CORONAVIRUS

Vaccine breakthrough hypoxemic COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs

Paul Bastard[1,2,3,4]†, Sara E. Vazquez[5,6,7]†, Jamin Liu[8,9]†, Matthew T. Laurie[8]†, Chung Yu Wang[10]†, Adrian Gervais[1,2]†, Tom Le Voyer[1,2]†, Lucy Bizien[1,2]‡, Colin Zamecnik[11]‡, Quentin Philippot[1,2]‡, Jérémie Rosain[1,2]‡, Emilie Catherinot[12], Andrew Willmore[10], Anthea M. Mitchell[10], Rebecca Bair[11], Pierre Garçon[13], Heather Kenney[14], Arnaud Fekkar[1,2,15], Maria Salagianni[16], Garyphallia Poulakou[17], Eleni Siouti[16], Sabina Sahanic[18], Ivan Tancevski[18], Günter Weiss[18], Laurenz Nagl[19], Jérémy Manry[1,2], Sotirija Duvlis[20,21], Daniel Arroyo-Sánchez[22], Estela Paz Artal[22], Luis Rubio[8], Cristiano Perani[23], Michela Bezzi[24], Alessandra Sottini[25], Virginia Quaresima[25], Lucie Roussel[26,27], Donald C. Vinh[26,27], Luis Felipe Reyes[28,29], Margaux Garzaro[30], Nevin Hatipoglu[31], David Boutboul[32], Yacine Tandjaoui-Lambiotte[33,34,35], Alessandro Borghesi[36], Anna Aliberti[37], Irene Cassaniti[38], Fabienne Venet[39,40,41], Guillaume Monneret[39,40], Rabih Halwani[42,43], Narjes Saheb Sharif-Askari[42], Jeffrey Danielson[14], Sonia Burrel[44], Caroline Morbieu[45], Yurii Stepanovskyy[46], Anastasia Bondarenko[46], Alla Volokha[46], Oksana Boyarchuk[47], Alenka Gagro[48], Mathilde Neuville[49], Bénédicte Neven[50], Sevgi Keles[51], Romain Hernu[52], Antonin Bal[53], Antonio Novelli[54], Giuseppe Novelli[55], Kahina Saker[56], Oana Ailioaie[57], Arnau Antolí[58], Eric Jeziorski[59], Gemma Rocamora-Blanch[58], Carla Teixeira[60], Clarisse Delaunay[61], Marine Lhuillier[62], Paul Le Turnier[61], Yu Zhang[14,63], Matthieu Mahevas[64,65,66], Qiang Pan-Hammarström[67], Hassan Abolhassani[67], Thierry Bompoil[68], Karim Dorgham[69], COVID HGE Consortium§, French COVID Study Group§, COMET Consortium§, Guy Gorochov[69,70], Cédric Laouenan[33,71,72], Carlos Rodríguez-Gallego[73,74], Lisa F. P. Ng[75], Laurent Renia[75,76,77], Aurora Pujol[78], Alexandre Belot[56,79], François Raffi[61], Luis M. Allende[22], Javier Martinez-Picado[80,81,82,83], Tayfun Ozcelik[84], Luisa Imberti[25], Luigi D. Notarangelo[14], Jesus Troya[85], Xavier Solanich[58], Shen-Ying Zhang[1,2,3], Anne Puel[1,2,3], Michael R. Wilson[11], Sophie Trouillet-Assant[86], Laurent Abel[1,2,3], Emmanuelle Jouanguy[1,2,3], Chun Jimmie Ye[10,87,88,89,90]||, Aurélie Cobat[1,2,3]||, Leslie M. Thompson[91]||, Evangelos Andreakos[16]||, Qian Zhang[1,2,3]||, Mark S. Anderson[7,92]*¶, Jean-Laurent Casanova[1,2,3,4,93]*¶, Joseph L. DeRisi[8,10]*¶

Life-threatening "breakthrough" cases of critical COVID-19 are attributed to poor or waning antibody (Ab) response to SARS-CoV-2 vaccines in individuals already at risk. Preexisting auto-Abs neutralizing type I IFNs underlie at least 15% of critical COVID-19 pneumonia cases in unvaccinated individuals; their contribution to hypoxemic breakthrough cases in vaccinated people is unknown. We studied a cohort of 48 individuals (aged 20 to 86 years) who received two doses of a messenger RNA (mRNA) vaccine and developed a breakthrough infection with hypoxemic COVID-19 pneumonia 2 weeks to 4 months later. Ab levels to the vaccine, neutralization of the virus, and auto-Abs to type I IFNs were measured in the plasma. Forty-two individuals had no known deficiency of B cell immunity and a normal Ab response to the vaccine. Among them, 10 (24%) had auto-Abs neutralizing type I IFNs (aged 43 to 86 years). Eight of these 10 patients had auto-Abs neutralizing both IFN-α2 and IFN-ω, whereas two neutralized IFN-ω only. No patient neutralized IFN-β. Seven neutralized type I IFNs at 10 ng/ml and three at 100 pg/ml only. Seven patients neutralized SARS-CoV-2 D614G and Delta efficiently, whereas one patient neutralized Delta slightly less efficiently. Two of the three patients neutralizing only type I IFNs at 100 pg/ml neutralized both D614G and Delta less efficiently. Despite two mRNA vaccine inoculations and the presence of circulating Abs capable of neutralizing SARS-CoV-2, auto-Abs neutralizing type I IFNs may underlie a notable proportion of hypoxemic COVID-19 pneumonia cases, highlighting the importance of this particularly vulnerable population.

