinburgh, Edinburgh, United Kingdom <sup>132</sup>University of Exeter, Exeter, United Kingdom <sup>133</sup>University of Liverpool, Liverpool, United Kingdom <sup>134</sup>University of Sheffield, Sheffield, United Kingdom <sup>135</sup>University of Warwick, Warwick, United Kingdom <sup>136</sup>University of Cambridge, Cambridge, United Kingdom <sup>137</sup>Viapath, Guy's and St Thomas' NHS Foundation Trust, and King's College Hospital NHS Foundation Trust, London, United Kingdom <sup>138</sup>Virology, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, United Kingdom <sup>139</sup>Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom <sup>140</sup>Wellcome Sanger Institute, London, United Kingdom <sup>141</sup>West of Scotland Specialist Virology Centre, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom <sup>142</sup>Department of Medicine, University of Cambridge, Cambridge, United Kingdom <sup>143</sup>Ministry of Health, Colombo, Sri Lanka <sup>144</sup>NIHR Health Protection Research Unit in HCAI and AMR, Imperial College London, London, United Kingdom <sup>145</sup>North West London Pathology, London, United Kingdom <sup>146</sup>NU-OMICS, Northumbria University, Northumbria, United Kingdom <sup>147</sup>University of Kent, Kent, United Kingdom <sup>148</sup>University of Oxford, Oxford, United Kingdom <sup>149</sup>University of Southampton, Southampton, United Kingdom <sup>150</sup>University of Southampton School of Health Sciences, Southampton, United Kingdom <sup>151</sup>University of Southampton School of Medicine, Southampton, United Kingdom <sup>152</sup>University of Surrey, Guildford, United Kingdom <sup>153</sup>Warwick Medical School and Institute of Precision Diagnostics, Pathology, UHCW NHS Trust, Warwick, United Kingdom

, Katherine Sharrocks<sup>4</sup>, Elizabeth Blane<sup>3</sup>, Yorgo Modis<sup>8</sup>, Kendra Leigh<sup>8</sup>, John Briggs<sup>8</sup>, Marit van Gils<sup>9</sup>, Kenneth GC Smith<sup>2,3</sup>, John R Bradley<sup>3,10</sup>, Chris Smith<sup>11</sup>, Rainer Doffinger<sup>13</sup>, Lourdes Ceron-Gutierrez<sup>13</sup>, Gabriela Barcenas-Morales<sup>13,14</sup>, David D Pollock<sup>15</sup>, Richard A Goldstein<sup>1</sup>, Anna Smielewska<sup>5,11</sup>, Jordan P Skittrall<sup>4,12,16</sup>, Theodore Gouliouris<sup>4</sup>, Ian G Goodfellow<sup>5</sup>, Effrossyni Gkrania-Klotsas<sup>4</sup>, Christopher JR Illingworth<sup>12,17</sup>, Laura E McCoy<sup>1</sup>, Ravindra K Gupta<sup>2,3,18</sup>

<sup>1</sup>Division of Infection and Immunity, University College London, London, UK <sup>2</sup> Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), Cambridge, UK <sup>3</sup>Department of Medicine, University of Cambridge, Cambridge, UK <sup>4</sup>Department of Infectious Diseases, Cambridge University NHS Hospitals Foundation Trust, Cambridge, UK <sup>5</sup>Department of Pathology, University of Cambridge, Cambridge <sup>6</sup> NHS Blood and Transplant, Oxford and BRC Haematology Theme, University of Oxford, UK <sup>7</sup>Viral Pseudotype Unit, Medway School of Pharmacy, University of Kent, UK <sup>8</sup>Medical Research Council Laboratory of Molecular Biology, Cambridge, UK <sup>9</sup>Department of Medical Microbiology, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Infection and Immunity, Amsterdam, Netherlands <sup>10</sup> NIHR Cambridge Clinical Research Facility, Cambridge, UK <sup>11</sup>Department of Virology, Cambridge University NHS Hospitals Foundation Trust <sup>12</sup>Department of Applied Mathematics and Theoretical Physics, University of Cambridge, UK <sup>13</sup> Department of Clinical Biochemistry and Immunology, Addenbrookes Hospital <sup>14</sup> FES-Cuautitlán, UNAM, Mexico <sup>15</sup>Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado, USA; <sup>16</sup>Clinical Microbiology and Public Health Laboratory, Addenbrookes' Hospital, Cambridge, UK <sup>17</sup> MRC Biostatistics Unit, University of Cambridge, Cambridge, UK <sup>18</sup>Africa Health Research Institute, Durban, South Africa

# These authors contributed equally to this work.

## Summary

SARS-CoV-2 Spike protein is critical for virus infection via engagement of ACE2<sup>1</sup>, and is a major antibody target. Here we report chronic SARS-CoV-2 with reduced sensitivity to neutralising antibodies in an immune suppressed individual treated with convalescent plasma, generating whole genome ultradeep sequences over 23 time points spanning 101 days. Little change was observed in the overall viral population structure following two courses of remdesivir over the first 57 days. However, following convalescent plasma therapy we observed large, dynamic virus population shifts, with the emergence of a dominant viral strain bearing D796H in S2 and H69/V70 in the S1 N-terminal domain NTD of the Spike protein. As passively transferred serum antibodies diminished, viruses with the escape genotype diminished in frequency, before returning during a final, unsuccessful course of convalescent plasma. *In vitro*, the Spike escape double mutant bearing H69/V70 and D796H conferred modestly decreased sensitivity to convalescent plasma, whilst maintaining infectivity similar to wild type. D796H appeared to be the main contributor to decreased susceptibility but incurred an infectivity defect. The H69/V70 single mutant had two-fold higher infectivity compared to wild type, possibly compensating for the reduced infectivity of D796H. These data reveal strong selection on SARS-CoV-2 during convalescent plasma therapy associated with emergence of viral variants with evidence of reduced susceptibility to neutralising antibodies.



## Keywords

SARS-CoV-2; COVID-19; antibody escape, Convalescent plasma; neutralising antibodies; mutation; evasion; resistance; immune suppression

## Clinical case history of SARS-CoV-2 infection in setting of immune-compromised host

A septuagenarian male was admitted to a tertiary hospital in summer of 2020 and had tested positive for SARS-CoV-2 RT-PCR 35 days previously on a nasopharyngeal swab (Day 1) at a local hospital (Extended data 1 and 2). His past medical history was significant for marginal B cell lymphoma diagnosed in 2012, with previous chemotherapy including vincristine, prednisolone, cyclophosphamide and anti-CD20 B cell depletion with rituximab. It is likely that both chemotherapy and underlying lymphoma contributed to B and T cell combined immunodeficiency (Extended data 2 and 3, Supplementary Table 1). Computed tomography (CT) of the chest showed widespread abnormalities consistent with COVID-19 pneumonia (Supplementary Figure 1). Treatment included two 10-day courses of remdesivir with a five day gap in between (Extended data 1). Two units of convalescent plasma were administered on days 63 and 65 (Extended data 3). Following clinical deterioration, remdesivir and a unit of convalescent plasma were administered on day 95, but the individual unfortunately died on day 102 (Supplementary text).

## Virus genomic comparative analysis of 23 sequential respiratory samples over 101 days

The majority of samples were respiratory samples from nose and throat or endotracheal aspirates during the period of intubation (Supplementary Table 3). Ct values ranged from 16-34 and all 23 respiratory samples were successfully sequenced by standard single molecule sequencing approach as per the ARTIC protocol implemented by COG-UK; of these 20 additionally underwent short-read deep sequencing using the Illumina platform (Supplementary table 4). There was general agreement between the two methods (Extended data 4). However due to the higher reliability of Illumina for low frequency variants, this was used for formal analysis<sup>2,3</sup>. Additionally, single genome amplification and sequencing of Spike using extracted RNA from respiratory samples was used as an independent method to detect mutations observed (Extended data 4). Finally, we detected no evidence of recombination, based on two independent methods.

Maximum likelihood analysis of patient-derived whole genome consensus sequences demonstrated clustering with other local sequences from the same region (Figure 1). The infecting strain was assigned to lineage 20B bearing the D614G Spike variant. Environmental sampling showed evidence of virus on surfaces such as telephone and call bell. Sequencing of these surface viruses showed clustering with those derived from the respiratory tract (Extended data 2). All samples were consistent with having arisen from a single underlying viral population. In our phylogenetic analysis, we included sequential sequences from three other local patients identified with persistent viral RNA shedding over

a period of 4 weeks or more as well as two long term immunosuppressed SARS-CoV-2 ‘shedders’ recently reported<sup>4,5</sup>, (Extended data 2, Supplementary Table 2). While the sequences from the three local patients as well as from Avanzato et al<sup>5</sup> showed little divergence with no amino acid changes in Spike over time, the case patient showed significant diversification. The Choi et al report<sup>4</sup> showed similar degree of diversification as the case patient. Further investigation of the sequence data suggested the existence of an underlying structure to the viral population in our patient, with samples collected at days 93 and 95 being rooted within, but significantly divergent from the original population (Extended data 5 and 6). The relationship of the divergent samples to those at earlier time points argues against superinfection.

## SARS-CoV-2 viral diversity

All samples tested positive by RT-PCR and there was no sustained change in Ct values throughout the 101 days following the first two courses of remdesivir (days 41 and 54), or the first two units of convalescent plasma with polyclonal antibodies (days 63 and 65, Extended data 3). Of note we were not able to culture virus from stored swab samples. Consensus sequences from short read deep sequence Illumina data revealed dynamic population changes after day 65, as shown by a highlighter plot (Extended data 6). In addition, we were also able to follow the dynamics of virus populations down to low frequencies during the entire period (Figure 2, Supplementary Table 4). Following remdesivir at day 41 the low frequency variant analysis allowed us to observe transient amino acid changes in populations at below 50% abundance in Orf 1b, 3a and Spike, with a T39I (C27509T) mutation in ORF7a reaching 79% on day 45 (Figure 2, pink, supplementary information). At day 66 we noted I513T in NSP2 (T2343C) and V157L (G13936T) in RdRp had emerged from undetectable at day 54 to almost 100% frequency (Figure 2, red and green dashed lines), with the polymerase being the more plausible candidate for driving this sweep. Notably, spike variant N501Y, which can increase the ACE2 receptor affinity<sup>6</sup>, and which is present in the new UK B.1.1.7 lineage<sup>7</sup>, was observed on day 55 at 33% frequency, but was eliminated by the sweep of the NSP2/RdRp variant.

In contrast to the early period of infection, between days 66 and 82, following the first two administrations of convalescent sera, a shift in the virus population was observed, with a variant bearing D796H in S2 and H69/ V70 in the S1 N-terminal domain (NTD) becoming the dominant population at day 82. This was identified in a nose and throat swab sample with high viral load as indicated by Ct of 23 (Figure 3A). The deletion was detected transiently at baseline according to short read deep sequencing. H69/ V70 was due to an out of frame six nucleotide deletion resulting in the sequence of codon 68 changing from ATA to ATC.

On Days 86 and 89, viruses obtained from upper respiratory tract samples were characterised by the Spike mutations Y200H and T240I, with the deletion/mutation pair observed on day 82 having fallen to frequencies of 10% or less (Figure 2 and 3). The Spike mutations Y200H and T240I were accompanied at high frequency by two other non-synonymous variants with similar allele frequencies, coding for I513T in NSP2, V157L in RdRp and N177S in NSP15 (Figure 2A). Both of these were also previously observed at

>98% frequency in the sample on day 66 (Figure 2A, red and green lines), arguing that this new lineage emerged out of a previously existing population.

Sequencing of a nose and throat swab sample at day 93 identified viruses characterised by Spike mutations P330S at the edge of the RBD and W64G in S1 NTD at close to 100% abundance, with D796H along with H69/ V70 at <1% abundance and the variants Y200H and T240I at frequencies of <2%. Viruses with the P330S variant were detected in two independent samples from different sampling sites, arguing against the possibility of contamination. The divergence of these samples from the remainder of the population (Figure 2, 3B and Extended data 5 and 6) suggests the possibility that they represent a compartmentalised subpopulation.

Patterns in the variant frequencies suggest competition between virus populations carrying different mutations, viruses with the D796H/ H69/ V70 deletion/mutation pair rising to high frequency during CP therapy, then being outcompeted by another population in the absence of therapy. Specifically, these data are consistent with a lineage of viruses with the NSP2 I513T and RdRp V157L variant, dominant on day 66, being outcompeted during therapy by the mutation/deletion variant. With the lapse in therapy, the original strain, having acquired NSP15 N1773S and the Spike mutations Y200H and T240I, regained dominance, followed by the emergence of a separate population with the W64G and P330S mutations.

In a final attempt to reduce the viral load, a third course of remdesivir (day 93) and third dose of CP (day 95) were administered. We observed a re-emergence of the D796H + H69/ V70 viral population (Figure 2, 3). The inferred linkage of D796H and H69/ V70 was maintained as evidenced by the highly similar frequencies of the two variants, suggesting that the third unit of CP led to the re-emergence of this population under renewed positive selection. In further support of our proposed idea of competition, noted above, frequencies of these two variants appeared to mirror changes in the NSP2 I513T mutation (Figure 2), suggesting these as markers of opposing clades in the viral population. Ct values remained low throughout this period with hyperinflammation, eventually leading to multi-organ failure and death at day 102. The repeated increase in frequency of the viral population with CP therapy strongly supports the hypothesis that the deletion/mutation combination conferred selective advantage.

## **Spike mutants emerging post convalescent plasma impair neutralising antibody potency**

Using lentiviral pseudotyping we generated wild type, H69/ V70 + D796H and single mutant Spike proteins in enveloped virions in order to measure neutralisation activity of CP against these viruses (Figure 4). This system has been shown to give generally similar results to replication competent virus<sup>8,9</sup>. Spike protein from each mutant was detected in pelleted virions (Figure 4A). We also probed with an HIV-1 p24 antibody to monitor levels of lentiviral particle production (Figure 4A, Supplementary Figure 2). We then measured infectivity of the pseudoviruses, correcting for virus input using reverse transcriptase activity measurement, and found that H69/ V70 appeared to have two-fold higher infectivity over

a single round of infection compared to wild type (Figure 4B, Extended data 7). By contrast, the D796H single mutant had significantly lower infectivity as compared to wild type and double mutant had similar infectivity to wild type (Figure 4B, Extended data 7).

We found that D796H alone and the D796H + H69/ V70 double mutant were less sensitive to neutralisation by convalescent plasma samples (Figure 4C-E, Extended data 7). By contrast the H69/ V70 single mutant did not reduce neutralisation sensitivity. In addition, patient derived serum from days 64 and 66 (one day either side of CP2 infusion) similarly showed lower potency against the D796H + H69/ V70 mutants (Figure 4F, G).

A panel of nineteen monoclonal antibodies (mAbs) isolated from three donors was previously identified to neutralize SARS-CoV-2. To establish if the mutations incurring *in vivo* (D796H and H69/ V70) resulted in a global change in neutralization sensitivity we tested neutralising mAbs targeting the seven major epitope clusters previously described (excluding non-neutralising clusters II, V and small [n = <2] neutralising clusters IV, X). The eight RBD-specific mAbs (Extended data 8) exhibited no major change in neutralisation potency and non-RBD specific COVA1-21 showing 3-5 fold reduction in potency against H69/ V70+D796H and H69/ V70, but not D796H alone<sup>9</sup> (Extended data 8). We observed no differences in neutralisation between single/double mutants and wild type, suggesting that the mechanism of escape was likely outside these epitopes in the RBD. These data confirm the specificity of the findings from convalescent plasma and suggest that mutations observed are related to antibodies targeting regions outside the RBD. Interestingly, H69/ V70 containing viruses showed reduced neutralisation sensitivity to the mAb COVA1-21, targeting an as yet undefined epitope outside the RBD.<sup>10</sup>

To understand how the H69/ V70 and D796H might confer antibody resistance, we assessed how they might affect the Spike structure (Extended data 9). We based this analysis primarily on a structure lacking stabilising modifications (PDB 6xr8)<sup>11</sup>, but also referred to stabilised structures determined at different pH values<sup>12</sup>. H69/ V70 is located in a disordered, glycosylated loop at the distal surface of the NTD, near the binding site of polyclonal antibodies derived from COV57 plasma<sup>13,14</sup> (Extended data 9). As this loop is flexible and highly accessible, H69/V70 could in principle affect antibody binding in this region. D796 is located near the base of Spike, in a surface loop that is structurally somewhat disordered in the prefusion conformation and becomes part of a large disordered region in the post fusion S2 trimer<sup>11</sup> (Extended data 9). The loop containing residue 796 is proposed to be targeted by antibodies<sup>15</sup>, despite mutations at position 796 being relatively uncommon (Extended data 9). In the RBD-down Spike structures<sup>11,12</sup>, D796 forms contacts with residues in the neighbouring protomer, including the glycosylated residue N709 (Extended data 9).

## Discussion

Here we have documented a repeated evolutionary response by SARS-CoV-2 in the presence of antibody therapy during the course of a persistent infection in an immunocompromised host. The observation of potential selection for specific variants coinciding with the presence of antibodies from convalescent plasma is supported by the experimental finding of two-fold

reduced susceptibility of these viruses to convalescent plasma containing polyclonal antibodies. In this case the emergence of the variant was not the primary reason for treatment failure. We have noted in our analysis signs of compartmentalised viral replication based on the sequences recovered in upper respiratory tract samples. Both population genetic and small animal studies have shown a lack of reassortment between influenza viruses within a single host during an infection, suggesting that acute respiratory viral infection may be characterised by spatially distinct viral populations<sup>16,17</sup>. In the analysis of data, it is important to distinguish genetic changes which occur in the primary viral population from apparent changes that arise from the stochastic observation of spatially distinct subpopulations in the host. While the samples we observe on days 93 and 95 of infection are genetically distinct from the others, the remaining samples are consistent with arising from a consistent viral population. We note that Choi et al reported the detection in post-mortem tissue of viral RNA not only in lung tissue, but also in the spleen, liver, and heart<sup>4</sup>. Mixing of virus from different compartments, for example via blood, or movement of secretions from lower to upper respiratory tract, could lead to fluctuations in viral populations at particular sampling sites.

This is a single case report and therefore limited conclusions can be drawn about generalisability.

An important limitation is that the data were derived from sampling from the upper respiratory tract and not the lower tract, thus limiting the inferences that can be drawn regarding viral populations in this single case.

In addition to documenting the emergence of SARS-CoV-2 Spike H69/ V70 *in vivo*, we show that this mutation modestly increases infectivity of the Spike protein in a pseudotyping assay. The deletion was observed contemporaneously with the rare S2 mutation D796H after two separate courses of CP, with other viral populations emerging. D796H, but not H69/ V70, conferred reduction in susceptibility to polyclonal antibodies in the units of CP administered, though we cannot speculate as to their individual impacts on sera from other individuals. It is intriguing that the H69/ V70 + D796H double mutant diminished in between CP courses, suggesting that there were other selective forces at play in the intervening period, possibly driven by the inflammation observed in the individual. This includes the possibility that the haplotype with H69/ V70 + D796H may have carried mutations in other regions deleterious during that intervening period. Although H69/V70 is expanding at a high rate<sup>18</sup>, D796 mutations are also increasing. D796H has been documented in 0.02% of global sequences and D796Y appears in 0.05% of global sequences (Extended data 9).

The effects of CP on virus evolution seen here are unlikely to apply in immune competent hosts where viral diversity is likely to be lower due to better immune control. Our data highlight that infection control measures may need to be tailored to the needs of immunocompromised patients and also caution in interpretation of CDC guidelines that recommend 20 days as the upper limit of infection prevention precautions in immune compromised patients who are afebrile<sup>19</sup>. Due to the difficulty with culturing clinical isolates, use of surrogates are warranted<sup>20</sup>. However, where detection of ongoing viral

evolution is possible, this serves as a clear proxy for the existence of infectious virus. In our case we detected environmental contamination whilst in a single occupancy room and the patient was moved to a negative-pressure high air-change infectious disease isolation room.

Clinical efficacy of convalescent plasma in severe COVID-19 has not been demonstrated<sup>21</sup>, and its use in different stages of infection and disease remains experimental; as such, we suggest that it should be reserved for use within clinical trials, with rigorous monitoring of clinical and virological parameters. The data from this single case report might warrant caution in use of convalescent plasma in patients with immune suppression of both T cell and B cell arms; in such cases, the antibodies administered have little support from cytotoxic T cells, thereby reducing chances of clearance and theoretically raising the potential for escape mutations. Whilst we await further data, where clinical trial enrolment is not possible, convalescent plasma administered for clinical need in immune suppression should ideally only be considered as part of observational studies, undertaken preferably in single occupancy rooms with enhanced infection control precautions, including SARS-CoV-2 environmental sampling and real-time sequencing. Understanding of viral dynamics and characterisation of viral evolution in response to different selection pressures in the immunocompromised host is necessary not only for improved patient management but also for public health benefit.

## Methods

### Clinical Sample Collection and Next generation sequencing

Serial samples were collected from the patient periodically from the lower respiratory tract (sputum or endotracheal aspirate), upper respiratory tract (throat and nasal swab), and from stool. Nucleic acid extraction was done from 500µl of sample with a dilution of MS2 bacteriophage to act as an internal control, using the easyMAG platform (Biomerieux, Marcy-l'Étoile) according to the manufacturers' instructions. All samples were tested for presence of SARS-CoV-2 with a validated one-step RT q-PCR assay developed in conjunction with the Public Health England Clinical Microbiology<sup>22</sup>. Amplification reaction were all performed on a Rotorgene™ PCR instrument. Samples which generated a CT of 36 were considered to be positive.

Sera from recovered patients in the COVIDx study<sup>23</sup> were used for testing of neutralisation activity by SARS-CoV-2 mutants.

### SARS-CoV-2 serology by multiplex particle-based flow cytometry (Luminex)

Recombinant SARS-CoV-2 N, S and RBD were covalently coupled to distinct carboxylated bead sets (Luminex; Netherlands) to form a 3-plex and analyzed as previously described (Xiong et al. 2020). Specific binding was reported as mean fluorescence intensities (MFI).

### Whole blood T cell and innate stimulation assay

Whole blood was diluted 1:5 in RPMI into 96-well F plates (Corning) and activated by single stimulation with phytohemagglutinin (PHA; 10 µg/ml; Sigma-Aldrich), or LPS (1 µg/ml, List Biochemicals) or by co-stimulating with anti-CD3 (MEM57, Abcam, 200 ng/ml,

1:1000) and IL-2 (Immunotools, 1430U/ml, 1:1000). Supernatants were taken after 24 hours. Levels (pg/ml) are shown for IFN $\gamma$ , IL17, IL2, TNF $\alpha$ , IL6, IL1 $\beta$  and IL10. Cytokines were measured by multiplexed particle based Flow cytometry on a Luminex analyzer (BioPlex, Bio-Rad, UK) using an R&D Systems custom kit (R&D Systems, UK).

For viral genomic sequencing, total RNA was extracted from samples as described. Samples were sequenced using MinION flow cells version 9.4.1 (Oxford Nanopore Technologies) following the ARTICnetwork V3 protocol (<https://dx.doi.org/10.17504/protocols.io.bbmuik6w>) and BAM files assembled using the ARTICnetwork assembly pipeline (<https://artic.network/ncov-2019/ncov2019-bioinformatics-sop.html>). A representative set of 10 sequences were selected and also sequenced using the Illumina MiSeq platform. Amplicons were diluted to 2 ng/ $\mu$ l and 25  $\mu$ l (50 ng) were used as input for each library preparation reaction. The library preparation used KAPA Hyper Prep kit (Roche) according to manufacturer's instructions. Briefly, amplicons were end-repaired and had A-overhang added; these were then ligated with 15mM of NEXTflex DNA Barcodes (Bio Scientific, Texas, USA). Post-ligation products were cleaned using AMPure beads and eluted in 25  $\mu$ l. Then, 20  $\mu$ l were used for library amplification by 5 cycles of PCR. For the negative controls, 1ng was used for ligation-based library preparation. All libraries were assayed using TapeStation (Agilent Technologies, California, USA) to assess fragment size and quantified by QPCR. All libraries were then pooled in equimolar accordingly. Libraries were loaded at 15nM and spiked in 5% PhiX (Illumina, California, USA) and sequenced on one MiSeq 500 cycle using a Miseq Nano v2 with 2x 250 paired-end sequencing. A minimum of ten reads were required for a variant call.

### Bioinformatics Processes

For long-read sequencing, genomes were assembled with reference-based assembly and a curated bioinformatics pipeline with 20x minimum coverage across the whole-genome<sup>24</sup>. For short-read sequencing, FASTQs were downloaded, poor-quality reads were identified and removed, and both Illumina and PHiX adapters were removed using TrimGalore v0.6.6<sup>25</sup>. Trimmed paired-end reads were mapped to the National Center for Biotechnology Information SARS-CoV-2 reference sequence MN908947.3 using MiniMap2-2.17 with arguments -ax and sr<sup>26</sup>. BAM files were then sorted and indexed with samtools v1.11 and PCR optical duplicates removed using Picard (<http://broadinstitute.github.io/picard>). A consensus sequences of nucleic acids with a minimum whole-genome coverage of at least 20x were generated with BCFtools using a 0% majority threshold.