INTRODUCTION

Since the start of the coronavirus disease 19 (COVID-19) pandemic (*1*), caused by severe respiratory syndrome coronavirus 2 (SARS-CoV-2), at least 6 million people have died from COVID-19 (*2*). Although most of the infected individuals recover, it remains important to identify the factors that put patients at greater risk for severe disease. Age is the major epidemiological risk factor of death from pneumonia, the risk doubling every 5 years of age from childhood onward (*3*–*5*). Patients with inborn errors (IEs) of immunity affecting the production of, and/or response to, type I interferons (IFNs) are prone to critical COVID-19 pneumonia (*6*–*12*). These findings established the crucial role of type I IFNs in fending off

SARS-CoV-2 (*13*). Moreover, autoantibodies (auto-Abs) neutralizing high concentrations (10 ng/ml in plasma diluted 1/10) of IFN-α2 and/or IFN-ω were found in at least 10% of individuals with critical COVID-19 (*14*), an observation replicated in various regions of the world (*15*–*33*). Patients with autoimmune polyendocrine syndrome type I (APS-1) harbor these neutralizing auto-Abs from early childhood and are at high risk of life-threatening COVID-19 (*24*, *25*). Moreover, at least 13.6% of unvaccinated patients with critical COVID-19 had auto-Abs neutralizing lower, more physiological concentrations (100 pg/ml in plasma diluted 1/10) of IFN-α2 and/or IFN-ω, whereas auto-Abs neutralizing IFN-β were found in another 1% of patients (*34*). In more than 34,000 uninfected individuals aged 18 to 100 years,