### Variant calling

Variant frequencies were validated using custom code as part of the *AnCovMulti* package ([github.com/PollockLaboratory/AnCovMulti](https://github.com/PollockLaboratory/AnCovMulti)). The main idea behind this validation was to identify and remove consistent potential amplification errors and mutability near the end of Illumina reads. Furthermore, stringent filtering was applied to remove biased amplification of early laboratory-induced mutations or very low copy variations.

Filtering consisted of requiring exact initiation at a primer within two bp of the start of a read, a minimum of 247 bp length read, fewer than four well-separated sites divergent from

the reference sequence, a maximum insertion size of three nucleotides, a maximum deletion size of 11 bp, and resolution of conflicting signal from different primers.

### Single Genome Amplification and sequencing

Viral RNA extracts were reverse transcribed from each sample to sufficiently capture the diversity of the viral population without introducing resampling bias. SuperScript IV (ThermoFisher Scientific) and the gene specific primers were used for reverse transcription. Template RNA was degraded with RNase H (ThermoFisher Scientific). All primers used were 'in-house' primers designed using the multiple sequence alignment of the patient's consensus NGS sequences. Partial Spike (amino acids 21-800) was amplified as 1 continuous length of DNA (Spike ~ 1.8 kb) by nested PCR. Terminally diluted cDNA was PCR-amplified using Platinum<sup>®</sup> Taq DNA Polymerase High Fidelity (Invitrogen, Carlsbad, CA) so that 30% of reactions were positive<sup>27</sup>. By Poisson statistics, sequences were deemed 80% likely to be derived from HIV-1 single genomes. We obtained between 20–60 single genomes at each sample time point to achieve 90% confidence of detecting variants present at 8% of the viral population in vivo<sup>28,29</sup>. Partial spike amplicons obtained from terminal dilution PCR amplification were Sanger sequenced to form a contiguous sequence using another set of 8 in-house primers. Sanger sequencing was provided by Genewiz UK and manual sequence editing was performed using DNA Dynamo software (Blue Tractor Software Ltd, UK).

### Phylogenetic Analysis

All available full-genome SARS-CoV-2 sequences were downloaded from the GISAID database (<http://gisaid.org/>)<sup>30</sup> on 16<sup>th</sup> December. Duplicate and low-quality sequences (>5% N regions) were removed, leaving a dataset of 212,297 sequences with a length of >29,000bp. All sequences were sorted by name and only sequences sequenced with United Kingdom / England identifiers were retained. From this dataset, sequences were de-duplicated and where background sequences were required in figures, randomly subsampled using seqtk (<https://github.com/lh3/seqtk>). All sequences were aligned to the SARS-CoV-2 reference strain MN908947.3, using MAFFT v7.475 with automatic flavour selection<sup>31</sup>. Major SARS-CoV-2 clade memberships were assigned to all sequences using both the Nextclade server v0.9 (<https://clades.nextstrain.org/>) and Phylogenetic Assignment Of Named Global Outbreak Lineages (pangolin)<sup>32</sup>.

Maximum likelihood phylogenetic trees were produced using the above curated dataset using IQ-TREE v2.1.2<sup>33</sup>. Evolutionary model selection for trees were inferred using ModelFinder<sup>34</sup> and trees were estimated using the GTR+F+I model with 1000 ultrafast bootstrap replicates<sup>35</sup>. All trees were visualised with Figtree v.1.4.4 (<http://tree.bio.ed.ac.uk/software/figtree/>), rooted on the SARS-CoV-2 reference sequence and nodes arranged in descending order. Nodes with bootstraps values of <50 were collapsed using an in-house script.

### In-depth allele frequency variant calling

The SAMFIRE package version 1.06<sup>36</sup> was used to call allele frequency trajectories from BAM file data. Reads were included in this analysis if they had a median PHRED score of at



least 30, trimming the ends of reads to achieve this if necessary. Nucleotides were then filtered to have a PHRED score of at least 30; reads with fewer than 30 such reads were discarded. Distances between sequences, accounting for low-frequency variant information, was also conducted using SAMFIRE. The sequence distance metric, described in an earlier paper<sup>37</sup>, combines allele frequencies across the whole genome. Where  $L$  is the length of the genome, we define  $q(t)$  as a  $4 \times L$  element vector describing the frequencies of each of the nucleotides A, C, G, and T at each locus in the viral genome sampled at time  $t$ . For any given locus  $i$  in the genome we calculate the change in allele frequencies between the times  $t_1$  and  $t_2$  via a generalisation of the Hamming distance

$$d(q_i(t_1), q_i(t_2)) = \frac{1}{2} \sum_{a \in \{A, C, G, T\}} |q_i^a(t_1) - q_i^a(t_2)|$$

where the vertical lines indicate the absolute value of the difference. These statistics were then combined across the genome to generate the pairwise sequence distance metric

$$D(q(t_1), q(t_2)) = \sum_i d(q_i(t_1), q_i(t_2))$$

The Mathematica software package was used to conduct a regression analysis of pairwise sequence distances against time, leading to an estimate of a mean rate of within-host sequence evolution. In contrast to the phylogenetic analysis, this approach assumed the samples collected on days 93 and 95 to arise via stochastic emission from a spatially separated subpopulation within the host, leading to a lower inferred rate of viral evolution for the bulk of the viral population.

All variants were independently validated using custom code as part of the AnCovMulti package, found at <https://github.com/PollockLaboratory/AnCovMulti>.

### Western blot analysis

Forty-eight hours after transfection of cells with plasmid preparations, the culture supernatant was harvested and passed through a 0.45- $\mu\text{m}$ -pore-size filter to remove cellular debris. The filtrate was centrifuged at 15,000 rpm for 120 min to pellet virions. The pelleted virions were lysed in Laemmli reducing buffer (1 M Tris-HCl [pH 6.8], SDS, 100% glycerol,  $\beta$ -mercaptoethanol, and bromophenol blue). Pelleted virions were subjected to electrophoresis on SDS-4 to 12% bis-Tris protein gels (Thermo Fisher Scientific) under reducing conditions. This was followed by electroblotting onto polyvinylidene difluoride (PVDF) membranes. The SARS-CoV-2 Spike proteins were visualized by a ChemiDoc<sup>MP</sup> imaging system (Biorad) using anti-Spike S2 (Invitrogen at 1:1000 dilution) and anti-p24 Gag antibodies (NIH AIDS Reagents 1:1000 dilution).

### Recombination Detection

All sequences were tested for potential recombination, as this would impact on evolutionary estimates. Potential recombination events were explored with nine algorithms (RDP, MaxChi, SisScan, GeneConv, Bootscan, PhylPro, Chimera, LARD and 3SEQ), implemented

in RDP5 with default settings<sup>38</sup>. To corroborate any findings, ClonalFrameML v1.12<sup>39</sup> was also used to infer recombination breakpoints. Neither programs indicated evidence of recombination in our data.

### Structural Viewing

The Pymol Molecular Graphics System v2.4.0 (<https://github.com/schrodinger/pymol-open-source/releases>) was used to map the location of the four spike mutations of interest onto a SARS-CoV-2 spike structure visualised by Wrobel et al (PDB: 6ZGE)<sup>40</sup>.

### Testing of convalescent plasma for antibody titres

The Anti-SARS-CoV-2 ELISA (IgG) assay used to test CP for *antibody titres* was Euroimmun Medizinische Labordiagnostika AG. This indirect ELISA based assay uses a recombinant structural spike 1 (S1) protein of SARS-CoV-2 expressed in the human cell line HEK 293 for the detection of SARS-CoV2 IgG.

### Generation of Spike mutants

Amino acid substitutions were introduced into the D614G pCDNA\_SARS-CoV-2\_Spike plasmid as previously described<sup>41</sup> using the QuikChange Lightning Site-Directed Mutagenesis kit, following the manufacturer's instructions (Agilent Technologies, Inc., Santa Clara, CA).

### Pseudotype virus preparation

Viral vectors were prepared by transfection of 293T cells by using Fugene HD transfection reagent (Promega). 293T cells were transfected with a mixture of 11  $\mu$ l of Fugene HD, 1  $\mu$ g of pCDNAp19Spike-HA, 1  $\mu$ g of p8.91 HIV-1 gag-pol expression vector<sup>42,43</sup>, and 1.5  $\mu$ g of pCSFLW (expressing the firefly luciferase reporter gene with the HIV-1 packaging signal). Viral supernatant was collected at 48 and 72h after transfection, filtered through 0.45  $\mu$ m filter and stored at -8°C. The 50% tissue culture infectious dose (TCID50) of SARS-CoV-2 pseudovirus was determined using Steady-Glo Luciferase assay system (Promega).

### Standardisation of virus input by SYBR Green-based product-enhanced PCR assay (SG-PERT)

The reverse transcriptase activity of virus preparations was determined by qPCR using a SYBR Green-based product-enhanced PCR assay (SG-PERT) as previously described<sup>44</sup>. Briefly, 10-fold dilutions of virus supernatant were lysed in a 1:1 ratio in a 2x lysis solution (made up of 40% glycerol v/v 0.25% Triton X-100 v/v 100mM KCl, RNase inhibitor 0.8 U/ml, TrisHCL 100mM, buffered to pH7.4) for 10 minutes at room temperature.

12  $\mu$ l of each sample lysate was added to thirteen 13  $\mu$ l of a SYBR Green master mix (containing 0.5  $\mu$ M of MS2-RNA Fwd and Rev primers, 3.5 pmol/ml of MS2-RNA, and 0.125 U/ $\mu$ l of Ribolock RNase inhibitor and cycled in a QuantStudio. Relative amounts of reverse transcriptase activity were determined as the rate of transcription of bacteriophage MS2 RNA, with absolute RT activity calculated by comparing the relative amounts of RT to an RT standard of known activity.

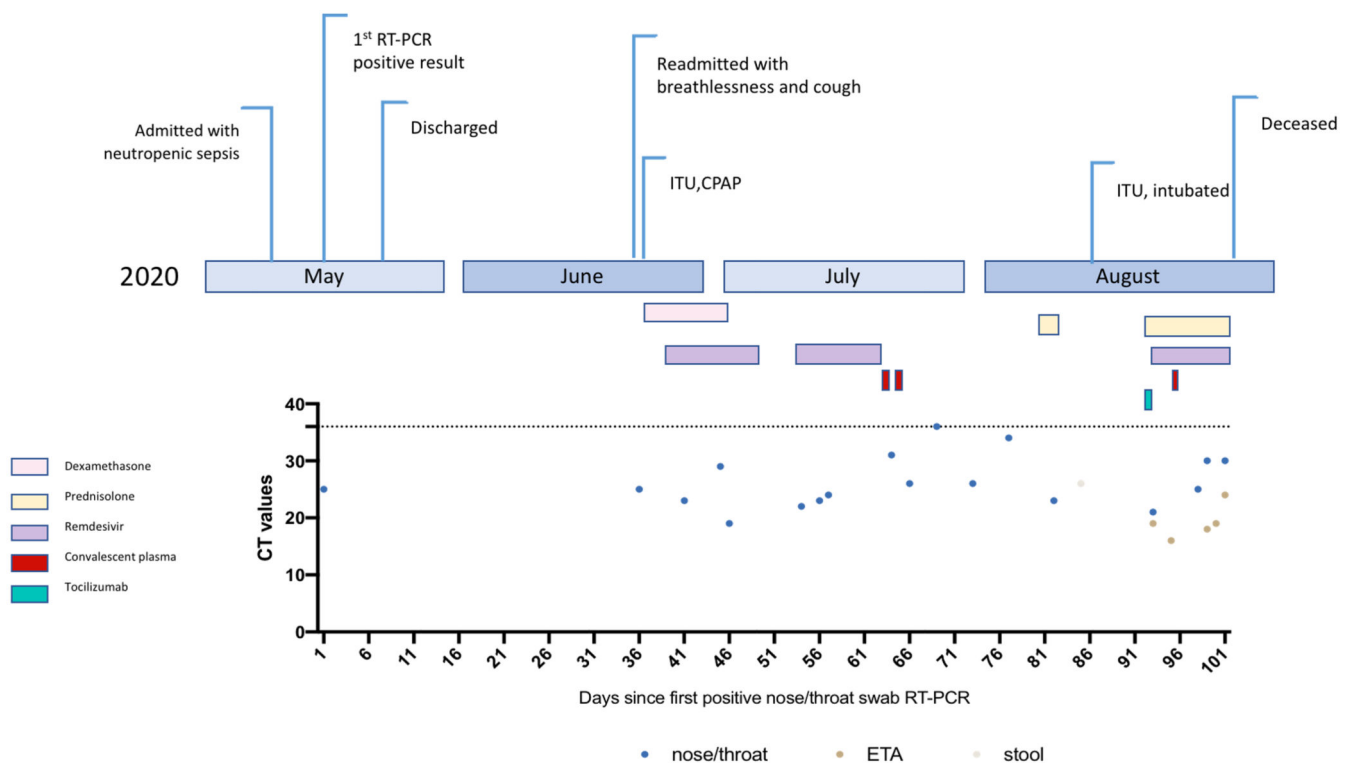
## Serum/plasma pseudotype neutralization assay

Spike pseudotype assays have been shown to have similar characteristics as neutralisation testing using fully infectious wild type SARS-CoV-2<sup>8</sup>. Virus neutralisation assays were performed on 293T cell transiently transfected with ACE2 and TMPRSS2 using SARS-CoV-2 Spike pseudotyped virus expressing luciferase<sup>45</sup>. Pseudotyped virus was incubated with serial dilution of heat inactivated human serum samples or convalescent plasma in duplicate for 1h at 37°C. Virus and cell only controls were also included. Then, freshly trypsinized 293T ACE2/TMPRSS2 expressing cells were added to each well. Following 48h incubation in a 5% CO<sub>2</sub> environment at 37°C, the luminescence was measured using Steady-Glo Luciferase assay system (Promega).

## mAb pseudotype neutralisation assay

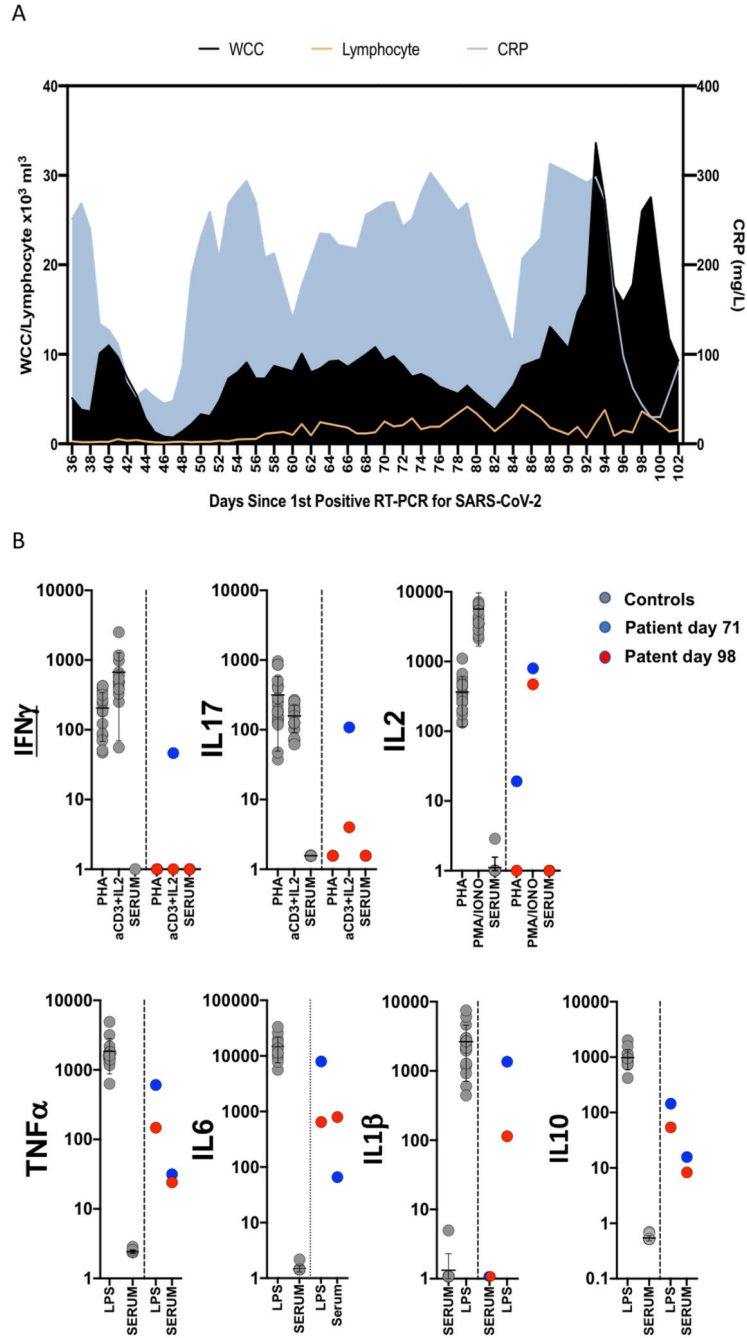
Virus neutralisation assays were performed on HeLa cells stably expressing ACE2 and using SARS-CoV-2 Spike pseudotyped virus expressing luciferase as previously described<sup>46</sup>. Pseudotyped virus was incubated with serial dilution of purified mAbs<sup>9</sup> in duplicate for 1h at 37°C. Then, freshly trypsinized HeLa ACE2-expressing cells were added to each well. Following 48h incubation in a 5% CO<sub>2</sub> environment at 37°C, the luminescence was measured using Bright-Glo Luciferase assay system (Promega) and neutralization calculated relative to virus only controls. IC<sub>50</sub> values were calculated in GraphPad Prism.

## Extended Data



Extended Data Figure 1.

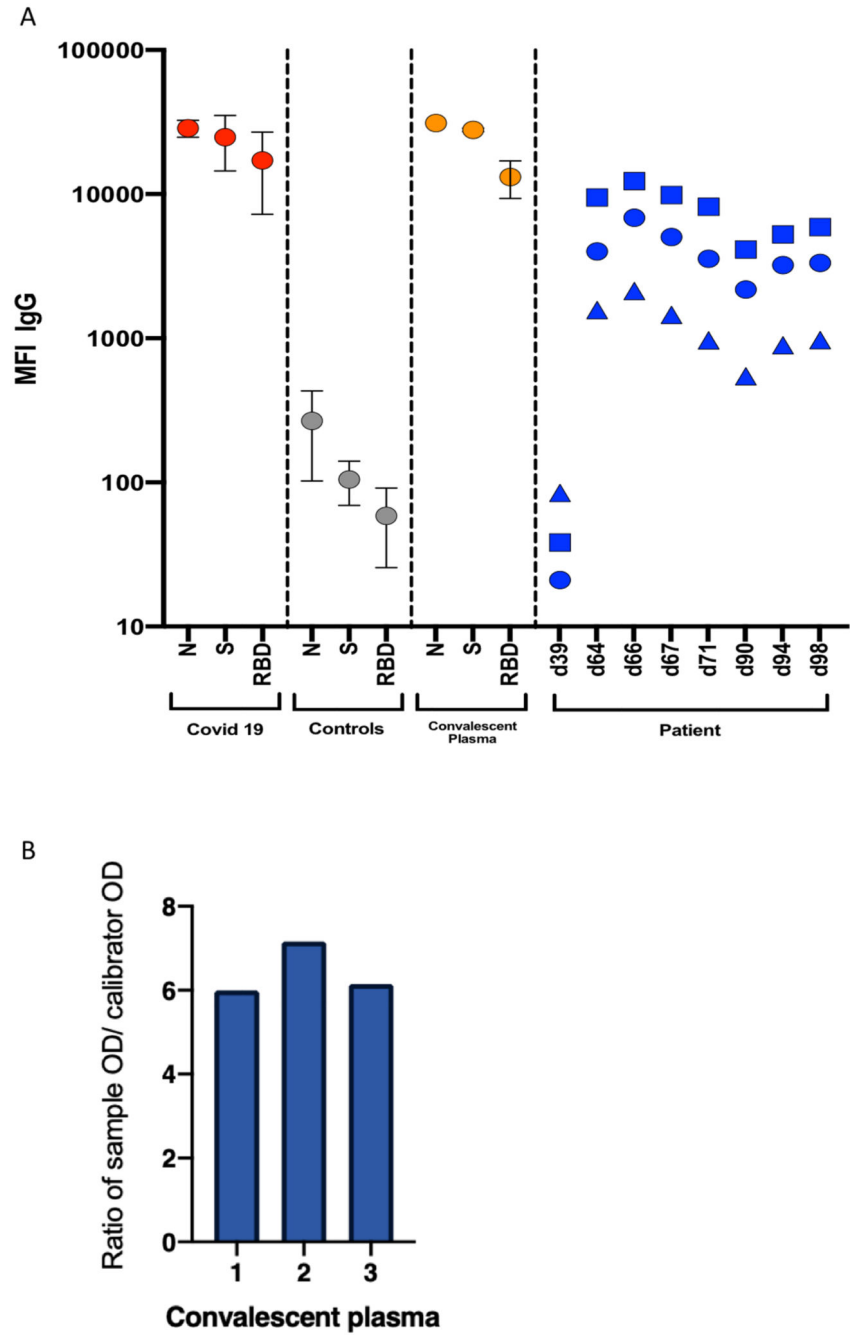
**Clinical time line of events with longitudinal respiratory sample CT values.** CT – cycle threshold.



**Extended data 2.**

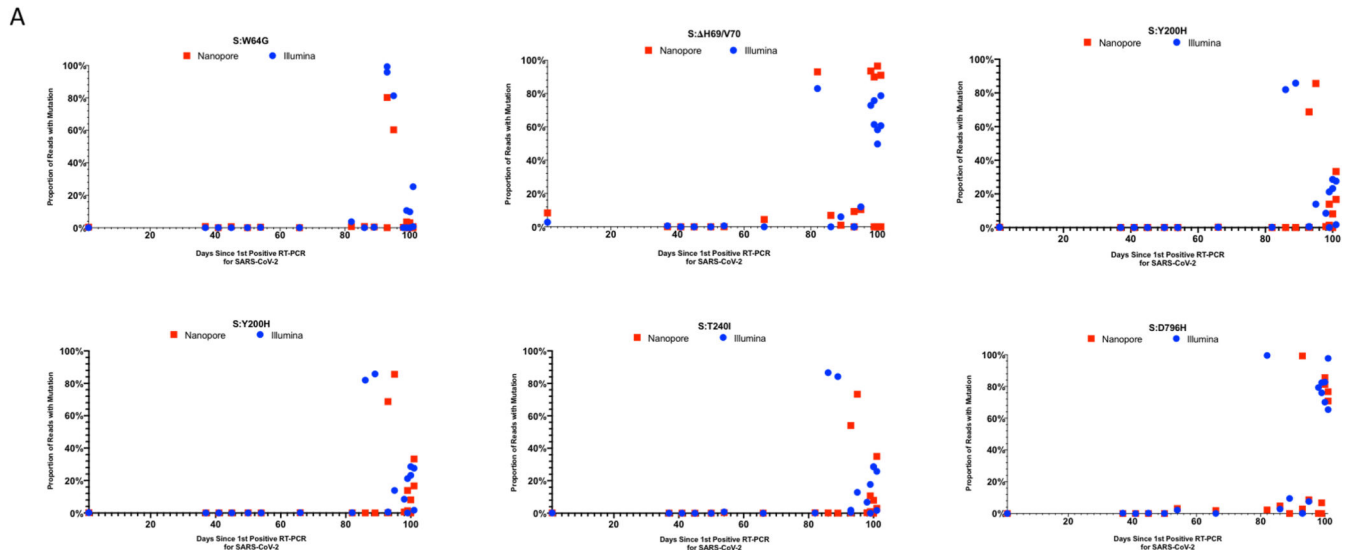
**A. Blood parameters over time in patient case:** White cell count (WCC) and lymphocyte counts are expressed as  $\times 10^3$  Cells/mm<sup>3</sup>. CRP: C reactive protein. **B. Assessment of T cell and innate function.** Whole blood cytokines were measured in whole blood after 24 hours stimulation either after T-cell stimulation with PHA or anti CD3/IL2 or innate stimulation

with LPS. Healthy controls are shown as grey circles (N=15), Patient at d71 and d98 is shown as blue circles or red circles respectively. Cytokine levels are shown as pg/ml stimulation. Mean is shown by line and whiskers representing standard deviation.



Extended Data Figure 3. **A. Serum SARS-CoV-2 antibody levels and virus population changes in chronic SARS-CoV-2 infection. Anti SARS-CoV2 IgG antibodies in patient and pre/post convalescent plasma compared to RNA+ Covid19 patients and prepanemic healthy controls: Red,**

**grey and gold:** IgG antibodies to SARS-CoV2 nucleocapsid protein (N), trimeric S protein (S) and the receptor binding domain (RBD) were measured by multiplexed particle based flow cytometry (Luminex) in RNA+ COVID-19 patients (N=20, red dots), Pre-pandemic healthy controls (N=20, grey dots) and in the convalescent donor plasma (orange dots); Results are shown as mean fluorescent intensity (MFI) +/- SD. **Patient sera over time in blue:** Anti SARS-CoV2 IgG to N (blue squares), S (blue circles) and RBD (blue triangles). Timing of CP units is also shown. **B. SARS-CoV-2 antibody titres in patient and in convalescent plasma.** Measurement of SARS-CoV-2 specific IgG antibody titres in three units of convalescent plasma (CP) by Euroimmun assay.