[1]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France. [2]Imagine Institute, University of Paris Cité, Paris, France. [3]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA. [4]Department of Pediatrics, Necker Hospital for Sick Children, AP-HP, Paris, France. [5]Medical Scientist Training Program, University of California, San Francisco, San Francisco, CA 94143, USA. [6]Tetrad Graduate Program, University of California, San Francisco, San Francisco, CA 94143, USA. [7]Diabetes Center, University of California, San Francisco, San Francisco, CA 94143, USA. [8]Department of Biochemistry and Biophysics, University of California, San Francisco, San Francisco, CA 94158, USA. [9]University of California, Berkeley–University of California, San Francisco Graduate Program in Bioengineering, University of California, San Francisco, San Francisco, CA, USA. [10]Chan Zuckerberg Biohub, San Francisco, CA 94158, USA. [11]Weill Institute for Neurosciences, Department of Neurology, University of California, San Francisco, San Francisco, CA, USA. [12]Pneumology Department, Foch Hospital, Suresne, France. [13]Intensive Care Unit, Grand Hôpital de l'Est Francilien Site de Marne-la-Vallée, Jossigny, France. [14]Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. [15]Service de Parasitologie-Mycologie, Groupe Hospitalier Pitié Salpêtrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. [16]Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. [17]3rd Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, "Sotiria" General Hospital of Chest Diseases, Athens, Greece. [18]Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria. [19]Department of Internal Medicine V, Medical University of Innsbruck, Innsbruck, Austria. [20]Faculty of Medical Sciences, University "Goce Delchev", Stip, Republic of North Macedonia. [21]Institute of Public Health, Skopje, Republic of North Macedonia. [22]Department of Immunology, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12) and Department of Immunology, Ophthalmology and ENT, Complutense University School of Medicine, CIBERINFEC, Madrid, Spain. [23]Emergency Room, ASST Spedali Civili di Brescia, Brescia, Italy. [24]Covid Unit, ASST Spedali Civili, Brescia, Italy. [25]CREA Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia, Brescia, Italy. [26]Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, Québec, Canada. [27]Infectious Disease Susceptibility Program, Research Institute-McGill University Health Centre, Montréal, Québec, Canada. [28]Department of Microbiology, Universidad de La Sabana, Chía, Colombia. [29]Department of Critical Care Medicine, Clínica Universidad de La Sabana, Chía, Colombia. [30]Department of Infectious Diseases, Necker Hospital for Sick Children, AP-HP, Paris, France. [31]Pediatric Infectious Diseases Unit, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. [32]Department of Immunology, Saint-Louis Hospital, AP-HP, Paris, France. [33]INSERM UMR 1137 IAME, Paris, France. [34]INSERM UMR 1272 Hypoxie and Poumon, Bobigny, France. [35]Pneumology and Infectiology Department, CH Saint Denis, Saint-Denis, France. [36]Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [37]Anesthesia and Intensive Care, Rianimazione I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [38]Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. [39]Laboratoire d'Immunologie, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France. [40]EA 7426, Pathophysiology of Injury-Induced Immunosuppression, Université Claude Bernard Lyon 1, Hospices Civils de Lyon, Hôpital Edouard Herriot-BioMérieux, Lyon, France. [41]CIRI, INSERM U1111, CNRS, UMR5308, Ecole Normale Supérieure de Lyon, Université Claude Bernard Lyon 1, Lyon, France. [42]Sharjah Institute for Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates. [43]Immunology Research Laboratory, College of Medicine, King Saud University, Riyadh, Saudi Arabia. [44]Sorbonne Université, INSERM U1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique (iPLESP), AP-HP, Hôpital Pitié Salpêtrière, Service de Virologie, Paris, France. [45]Internal Medicine Department, Louis Mourier Hospital, AP-HP, Paris, France. [46]Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. [47]Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. [48]Department of Pediatrics, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Josip Juraj Strossmayer University of Osijek, Medical Faculty Osijek, Osijek, Croatia. [49]Intensive Care Unit, Foch Hospital, Suresnes, France. [50]Department of Pediatrics Hematology Immunology and Rheumatology, Necker Hospital for Sick Children, AP-HP, Paris, France. [51]Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey. [52]Service des Urgences, Groupement Hospitalier Nord, Hospices Civils de Lyon, Lyon, France. [53]Laboratoire de virologie, Institut Agent Infectieux, Groupement Hospitalier Nord, Hospices Civils de Lyon, Lyon, France. [54]Laboratory of Medical Genetics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. [55]Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy. [56]Joint Research Unit, Hospices Civils de Lyon-bio Mérieux, Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France; and International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. [57]Service de Génétique, Hôpital Raymond Poincaré, AP-HP, Garches, France. [58]Department of Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. [59]General Pediatric Department, PCCEI, CeRéMAIA, University of Montpellier, CHU Montpellier, Montpellier, France. [60]Unidade de Infeciologia e Imunodeficiências, Centro Materno-infantil do Norte, Centro Hospitalar Universitário do Porto, Porto, Portugal. [61]Department of Infectious Diseases, CHU Nantes, and INSERM UIC 1413, CHU, Nantes, France. [62]Geriatric Department, CHU Nantes, Hopital Bellier, Nantes, France. [63]NIAID Clinical Genomics Program, NIH, Bethesda, MD, USA. [64]Necker Enfants Malades Institute (INEM), INSERM U1151/CNRS UMR 8253, University of Paris Cité, Paris, France. [65]Departement of Internal Medicine, Henri Mondor University Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris-Est Créteil University (UPEC), Créteil, France. [66]INSERM U955, Team 2, Mondor Biomedical Research Institute (IMRB), Paris-Est Créteil University (UPEC), Créteil, France. [67]Department of Biosciences and Nutrition, Karolinska Institutet, SE14183 Huddinge, Sweden. [68]Biologie/Pathologie, CHU-Nantes–Hôtel Dieu, Institut de Biologie, Nantes, France. [69]Sorbonne Université, Inserm, Centre d'Immunologie et des Maladies Infectieuses, (CIMI-Paris), Paris, France. [70]Département d'Immunologie, Assistance Publique Hôpitaux de Paris (AP-HP), Hôpital Pitié-Salpétrière, Paris, France. [71]Université de Paris, IAME UMR-S 1137, INSERM, Paris, France. [72]Département Epidémiologie Biostatistiques et Recherche Clinique, Hôpital Bichat, AP-HP, Paris, France. [73]Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Canary Islands, Spain. [74]Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. [75]A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore, Singapore. [76]Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore, Singapore. [77]School of Biological Sciences, Nanyang Technology University, Singapore, Singapore. [78]Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, CIBERER U759, and Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain. [79]CNRS UMR 5308, ENS, UCBL, Lyon, France; National Referee Centre for Rheumatic, and Autoimmune and Systemic Diseases in Children (RAISE), Lyon, France; and Immunopathology Federation LIFE, Hospices Civils de Lyon, Lyon, France. [80]IrsiCaixa AIDS Research Institute and Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona, Spain. [81]Infectious Diseases and Immunity, Center for Health and Social Care Research (CESS), Faculty of Medicine, University of Vic-Central University of Catalonia (UVic-UCC), Vic, Spain. [82]Catalan Institution for Research and Advanced Studies (ICREA), Barcelona, Spain. [83]CIBER de Enfermedades Infecciosas, Instituto de Salud Carlos III, Madrid, Spain. [84]Department of Molecular Biology and Genetics, Bilkent University, Ankara, Turkey. [85]Department of Internal Medicine, Infanta Leonor University Hospital, Madrid, Spain. [86]Hospices Civils de Lyon, Lyon, France; and International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. [87]ImmunoX Initiative, University of California, San Francisco, San Francisco, CA 94143, USA. [88]Departments of Epidemiology and Biostatistics and Bioengineering and Therapeutic Sciences, University of California, San Francisco, San Francisco, CA 94143, USA. [89]Bakar Computational Health Sciences Institute, University of California, San Francisco, San Francisco, CA 94143, USA. [90]Parker Institute for Cancer Immunotherapy, San Francisco, CA 94129, USA. [91]Departments of Psychiatry and Human Behavior and Neurobiology and Behavior, University of California, Irvine, Irvine, CA, USA. [92]Division of Endocrinology and Metabolism, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143, USA. [93]Howard Hughes Medical Institute, New York, NY, USA.
*Corresponding author. Email: mark.anderson@ucsf.edu (M.S.A.); jean-laurent.casanova@rockefeller.edu (J.-L.C.); jderisi@gmail.com (J.L.D.)
†These authors contributed equally to this work.
‡These authors contributed equally to this work.
§All collaborators and their affiliations appear at the end of this paper.
||These authors contributed equally to this work.
¶These authors contributed equally to this work.