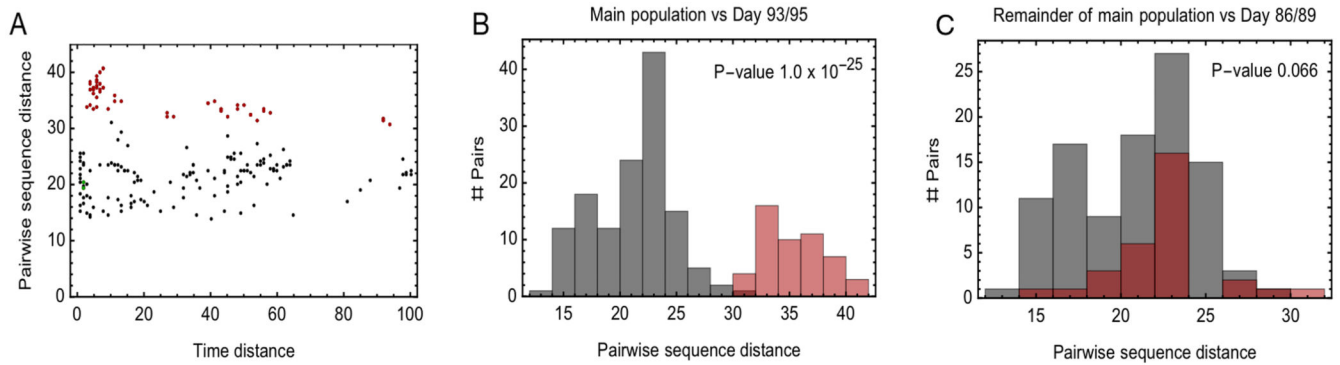


**B**

	W64G	P330S	ΔH69/V70	D796H	T200I	Y240H
Day 1 (n=7)	0	0	0	0	0	0
Day 37 (n=38)	0	0	0	0	0	0
Day 98 (n=21)	1 (4.8)	1 (4.8)	17 (81.0)	13*(68.4)	3 (14.3)	3 (14.3)

**Extended data 4. Comparison between short-read (Illumina) and long-read single molecule (Oxford Nanopore) sequencing methods for the six observed Spike mutations.**

Concordance was generally good between the majority of timepoints, however due to large discrepancies in a number of timepoints, we suggest that due to the high base calling error rate, Nanopore is not yet suitable for calling minority variants. As such, all figures in the main paper were produced using Illumina data only. **B. Single genome sequencing (SGS) data from respiratory samples at indicated days.** Indicated are the number of single genomes obtained at each time point with the mutations of interest (identified by deep sequencing). \*denominator is 19 as for 2 samples the primer reads were poor quality at amino acid 796 at day 98. Amino acid variant and corresponding nucleotide position: S:W64G = 21752, S: 69 = 21765-21770, S:Y200H = 22160, S:T240I = 22281, S:P330S = 22550, S:D795H = 23948



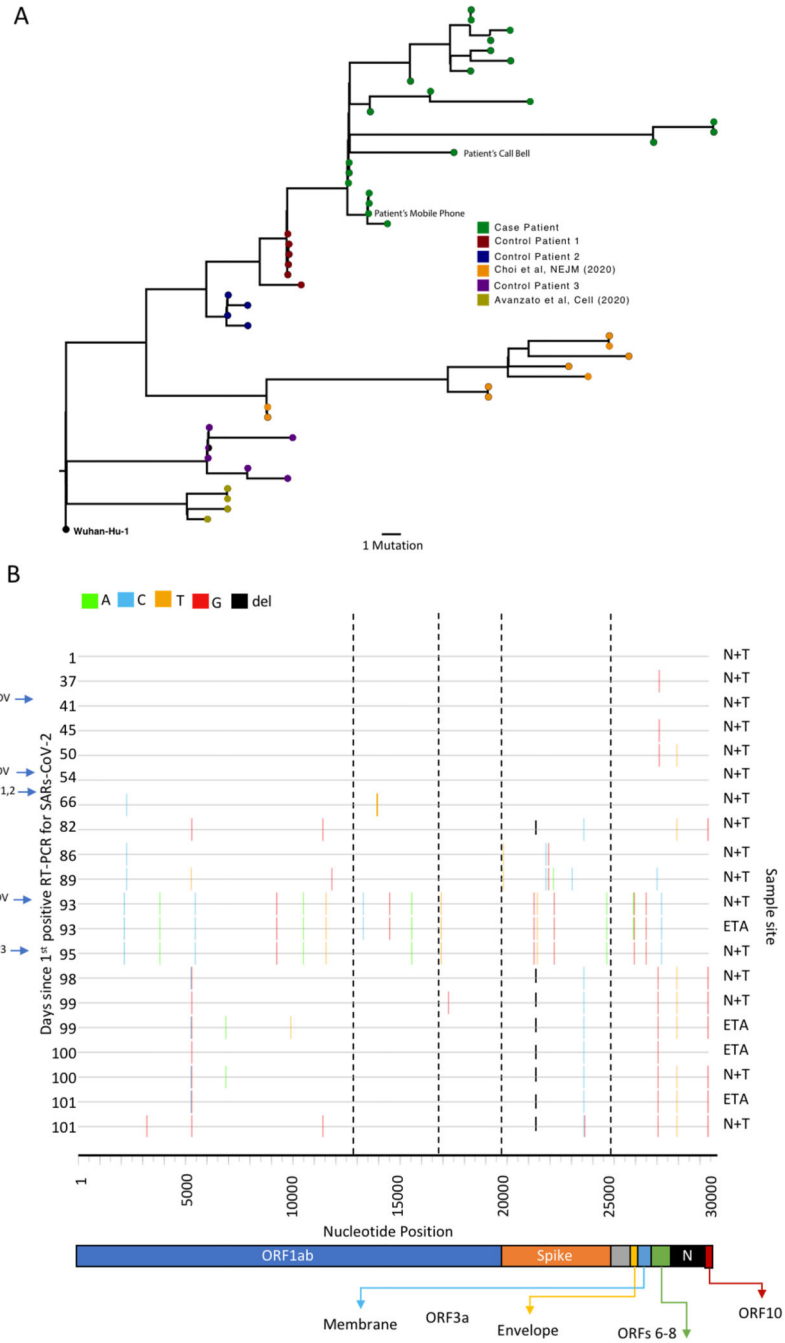
**Extended Data Figure 5. Evidence for within-host cladal structure.**

**A.** Pairwise distances between samples measured using the all-locus distance metric plotted against pairwise distances in time (measured in days) between samples being collected.

Internal distances between samples in the proposed main clade are shown in black, distances between samples in the main clade and samples collected on days 93 and 95 are shown in red, and internal distances between samples collected on days 93 and 95 are shown in green.

**B.** Pairwise distances between samples in the larger clade (black) and between these samples and those collected on days 93 and 95 (red). The median values of the distributions of these values are significantly different according to a Mann Whitney test. **C.** Pairwise distances between samples in the main clade, once those collected on days 86, 89, 93, 95 have been removed (black) and between these samples and those collected on days 86 and 89 (red).

The median values of the distributions of these values are not significantly different at the 5 level according to a Mann Whitney test.

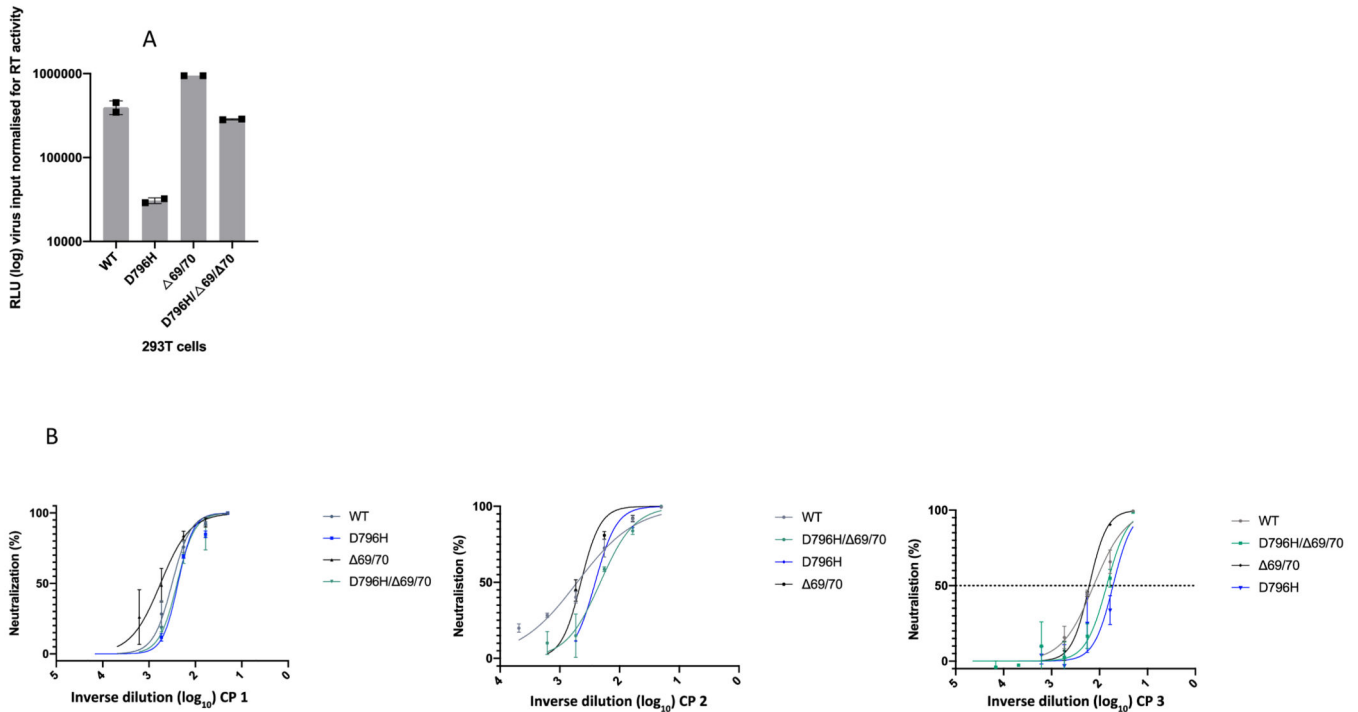


**Extended Data Figure 6.**

**A. Close-view maximum-likelihood phylogenetic tree** indicating the diversity of the case patient and three other long-term shedders from the local area (red, blue and purple), compared to recently published sequences from Choi et al (orange) and Avanzato et al (gold). Control patients generally showed limited diversity temporally, though the Choi et al sequences were highly divergent. Environmental samples (patient’s call bell, and patient’s mobile phone) are indicated. Tree branched have been collapsed where bootstrap support was <60.



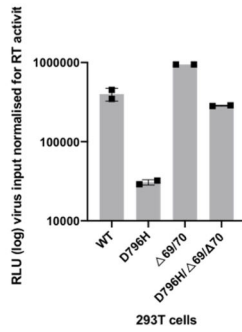
**B. Highlighter plot indicating nucleotide changes at consensus level in sequential respiratory samples compared to the consensus sequence at first diagnosis of COVID-19.** Each row indicates the timepoint the sample was collected (number of days from first positive SARS-CoV-2 RT-PCR). Black dashed lines indicate the RNA-dependent RNA polymerase (RdRp) and Spike regions of the genome. There were few nucleotide substitutions between days 1-54, despite the patient receiving two courses of remdesivir. The first major changes in the spike genome occurred on day 82, following convalescent plasma given on days 63 and 65. The amino acid deletion in S1, H69/V70 is indicated by the black lines. Sites: Endotracheal aspirate (ETA) or Nose/throat swabs (N+T).



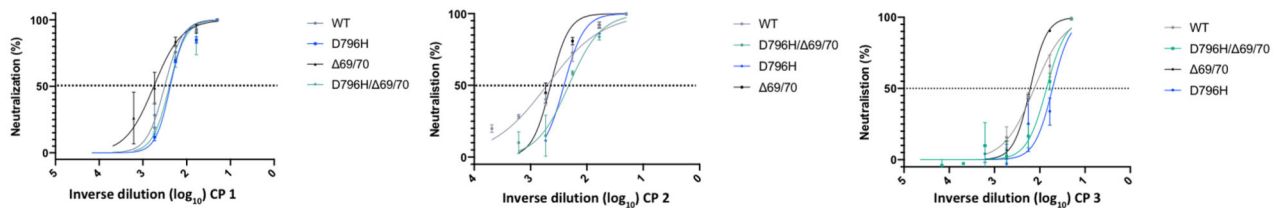
**Extended Data 7. In vitro infectivity and neutralisation sensitivity of Spike pseudotyped lentiviruses.**

**A.** infection of target 293T cells expressing TMPRSS2 and ACE2 receptors using equal amounts of virus as determined by reverse transcriptase activity. Data points represent technical replicates (n=2), with mean shown with error bars representing standard deviation. Data are representative of n=2 independent experiments (n=2). **B.** Representative Inverse dilution plots for Spike variants against convalescent plasma units 1-3. Data points represent mean neutralisation of technical replicates and error bars represent standard error of the mean of replicates. Data are representative of two independent experiments (n=2).

A

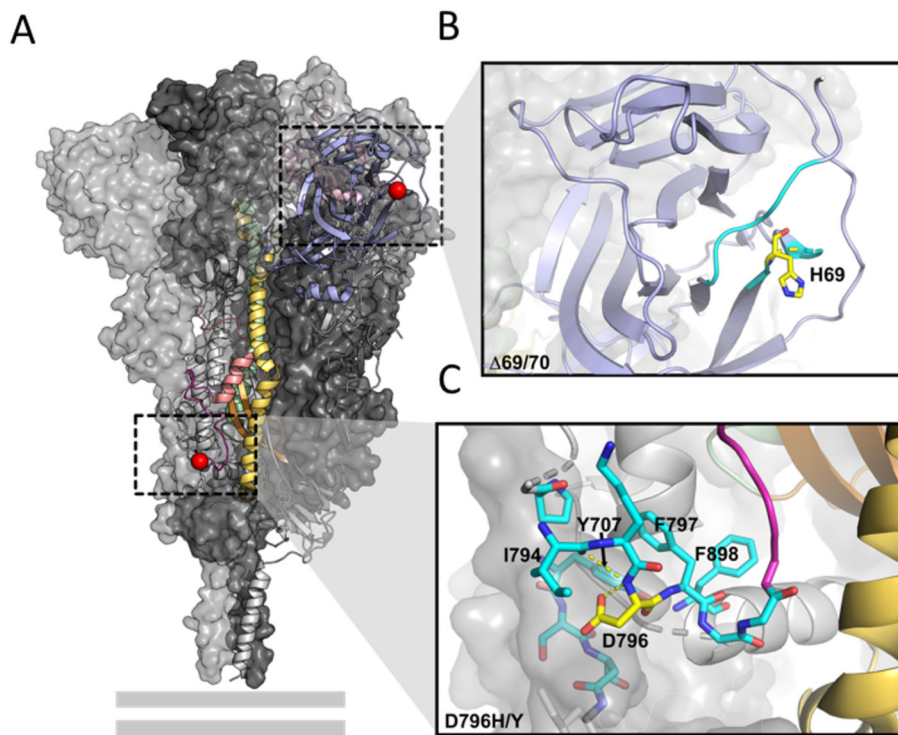


B



### Extended Data Figure 8.

**A. Neutralization potency of a panel of monoclonal antibodies targeting the RBD is not impacted by Spike mutations D796H or H69/V70.** Lentivirus pseudotyped with SARS-CoV-2 Spike protein: WT (D614G background), D796H, H69/V70, D796H+ H69/V70 were produced in 293T cells and used to infect target Hela cells stably expressing ACE2 in the presence of serial dilutions of indicated monoclonal antibodies. Data are means of technical replicates with error bars representing SD. Data are representative of at least two independent experiments. RBD: receptor binding domain. **B. Classes of RBD binding antibodies and fold changes for Spike mutations D796H or H69/V70** are indicated based Bouwer et al. Clusters II, V contain only non-neutralising mAbs, smaller neutralising mAb clusters IV (n=2) and X (n=1) were not tested. Red indicates significant fold changes.



**D**

Mutation	Number of Sequences	Global Prevalence (%)
W64G	0	0.00
$\Delta$ H69/V70	12883	4.32
Y200H	7	<0.01
T240I	77	0.02
P330S	167	0.06
D796H	65	0.02
D796Y	141	0.05

**Extended Data 9. Location of Spike mutations H69/Y70 and D796H.**

**A.** The SARS-CoV-2 spike trimer (PDB ID: 6xr8) with two protomers represented as surfaces and one protomer represented as a ribbon. The NTD is coloured in light blue, the RBD in light pink, the fusion peptide in dark pink, the HR1 domain in yellow, the CH domain in pale green, and the CD domain in brown. The location of D796 and H69 are indicated by red spheres. The loop connecting D796 to the fusion peptide is coloured magenta to improve visibility. The double grey lines provide orientation relative to the membrane. **B.** A close-up of the region defined by the box around H69 in panel A. H69 is highlighted in yellow. Residues containing atoms that are within 6 Å of H69 are highlighted in cyan. **C.** A close-up of the region defined by the box around D796 in panel A. D796 is

highlighted in yellow. Residues containing atoms that are within 6 Å of D796 are highlighted in cyan. Hydrogen bonds are indicated by dashed yellow lines. Hydrophobic residues in the vicinity of D796 have been labelled. Y707 is from the neighbouring protomer. **D. Global prevalence of selected spike mutations detailed in this paper.** All high coverage sequences were downloaded from the GISAID database on 6<sup>th</sup> January and aligned using MAFFT; as of this date there were 298254 sequences available. The global prevalence of each of the six spike mutations W64G, H69/V70, Y200H, T240I, P330S and D796H were assessed by viewing the multiple sequence alignment in AliView, sorting by the column of interest, and counting the number of mutations.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Authors

**Steven A Kemp<sup>#1</sup>, Dami A Collier<sup>#1,2,3</sup>, Rawlings P Datir<sup>#2,3</sup>, Isabella ATM Ferreira<sup>2,3</sup>, Salma Gayed<sup>4</sup>, Aminu Jahun<sup>5</sup>, Myra Hosmillo<sup>5</sup>, Chloe Rees-Spear<sup>1</sup>, Petra Mlcochova<sup>2,3</sup>, Ines Ushiro Lumb<sup>6</sup>, David J Roberts<sup>6</sup>, Anita Chandra<sup>2,3</sup>, Nigel Temperton<sup>7</sup>, The CITIID-NIHR BioResource COVID-19 Collaboration Stephen Baker<sup>2,3</sup> [Principal Investigators], Gordon Dougan<sup>2,3</sup> [Principal Investigators], Christoph Hess<sup>2,3,26,27</sup> [Principal Investigators], Nathalie Kingston<sup>20,12</sup> [Principal Investigators], Paul J. Lehner<sup>2,3</sup> [Principal Investigators], Paul A. Lyons<sup>2,3</sup> [Principal Investigators], Nicholas J. Matheson<sup>2,3</sup> [Principal Investigators], Willem H. Owehand<sup>20</sup> [Principal Investigators], Caroline Saunders<sup>19</sup> [Principal Investigators], Charlotte Summers<sup>3,24,25,28</sup> [Principal Investigators], James E.D. Thaventhiran<sup>2,3,22</sup> [Principal Investigators], Mark Toshner<sup>3,24,25</sup> [Principal Investigators], Michael P. Weekes<sup>2</sup> [Principal Investigators], Ashlea Bucke<sup>19</sup> [CRF and Volunteer Research Nurses], Jo Calder<sup>19</sup> [CRF and Volunteer Research Nurses], Laura Canna<sup>19</sup> [CRF and Volunteer Research Nurses], Jason Domingo<sup>19</sup> [CRF and Volunteer Research Nurses], Anne Elmer<sup>19</sup> [CRF and Volunteer Research Nurses], Stewart Fuller<sup>19</sup> [CRF and Volunteer Research Nurses], Julie Harris<sup>41</sup> [CRF and Volunteer Research Nurses], Sarah Hewitt<sup>19</sup> [CRF and Volunteer Research Nurses], Jane Kennet<sup>19</sup> [CRF and Volunteer Research Nurses], Sherly Jose<sup>19</sup> [CRF and Volunteer Research Nurses], Jenny Kourampa<sup>19</sup> [CRF and Volunteer Research Nurses], Anne Meadows<sup>19</sup> [CRF and Volunteer Research Nurses], Criona O'Brien<sup>41</sup> [CRF and Volunteer Research Nurses], Jane Price<sup>19</sup> [CRF and Volunteer Research Nurses], Cherry Publico<sup>19</sup> [CRF and Volunteer Research Nurses], Rebecca Rastall<sup>19</sup> [CRF and Volunteer Research Nurses], Carla Ribeiro<sup>19</sup> [CRF and Volunteer Research Nurses], Jane Rowlands<sup>19</sup> [CRF and Volunteer Research Nurses], Valentina Ruffolo<sup>19</sup> [CRF and Volunteer Research Nurses], Hugo Tordesillas<sup>19</sup> [CRF and Volunteer Research Nurses], Ben Bullman<sup>2</sup> [Sample Logistics], Benjamin J Dunmore<sup>3</sup> [Sample Logistics], Stuart Fawke<sup>30</sup> [Sample Logistics], Stefan Gräf<sup>3,12,20</sup> [Sample Logistics], Josh Hodgson<sup>3</sup> [Sample Logistics], Christopher Huang<sup>3</sup>**

[Sample Logistics], Kelvin Hunter<sup>2,3</sup> [Sample Logistics], Emma Jones<sup>29</sup>  
 [Sample Logistics], Ekaterina Legchenko<sup>3</sup> [Sample Logistics], Cecilia Matara<sup>3</sup>  
 [Sample Logistics], Jennifer Martin<sup>3</sup> [Sample Logistics], Federica Mescia<sup>2,3</sup>  
 [Sample Logistics], Ciara O'Donnell<sup>3</sup> [Sample Logistics], Linda Pointon<sup>3</sup>  
 [Sample Logistics], Nicole Pond<sup>2,3</sup> [Sample Logistics], Joy Shih<sup>3</sup> [Sample  
 Logistics], Rachel Sutcliffe<sup>3</sup> [Sample Logistics], Tobias Tilly<sup>3</sup> [Sample  
 Logistics], Carmen Treacy<sup>3</sup> [Sample Logistics], Zhen Tong<sup>3</sup> [Sample  
 Logistics], Jennifer Wood<sup>3</sup> [Sample Logistics], Marta Wylot<sup>36</sup> [Sample  
 Logistics], Laura Bergamaschi<sup>2,3</sup> [Sample Processing and Data Acquisition],  
 Ariana Betancourt<sup>2,3</sup> [Sample Processing and Data Acquisition], Georgie  
 Bower<sup>2,3</sup> [Sample Processing and Data Acquisition], Chiara Cossetti<sup>2,3</sup>  
 [Sample Processing and Data Acquisition], Aloka De Sa<sup>3</sup> [Sample Processing  
 and Data Acquisition], Madeline Epping<sup>2,3</sup> [Sample Processing and Data  
 Acquisition], Stuart Fawke<sup>32</sup> [Sample Processing and Data Acquisition], Nick  
 Gleadall<sup>20</sup> [Sample Processing and Data Acquisition], Richard Grenfell<sup>31</sup>  
 [Sample Processing and Data Acquisition], Andrew Hinch<sup>2,3</sup> [Sample  
 Processing and Data Acquisition], Oisín Huhn<sup>32</sup> [Sample Processing and Data  
 Acquisition], Sarah Jackson<sup>3</sup> [Sample Processing and Data Acquisition],  
 Isobel Jarvis<sup>3</sup> [Sample Processing and Data Acquisition], Daniel Lewis<sup>3</sup>  
 [Sample Processing and Data Acquisition], Joe Marsden<sup>3</sup> [Sample Processing  
 and Data Acquisition], Francesca Nice<sup>39</sup> [Sample Processing and Data  
 Acquisition], Georgina Okecha<sup>3</sup> [Sample Processing and Data Acquisition],  
 Ommar Omarjee<sup>3</sup> [Sample Processing and Data Acquisition], Marianne  
 Perera<sup>3</sup> [Sample Processing and Data Acquisition], Nathan Richoz<sup>3</sup> [Sample  
 Processing and Data Acquisition], Veronika Romashova<sup>2,3</sup> [Sample  
 Processing and Data Acquisition], Natalia Savinykh Yarkoni<sup>3</sup> [Sample  
 Processing and Data Acquisition], Rahul Sharma<sup>3</sup> [Sample Processing and  
 Data Acquisition], Luca Stefanucci<sup>20</sup> [Sample Processing and Data  
 Acquisition], Jonathan Stephens<sup>20</sup> [Sample Processing and Data Acquisition],  
 Mateusz Strezlecki<sup>31</sup> [Sample Processing and Data Acquisition], Lori Turner<sup>2,3</sup>  
 [Sample Processing and Data Acquisition], Eckart M.D.D. De Bie<sup>3</sup> [Clinical  
 Data Collection], Katherine Bunclark<sup>3</sup> [Clinical Data Collection], Masa  
 Josipovic<sup>40</sup> [Clinical Data Collection], Michael Mackay<sup>3</sup> [Clinical Data  
 Collection], Federica Mescia<sup>2,3</sup> [Clinical Data Collection], Alice Michael<sup>25</sup>  
 [Clinical Data Collection], Sabrina Rossi<sup>35</sup> [Clinical Data Collection], Mayurun  
 Selvan<sup>3</sup> [Clinical Data Collection], Sarah Spencer<sup>15</sup> [Clinical Data Collection],  
 Cissy Yong<sup>35</sup> [Clinical Data Collection], Ali Ansari<sup>25</sup> [Royal Papworth  
 Hospital ICU], Alice Michael<sup>25</sup> [Royal Papworth Hospital ICU], Lucy Mwaura<sup>25</sup>  
 [Royal Papworth Hospital ICU], Caroline Patterson<sup>25</sup> [Royal Papworth Hospital  
 ICU], Gary Polwarth<sup>25</sup> [Royal Papworth Hospital ICU], Petra Polgarova<sup>28</sup>  
 [Addenbrooke's Hospital ICU], Giovanni di Stefano<sup>28</sup> [Addenbrooke's Hospital  
 ICU], Codie Fahey<sup>34</sup> [Cambridge and Peterborough Foundation Trust], Rachel  
 Michel<sup>34</sup> [Cambridge and Peterborough Foundation Trust], Sze-How Bong<sup>21</sup>  
 [ANPC and Centre for Molecular Medicine and Innovative Therapeutics],  
 Jerome D. Coudert<sup>33</sup> [ANPC and Centre for Molecular Medicine and Innovative

Therapeutics], Elaine Holmes<sup>37</sup> [ANPC and Centre for Molecular Medicine and Innovative Therapeutics], John Allison<sup>20,12</sup> [NIHR BioResource], Helen Butcher<sup>12,38</sup> [NIHR BioResource], Daniela Caputo<sup>12,38</sup> [NIHR BioResource], Debbie Clapham-Riley<sup>12,38</sup> [NIHR BioResource], Eleanor Dewhurst<sup>12,38</sup> [NIHR BioResource], Anita Furlong<sup>12,38</sup> [NIHR BioResource], Barbara Graves<sup>12,38</sup> [NIHR BioResource], Jennifer Gray<sup>12,38</sup> [NIHR BioResource], Tasmin Ivers<sup>12,38</sup> [NIHR BioResource], Mary Kasanicki<sup>12,28</sup> [NIHR BioResource], Emma Le Gresley<sup>12,38</sup> [NIHR BioResource], Rachel Linger<sup>12,38</sup> [NIHR BioResource], Sarah Meloy<sup>12,38</sup> [NIHR BioResource], Francesca Muldoon<sup>12,38</sup> [NIHR BioResource], Nigel Ovington<sup>12,20</sup> [NIHR BioResource], Sofia Papadia<sup>12,38</sup> [NIHR BioResource], Isabel Phelan<sup>12,38</sup> [NIHR BioResource], Hannah Stark<sup>12,38</sup> [NIHR BioResource], Kathleen E Stirrups<sup>12,20</sup> [NIHR BioResource], Paul Townsend<sup>12,20</sup> [NIHR BioResource], Neil Walker<sup>12,20</sup> [NIHR BioResource], Jennifer Webster<sup>12,38</sup> [NIHR BioResource]

<sup>19</sup>Cambridge Clinical Research Centre, NIHR Clinical Research Facility, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>20</sup>Department of Haematology, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>21</sup>Australian National Phenome Centre, Murdoch University, Murdoch, Western Australia WA 6150, Australia <sup>22</sup>MRC Toxicology Unit, School of Biological Sciences, University of Cambridge, Cambridge CB2 1QR, UK <sup>23</sup>R&D Department, Hycult Biotech, 5405 PD Uden, The Netherlands <sup>24</sup>Heart and Lung Research Institute, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>25</sup>Royal Papworth Hospital NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>26</sup>Department of Biomedicine, University and University Hospital Basel, 4031Basel, Switzerland <sup>27</sup>Botnar Research Centre for Child Health (BRCCH) University Basel & ETH Zurich, 4058 Basel, Switzerland <sup>28</sup>Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>29</sup>Department of Veterinary Medicine, Madingley Road, Cambridge, CB3 0ES, UK <sup>30</sup>Cambridge Institute for Medical Research, Cambridge Biomedical Campus, Cambridge CB2 0XY, UK <sup>31</sup>Cancer Research UK, Cambridge Institute, University of Cambridge CB2 0RE, UK <sup>32</sup>Department of Obstetrics & Gynaecology, The Rosie Maternity Hospital, Robinson Way, Cambridge CB2 0SW, UK <sup>33</sup>Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute, Murdoch University, Perth, WA, Australia <sup>34</sup>Cambridge and Peterborough Foundation Trust, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EF, UK <sup>35</sup>Department of Surgery, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>36</sup>Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK <sup>37</sup>Centre of Computational and Systems Medicine, Health Futures Institute, Murdoch University, Harry Perkins Building, Perth, WA 6150, Australia <sup>38</sup>Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK <sup>39</sup>Cancer Molecular Diagnostics Laboratory, Department of Oncology, University of Cambridge, Cambridge CB2 0AH, UK <sup>40</sup>Metabolic

Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK

<sup>41</sup>Department of Paediatrics, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK

, The COVID-19 Genomics UK (COG-UK) Consortium

Samuel C Robson<sup>54</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], Nicholas J Loman<sup>82</sup>, Thomas R Connor<sup>51,110</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Software and analysis tools], Tanya Golubchik<sup>46</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], Rocio T Martinez Nunez<sup>83</sup> [Funding acquisition, Metadata curation, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], Catherine Ludden<sup>129</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Project administration, and Samples and logistics], Sally Corden<sup>110</sup> [Funding acquisition, Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Ian Johnston<sup>140</sup>, David Bonsall<sup>46</sup> [Funding acquisition, Leadership and supervision, Project administration, Samples and logistics, and Sequencing and analysis], Colin P Smith<sup>128</sup>, Ali R Awan<sup>69</sup> [Funding acquisition, Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation], Giselda Bucca<sup>128</sup> [Funding acquisition, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation], M. Estee Torok<sup>63,142</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Kordo Saeed<sup>122,151</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Visualisation], Jacqui A Prieto<sup>124,150</sup> [Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Visualisation], David K Jackson<sup>140</sup> [Leadership and supervision, Metadata curation, Project administration, Sequencing and analysis, and Software and analysis tools], William L Hamilton<sup>63</sup> [Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Software and analysis tools], Luke B Snell<sup>52</sup> [Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Visualisation], Catherine Moore<sup>110</sup> [Funding acquisition, Leadership and supervision, Metadata curation, and Samples and logistics], Ewan M Harrison<sup>129,140</sup> [Funding acquisition, Leadership and supervision, Project administration, and Samples and logistics], Sonia Goncalves<sup>140</sup> [Leadership and supervision, Metadata curation, Project administration, and Samples and logistics], Derek J Fairley<sup>44,113</sup> [Leadership and supervision, Metadata

curation, Samples and logistics, and Sequencing and analysis], Matthew W Loose<sup>59</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Joanne Watkins<sup>110</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis], Rich Livett<sup>140</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Software and analysis tools], Samuel Moses<sup>66,147</sup> [Leadership and supervision, Metadata curation, Samples and logistics, and Visualisation], Roberto Amato<sup>140</sup> [Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools], Sam Nicholls<sup>82</sup> [Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools], Matthew Bull<sup>110</sup> [Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools], Darren L Smith<sup>1,99,146</sup> [Leadership and supervision, Project administration, Samples and logistics, and Sequencing and analysis], Jeff Barrett<sup>140</sup> [Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation], David M Aanensen<sup>55</sup> [Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation], Martin D Curran<sup>106</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Surendra Parmar<sup>106</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Dinesh Aggarwal<sup>1,140,105</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], James G Shepherd<sup>89</sup> [Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis], Matthew D Parker<sup>134</sup> [Metadata curation, Project administration, Sequencing and analysis, and Software and analysis tools], Sharon Glaysher<sup>102</sup> [Metadata curation, Samples and logistics, Sequencing and analysis, and Visualisation], Matthew Bashton<sup>78,99</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Anthony P Underwood<sup>55</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Nicole Pacchiarini<sup>110</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Katie F Loveson<sup>118</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Alessandro M Carabelli<sup>129</sup> [Project administration, Sequencing and analysis, Software and analysis tools, and Visualisation], Kate E Templeton<sup>94,131</sup> [Funding acquisition, Leadership and supervision, and Metadata curation], Cordelia F Langford<sup>140</sup> [Funding acquisition, Leadership and supervision, and Project administration], John Sillitoe<sup>140</sup> [Funding acquisition, Leadership and supervision, and Project administration], Thushan I de Silva<sup>134</sup> [Funding acquisition, Leadership and supervision, and Project administration], Dennis Wang<sup>134</sup> [Funding acquisition, Leadership and supervision, and Project administration], Dominic Kwiatkowski<sup>140,148</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Andrew Rambaut<sup>131</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Justin O'Grady<sup>111,130</sup> [Funding acquisition, Leadership and



supervision, and Sequencing and analysis], Simon Cottrell<sup>110</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Matthew T.G. Holden<sup>109</sup> [Leadership and supervision, Metadata curation, and Sequencing and analysis], Emma C Thomson<sup>89</sup> [Leadership and supervision, Metadata curation, and Sequencing and analysis], Husam Osman<sup>77,105</sup> [Leadership and supervision, Project administration, and Samples and logistics], Monique Andersson<sup>100</sup> [Leadership and supervision, Project administration, and Samples and logistics], Anoop J Chauhan<sup>102</sup> [Leadership and supervision, Project administration, and Samples and logistics], Mohammed O Hassan-Ibrahim<sup>47</sup> [Leadership and supervision, Project administration, and Samples and logistics], Mara Lawniczak<sup>140</sup> [Leadership and supervision, Project administration, and Sequencing and analysis], Alex Alderton<sup>140</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Meera Chand<sup>107</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Chrystala Constantinidou<sup>135</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Meera Unnikrishnan<sup>135</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Alistair C Darby<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Julian A Hiscox<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Steve Paterson<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Inigo Martincorena<sup>140</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], David L Robertson<sup>89</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Erik M Volz<sup>80</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Andrew J Page<sup>111</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Oliver G Pybus<sup>64</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Andrew R Bassett<sup>140</sup> [Leadership and supervision, Sequencing and analysis, and Visualisation], Cristina V Ariani<sup>140</sup> [Metadata curation, Project administration, and Samples and logistics], Michael H Spencer Chapman<sup>129,140</sup> [Metadata curation, Project administration, and Samples and logistics], Kathy K Li<sup>89</sup> [Metadata curation, Project administration, and Samples and logistics], Rajiv N Shah<sup>89</sup> [Metadata curation, Project administration, and Samples and logistics], Natasha G Jesudason<sup>89</sup> [Metadata curation, Project administration, and Samples and logistics], Yusri Taha<sup>91</sup> [Metadata curation, Project administration, and Samples and logistics], Martin P McHugh<sup>94</sup> [Metadata curation, Project administration, and Sequencing and analysis], Rebecca Dewar<sup>94</sup> [Metadata curation, Project administration, and Sequencing and analysis], Aminu S Jahun<sup>65</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Claire McMurray<sup>82</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Sarojini Pandey<sup>125</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], James P McKenna<sup>44</sup> [Metadata

curation, Samples and logistics, and Sequencing and analysis], Andrew Nelson<sup>99,146</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Gregory R Young<sup>78,99</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Clare M McCann<sup>99,146</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Scott Elliott<sup>102</sup> [Metadata curation, Samples and logistics, and Sequencing and analysis], Hannah Lowe<sup>66</sup> [Metadata curation, Samples and logistics, and Visualisation], Ben Temperton<sup>132</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Sunando Roy<sup>123</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Anna Price<sup>51</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Sara Rey<sup>110</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Matthew Wyles<sup>134</sup> [Metadata curation, Sequencing and analysis, and Software and analysis tools], Stefan Rooke<sup>131</sup> [Metadata curation, Sequencing and analysis, and Visualisation], Sharif Shaaban<sup>109</sup> [Metadata curation, Sequencing and analysis, and Visualisation], Mariateresa de Cesare<sup>139</sup> [Project administration, Samples and logistics, Sequencing and analysis], Laura Letchford<sup>140</sup> [Project administration, Samples and logistics, and Software and analysis tools], Siona Silveira<sup>122</sup> [Project administration, Samples and logistics, and Visualisation], Emanuela Pelosi<sup>122</sup> [Project administration, Samples and logistics, and Visualisation], Eleri Wilson-Davies<sup>122</sup> [Project administration, Samples and logistics, and Visualisation], Myra Hosmillo<sup>65</sup> [Samples and logistics, Sequencing and analysis, and Software and analysis tools], Áine O'Toole<sup>131</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Andrew R Hesketh<sup>128</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Richard Stark<sup>135</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Louis du Plessis<sup>64</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Chris Ruis<sup>129</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Helen Adams<sup>45</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Yann Bourgeois<sup>117</sup> [Sequencing and analysis, Software and analysis tools, and Visualisation], Stephen L Michell<sup>132</sup> [Funding acquisition, and Leadership and supervision], Dimitris Gramatopoulos<sup>125,153</sup> [Funding acquisition, and Leadership and supervision], Jonathan Edgeworth<sup>53</sup> [Funding acquisition, and Leadership and supervision], Judith Breuer<sup>71,123</sup> [Funding acquisition, and Leadership and supervision], John A Todd<sup>139</sup> [Funding acquisition, and Leadership and supervision], Christophe Fraser<sup>46</sup> [Funding acquisition, and Leadership and supervision], David Buck<sup>139</sup> [Funding acquisition, and Project administration], Michaela John<sup>50</sup> [Funding acquisition, and Project administration], Gemma L Kay<sup>111</sup> [Leadership and supervision, and Metadata curation], Steve Palmer<sup>140</sup> [Leadership and supervision, and Project administration], Sharon J Peacock<sup>129,105</sup> [Leadership and supervision, and Project administration], David Heyburn<sup>110</sup> [Leadership and supervision, and Project administration], Danni Weldon<sup>140</sup> [Leadership and supervision, and

Samples and logistics], Esther Robinson<sup>105,77</sup> [Leadership and supervision, and Samples and logistics], Alan McNally<sup>82,127</sup> [Leadership and supervision, and Samples and logistics], Peter Muir<sup>105</sup> [Leadership and supervision, and Samples and logistics], Ian B Vipond<sup>105</sup> [Leadership and supervision, and Samples and logistics], John BoYes<sup>70</sup> [Leadership and supervision, and Samples and logistics], Venkat Sivaprakasam<sup>87</sup> [Leadership and supervision, and Samples and logistics], Tranpriet Salluja<sup>116</sup> [Leadership and supervision, and Samples and logistics], Samir Dervisevic<sup>95</sup> [Leadership and supervision, and Samples and logistics], Emma J Meader<sup>95</sup> [Leadership and supervision, and Samples and logistics], Naomi R Park<sup>140</sup> [Leadership and supervision, and Sequencing and analysis], Karen Oliver<sup>140</sup> [Leadership and supervision, and Sequencing and analysis], Aaron R Jeffries<sup>132</sup> [Leadership and supervision, and Sequencing and analysis], Sascha Ott<sup>135</sup> [Leadership and supervision, and Sequencing and analysis], Ana da Silva Filipe<sup>89</sup> [Leadership and supervision, and Sequencing and analysis], David A Simpson<sup>113</sup> [Leadership and supervision, and Sequencing and analysis], Chris Williams<sup>110</sup> [Leadership and supervision, and Sequencing and analysis], Jane AH Masoli<sup>114,132</sup> [Leadership and supervision, and Visualisation], Bridget A Knight<sup>114,132</sup> [Metadata curation, and Samples and logistics], Christopher R Jones<sup>114,132</sup> [Metadata curation, and Samples and logistics], Cherian Koshy<sup>42</sup> [Metadata curation, and Samples and logistics], Amy Ash<sup>42</sup> [Metadata curation, and Samples and logistics], Anna Casey<sup>112</sup> [Metadata curation, and Samples and logistics], Andrew Bosworth<sup>105,77</sup> [Metadata curation, and Samples and logistics], Liz Ratcliffe<sup>112</sup> [Metadata curation, and Samples and logistics], Li Xu-McCrae<sup>77</sup> [Metadata curation, and Samples and logistics], Hannah M Pymont<sup>105</sup> [Metadata curation, and Samples and logistics], Stephanie Hutchings<sup>105</sup> [Metadata curation, and Samples and logistics], Lisa Berry<sup>125</sup> [Metadata curation, and Samples and logistics], Katie Jones<sup>125</sup> [Metadata curation, and Samples and logistics], Fenella Halstead<sup>87</sup> [Metadata curation, and Samples and logistics], Thomas Davis<sup>62</sup> [Metadata curation, and Samples and logistics], Christopher Holmes<sup>57</sup> [Metadata curation, and Samples and logistics], Miren Iturriza-Gomara<sup>133</sup> [Metadata curation, and Samples and logistics], Anita O Lucaci<sup>133</sup> [Metadata curation, and Samples and logistics], Paul Anthony Randell<sup>79,145</sup> [Metadata curation, and Samples and logistics], Alison Cox<sup>79,145</sup> [Metadata curation, and Samples and logistics], Pinglawathee Madona<sup>79,145</sup> [Metadata curation, and Samples and logistics], Kathryn Ann Harris<sup>71</sup> [Metadata curation, and Samples and logistics], Julianne Rose Brown<sup>71</sup> [Metadata curation, and Samples and logistics], Tabitha W Mahungu<sup>115</sup> [Metadata curation, and Samples and logistics], Dianne Irish-Tavares<sup>115</sup> [Metadata curation, and Samples and logistics], Tanzina Haque<sup>115</sup> [Metadata curation, and Samples and logistics], Jennifer Hart<sup>115</sup> [Metadata curation, and Samples and logistics], Eric Witele<sup>115</sup> [Metadata curation, and Samples and logistics], Melisa Louise Fenton<sup>116</sup> [Metadata curation, and Samples and logistics], Steven Liggett<sup>120</sup> [Metadata curation, and Samples and logistics], Clive Graham<sup>97</sup> [Metadata curation, and

Samples and logistics], Emma Swindells<sup>98</sup> [Metadata curation, and Samples and logistics], Jennifer Collins<sup>91</sup> [Metadata curation, and Samples and logistics], Gary Eltringham<sup>91</sup> [Metadata curation, and Samples and logistics], Sharon Campbell<sup>58</sup> [Metadata curation, and Samples and logistics], Patrick C McClure<sup>138</sup> [Metadata curation, and Samples and logistics], Gemma Clark<sup>56</sup> [Metadata curation, and Samples and logistics], Tim J Sloan<sup>101</sup> [Metadata curation, and Samples and logistics], Carl Jones<sup>56</sup> [Metadata curation, and Samples and logistics], Jessica Lynch<sup>43,152</sup> [Metadata curation, and Samples and logistics], Ben Warne<sup>49</sup> [Metadata curation, and Sequencing and analysis], Steven Leonard<sup>140</sup> [Metadata curation, and Sequencing and analysis], Jillian Durham<sup>140</sup> [Metadata curation, and Sequencing and analysis], Thomas Williams<sup>131</sup> [Metadata curation, and Sequencing and analysis], Sam T Haldenby<sup>133</sup> [Metadata curation, and Sequencing and analysis], Nathaniel Storey<sup>71</sup> [Metadata curation, and Sequencing and analysis], Nabil-Fareed Alikhan<sup>111</sup> [Metadata curation, and Sequencing and analysis], Nadine Holmes<sup>59</sup> [Metadata curation, and Sequencing and analysis], Christopher Moore<sup>59</sup> [Metadata curation, and Sequencing and analysis], Matthew Carlile<sup>59</sup> [Metadata curation, and Sequencing and analysis], Malorie Perry<sup>110</sup> [Metadata curation, and Sequencing and analysis], Noel Craine<sup>140</sup> [Metadata curation, and Sequencing and analysis], Ronan A Lyons<sup>140</sup> [Metadata curation, and Sequencing and analysis], Angela H Beckett<sup>54</sup> [Metadata curation, and Sequencing and analysis], Salman Goudarzi<sup>118</sup> [Metadata curation, and Sequencing and analysis], Christopher Fearn<sup>118</sup> [Metadata curation, and Sequencing and analysis], Kate Cook<sup>118</sup> [Metadata curation, and Sequencing and analysis], Hannah Dent<sup>118</sup> [Metadata curation, and Sequencing and analysis], Hannah Paul<sup>118</sup> [Metadata curation, and Sequencing and analysis], Robert Davies<sup>140</sup> [Metadata curation, and Software and analysis tools], Beth Blane<sup>140</sup> [Project administration, and Samples and logistics], Sophia T Girgis<sup>140</sup> [Project administration, and Samples and logistics], Mathew A Beale<sup>140</sup> [Project administration, and Samples and logistics], Katherine L Bellis<sup>140,129</sup> [Project administration, and Samples and logistics], Matthew J Dorman<sup>140</sup> [Project administration, and Samples and logistics], Eleanor Drury<sup>140</sup> [Project administration, and Samples and logistics], Leanne Kane<sup>140</sup> [Project administration, and Samples and logistics], Sally Kay<sup>140</sup> [Project administration, and Samples and logistics], Samantha McGuigan<sup>140</sup> [Project administration, and Samples and logistics], Rachel Nelson<sup>140</sup> [Project administration, and Samples and logistics], Liam Prestwood<sup>140</sup> [Project administration, and Samples and logistics], Shavanthi Rajatileka<sup>140</sup> [Project administration, and Samples and logistics], Rahul Batra<sup>140</sup> [Project administration, and Samples and logistics], Rachel J Williams<sup>123</sup> [Project administration, and Samples and logistics], Mark Kristiansen<sup>123</sup> [Project administration, and Samples and logistics], Angie Green<sup>139</sup> [Project administration, and Samples and logistics], Anita Justice<sup>140</sup> [Project administration, and Samples and logistics], Adhyana I.K Mahanama<sup>122,143</sup> [Project administration, and Samples and logistics],

Buddhini Samaraweera<sup>122,143</sup> [Project administration, and Samples and logistics], Nazreen F Hadjirin<sup>129</sup> [Project administration, and Sequencing and analysis], Joshua Quick<sup>82</sup> [Project administration, and Sequencing and analysis], Radoslaw Poplawski<sup>82</sup> [Project administration, and Software and analysis tools], Leanne M Kermack<sup>129</sup> [Samples and logistics, and Sequencing and analysis], Nicola Reynolds<sup>48</sup> [Samples and logistics, and Sequencing and analysis], Grant Hall<sup>65</sup> [Samples and logistics, and Sequencing and analysis], Yasmin Chaudhry<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Malte L Pinckert<sup>65</sup> [Samples and logistics, and Sequencing and analysis], Iliana Georgana<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Robin J Moll<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Alicia Thornton<sup>107</sup> [Samples and logistics, and Sequencing and analysis], Richard Myers<sup>107</sup> [Samples and logistics, and Sequencing and analysis], Joanne Stockton<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Charlotte A Williams<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Wen C Yew<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Alexander J Trotter<sup>111</sup> [Samples and logistics, and Sequencing and analysis], Amy Trebes<sup>140</sup> [Samples and logistics, and Sequencing and analysis], George MacIntyre-Cockett<sup>139</sup> [Samples and logistics, and Sequencing and analysis], Alec Birchley<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Alexander Adams<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Amy Plimmer<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Bree Gatica-Wilcox<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Caoimhe McKerr<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Ember Hilvers<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Hannah Jones<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Hibo Asad<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Jason Coombes<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Johnathan M Evans<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Laia Fina<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Lauren Gilbert<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Lee Graham<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Michelle Cronin<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Sara Kumziene-SummerhaYes<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Sarah Taylor<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Sophie Jones<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Danielle C Groves<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Peijun Zhang<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Marta Gallis<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Stavroula F Louka<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Igor Starinskij<sup>89</sup> [Samples and logistics, and Software and analysis tools], Chris Jackson<sup>88</sup> [Sequencing and analysis, and Software and analysis tools], Marina Gourtovaia<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Gerry Tonkin-Hill<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Kevin Lewis<sup>140</sup>

[Sequencing and analysis, and Software and analysis tools], Jaime M Tovar-Corona<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Keith James<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Laura Baxter<sup>135</sup> [Sequencing and analysis, and Software and analysis tools], Mohammad T Alam<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Richard J Orton<sup>89</sup> [Sequencing and analysis, and Software and analysis tools], Joseph Hughes<sup>89</sup> [Sequencing and analysis, and Software and analysis tools], Sreenu Vattipally<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Manon Ragonnet-Cronin<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], Fabricia F Nascimento<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], David Jorgensen<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], Olivia Boyd<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], Lily Geidelberg<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Alex E Zarebski<sup>64</sup> [Sequencing and analysis, and Software and analysis tools], Jayna Raghvani<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Moritz UG Kraemer<sup>64</sup> [Sequencing and analysis, and Software and analysis tools], Joel Southgate<sup>51,110</sup> [Sequencing and analysis, and Software and analysis tools], Benjamin B Lindsey<sup>134</sup> [Sequencing and analysis, and Software and analysis tools], Timothy M Freeman<sup>134</sup> [Sequencing and analysis, and Software and analysis tools], Jon-Paul Keatley<sup>140</sup> [Software and analysis tools, and Visualisation], Joshua B Singer<sup>140</sup> [Software and analysis tools, and Visualisation], Leonardo de Oliveira Martins<sup>140</sup> [Software and analysis tools, and Visualisation], Corin A Yeats<sup>55</sup> [Software and analysis tools, and Visualisation], Khalil Abudahab<sup>140,140</sup> [Software and analysis tools, and Visualisation], Ben EW Taylor<sup>140</sup> [Software and analysis tools, and Visualisation], Mirko Menegazzo<sup>55</sup> [Software and analysis tools, and Visualisation], John Danesh<sup>140</sup> [Leadership and supervision], Wendy Hogsden<sup>87</sup> [Leadership and supervision], Sahar Eldirdiri<sup>62</sup> [Leadership and supervision], Anita Kenyon<sup>62</sup> [Leadership and supervision], Jenifer Mason<sup>140</sup> [Leadership and supervision], Trevor I Robinson<sup>84</sup> [Leadership and supervision], Alison Holmes<sup>140,144</sup> [Leadership and supervision], James Price<sup>140,140</sup> [Leadership and supervision], John A Hartley<sup>123</sup> [Leadership and supervision], Tanya Curran<sup>140</sup> [Leadership and supervision], Alison E Mather<sup>111</sup> [Leadership and supervision], Giri Shankar<sup>110</sup> [Leadership and supervision], Rachel Jones<sup>110</sup> [Leadership and supervision], Robin Howe<sup>110</sup> [Leadership and supervision], Sian Morgan<sup>50</sup> [Leadership and supervision], Elizabeth Wastenge<sup>140</sup> [Metadata curation], Michael R Chapman<sup>1,129,140</sup> [Metadata curation], Siddharth Mookerjee<sup>79,144</sup> [Metadata curation], Rachael Stanley<sup>95</sup> [Metadata curation], Wendy Smith<sup>56</sup> [Metadata curation], Timothy Peto<sup>100</sup> [Metadata curation], David Eyre<sup>100</sup> [Metadata curation], Derrick Crook<sup>100</sup> [Metadata curation], Gabrielle Vernet<sup>74</sup> [Metadata curation], Christine Kitchen<sup>51</sup> [Metadata curation], Huw Gulliver<sup>51</sup> [Metadata curation], Ian Merrick<sup>51</sup> [Metadata curation], Martyn Guest<sup>51</sup> [Metadata curation], Robert Munn<sup>140</sup> [Metadata curation], Declan T

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Hermione J Webster<sup>140</sup> [Sequencing and analysis], Chloe L Fisher<sup>140</sup> [Sequencing and analysis], Adrian W Signell<sup>61</sup> [Sequencing and analysis], Gilberto Betancor<sup>140</sup> [Sequencing and analysis], Harry D Wilson<sup>61</sup> [Sequencing and analysis], Gaia Nebbia<sup>53</sup> [Sequencing and analysis], Flavia Flaviani<sup>140</sup> [Sequencing and analysis], Alberto C Cerda<sup>140</sup> [Sequencing and analysis], Tammy V Merrill<sup>140</sup> [Sequencing and analysis], Rebekah E Wilson<sup>137</sup> [Sequencing and analysis], Marius Cotic<sup>123</sup> [Sequencing and analysis], Nadua Bayzid<sup>123</sup> [Sequencing and analysis], Thomas Thompson<sup>113</sup> [Sequencing and analysis], Erwan Acheson<sup>113</sup> [Sequencing and analysis], Steven Rushton<sup>140</sup> [Sequencing and analysis], Sarah O'Brien<sup>140</sup> [Sequencing and analysis], David J Baker<sup>111</sup> [Sequencing and analysis], Steven Rudder<sup>111</sup> [Sequencing and analysis], Alp Aydin<sup>111</sup> [Sequencing and analysis], Fei Sang<sup>59</sup> [Sequencing and analysis], Johnny Debebe<sup>59</sup> [Sequencing and analysis], Sarah Francois<sup>140</sup> [Sequencing and analysis], Tetyana I Vasylyeva<sup>140</sup> [Sequencing and analysis], Marina Escalera Zamudio<sup>64</sup> [Sequencing and analysis], Bernardo Gutierrez<sup>64</sup> [Sequencing and analysis], Angela Marchbank<sup>51</sup> [Sequencing and analysis], Joshua Maksimovic<sup>50</sup> [Sequencing and analysis], Karla Spellman<sup>50</sup> [Sequencing and analysis], Kathryn McCluggage<sup>50</sup> [Sequencing and analysis], Mari Morgan<sup>110</sup> [Sequencing and analysis], Robert Beer<sup>50</sup> [Sequencing and analysis], Safiah Afifi<sup>50</sup> [Sequencing and analysis], Trudy Workman<sup>51</sup> [Sequencing and analysis], William Fuller<sup>51</sup> [Sequencing and analysis], Catherine Bresner<sup>51</sup> [Sequencing and analysis], Adrienn Angyal<sup>140</sup> [Sequencing and analysis], Luke R Green<sup>140</sup> [Sequencing and analysis], Paul J Parsons<sup>140</sup> [Sequencing and analysis], Rachel M Tucker<sup>134</sup> [Sequencing and analysis], Rebecca Brown<sup>134</sup> [Sequencing and analysis], Max Whiteley<sup>134</sup> [Sequencing and analysis], James Bonfield<sup>140</sup> [Software and analysis tools], Christoph Puethe<sup>140</sup> [Software and analysis tools], Andrew Whitwham<sup>140</sup> [Software and analysis tools], Jennifer Liddle<sup>140</sup> [Software and analysis tools], Will Rowe<sup>82</sup> [Software and analysis tools], Igor Siveroni<sup>140</sup> [Software and analysis tools], Thanh Le-Viet<sup>140</sup> [Software and analysis tools], Amy Gaskin<sup>110</sup> [Software and analysis tools], Rob Johnson<sup>80</sup> [Visualisation]

<sup>42</sup>Barking, Havering and Redbridge University Hospitals NHS Trust, Barking, United Kingdom <sup>43</sup>Basingstoke Hospital, Basingstoke, United Kingdom <sup>44</sup>Belfast Health & Social Care Trust, Belfast, United Kingdom <sup>45</sup>Betsi Cadwaladr University Health Board, Betsi Cadwaladr, United Kingdom <sup>46</sup>Big Data Institute, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom <sup>47</sup>Brighton and Sussex University Hospitals NHS Trust, Brighton & Sussex, United Kingdom <sup>48</sup>Cambridge Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom <sup>49</sup>Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom <sup>50</sup>Cardiff and Vale University Health Board, Cardiff, United Kingdom <sup>51</sup>Cardiff University, Cardiff, United Kingdom <sup>52</sup>Centre for Clinical Infection & Diagnostics Research, St. Thomas' Hospital and Kings College London, London, United

Kingdom <sup>53</sup>Centre for Clinical Infection and Diagnostics Research, Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom <sup>54</sup>Centre for Enzyme Innovation, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>55</sup>Centre for Genomic Pathogen Surveillance, University of Oxford, Oxford, United Kingdom <sup>56</sup>Clinical Microbiology Department, Queens Medical Centre, Nottingham, United Kingdom <sup>57</sup>Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom <sup>58</sup>County Durham and Darlington NHS Foundation Trust, Durham, United Kingdom <sup>59</sup>Deep Seq, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, United Kingdom <sup>60</sup>Department of Infection Biology, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom <sup>61</sup>Department of Infectious Diseases, King's College London, London, United Kingdom <sup>62</sup>Department of Microbiology, Kettering General Hospital, Kettering, United Kingdom <sup>63</sup>Departments of Infectious Diseases and Microbiology, Cambridge University Hospitals NHS Foundation Trust; Cambridge, UK, Cambridge, United Kingdom <sup>64</sup>Department of Zoology, University of Oxford, Oxford, United Kingdom <sup>65</sup>Division of Virology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom <sup>66</sup>East Kent Hospitals University NHS Foundation Trust, Kent, United Kingdom <sup>67</sup>East Suffolk and North Essex NHS Foundation Trust, Suffolk, United Kingdom <sup>68</sup>Gateshead Health NHS Foundation Trust, Gateshead, United Kingdom <sup>69</sup>Genomics Innovation Unit, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom <sup>70</sup>Gloucestershire Hospitals NHS Foundation Trust, Gloucester, United Kingdom <sup>71</sup>Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom <sup>72</sup>Guy's and St. Thomas' BRC, London, United Kingdom <sup>73</sup>Guy's and St. Thomas' Hospitals, London, United Kingdom <sup>74</sup>Hampshire Hospitals NHS Foundation Trust, Hampshire, United Kingdom <sup>75</sup>Health Data Research UK Cambridge, Cambridge, United Kingdom <sup>76</sup>Health Services Laboratories, London, United Kingdom <sup>77</sup>Heartlands Hospital, Birmingham, Birmingham, United Kingdom <sup>78</sup>Hub for Biotechnology in the Built Environment, Northumbria University, Northumbria, United Kingdom <sup>79</sup>Imperial College Hospitals NHS Trust, London, United Kingdom <sup>80</sup>Imperial College London, London, United Kingdom <sup>81</sup>Institute of Biodiversity, Animal Health & Comparative Medicine, Glasgow, United Kingdom <sup>82</sup>Institute of Microbiology and Infection, University of Birmingham, Birmingham, United Kingdom <sup>83</sup>King's College London, London, United Kingdom <sup>84</sup>Liverpool Clinical Laboratories, Liverpool, United Kingdom <sup>85</sup>Maidstone and Tunbridge Wells NHS Trust, Maidstone, United Kingdom <sup>86</sup>Manchester University NHS Foundation Trust, Manchester, United Kingdom <sup>87</sup>Microbiology Department, Wye Valley NHS Trust, Hereford, United Kingdom <sup>88</sup>MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom <sup>89</sup>MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom <sup>90</sup>National Infection Service, PHE and Leeds Teaching

Hospitals Trust, Leeds, United Kingdom <sup>91</sup>Newcastle Hospitals NHS Foundation Trust, Newcastle, United Kingdom <sup>92</sup>Newcastle University, Newcastle, United Kingdom <sup>93</sup>NHS Greater Glasgow and Clyde, Glasgow, United Kingdom <sup>94</sup>NHS Lothian, Edinburgh, United Kingdom <sup>95</sup>Norfolk and Norwich University Hospital, Norfolk, United Kingdom <sup>96</sup>Norfolk County Council, Norfolk, United Kingdom <sup>97</sup>North Cumbria Integrated Care NHS Foundation Trust, Carlisle, United Kingdom <sup>98</sup>North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees, United Kingdom <sup>99</sup>Northumbria University, Northumbria, United Kingdom <sup>100</sup>Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom <sup>101</sup>PathLinks, Northern Lincolnshire & Goole NHS Foundation Trust, Lincolnshire, United Kingdom <sup>102</sup>Portsmouth Hospitals University NHS Trust, Portsmouth, United Kingdom <sup>103</sup>Princess Alexandra Hospital Microbiology Dept., Harlow, United Kingdom <sup>104</sup>Public Health Agency, London, United Kingdom <sup>105</sup>Public Health England, London, United Kingdom <sup>106</sup>Public Health England, Clinical Microbiology and Public Health Laboratory, Cambridge, United Kingdom <sup>107</sup>Public Health England, Colindale, London, United Kingdom <sup>108</sup>Public Health England, Colindale, London, United Kingdom <sup>109</sup>Public Health Scotland, Glasgow, United Kingdom <sup>110</sup>Public Health Wales NHS Trust, Cardiff, United Kingdom <sup>111</sup>Quadram Institute Bioscience, Norwich, United Kingdom <sup>112</sup>Queen Elizabeth Hospital, Birmingham, United Kingdom <sup>113</sup>Queen's University Belfast, Belfast, United Kingdom <sup>114</sup>Royal Devon and Exeter NHS Foundation Trust, Devon, United Kingdom <sup>115</sup>Royal Free NHS Trust, London, United Kingdom <sup>116</sup>Sandwell and West Birmingham NHS Trust, Sandwell, United Kingdom <sup>117</sup>School of Biological Sciences, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>118</sup>School of Pharmacy and Biomedical Sciences, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>119</sup>Sheffield Teaching Hospitals, Sheffield, United Kingdom <sup>120</sup>South Tees Hospitals NHS Foundation Trust, Newcastle, United Kingdom <sup>121</sup>Swansea University, Swansea, United Kingdom <sup>122</sup>University Hospitals Southampton NHS Foundation Trust, Southampton, United Kingdom <sup>123</sup>University College London, London, United Kingdom <sup>124</sup>University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom <sup>125</sup>University Hospitals Coventry and Warwickshire, Coventry, United Kingdom <sup>126</sup>University of Birmingham, Birmingham, United Kingdom <sup>127</sup>University of Birmingham Turnkey Laboratory, Birmingham, United Kingdom <sup>128</sup>University of Brighton, Brighton, United Kingdom <sup>129</sup>University of Cambridge, Cambridge, United Kingdom <sup>130</sup>University of East Anglia, East Anglia, United Kingdom <sup>131</sup>University of Edinburgh, Edinburgh, United Kingdom <sup>132</sup>University of Exeter, Exeter, United Kingdom <sup>133</sup>University of Liverpool, Liverpool, United Kingdom <sup>134</sup>University of Sheffield, Sheffield, United Kingdom <sup>135</sup>University of Warwick, Warwick, United Kingdom <sup>136</sup>University of Cambridge, Cambridge, United Kingdom <sup>137</sup>Viapath, Guy's and St Thomas' NHS Foundation Trust, and King's College Hospital NHS Foundation Trust, London, United Kingdom

<sup>138</sup>Virology, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, United Kingdom <sup>139</sup>Wellcome Centre for Human Genetics, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom <sup>140</sup>Wellcome Sanger Institute, London, United Kingdom <sup>141</sup>West of Scotland Specialist Virology Centre, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom <sup>142</sup>Department of Medicine, University of Cambridge, Cambridge, United Kingdom <sup>143</sup>Ministry of Health, Colombo, Sri Lanka <sup>144</sup>NIHR Health Protection Research Unit in HCAI and AMR, Imperial College London, London, United Kingdom <sup>145</sup>North West London Pathology, London, United Kingdom <sup>146</sup>NU-OMICS, Northumbria University, Northumbria, United Kingdom <sup>147</sup>University of Kent, Kent, United Kingdom <sup>148</sup>University of Oxford, Oxford, United Kingdom <sup>149</sup>University of Southampton, Southampton, United Kingdom <sup>150</sup>University of Southampton School of Health Sciences, Southampton, United Kingdom <sup>151</sup>University of Southampton School of Medicine, Southampton, United Kingdom <sup>152</sup>University of Surrey, Guildford, United Kingdom <sup>153</sup>Warwick Medical School and Institute of Precision Diagnostics, Pathology, UHCW NHS Trust, Warwick, United Kingdom

, Katherine Sharrocks<sup>4</sup>, Elizabeth Blane<sup>3</sup>, Yorgo Modis<sup>8</sup>, Kendra Leigh<sup>8</sup>, John Briggs<sup>8</sup>, Marit van Gils<sup>9</sup>, Kenneth GC Smith<sup>2,3</sup>, John R Bradley<sup>3,10</sup>, Chris Smith<sup>11</sup>, Rainer Doffinger<sup>13</sup>, Lourdes Ceron-Gutierrez<sup>13</sup>, Gabriela Barcenas-Morales<sup>13,14</sup>, David D Pollock<sup>15</sup>, Richard A Goldstein<sup>1</sup>, Anna Smielewska<sup>5,11</sup>, Jordan P Skittrall<sup>4,12,16</sup>, Theodore Gouliouris<sup>4</sup>, Ian G Goodfellow<sup>5</sup>, Effrossyni Gkrania-Klotsas<sup>4</sup>, Christopher JR Illingworth<sup>12,17</sup>, Laura E McCoy<sup>1</sup>, Ravindra K Gupta<sup>2,3,18</sup>

Stephen Baker<sup>2,3</sup> [Principal Investigators], Gordon Dougan<sup>2,3</sup> [Principal Investigators], Christoph Hess<sup>2,3,26,27</sup> [Principal Investigators], Nathalie Kingston<sup>20,12</sup> [Principal Investigators], Paul J. Lehner<sup>2,3</sup> [Principal Investigators], Paul A. Lyons<sup>2,3</sup> [Principal Investigators], Nicholas J. Matheson<sup>2,3</sup> [Principal Investigators], Willem H. Owehand<sup>20</sup> [Principal Investigators], Caroline Saunders<sup>19</sup> [Principal Investigators], Charlotte Summers<sup>3,24,25,28</sup> [Principal Investigators], James E.D. Thaventhiran<sup>2,3,22</sup> [Principal Investigators], Mark Toshner<sup>3,24,25</sup> [Principal Investigators], Michael P. Weekes<sup>2</sup> [Principal Investigators], Ashlea Bucke<sup>19</sup> [CRF and Volunteer Research Nurses], Jo Calder<sup>19</sup> [CRF and Volunteer Research Nurses], Laura Canna<sup>19</sup> [CRF and Volunteer Research Nurses], Jason Domingo<sup>19</sup> [CRF and Volunteer Research Nurses], Anne Elmer<sup>19</sup> [CRF and Volunteer Research Nurses], Stewart Fuller<sup>19</sup> [CRF and Volunteer Research Nurses], Julie Harris<sup>41</sup> [CRF and Volunteer Research Nurses], Sarah Hewitt<sup>19</sup> [CRF and Volunteer Research Nurses], Jane Kennet<sup>19</sup> [CRF and Volunteer Research Nurses], Sherly Jose<sup>19</sup> [CRF and Volunteer Research Nurses], Jenny Kourampa<sup>19</sup> [CRF and Volunteer Research Nurses], Anne Meadows<sup>19</sup> [CRF and Volunteer Research Nurses], Criona O'Brien<sup>41</sup> [CRF and Volunteer Research Nurses], Jane Price<sup>19</sup> [CRF and Volunteer Research Nurses], Cherry Publico<sup>19</sup> [CRF and Volunteer Research

**Nurses**], Rebecca Rastall<sup>19</sup> [**CRF and Volunteer Research Nurses**], Carla Ribeiro<sup>19</sup> [**CRF and Volunteer Research Nurses**], Jane Rowlands<sup>19</sup> [**CRF and Volunteer Research Nurses**], Valentina Ruffolo<sup>19</sup> [**CRF and Volunteer Research Nurses**], Hugo Tordesillas<sup>19</sup> [**CRF and Volunteer Research Nurses**], Ben Bullman<sup>2</sup> [**Sample Logistics**], Benjamin J Dunmore<sup>3</sup> [**Sample Logistics**], Stuart Fawke<sup>30</sup> [**Sample Logistics**], Stefan Gräf<sup>3,12,20</sup> [**Sample Logistics**], Josh Hodgson<sup>3</sup> [**Sample Logistics**], Christopher Huang<sup>3</sup> [**Sample Logistics**], Kelvin Hunter<sup>2,3</sup> [**Sample Logistics**], Emma Jones<sup>29</sup> [**Sample Logistics**], Ekaterina Legchenko<sup>3</sup> [**Sample Logistics**], Cecilia Matara<sup>3</sup> [**Sample Logistics**], Jennifer Martin<sup>3</sup> [**Sample Logistics**], Federica Mescia<sup>2,3</sup> [**Sample Logistics**], Ciara O'Donnell<sup>3</sup> [**Sample Logistics**], Linda Pointon<sup>3</sup> [**Sample Logistics**], Nicole Pond<sup>2,3</sup> [**Sample Logistics**], Joy Shih<sup>3</sup> [**Sample Logistics**], Rachel Sutcliffe<sup>3</sup> [**Sample Logistics**], Tobias Tilly<sup>3</sup> [**Sample Logistics**], Carmen Treacy<sup>3</sup> [**Sample Logistics**], Zhen Tong<sup>3</sup> [**Sample Logistics**], Jennifer Wood<sup>3</sup> [**Sample Logistics**], Marta Wylot<sup>36</sup> [**Sample Logistics**], Laura Bergamaschi<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Ariana Betancourt<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Georgie Bower<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Chiara Cossetti<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Aloka De Sa<sup>3</sup> [**Sample Processing and Data Acquisition**], Madeline Epping<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Stuart Fawke<sup>32</sup> [**Sample Processing and Data Acquisition**], Nick Gleadall<sup>20</sup> [**Sample Processing and Data Acquisition**], Richard Grenfell<sup>31</sup> [**Sample Processing and Data Acquisition**], Andrew Hinch<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Oisin Huhn<sup>32</sup> [**Sample Processing and Data Acquisition**], Sarah Jackson<sup>3</sup> [**Sample Processing and Data Acquisition**], Isobel Jarvis<sup>3</sup> [**Sample Processing and Data Acquisition**], Daniel Lewis<sup>3</sup> [**Sample Processing and Data Acquisition**], Joe Marsden<sup>3</sup> [**Sample Processing and Data Acquisition**], Francesca Nice<sup>39</sup> [**Sample Processing and Data Acquisition**], Georgina Okecha<sup>3</sup> [**Sample Processing and Data Acquisition**], Ommar Omarjee<sup>3</sup> [**Sample Processing and Data Acquisition**], Marianne Perera<sup>3</sup> [**Sample Processing and Data Acquisition**], Nathan Richoz<sup>3</sup> [**Sample Processing and Data Acquisition**], Veronika Romashova<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Natalia Savinykh Yarkoni<sup>3</sup> [**Sample Processing and Data Acquisition**], Rahul Sharma<sup>3</sup> [**Sample Processing and Data Acquisition**], Luca Stefanucci<sup>20</sup> [**Sample Processing and Data Acquisition**], Jonathan Stephens<sup>20</sup> [**Sample Processing and Data Acquisition**], Mateusz Strezlecki<sup>31</sup> [**Sample Processing and Data Acquisition**], Lori Turner<sup>2,3</sup> [**Sample Processing and Data Acquisition**], Eckart M.D.D. De Bie<sup>3</sup> [**Clinical Data Collection**], Katherine Bunclark<sup>3</sup> [**Clinical Data Collection**], Masa Josipovic<sup>40</sup> [**Clinical Data Collection**], Michael Mackay<sup>3</sup> [**Clinical Data Collection**], Federica Mescia<sup>2,3</sup> [**Clinical Data Collection**], Alice Michael<sup>25</sup> [**Clinical Data Collection**], Sabrina Rossi<sup>35</sup> [**Clinical Data Collection**], Mayurun Selvan<sup>3</sup> [**Clinical Data Collection**], Sarah Spencer<sup>15</sup> [**Clinical Data Collection**], Cissy Yong<sup>35</sup> [**Clinical Data Collection**], Ali Ansari-pour<sup>25</sup> [**Royal Papworth Hospital ICU**], Alice Michael<sup>25</sup> [**Royal Papworth Hospital ICU**], Lucy Mwaura<sup>25</sup> [**Royal Papworth**

**Hospital ICU**, Caroline Patterson<sup>25</sup> [**Royal Papworth Hospital ICU**], Gary Polwarth<sup>25</sup> [**Royal Papworth Hospital ICU**], Petra Polgarova<sup>28</sup> [**Addenbrooke's Hospital ICU**], Giovanni di Stefano<sup>28</sup> [**Addenbrooke's Hospital ICU**], Codie Fahey<sup>34</sup> [**Cambridge and Peterborough Foundation Trust**], Rachel Michel<sup>34</sup> [**Cambridge and Peterborough Foundation Trust**], Sze-How Bong<sup>21</sup> [**ANPC and Centre for Molecular Medicine and Innovative Therapeutics**], Jerome D. Coudert<sup>33</sup> [**ANPC and Centre for Molecular Medicine and Innovative Therapeutics**], Elaine Holmes<sup>37</sup> [**ANPC and Centre for Molecular Medicine and Innovative Therapeutics**], John Allison<sup>20,12</sup> [**NIHR BioResource**], Helen Butcher<sup>12,38</sup> [**NIHR BioResource**], Daniela Caputo<sup>12,38</sup> [**NIHR BioResource**], Debbie Clapham-Riley<sup>12,38</sup> [**NIHR BioResource**], Eleanor Dewhurst<sup>12,38</sup> [**NIHR BioResource**], Anita Furlong<sup>12,38</sup> [**NIHR BioResource**], Barbara Graves<sup>12,38</sup> [**NIHR BioResource**], Jennifer Gray<sup>12,38</sup> [**NIHR BioResource**], Tasmin Ivers<sup>12,38</sup> [**NIHR BioResource**], Mary Kasanicki<sup>12,28</sup> [**NIHR BioResource**], Emma Le Gresley<sup>12,38</sup> [**NIHR BioResource**], Rachel Linger<sup>12,38</sup> [**NIHR BioResource**], Sarah Meloy<sup>12,38</sup> [**NIHR BioResource**], Francesca Muldoon<sup>12,38</sup> [**NIHR BioResource**], Nigel Ovington<sup>12,20</sup> [**NIHR BioResource**], Sofia Papadia<sup>12,38</sup> [**NIHR BioResource**], Isabel Phelan<sup>12,38</sup> [**NIHR BioResource**], Hannah Stark<sup>12,38</sup> [**NIHR BioResource**], Kathleen E Stirrups<sup>12,20</sup> [**NIHR BioResource**], Paul Townsend<sup>12,20</sup> [**NIHR BioResource**], Neil Walker<sup>12,20</sup> [**NIHR BioResource**], Jennifer Webster<sup>12,38</sup> [**NIHR BioResource**]

Samuel C Robson<sup>54</sup> [**Funding acquisition, Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation**], Nicholas J Loman<sup>82</sup>, Thomas R Connor<sup>51,110</sup> [**Funding acquisition, Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Software and analysis tools**], Tanya Golubchik<sup>46</sup> [**Leadership and supervision, Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation**], Rocio T Martinez Nunez<sup>83</sup> [**Funding acquisition, Metadata curation, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation**], Catherine Ludden<sup>129</sup> [**Funding acquisition, Leadership and supervision, Metadata curation, Project administration, and Samples and logistics**], Sally Corden<sup>110</sup> [**Funding acquisition, Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis**], Ian Johnston<sup>140</sup>, David Bonsall<sup>46</sup> [**Funding acquisition, Leadership and supervision, Project administration, Samples and logistics, and Sequencing and analysis**], Colin P Smith<sup>128</sup>, Ali R Awan<sup>69</sup> [**Funding acquisition, Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation**], Giselda Bucca<sup>128</sup> [**Funding acquisition, Samples and logistics, Sequencing and analysis, Software and analysis tools, and Visualisation**], M. Estee Torok<sup>63,142</sup> [**Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis**], Kordo Saeed<sup>122,151</sup> [**Leadership and supervision, Metadata curation,**

**Project administration, Samples and logistics, and Visualisation]**, Jacqui A Prieto<sup>124,150</sup> [**Leadership and supervision, Metadata curation, Project administration, Samples and logistics, and Visualisation]**, David K Jackson<sup>140</sup> [**Leadership and supervision, Metadata curation, Project administration, Sequencing and analysis, and Software and analysis tools]**, William L Hamilton<sup>63</sup> [**Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Software and analysis tools]**, Luke B Snell<sup>52</sup> [**Metadata curation, Project administration, Samples and logistics, Sequencing and analysis, and Visualisation]**, Catherine Moore<sup>110</sup> [**Funding acquisition, Leadership and supervision, Metadata curation, and Samples and logistics]**, Ewan M Harrison<sup>129,140</sup> [**Funding acquisition, Leadership and supervision, Project administration, and Samples and logistics]**, Sonia Goncalves<sup>140</sup> [**Leadership and supervision, Metadata curation, Project administration, and Samples and logistics]**, Derek J Fairley<sup>44,113</sup> [**Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis]**, Matthew W Loose<sup>59</sup> [**Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis]**, Joanne Watkins<sup>110</sup> [**Leadership and supervision, Metadata curation, Samples and logistics, and Sequencing and analysis]**, Rich Livett<sup>140</sup> [**Leadership and supervision, Metadata curation, Samples and logistics, and Software and analysis tools]**, Samuel Moses<sup>66,147</sup> [**Leadership and supervision, Metadata curation, Samples and logistics, and Visualisation]**, Roberto Amato<sup>140</sup> [**Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools]**, Sam Nicholls<sup>82</sup> [**Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools]**, Matthew Bull<sup>110</sup> [**Leadership and supervision, Metadata curation, Sequencing and analysis, and Software and analysis tools]**, Darren L Smith<sup>1,99,146</sup> [**Leadership and supervision, Project administration, Samples and logistics, and Sequencing and analysis]**, Jeff Barrett<sup>140</sup> [**Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation]**, David M Aanensen<sup>55</sup> [**Leadership and supervision, Sequencing and analysis, Software and analysis tools, and Visualisation]**, Martin D Curran<sup>106</sup> [**Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis]**, Surendra Parmar<sup>106</sup> [**Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis]**, Dinesh Aggarwal<sup>1,140,105</sup> [**Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis]**, James G Shepherd<sup>89</sup> [**Metadata curation, Project administration, Samples and logistics, and Sequencing and analysis]**, Matthew D Parker<sup>134</sup> [**Metadata curation, Project administration, Sequencing and analysis, and Software and analysis tools]**, Sharon Glaysher<sup>102</sup> [**Metadata curation, Samples and logistics, Sequencing and analysis, and Visualisation]**, Matthew Bashton<sup>78,99</sup> [**Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation]**, Anthony P Underwood<sup>55</sup> [**Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation]**, Nicole Pacchiarini<sup>110</sup> [**Metadata**



curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Katie F Loveson<sup>118</sup> [Metadata curation, Sequencing and analysis, Software and analysis tools, and Visualisation], Alessandro M Carabelli<sup>129</sup> [Project administration, Sequencing and analysis, Software and analysis tools, and Visualisation], Kate E Templeton<sup>94,131</sup> [Funding acquisition, Leadership and supervision, and Metadata curation], Cordelia F Langford<sup>140</sup> [Funding acquisition, Leadership and supervision, and Project administration], John Sillitoe<sup>140</sup> [Funding acquisition, Leadership and supervision, and Project administration], Thushan I de Silva<sup>134</sup> [Funding acquisition, Leadership and supervision, and Project administration], Dennis Wang<sup>134</sup> [Funding acquisition, Leadership and supervision, and Project administration], Dominic Kwiatkowski<sup>140,148</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Andrew Rambaut<sup>131</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Justin O'Grady<sup>111,130</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Simon Cottrell<sup>110</sup> [Funding acquisition, Leadership and supervision, and Sequencing and analysis], Matthew T.G. Holden<sup>109</sup> [Leadership and supervision, Metadata curation, and Sequencing and analysis], Emma C Thomson<sup>89</sup> [Leadership and supervision, Metadata curation, and Sequencing and analysis], Husam Osman<sup>77,105</sup> [Leadership and supervision, Project administration, and Samples and logistics], Monique Andersson<sup>100</sup> [Leadership and supervision, Project administration, and Samples and logistics], Anoop J Chauhan<sup>102</sup> [Leadership and supervision, Project administration, and Samples and logistics], Mohammed O Hassan-Ibrahim<sup>47</sup> [Leadership and supervision, Project administration, and Samples and logistics], Mara Lawniczak<sup>140</sup> [Leadership and supervision, Project administration, and Sequencing and analysis], Alex Alderton<sup>140</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Meera Chand<sup>107</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Chrystala Constantinidou<sup>135</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Meera Unnikrishnan<sup>135</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Alistair C Darby<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Julian A Hiscox<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Steve Paterson<sup>133</sup> [Leadership and supervision, Samples and logistics, and Sequencing and analysis], Inigo Martincorena<sup>140</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], David L Robertson<sup>89</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Erik M Volz<sup>80</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Andrew J Page<sup>111</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Oliver G Pybus<sup>64</sup> [Leadership and supervision, Sequencing and analysis, and Software and analysis tools], Andrew R Bassett<sup>140</sup> [Leadership and supervision, Sequencing and analysis, and Visualisation],

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M Evans<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Laia Fina<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Lauren Gilbert<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Lee Graham<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Michelle Cronin<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Sara Kumziene-SummerhaYes<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Sarah Taylor<sup>110</sup> [Samples and logistics, and Sequencing and analysis], Sophie Jones<sup>140</sup> [Samples and logistics, and Sequencing and analysis], Danielle C Groves<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Peijun Zhang<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Marta Gallis<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Stavroula F Louka<sup>134</sup> [Samples and logistics, and Sequencing and analysis], Igor Starinskij<sup>89</sup> [Samples and logistics, and Software and analysis tools], Chris Jackson<sup>88</sup> [Sequencing and analysis, and Software and analysis tools], Marina Gourtovaia<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Gerry Tonkin-Hill<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Kevin Lewis<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Jaime M Tovar-Corona<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Keith James<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Laura Baxter<sup>135</sup> [Sequencing and analysis, and Software and analysis tools], Mohammad T Alam<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Richard J Orton<sup>89</sup> [Sequencing and analysis, and Software and analysis tools], Joseph Hughes<sup>89</sup> [Sequencing and analysis, and Software and analysis tools], Sreenu Vattipally<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Manon Ragonnet-Cronin<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], Fabricia F Nascimento<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], David Jorgensen<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], Olivia Boyd<sup>80</sup> [Sequencing and analysis, and Software and analysis tools], Lily Geidelberg<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Alex E Zarebski<sup>64</sup> [Sequencing and analysis, and Software and analysis tools], Jayna Raghwan<sup>140</sup> [Sequencing and analysis, and Software and analysis tools], Moritz UG Kraemer<sup>64</sup> [Sequencing and analysis, and Software and analysis tools], Joel Southgate<sup>51,110</sup> [Sequencing and analysis, and Software and analysis tools], Benjamin B Lindsey<sup>134</sup> [Sequencing and analysis, and Software and analysis tools], Timothy M Freeman<sup>134</sup> [Sequencing and analysis, and Software and analysis tools], Jon-Paul Keatley<sup>140</sup> [Software and analysis tools, and Visualisation], Joshua B Singer<sup>140</sup> [Software and analysis tools, and Visualisation], Leonardo de Oliveira Martins<sup>140</sup> [Software and analysis tools, and Visualisation], Corin A Yeats<sup>55</sup> [Software and analysis tools, and Visualisation], Khalil Abudahab<sup>140,140</sup> [Software and analysis tools, and Visualisation], Ben EW Taylor<sup>140</sup> [Software and analysis tools, and Visualisation], Mirko Menegazzo<sup>55</sup> [Software and analysis tools, and Visualisation], John Danesh<sup>140</sup> [Leadership and supervision], Wendy

Hogsden<sup>87</sup> [Leadership and supervision], Sahar Eldirdiri<sup>62</sup> [Leadership and supervision], Anita Kenyon<sup>62</sup> [Leadership and supervision], Jenifer Mason<sup>140</sup> [Leadership and supervision], Trevor I Robinson<sup>84</sup> [Leadership and supervision], Alison Holmes<sup>140,144</sup> [Leadership and supervision], James Price<sup>140,140</sup> [Leadership and supervision], John A Hartley<sup>123</sup> [Leadership and supervision], Tanya Curran<sup>140</sup> [Leadership and supervision], Alison E Mather<sup>111</sup> [Leadership and supervision], Giri Shankar<sup>110</sup> [Leadership and supervision], Rachel Jones<sup>110</sup> [Leadership and supervision], Robin Howe<sup>110</sup> [Leadership and supervision], Sian Morgan<sup>50</sup> [Leadership and supervision], Elizabeth Wastenge<sup>140</sup> [Metadata curation], Michael R Chapman<sup>1,129,140</sup> [Metadata curation], Siddharth Mookerjee<sup>79,144</sup> [Metadata curation], Rachael Stanley<sup>95</sup> [Metadata curation], Wendy Smith<sup>56</sup> [Metadata curation], Timothy Peto<sup>100</sup> [Metadata curation], David Eyre<sup>100</sup> [Metadata curation], Derrick Crook<sup>100</sup> [Metadata curation], Gabrielle Vernet<sup>74</sup> [Metadata curation], Christine Kitchen<sup>51</sup> [Metadata curation], Huw Gulliver<sup>51</sup> [Metadata curation], Ian Merrick<sup>51</sup> [Metadata curation], Martyn Guest<sup>51</sup> [Metadata curation], Robert Munn<sup>140</sup> [Metadata curation], Declan T Bradley<sup>140,113</sup> [Metadata curation], Tim Wyatt<sup>104</sup> [Metadata curation], Charlotte Beaver<sup>140</sup> [Project administration], Luke Foulser<sup>140</sup> [Project administration], Sophie Palmer<sup>140</sup> [Project administration], Carol M Churcher<sup>129</sup> [Project administration], Ellena Brooks<sup>140</sup> [Project administration], Kim S Smith<sup>129</sup> [Project administration], Katerina Galai<sup>140</sup> [Project administration], Georgina M McManus<sup>129</sup> [Project administration], Frances Bolt<sup>79,144</sup> [Project administration], Francesc Coll<sup>60</sup> [Project administration], Lizzie Meadows<sup>140</sup> [Project administration], Stephen W Attwood<sup>64</sup> [Project administration], Alisha Davies<sup>140</sup> [Project administration], Elen De Lacy<sup>110</sup> [Project administration], Fatima Downing<sup>110</sup> [Project administration], Sue Edwards<sup>140</sup> [Project administration], Garry P Scarlett<sup>117</sup> [Project administration], Sarah Jeremiah<sup>124</sup> [Project administration], Nikki Smith<sup>134</sup> [Project administration], Danielle Leek<sup>129</sup> [Samples and logistics], Sushmita Sridhar<sup>140,140</sup> [Samples and logistics], Sally Forrest<sup>129</sup> [Samples and logistics], Claire Cormie<sup>140</sup> [Samples and logistics], Harmeet K Gill<sup>129</sup> [Samples and logistics], Joana Dias<sup>140</sup> [Samples and logistics], Ellen E Higginson<sup>129</sup> [Samples and logistics], Mailis Maes<sup>129</sup> [Samples and logistics], Jamie Young<sup>129</sup> [Samples and logistics], Michelle Wantoch<sup>140</sup> [Samples and logistics], Sanger Covid Team<sup>140</sup> [Samples and logistics], Dorota Jamrozy<sup>140</sup> [Samples and logistics], Stephanie Lo<sup>140</sup> [Samples and logistics], Minal Patel<sup>140</sup> [Samples and logistics], Verity Hill<sup>140</sup> [Samples and logistics], Claire M Bewshea<sup>132</sup> [Samples and logistics], Sian Ellard<sup>114,132</sup> [Samples and logistics], Cressida Auckland<sup>114</sup> [Samples and logistics], Ian Harrison<sup>107</sup> [Samples and logistics], Chloe Bishop<sup>107</sup> [Samples and logistics], Vicki Chalker<sup>107</sup> [Samples and logistics], Alex Richter<sup>126</sup> [Samples and logistics], Andrew Beggs<sup>126</sup> [Samples and logistics], Angus Best<sup>127</sup> [Samples and logistics], Benita Percival<sup>127</sup> [Samples and logistics], Jeremy Mirza<sup>127</sup> [Samples and logistics], Oliver Megram<sup>127</sup> [Samples and logistics], Megan Mayhew<sup>127</sup> [Samples and logistics], Liam Crawford<sup>127</sup>

**[Samples and logistics]**, Fiona Ashcroft<sup>140</sup> **[Samples and logistics]**, Emma Moles-Garcia<sup>127</sup> **[Samples and logistics]**, Nicola Cumley<sup>127</sup> **[Samples and logistics]**, Richard Hopes<sup>105</sup> **[Samples and logistics]**, Patawee Asamaphan<sup>140</sup> **[Samples and logistics]**, Marc O Niebel<sup>140</sup> **[Samples and logistics]**, Rory N Gunson<sup>141</sup> **[Samples and logistics]**, Amanda Bradley<sup>93</sup> **[Samples and logistics]**, Alasdair Maclean<sup>93</sup> **[Samples and logistics]**, Guy Mollett<sup>93</sup> **[Samples and logistics]**, Rachel Blacow<sup>93</sup> **[Samples and logistics]**, Paul Bird<sup>57</sup> **[Samples and logistics]**, Thomas Helmer<sup>57</sup> **[Samples and logistics]**, Karlie Fallon<sup>57</sup> **[Samples and logistics]**, Julian Tang<sup>140</sup> **[Samples and logistics]**, Antony D Hale<sup>140</sup> **[Samples and logistics]**, Louissa R Macfarlane-Smith<sup>140</sup> **[Samples and logistics]**, Katherine L Harper<sup>90</sup> **[Samples and logistics]**, Holli Carden<sup>140</sup> **[Samples and logistics]**, Nicholas W Machin<sup>86,105</sup> **[Samples and logistics]**, Kathryn A Jackson<sup>133</sup> **[Samples and logistics]**, Shazaad SY Ahmad<sup>86,105</sup> **[Samples and logistics]**, Ryan P George<sup>86</sup> **[Samples and logistics]**, Lance Turtle<sup>140</sup> **[Samples and logistics]**, Elaine O'Toole<sup>84</sup> **[Samples and logistics]**, Joanne Watts<sup>84</sup> **[Samples and logistics]**, Cassie Breen<sup>84</sup> **[Samples and logistics]**, Angela Cowell<sup>140</sup> **[Samples and logistics]**, Adela Alcolea-Medina<sup>73,137</sup> **[Samples and logistics]**, Themoula Charalampous<sup>140,83</sup> **[Samples and logistics]**, Amita Patel<sup>140</sup> **[Samples and logistics]**, Lisa J Levett<sup>76</sup> **[Samples and logistics]**, Judith Heaney<sup>76</sup> **[Samples and logistics]**, Aileen Rowan<sup>140</sup> **[Samples and logistics]**, Graham P Taylor<sup>80</sup> **[Samples and logistics]**, Divya Shah<sup>71</sup> **[Samples and logistics]**, Laura Atkinson<sup>140</sup> **[Samples and logistics]**, Jack CD Lee<sup>140</sup> **[Samples and logistics]**, Adam P Westhorpe<sup>123</sup> **[Samples and logistics]**, Riaz Jannoo<sup>140</sup> **[Samples and logistics]**, Helen L Lowe<sup>123</sup> **[Samples and logistics]**, Angeliki Karamani<sup>123</sup> **[Samples and logistics]**, Leah Ensell<sup>123</sup> **[Samples and logistics]**, Wendy Chatterton<sup>76</sup>, Monika Pusok<sup>76</sup> **[Samples and logistics]**, Ashok Dadrah<sup>116</sup> **[Samples and logistics]**, Amanda Symmonds<sup>116</sup> **[Samples and logistics]**, Graciela Sluga<sup>85</sup> **[Samples and logistics]**, Zoltan Molnar<sup>113</sup> **[Samples and logistics]**, Paul Baker<sup>120</sup> **[Samples and logistics]**, Stephen Bonner<sup>120</sup> **[Samples and logistics]**, Sarah Essex<sup>120</sup> **[Samples and logistics]**, Edward Barton<sup>97</sup> **[Samples and logistics]**, Debra Padgett<sup>97</sup> **[Samples and logistics]**, Garren Scott<sup>97</sup> **[Samples and logistics]**, Jane Greenaway<sup>140</sup> **[Samples and logistics]**, Brendan Al Payne<sup>140</sup> **[Samples and logistics]**, Shirelle Burton-Fanning<sup>91</sup> **[Samples and logistics]**, Sheila Waugh<sup>91</sup> **[Samples and logistics]**, Veena Raviprakash<sup>58</sup> **[Samples and logistics]**, Nicola Sheriff<sup>58</sup> **[Samples and logistics]**, Victoria Blakey<sup>140</sup> **[Samples and logistics]**, Lesley-Anne Williams<sup>58</sup> **[Samples and logistics]**, Jonathan Moore<sup>68</sup> **[Samples and logistics]**, Susanne Stonehouse<sup>68</sup> **[Samples and logistics]**, Louise Smith<sup>140</sup> **[Samples and logistics]**, Rose K Davidson<sup>130</sup> **[Samples and logistics]**, Luke Bedford<sup>67</sup> **[Samples and logistics]**, Lindsay Coupland<sup>95</sup> **[Samples and logistics]**, Victoria Wright<sup>140</sup> **[Samples and logistics]**, Joseph G Chappell<sup>138</sup> **[Samples and logistics]**, Theocharis Tsoleridis<sup>138</sup> **[Samples and logistics]**, Jonathan Ball<sup>138</sup> **[Samples and logistics]**, Manjinder Khakh<sup>140</sup> **[Samples and logistics]**, Vicki M Fleming<sup>140</sup> **[Samples and logistics]**, Michelle M Lister<sup>140</sup> **[Samples and logistics]**, Hannah C



Howson-Wells<sup>56</sup> [**Samples and logistics**], Louise Berry<sup>56</sup> [**Samples and logistics**], Tim Boswell<sup>56</sup> [**Samples and logistics**], Amelia Joseph<sup>56</sup> [**Samples and logistics**], Iona Willingham<sup>56</sup> [**Samples and logistics**], Nichola Duckworth<sup>101</sup> [**Samples and logistics**], Sarah Walsh<sup>101</sup> [**Samples and logistics**], Emma Wise<sup>140,152</sup> [**Samples and logistics**], Nathan Moore<sup>140,152</sup> [**Samples and logistics**], Matilde Mori<sup>140,140,152</sup> [**Samples and logistics**], Nick Cortes<sup>140,152</sup> [**Samples and logistics**], Stephen Kidd<sup>140,152</sup> [**Samples and logistics**], Rebecca Williams<sup>74</sup> [**Samples and logistics**], Laura Gifford<sup>110</sup> [**Samples and logistics**], Kelly Bicknell<sup>102</sup> [**Samples and logistics**], Sarah Wyllie<sup>102</sup> [**Samples and logistics**], Allyson Lloyd<sup>102</sup> [**Samples and logistics**], Robert Impey<sup>140</sup> [**Samples and logistics**], Cassandra S Malone<sup>140</sup> [**Samples and logistics**], Benjamin J Cogger<sup>47</sup> [**Samples and logistics**], Nick Levene<sup>103</sup> [**Samples and logistics**], Lynn Monaghan<sup>140</sup> [**Samples and logistics**], Alexander J Keeley<sup>140</sup> [**Samples and logistics**], David G Partridge<sup>140,134</sup> [**Samples and logistics**], Mohammad Raza<sup>119,134</sup> [**Samples and logistics**], Cariad Evans<sup>140,134</sup> [**Samples and logistics**], Kate Johnson<sup>119,134</sup> [**Samples and logistics**], Emma Betteridge<sup>140</sup> [**Sequencing and analysis**], Ben W Farr<sup>140</sup> [**Sequencing and analysis**], Scott Goodwin<sup>140</sup> [**Sequencing and analysis**], Michael A Quail<sup>140</sup> [**Sequencing and analysis**], Carol Scott<sup>140</sup> [**Sequencing and analysis**], Lesley Shirley<sup>140</sup> [**Sequencing and analysis**], Scott AJ Thurston<sup>140</sup> [**Sequencing and analysis**], Diana Rajan<sup>140</sup> [**Sequencing and analysis**], Iraad F Bronner<sup>140</sup> [**Sequencing and analysis**], Louise Aigrain<sup>140</sup> [**Sequencing and analysis**], Nicholas M Redshaw<sup>140</sup> [**Sequencing and analysis**], Stefanie V Lensing<sup>140</sup> [**Sequencing and analysis**], Shane McCarthy<sup>140</sup> [**Sequencing and analysis**], Alex Makunin<sup>140</sup> [**Sequencing and analysis**], Carlos E Balcazar<sup>140</sup> [**Sequencing and analysis**], Michael D Gallagher<sup>140</sup> [**Sequencing and analysis**], Kathleen A Williamson<sup>140</sup> [**Sequencing and analysis**], Thomas D Stanton<sup>140</sup> [**Sequencing and analysis**], Michelle L Michelsen<sup>140</sup> [**Sequencing and analysis**], Joanna Warwick-Dugdale<sup>132</sup> [**Sequencing and analysis**], Robin Manley<sup>132</sup> [**Sequencing and analysis**], Audrey Farbos<sup>140</sup> [**Sequencing and analysis**], James W Harrison<sup>140</sup> [**Sequencing and analysis**], Christine M Sambles<sup>140</sup> [**Sequencing and analysis**], David J Studholme<sup>132</sup> [**Sequencing and analysis**], Angie Lackenby<sup>107</sup> [**Sequencing and analysis**], Tamyo Mbisa<sup>107</sup> [**Sequencing and analysis**], Steven Platt<sup>107</sup> [**Sequencing and analysis**], Shahjahan Miah<sup>107</sup> [**Sequencing and analysis**], David Bibby<sup>107</sup> [**Sequencing and analysis**], Carmen Manso<sup>107</sup> [**Sequencing and analysis**], Jonathan Hubb<sup>107</sup> [**Sequencing and analysis**], Gavin Dabrera<sup>107</sup> [**Sequencing and analysis**], Mary Ramsay<sup>107</sup> [**Sequencing and analysis**], Daniel Bradshaw<sup>107</sup> [**Sequencing and analysis**], Ulf Schaefer<sup>107</sup> [**Sequencing and analysis**], Natalie Groves<sup>107</sup> [**Sequencing and analysis**], Eileen Gallagher<sup>107</sup> [**Sequencing and analysis**], David Lee<sup>107</sup> [**Sequencing and analysis**], David Williams<sup>107</sup> [**Sequencing and analysis**], Nicholas Ellaby<sup>107</sup> [**Sequencing and analysis**], Hassan Hartman<sup>107</sup> [**Sequencing and analysis**], Nikos Manesis<sup>107</sup> [**Sequencing and analysis**], Vineet Patel<sup>107</sup> [**Sequencing and analysis**], Juan Ledesma<sup>140</sup> [**Sequencing and analysis**], Katherine A Twohig<sup>108</sup> [**Sequencing and**

analysis], Elias Allara<sup>140,129</sup> [Sequencing and analysis], Clare Pearson<sup>140,140</sup> [Sequencing and analysis], Jeffrey K. J. Cheng<sup>135</sup> [Sequencing and analysis], Hannah E Bridgewater<sup>135</sup> [Sequencing and analysis], Lucy R Frost<sup>140</sup> [Sequencing and analysis], Grace Taylor-Joyce<sup>140</sup> [Sequencing and analysis], Paul E Brown<sup>135</sup> [Sequencing and analysis], Lily Tong<sup>89</sup> [Sequencing and analysis], Alice Broos<sup>89</sup> [Sequencing and analysis], Daniel Mair<sup>89</sup> [Sequencing and analysis], Jenna Nichols<sup>140</sup> [Sequencing and analysis], Stephen N Carmichael<sup>140</sup> [Sequencing and analysis], Katherine L Smollett<sup>81</sup> [Sequencing and analysis], Kyriaki Nomikou<sup>140</sup> [Sequencing and analysis], Elihu Aranday-Cortes<sup>89</sup> [Sequencing and analysis], Natasha Johnson<sup>89</sup> [Sequencing and analysis], Seema Nickbakhsh<sup>140,140</sup> [Sequencing and analysis], Edith E Vamos<sup>133</sup> [Sequencing and analysis], Margaret Hughes<sup>133</sup> [Sequencing and analysis], Lucille Rainbow<sup>133</sup> [Sequencing and analysis], Richard Eccles<sup>133</sup> [Sequencing and analysis], Charlotte Nelson<sup>133</sup> [Sequencing and analysis], Mark Whitehead<sup>133</sup> [Sequencing and analysis], Richard Gregory<sup>133</sup> [Sequencing and analysis], Matthew Gemmell<sup>133</sup> [Sequencing and analysis], Claudia Wierzbicki<sup>140</sup> [Sequencing and analysis], Hermione J Webster<sup>140</sup> [Sequencing and analysis], Chloe L Fisher<sup>140</sup> [Sequencing and analysis], Adrian W Signell<sup>61</sup> [Sequencing and analysis], Gilberto Betancor<sup>140</sup> [Sequencing and analysis], Harry D Wilson<sup>61</sup> [Sequencing and analysis], Gaia Nebbia<sup>53</sup> [Sequencing and analysis], Flavia Flaviani<sup>140</sup> [Sequencing and analysis], Alberto C Cerda<sup>140</sup> [Sequencing and analysis], Tammy V Merrill<sup>140</sup> [Sequencing and analysis], Rebekah E Wilson<sup>137</sup> [Sequencing and analysis], Marius Cotic<sup>123</sup> [Sequencing and analysis], Nadua Bayzid<sup>123</sup> [Sequencing and analysis], Thomas Thompson<sup>113</sup> [Sequencing and analysis], Erwan Acheson<sup>113</sup> [Sequencing and analysis], Steven Rushton<sup>140</sup> [Sequencing and analysis], Sarah O'Brien<sup>140</sup> [Sequencing and analysis], David J Baker<sup>111</sup> [Sequencing and analysis], Steven Rudder<sup>111</sup> [Sequencing and analysis], Alp Aydin<sup>111</sup> [Sequencing and analysis], Fei Sang<sup>59</sup> [Sequencing and analysis], Johnny Debebe<sup>59</sup> [Sequencing and analysis], Sarah Francois<sup>140</sup> [Sequencing and analysis], Tetyana I Vasylyeva<sup>140</sup> [Sequencing and analysis], Marina Escalera Zamudio<sup>64</sup> [Sequencing and analysis], Bernardo Gutierrez<sup>64</sup> [Sequencing and analysis], Angela Marchbank<sup>51</sup> [Sequencing and analysis], Joshua Maksimovic<sup>50</sup> [Sequencing and analysis], Karla Spellman<sup>50</sup> [Sequencing and analysis], Kathryn McCluggage<sup>50</sup> [Sequencing and analysis], Mari Morgan<sup>110</sup> [Sequencing and analysis], Robert Beer<sup>50</sup> [Sequencing and analysis], Safiah Affi<sup>50</sup> [Sequencing and analysis], Trudy Workman<sup>51</sup> [Sequencing and analysis], William Fuller<sup>51</sup> [Sequencing and analysis], Catherine Bresner<sup>51</sup> [Sequencing and analysis], Adrienn Angyal<sup>140</sup> [Sequencing and analysis], Luke R Green<sup>140</sup> [Sequencing and analysis], Paul J Parsons<sup>140</sup> [Sequencing and analysis], Rachel M Tucker<sup>134</sup> [Sequencing and analysis], Rebecca Brown<sup>134</sup> [Sequencing and analysis], Max Whiteley<sup>134</sup> [Sequencing and analysis], James Bonfield<sup>140</sup> [Software and analysis tools], Christoph Puehe<sup>140</sup> [Software and analysis tools], Andrew Whitwham<sup>140</sup> [Software and analysis tools], Jennifer Liddle<sup>140</sup> [Software and analysis tools],

Will Rowe<sup>82</sup> [Software and analysis tools], Igor Siveroni<sup>140</sup> [Software and analysis tools], Thanh Le-Viet<sup>140</sup> [Software and analysis tools], Amy Gaskin<sup>110</sup> [Software and analysis tools], Rob Johnson<sup>80</sup> [Visualisation]

## Affiliations

<sup>19</sup>Cambridge Clinical Research Centre, NIHR Clinical Research Facility, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>20</sup>Department of Haematology, University of Cambridge, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>21</sup>Australian National Phenome Centre, Murdoch University, Murdoch, Western Australia WA 6150, Australia <sup>22</sup>MRC Toxicology Unit, School of Biological Sciences, University of Cambridge, Cambridge CB2 1QR, UK <sup>23</sup>R&D Department, Hycult Biotech, 5405 PD Uden, The Netherlands <sup>24</sup>Heart and Lung Research Institute, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>25</sup>Royal Papworth Hospital NHS Foundation Trust, Cambridge Biomedical Campus, Cambridge CB2 0QQ, UK <sup>26</sup>Department of Biomedicine, University and University Hospital Basel, 4031 Basel, Switzerland <sup>27</sup>Botnar Research Centre for Child Health (BRCC) University Basel & ETH Zurich, 4058 Basel, Switzerland <sup>28</sup>Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>29</sup>Department of Veterinary Medicine, Madingley Road, Cambridge, CB3 0ES, UK <sup>30</sup>Cambridge Institute for Medical Research, Cambridge Biomedical Campus, Cambridge CB2 0XY, UK <sup>31</sup>Cancer Research UK, Cambridge Institute, University of Cambridge CB2 0RE, UK <sup>32</sup>Department of Obstetrics & Gynaecology, The Rosie Maternity Hospital, Robinson Way, Cambridge CB2 0SW, UK <sup>33</sup>Centre for Molecular Medicine and Innovative Therapeutics, Health Futures Institute, Murdoch University, Perth, WA, Australia <sup>34</sup>Cambridge and Peterborough Foundation Trust, Fulbourn Hospital, Fulbourn, Cambridge CB21 5EF, UK <sup>35</sup>Department of Surgery, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK <sup>36</sup>Department of Biochemistry, University of Cambridge, Cambridge, CB2 1QW, UK <sup>37</sup>Centre of Computational and Systems Medicine, Health Futures Institute, Murdoch University, Harry Perkins Building, Perth, WA 6150, Australia <sup>38</sup>Department of Public Health and Primary Care, School of Clinical Medicine, University of Cambridge, Cambridge Biomedical Campus, Cambridge, UK <sup>39</sup>Cancer Molecular Diagnostics Laboratory, Department of Oncology, University of Cambridge, Cambridge CB2 0AH, UK <sup>40</sup>Metabolic Research Laboratories, Wellcome Trust-Medical Research Council Institute of Metabolic Science, University of Cambridge, Cambridge CB2 0QQ, UK <sup>41</sup>Department of Paediatrics, University of Cambridge, Cambridge Biomedical Campus, Cambridge, CB2 0QQ, UK

<sup>42</sup>Barking, Havering and Redbridge University Hospitals NHS Trust, Barking, United Kingdom <sup>43</sup>Basingstoke Hospital, Basingstoke, United Kingdom <sup>44</sup>Belfast Health & Social Care Trust, Belfast, United Kingdom <sup>45</sup>Betsi Cadwaladr University Health Board, Betsi Cadwaladr, United Kingdom <sup>46</sup>Big Data Institute, Nuffield Department of Medicine, University of Oxford, Oxford, United Kingdom <sup>47</sup>Brighton and Sussex University Hospitals NHS Trust, Brighton & Sussex, United Kingdom <sup>48</sup>Cambridge Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom

<sup>49</sup>Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom <sup>50</sup>Cardiff and Vale University Health Board, Cardiff, United Kingdom <sup>51</sup>Cardiff University, Cardiff, United Kingdom <sup>52</sup>Centre for Clinical Infection & Diagnostics Research, St. Thomas' Hospital and Kings College London, London, United Kingdom <sup>53</sup>Centre for Clinical Infection and Diagnostics Research, Department of Infectious Diseases, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom <sup>54</sup>Centre for Enzyme Innovation, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>55</sup>Centre for Genomic Pathogen Surveillance, University of Oxford, Oxford, United Kingdom <sup>56</sup>Clinical Microbiology Department, Queens Medical Centre, Nottingham, United Kingdom <sup>57</sup>Clinical Microbiology, University Hospitals of Leicester NHS Trust, Leicester, United Kingdom <sup>58</sup>County Durham and Darlington NHS Foundation Trust, Durham, United Kingdom <sup>59</sup>Deep Seq, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, United Kingdom <sup>60</sup>Department of Infection Biology, Faculty of Infectious & Tropical Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom <sup>61</sup>Department of Infectious Diseases, King's College London, London, United Kingdom <sup>62</sup>Department of Microbiology, Kettering General Hospital, Kettering, United Kingdom <sup>63</sup>Departments of Infectious Diseases and Microbiology, Cambridge University Hospitals NHS Foundation Trust; Cambridge, UK, Cambridge, United Kingdom <sup>64</sup>Department of Zoology, University of Oxford, Oxford, United Kingdom <sup>65</sup>Division of Virology, Department of Pathology, University of Cambridge, Cambridge, United Kingdom <sup>66</sup>East Kent Hospitals University NHS Foundation Trust, Kent, United Kingdom <sup>67</sup>East Suffolk and North Essex NHS Foundation Trust, Suffolk, United Kingdom <sup>68</sup>Gateshead Health NHS Foundation Trust, Gateshead, United Kingdom <sup>69</sup>Genomics Innovation Unit, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom <sup>70</sup>Gloucestershire Hospitals NHS Foundation Trust, Gloucester, United Kingdom <sup>71</sup>Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom <sup>72</sup>Guy's and St. Thomas' BRC, London, United Kingdom <sup>73</sup>Guy's and St. Thomas' Hospitals, London, United Kingdom <sup>74</sup>Hampshire Hospitals NHS Foundation Trust, Hampshire, United Kingdom <sup>75</sup>Health Data Research UK Cambridge, Cambridge, United Kingdom <sup>76</sup>Health Services Laboratories, London, United Kingdom <sup>77</sup>Heartlands Hospital, Birmingham, Birmingham, United Kingdom <sup>78</sup>Hub for Biotechnology in the Built Environment, Northumbria University, Northumbria, United Kingdom <sup>79</sup>Imperial College Hospitals NHS Trust, London, United Kingdom <sup>80</sup>Imperial College London, London, United Kingdom <sup>81</sup>Institute of Biodiversity, Animal Health & Comparative Medicine, Glasgow, United Kingdom <sup>82</sup>Institute of Microbiology and Infection, University of Birmingham, Birmingham, United Kingdom <sup>83</sup>King's College London, London, United Kingdom <sup>84</sup>Liverpool Clinical Laboratories, Liverpool, United Kingdom <sup>85</sup>Maidstone and Tunbridge Wells NHS Trust, Maidstone, United Kingdom <sup>86</sup>Manchester University NHS Foundation Trust, Manchester, United Kingdom <sup>87</sup>Microbiology Department, Wye Valley NHS Trust, Hereford, United Kingdom <sup>88</sup>MRC Biostatistics Unit, University of Cambridge, Cambridge, United Kingdom <sup>89</sup>MRC-University of Glasgow Centre for Virus Research, Glasgow, United Kingdom

<sup>90</sup>National Infection Service, PHE and Leeds Teaching Hospitals Trust, Leeds, United Kingdom <sup>91</sup>Newcastle Hospitals NHS Foundation Trust, Newcastle, United Kingdom <sup>92</sup>Newcastle University, Newcastle, United Kingdom <sup>93</sup>NHS Greater Glasgow and Clyde, Glasgow, United Kingdom <sup>94</sup>NHS Lothian, Edinburgh, United Kingdom <sup>95</sup>Norfolk and Norwich University Hospital, Norfolk, United Kingdom <sup>96</sup>Norfolk County Council, Norfolk, United Kingdom <sup>97</sup>North Cumbria Integrated Care NHS Foundation Trust, Carlisle, United Kingdom <sup>98</sup>North Tees and Hartlepool NHS Foundation Trust, Stockton-on-Tees, United Kingdom <sup>99</sup>Northumbria University, Northumbria, United Kingdom <sup>100</sup>Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom <sup>101</sup>PathLinks, Northern Lincolnshire & Goole NHS Foundation Trust, Lincolnshire, United Kingdom <sup>102</sup>Portsmouth Hospitals University NHS Trust, Portsmouth, United Kingdom <sup>103</sup>Princess Alexandra Hospital Microbiology Dept., Harlow, United Kingdom <sup>104</sup>Public Health Agency, London, United Kingdom <sup>105</sup>Public Health England, London, United Kingdom <sup>106</sup>Public Health England, Clinical Microbiology and Public Health Laboratory, Cambridge, United Kingdom <sup>107</sup>Public Health England, Colindale, London, United Kingdom <sup>108</sup>Public Health England, Colindale, London, United Kingdom <sup>109</sup>Public Health Scotland, Glasgow, United Kingdom <sup>110</sup>Public Health Wales NHS Trust, Cardiff, United Kingdom <sup>111</sup>Quadram Institute Bioscience, Norwich, United Kingdom <sup>112</sup>Queen Elizabeth Hospital, Birmingham, United Kingdom <sup>113</sup>Queen's University Belfast, Belfast, United Kingdom <sup>114</sup>Royal Devon and Exeter NHS Foundation Trust, Devon, United Kingdom <sup>115</sup>Royal Free NHS Trust, London, United Kingdom <sup>116</sup>Sandwell and West Birmingham NHS Trust, Sandwell, United Kingdom <sup>117</sup>School of Biological Sciences, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>118</sup>School of Pharmacy and Biomedical Sciences, University of Portsmouth (PORT), Portsmouth, United Kingdom <sup>119</sup>Sheffield Teaching Hospitals, Sheffield, United Kingdom <sup>120</sup>South Tees Hospitals NHS Foundation Trust, Newcastle, United Kingdom <sup>121</sup>Swansea University, Swansea, United Kingdom <sup>122</sup>University Hospitals Southampton NHS Foundation Trust, Southampton, United Kingdom <sup>123</sup>University College London, London, United Kingdom <sup>124</sup>University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom <sup>125</sup>University Hospitals Coventry and Warwickshire, Coventry, United Kingdom <sup>126</sup>University of Birmingham, Birmingham, United Kingdom <sup>127</sup>University of Birmingham Turnkey Laboratory, Birmingham, United Kingdom <sup>128</sup>University of Brighton, Brighton, United Kingdom <sup>129</sup>University of Cambridge, Cambridge, United Kingdom <sup>130</sup>University of East Anglia, East Anglia, United Kingdom <sup>131</sup>University of Edinburgh, Edinburgh, United Kingdom <sup>132</sup>University of Exeter, Exeter, United Kingdom <sup>133</sup>University of Liverpool, Liverpool, United Kingdom <sup>134</sup>University of Sheffield, Sheffield, United Kingdom <sup>135</sup>University of Warwick, Warwick, United Kingdom <sup>136</sup>University of Cambridge, Cambridge, United Kingdom <sup>137</sup>Viapath, Guy's and St Thomas' NHS Foundation Trust, and King's College Hospital NHS Foundation Trust, London, United Kingdom <sup>138</sup>Virology, School of Life Sciences, Queens Medical Centre, University of Nottingham, Nottingham, United Kingdom <sup>139</sup>Wellcome Centre for Human Genetics, Nuffield Department of Medicine,

University of Oxford, Oxford, United Kingdom <sup>140</sup>Wellcome Sanger Institute, London, United Kingdom <sup>141</sup>West of Scotland Specialist Virology Centre, NHS Greater Glasgow and Clyde, Glasgow, United Kingdom <sup>142</sup>Department of Medicine, University of Cambridge, Cambridge, United Kingdom <sup>143</sup>Ministry of Health, Colombo, Sri Lanka <sup>144</sup>NIHR Health Protection Research Unit in HCAI and AMR, Imperial College London, London, United Kingdom <sup>145</sup>North West London Pathology, London, United Kingdom <sup>146</sup>NU-OMICS, Northumbria University, Northumbria, United Kingdom <sup>147</sup>University of Kent, Kent, United Kingdom <sup>148</sup>University of Oxford, Oxford, United Kingdom <sup>149</sup>University of Southampton, Southampton, United Kingdom <sup>150</sup>University of Southampton School of Health Sciences, Southampton, United Kingdom <sup>151</sup>University of Southampton School of Medicine, Southampton, United Kingdom <sup>152</sup>University of Surrey, Guildford, United Kingdom <sup>153</sup>Warwick Medical School and Institute of Precision Diagnostics, Pathology, UHCW NHS Trust, Warwick, United Kingdom

<sup>1</sup>Division of Infection and Immunity, University College London, London, UK <sup>2</sup> Cambridge Institute of Therapeutic Immunology & Infectious Disease (CITIID), Cambridge, UK <sup>3</sup>Department of Medicine, University of Cambridge, Cambridge, UK <sup>4</sup>Department of Infectious Diseases, Cambridge University NHS Hospitals Foundation Trust, Cambridge, UK <sup>5</sup>Department of Pathology, University of Cambridge, Cambridge <sup>6</sup> NHS Blood and Transplant, Oxford and BRC Haematology Theme, University of Oxford, UK <sup>7</sup>Viral Pseudotype Unit, Medway School of Pharmacy, University of Kent, UK <sup>8</sup>Medical Research Council Laboratory of Molecular Biology, Cambridge, UK <sup>9</sup>Department of Medical Microbiology, Academic Medical Center, University of Amsterdam, Amsterdam Institute for Infection and Immunity, Amsterdam, Netherlands <sup>10</sup> NIHR Cambridge Clinical Research Facility, Cambridge, UK <sup>11</sup>Department of Virology, Cambridge University NHS Hospitals Foundation Trust <sup>12</sup>Department of Applied Mathematics and Theoretical Physics, University of Cambridge, UK <sup>13</sup> Department of Clinical Biochemistry and Immunology, Addenbrookes Hospital <sup>14</sup> FES-Cuautitlán, UNAM, Mexico <sup>15</sup>Biochemistry and Molecular Genetics, University of Colorado School of Medicine, Aurora, Colorado, USA; <sup>16</sup>Clinical Microbiology and Public Health Laboratory, Addenbrookes' Hospital, Cambridge, UK <sup>17</sup> MRC Biostatistics Unit, University of Cambridge, Cambridge, UK <sup>18</sup>Africa Health Research Institute, Durban, South Africa

## Acknowledgements

We are immensely grateful to the patient and his family. We would also like to thank the staff at CUH and the NIHR Cambridge Clinical Research Facility. We would like to thank Dr Ruthiran Kugathanan and Professor Wendy Barclay for helpful discussions and Dr Martin Curran, Dr William Hamilton, and Dr. Dominic Sparkes. We would like to thank Prof Andres Floto and Prof Ferdia Gallagher. We thank Dr James Voss for the kind gift of HeLa cells stably expressing ACE2. We would like to thank James Nathan for RBD protein and Leo James for N protein. COG-UK is supported by funding from the Medical Research Council (MRC) part of UK Research & Innovation (UKRI), the National Institute of Health Research (NIHR) and Genome Research Limited, operating as the Wellcome Sanger Institute. RKG is supported by a Wellcome Trust Senior Fellowship in Clinical Science (WT108082AIA). LEM is supported by a Medical Research Council Career Development Award (MR/R008698/1).

SAK is supported by the Bill and Melinda Gates Foundation via PANGEA grant: OPP1175094. DAC is supported by a Wellcome Trust Clinical PhD Research Fellowship. CJRI acknowledges MRC funding (ref: MC\_UU\_00002/11). This research was supported by the National Institute for Health Research (NIHR) Cambridge Biomedical Research Centre, the Cambridge Clinical Trials Unit (CCTU) and by the UCL Coronavirus Response Fund and made possible through generous donations from UCL's supporters, alumni, and friends (LEM). JAGB is supported by the Medical Research Council (MC\_UP\_1201/16). IG is a Wellcome Senior Fellow and supported by the Wellcome Trust (207498/Z/17/Z). DDP is supported by NIH GM083127.

## Data Availability

Long-read sequencing data that support the findings of this study have been deposited in the NCBI SRA database with the accession codes SAMN16976824 - SAMN16976846 under BioProject PRJNA682013 (<https://www.ncbi.nlm.nih.gov/bioproject/PRJNA682013>). Short reads and data used to construct figures were deposited at [https://github.com/Steven-Kemp/sequence\\_files](https://github.com/Steven-Kemp/sequence_files). All data are also available from the corresponding author.

## Code Availability

The SAMFIRE package Version 1.06 was used for filtering and calling variants from the Illumina data. It is available at <https://github.com/cjri/samfire/> for review. Additional code was used to validate the variant frequencies and can be found at <https://github.com/PollockLaboratory/AnCovMulti>.

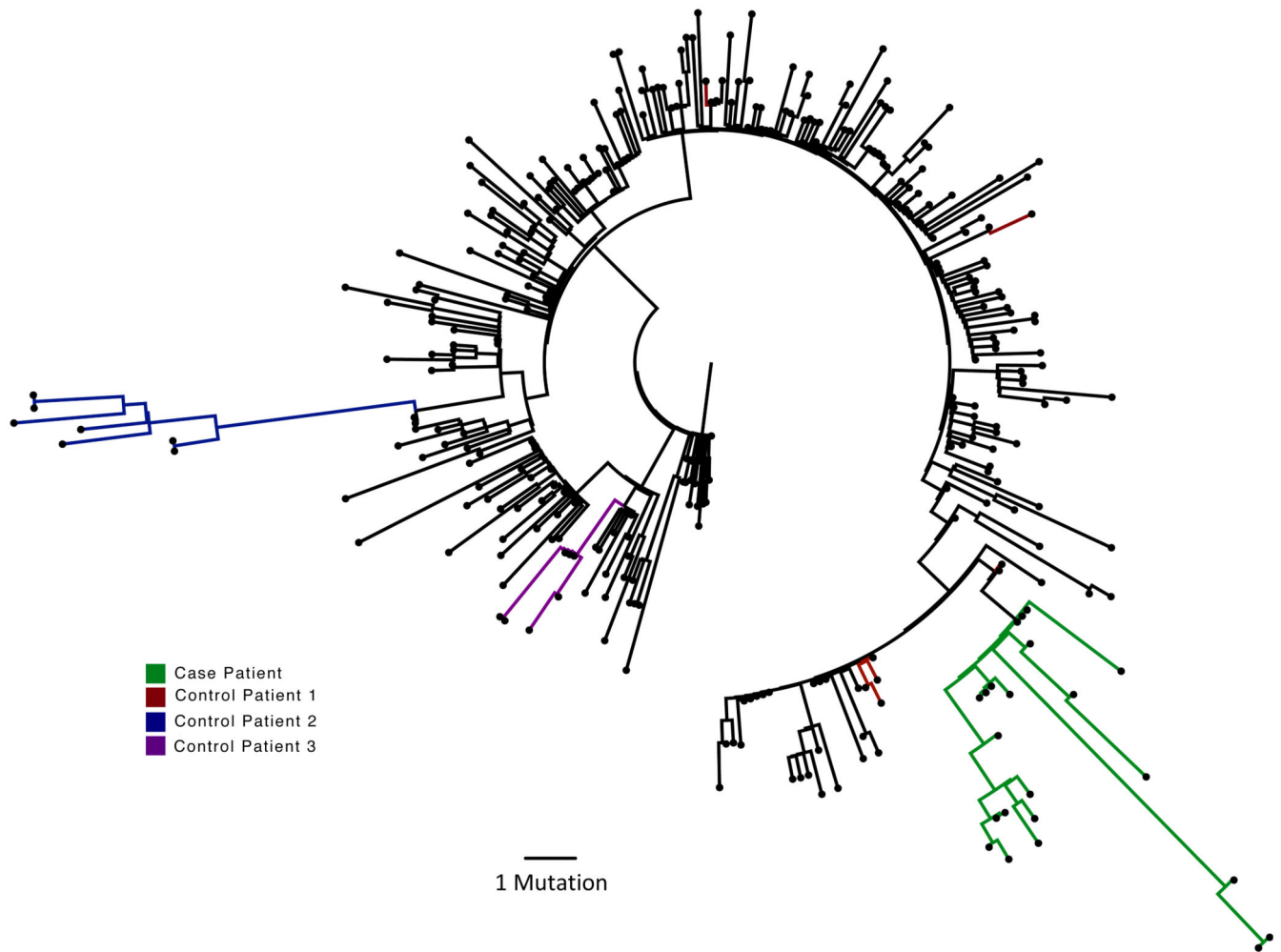
## References

- Hoffmann M, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020; 181:271–280 e278. DOI: 10.1016/j.cell.2020.02.052 [PubMed: 32142651]
- Kim KW, et al. Respiratory viral co-infections among SARS-CoV-2 cases confirmed by virome capture sequencing. 2020
- Bull RA, et al. Analytical validity of nanopore sequencing for rapid SARS-CoV-2 genome analysis. *Nat Commun*. 2020; 11:6272.doi: 10.1038/s41467-020-20075-6 [PubMed: 33298935]
- Choi B, et al. Persistence and Evolution of SARS-CoV-2 in an Immunocompromised Host. *The New England journal of medicine*. 2020; 383:2291–2293. DOI: 10.1056/NEJMc2031364 [PubMed: 33176080]
- Avanzato VA, et al. Case Study: Prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised cancer patient. *Cell*. 2020
- Starr TN, et al. Deep Mutational Scanning of SARS-CoV-2 Receptor Binding Domain Reveals Constraints on Folding and ACE2 Binding. *Cell*. 2020; 182:1295–1310 e1220. DOI: 10.1016/j.cell.2020.08.012 [PubMed: 32841599]
- Rambaut ALN, Pybus O, Barclay W, Carabelli AC, Connor T, Peacock T, Robertson DL, Volz E, COVID-19 Genomics Consortium UK (CoG-UK). Preliminary genomic characterisation of an emergent SARS-CoV-2 lineage in the UK defined by a novel set of spike mutations. 2020
- Schmidt F, et al. Measuring SARS-CoV-2 neutralizing antibody activity using pseudotyped and chimeric viruses. *bioRxiv*. 2020; doi: 10.1101/2020.06.08.140871
- Brouwer PJM, et al. Potent neutralizing antibodies from COVID-19 patients define multiple targets of vulnerability. *Science*. 2020; 369:643–650. DOI: 10.1126/science.abc5902 [PubMed: 32540902]
- Zussman ME, Bagby M, Benson DW, Gupta R, Hirsch R. Pulmonary vascular resistance in repaired congenital diaphragmatic hernia vs. age-matched controls. *Pediatr Res*. 2012; 71:697–700. DOI: 10.1038/pr.2012.16 [PubMed: 22456633]
- Cai Y, et al. Distinct conformational states of SARS-CoV-2 spike protein. *Science*. 2020; doi: 10.1126/science.abd4251

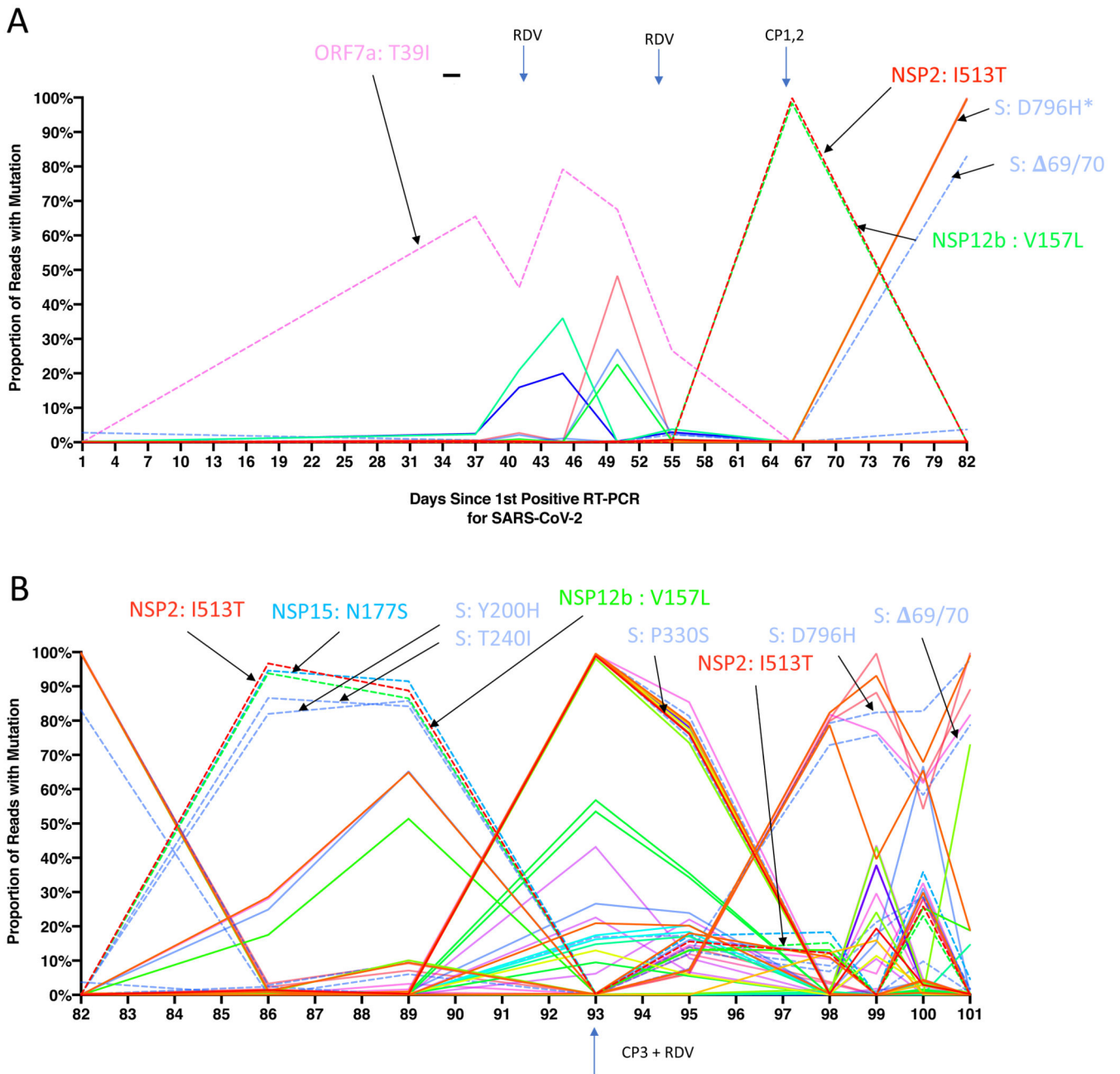
12. Zhou T, et al. Cryo-EM Structures of SARS-CoV-2 Spike without and with ACE2 Reveal a pH-Dependent Switch to Mediate Endosomal Positioning of Receptor-Binding Domains. *Cell Host & Microbe*. 2020; 28:867–879.e865. DOI: 10.1016/j.chom.2020.11.004 [PubMed: 33271067]
13. Robbiani DF, et al. Convergent antibody responses to SARS-CoV-2 in convalescent individuals. *Nature*. 2020; 584:437–442. DOI: 10.1038/s41586-020-2456-9 [PubMed: 32555388]
14. Barnes CO, et al. Structures of Human Antibodies Bound to SARS-CoV-2 Spike Reveal Common Epitopes and Recurrent Features of Antibodies. *Cell*. 2020; 182:828–842.e816. DOI: 10.1016/j.cell.2020.06.025 [PubMed: 32645326]
15. Shrock E, et al. Viral epitope profiling of COVID-19 patients reveals cross-reactivity and correlates of severity. *Science*. 2020; doi: 10.1126/science.abd4250
16. Sobel Leonard A, et al. The effective rate of influenza reassortment is limited during human infection. *PLoS Pathog*. 2017; 13:e1006203. doi: 10.1371/journal.ppat.1006203 [PubMed: 28170438]
17. Richard M, Herfst S, Tao H, Jacobs NT, Lowen AC. Influenza A Virus Reassortment Is Limited by Anatomical Compartmentalization following Coinfection via Distinct Routes. *J Virol*. 2018; 92:doi: 10.1128/JVI.02063-17
18. Kemp S, et al. Recurrent emergence and transmission of a SARS-CoV-2 Spike deletion H69/V70. *bioRxiv*. 2021; doi: 10.1101/2020.12.14.422555
19. CDC. Discontinuation of Transmission-Based Precautions and Disposition of Patients with COVID-19 in Healthcare Settings (Interim Guidance). 2020. <<https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html>>
20. Boshier FAT, et al. Remdesivir induced viral RNA and subgenomic RNA suppression, and evolution of viral variants in SARS-CoV-2 infected patients. *medRxiv*. 2020; doi: 10.1101/2020.11.18.20230599
21. Simonovich VA, et al. A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia. *N Engl J Med*. 2020; doi: 10.1056/NEJMoa2031304
22. Meredith LW, et al. Rapid implementation of SARS-CoV-2 sequencing to investigate cases of health-care associated COVID-19: a prospective genomic surveillance study. *The Lancet Infectious Diseases*. 2020; 20:1263–1272. DOI: 10.1016/S1473-3099(20)30562-4 [PubMed: 32679081]
23. Collier DA, et al. Point of Care Nucleic Acid Testing for SARS-CoV-2 in Hospitalized Patients: A Clinical Validation Trial and Implementation Study. *Cell Rep Med*. 2020; doi: 10.1016/j.xcrm.2020.100062
24. Loman N, Rowe W, Rambaut A. 2020
25. Martin M. Cutadapt removes adapter sequences from high-throughput sequencing reads. *EMBnet journal*. 2011; 17:10–12.
26. Li H. Minimap2: pairwise alignment for nucleotide sequences. *Bioinformatics (Oxford, England)*. 2018; 34:3094–3100. DOI: 10.1093/bioinformatics/bty191
27. Jordan MR, et al. Comparison of standard PCR/cloning to single genome sequencing for analysis of HIV-1 populations. *J Virol Methods*. 2010; 168:114–120. DOI: 10.1016/j.jviromet.2010.04.030 [PubMed: 20451557]
28. Palmer S, et al. Multiple, linked human immunodeficiency virus type 1 drug resistance mutations in treatment-experienced patients are missed by standard genotype analysis. *Journal of clinical microbiology*. 2005; 43:406–413. DOI: 10.1128/JCM.43.1.406-413.2005 [PubMed: 15635002]
29. Keele BF, et al. Identification and characterization of transmitted and early founder virus envelopes in primary HIV-1 infection. *Proceedings of the National Academy of Sciences of the United States of America*. 2008; 105:7552–7557. [PubMed: 18490657]
30. Shu Y, McCauley J. GISAID: Global initiative on sharing all influenza data - from vision to reality. *Euro surveillance: bulletin European sur les maladies transmissibles = European communicable disease bulletin*. 2017; 22:30494. doi: 10.2807/1560-7917.ES.2017.22.13.30494 [PubMed: 28382917]
31. Katoh K, Standley DM. MAFFT Multiple Sequence Alignment Software Version-7-Improvements in Performance and Usability. *Molecular Biology and Evolution*. 2013; 30:772–780. DOI: 10.1093/molbev/mst010 [PubMed: 23329690]



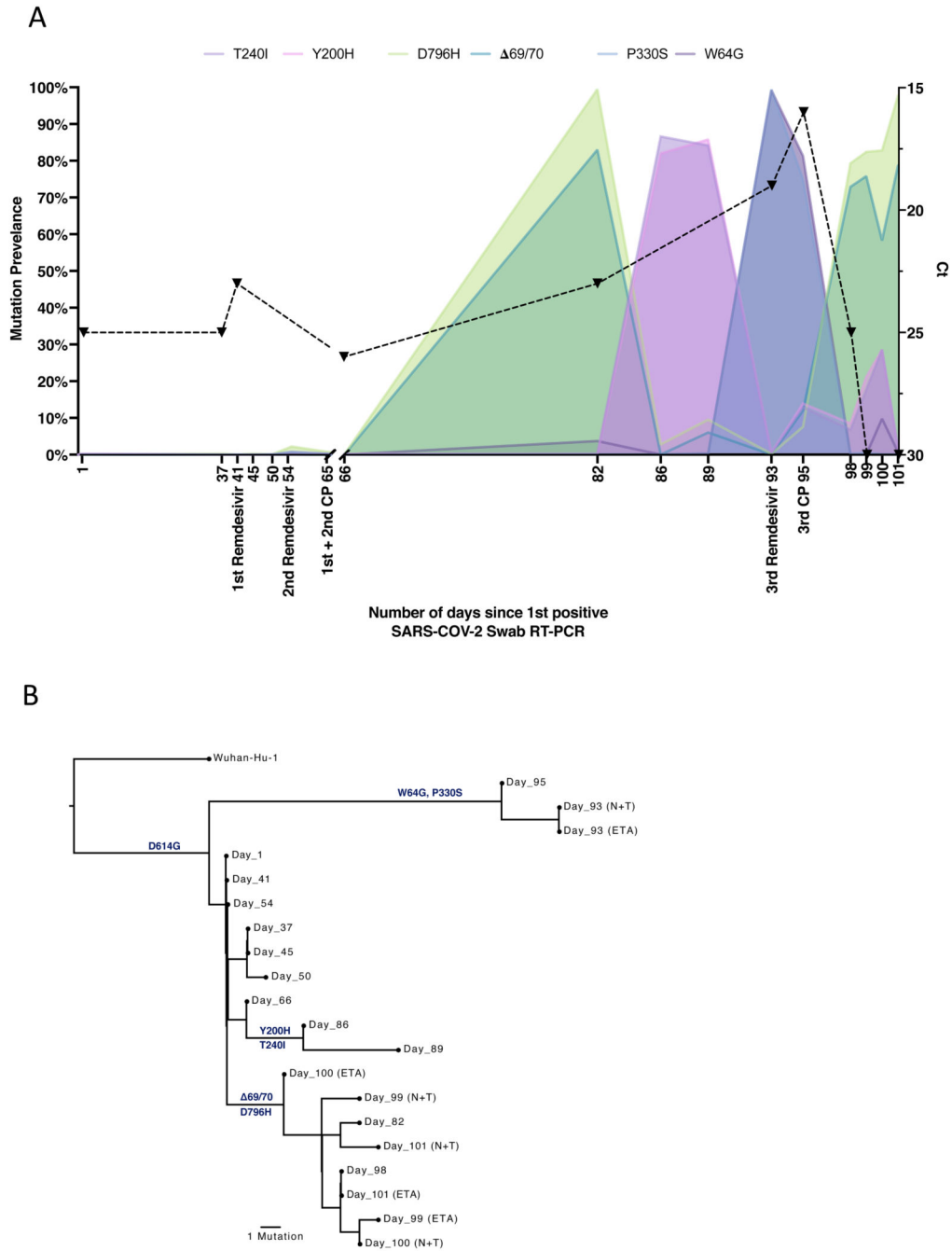
32. Rambaut A, et al. A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nature Microbiology*. 2020; 5:1403–1407. DOI: 10.1038/s41564-020-0770-5
33. Minh BQ, et al. IQ-TREE 2: New Models and Efficient Methods for Phylogenetic Inference in the Genomic Era. *Molecular Biology and Evolution*. 2020; 37:1530–1534. DOI: 10.1093/molbev/msaa015 [PubMed: 32011700]
34. Kalyaanamoorthy S, Minh BQ, Wong TKF, von Haeseler A, Jermini LS. ModelFinder: fast model selection for accurate phylogenetic estimates. *Nature Methods*. 2017; 14:587–589. DOI: 10.1038/nmeth.4285 [PubMed: 28481363]
35. Minh BQ, Nguyen MA, von Haeseler A. Ultrafast approximation for phylogenetic bootstrap. *Mol Biol Evol*. 2013; 30:1188–1195. DOI: 10.1093/molbev/mst024 [PubMed: 23418397]
36. Illingworth CJ. SAMFIRE: multi-locus variant calling for time-resolved sequence data. *Bioinformatics*. 2016; 32:2208–2209. DOI: 10.1093/bioinformatics/btw205 [PubMed: 27153641]
37. Lumby CK, Zhao L, Breuer J, Illingworth CJ. A large effective population size for established within-host influenza virus infection. *Elife*. 2020; 9doi: 10.7554/eLife.56915
38. Martin DP, Murrell B, Golden M, Khoosal A, Muhire B. RDP4: Detection and analysis of recombination patterns in virus genomes. *Virus evolution*. 2015; 1
39. Didelot X, Wilson DJ. ClonalFrameML: efficient inference of recombination in whole bacterial genomes. *PLoS Comput Biol*. 2015; 11:e1004041. [PubMed: 25675341]
40. Wrobel AG, et al. SARS-CoV-2 and bat RaTG13 spike glycoprotein structures inform on virus evolution and furin-cleavage effects. *Nature Structural & Molecular Biology*. 2020; 27:763–767. DOI: 10.1038/s41594-020-0468-7
41. Gregson J, et al. HIV-1 viral load is elevated in individuals with reverse transcriptase mutation M184V/I during virological failure of first line antiretroviral therapy and is associated with compensatory mutation L74I. *Journal of Infectious Diseases*. 2019
42. Naldini L, Blomer U, Gage FH, Trono D, Verma IM. Efficient transfer, integration, and sustained long-term expression of the transgene in adult rat brains injected with a lentiviral vector. *Proc Natl Acad Sci U S A*. 1996; 93:11382–11388. DOI: 10.1073/pnas.93.21.11382 [PubMed: 8876144]
43. Gupta RK, et al. Full length HIV-1 gag determines protease inhibitor susceptibility within in vitro assays. *AIDS*. 2010; 24:1651. [PubMed: 20597164]
44. Vermeire J, et al. Quantification of reverse transcriptase activity by real-time PCR as a fast and accurate method for titration of HIV, lenti- and retroviral vectors. *PloS one*. 2012; 7:e50859–e50859. DOI: 10.1371/journal.pone.0050859 [PubMed: 23227216]
45. Milcochova P, et al. Combined point of care nucleic acid and antibody testing for SARS-CoV-2 following emergence of D614G Spike Variant. *Cell Rep Med*. 2020; doi: 10.1016/j.xcrm.2020.100099
46. Seow J, et al. Longitudinal observation and decline of neutralizing antibody responses in the three months following SARS-CoV-2 infection in humans. *Nat Microbiol*. 2020; 5:1598–1607. DOI: 10.1038/s41564-020-00813-8 [PubMed: 33106674]



**Figure 1.** Analysis of 23 Patient derived whole SARS-CoV-2 genome sequences in context of local sequences and other cases of chronic SARS-CoV-2 shedding. Circularised maximum-likelihood phylogenetic tree rooted on the Wuhan-Hu-1 reference sequence, showing a subset of 250 local SARS-CoV-2 genomes from GISAID. This diagram highlights significant diversity of the case patient (green) compared to three other local patients with prolonged shedding (blue, red and purple sequences). All “United Kingdom / English” SARS-CoV-2 genomes were downloaded from the GISAID database and a random subset of 250 selected as background.



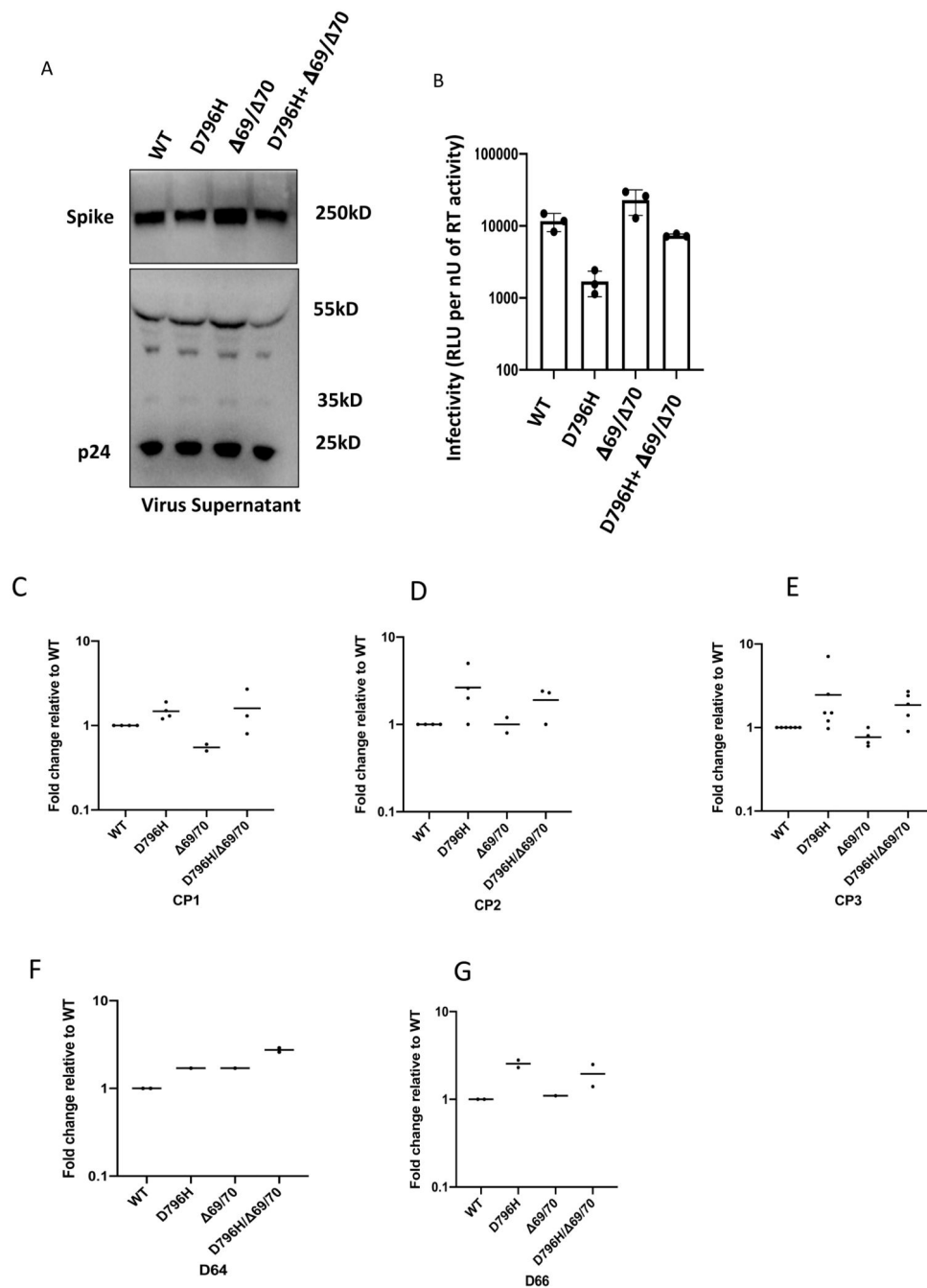
**Figure 2. Whole genome variant trajectories showing amino acids and relationship to treatments.** Data based on Illumina short read ultra deep sequencing at 1000x coverage. Variants shown reached a frequency of at least 10% in at least 2 samples. Treatments indicated are convalescent plasma (CP) and Remdesivir (RDV). Variants described in the text are designated by labels using the same colouring as the position in the genome. Variants labelled are represented by dashed lines. **A.** Variants detected in the patient from days 1-82. \*D796H (light blue) is at the same frequency as NSP3 K902N (orange) therefore it is hidden beneath **B.** Variants detected in the patient from days 82-101.



**Figure 3. Longitudinal variant frequencies and phylogenetic relationships for virus populations bearing six Spike (S) mutations**

**A.** At baseline, all six S variants (Illumina sequencing) except for H69/V70 were absent (<1% and <20 reads). Approximately two weeks after receiving two units of convalescent plasma (CP), viral populations carrying H69/V70 and D796H mutants rose to frequencies >80% but decreased significantly four days later. This population was replaced by a population bearing Y200H and T240I, detected in two samples over a period of 6 days. These viral populations were then replaced by virus carrying W64G and P330S mutations in

Spike, which both dominated at day 93. Following a 3<sup>rd</sup> course of remdesivir and an additional unit of convalescent plasma, the H69/V70 and D796H virus population re-emerged to become the dominant viral strain reaching variant frequencies of >75%. Pairs of mutations arose and disappeared simultaneously indicating linkage on the same viral haplotype. CT values from respiratory samples are indicated on the right y-axis (black dashed line and triangles). Where there were duplicate readings on the same day, to remain consistent, N+T samples were plotted **B**. Maximum likelihood phylogenetic tree of the case patient with day of sampling indicated. Spike mutations defining each of the clades are shown ancestrally on the branches on which they arose. On dates where multiple samples were collect, these are indicated as endotracheal aspirate (ETA) and Nose + throat swabs (N+T).



**Figure 4. Spike mutant D796H + H69/V70 infectivity and sensitivity convalescent plasma (CP).** **A.** western blot of virus pellets after centrifugation of supernatants from cells transfected with lentiviral pseudotyping plasmids including Spike protein. Blots are representative of two independent transfections. **B.** Single round Infectivity of luciferase expressing lentivirus pseudotyped with SARS-CoV-2 Spike protein (WT versus mutant) on 293T cells co-transfected with ACE2 and TMPRSS2 plasmids. Infectivity is corrected for reverse transcriptase activity in virus supernatant as measured by real time PCR. Data points represent technical replicates (n=3) with mean and error bars representing standard error of

mean; data are representative of two independent experiments **C-E**. convalescent plasma (CP units 1-3) neutralization potency against pseudovirus virus bearing Spike mutants D796H, H69/V70 and D796H + H69/V70 **F, G** patient serum neutralisation potency against pseudovirus virus bearing Spike mutants D796H, H69/V70 and D796H + H69/V70. Patient serum was taken at indicated Day (D). Indicated is serum dilution required to inhibit 50% of virus infection (ID50), expressed as fold change relative to WT. Data points represent means of technical replicates and each data point is an independent experiment (n=2-6). Mean of data points in C-G is shown by horizontal bars.