the prevalence of auto-Abs neutralizing IFN-α2 or IFN-ω at 10 ng/ml (or 100 pg/ml) increased significantly with age, with 0.17% (1.1%) of individuals positive for these auto-Abs under 70 years old and more than 1.4% (4.4%) positive over 70 years old, consistent with the higher risk of life-threatening COVID-19 in the elderly population (*34*). These auto-Abs thus precede infection and are strong determinants of critical disease, only second to age among common risk factors (*35*). The odds ratios (ORs) of critical disease are the highest in individuals with auto-Abs neutralizing both IFN-α2 and IFN-ω (10 ng/ml; OR = 67; $P = 7.8 \times 10^{-13}$) (*34*, *35*).

RNA vaccines are highly effective at protecting against severe COVID-19 pneumonia (*36*, *37*). Despite their efficacy, "breakthrough" cases, i.e., individuals diagnosed with SARS-CoV-2 infection despite being vaccinated with two doses, have been reported worldwide (*38*, *39*). Most breakthrough cases are asymptomatic or mild (*38*), but in rare cases, they are severe, critical, or even fatal (*40*, *41*). It is thought that these severe or critical cases can result from a pathologically deficient (including inherited and acquired deficiencies of adaptive immunity) or a physiologically waning Ab response to the vaccine (especially in aging individuals). Incomplete protection from viral genotypes with vaccine-resilient mutations (such as Delta or Omicron) can also result in insufficient viral neutralization in vivo, in individuals otherwise at risk of hypoxemic pneumonia (for example, due to their age, sex, comorbidity, rare or common genetic variant, or auto-Abs to type I IFNs) (*13*). In other words, breakthrough critical cases are thought to be due to a poor Ab response to the vaccine in at-risk individuals (*42*). However, the human genetic and immunological determinants of critical breakthrough cases remain unclear, especially in patients with normal Ab response to the vaccine. Moreover, the biological and clinical efficacy of RNA vaccines in patients with known genetic or immunological determinants of critical COVID-19 pneumonia, i.e., in patients with IE of, or auto-Abs to, type I IFNs, is not clear. With the COVID Human Genetic Effort (CHGE; www.covidhge.com), we recruited and tested patients with breakthrough COVID-19 and hypoxemic pneumonia. We tested the double hypothesis that some of these breakthrough cases of severe or critical COVID-19 pneumonia may have a normal Ab response to the vaccine and may also harbor auto-Abs to type I IFNs.

RESULTS

Forty-two of 48 patients have normal Ab response to the vaccine

Forty-eight patients who suffered from hypoxemic COVID-19 pneumonia (severe or critical), despite having received two doses of mRNA vaccine at least 2 weeks and up to 16 weeks (mean, 8 weeks) before infection, were recruited from six countries (France, Greece, North Macedonia, Turkey, Ukraine, and United States). All CHGE patients whose samples were available were recruited; they had not been previously infected with SARS-CoV-2, as attested by the clinical information collected and/or a negative serology at the time of vaccination or performed at the onset of disease. These patients were aged 20 to 86 years (mean, 53 years old) and included 34 men and 14 women. Five of them had a known deficiency of B cell immunity [immunosuppressive therapy in three individuals, HIV infection in one individual, and lymphoma with chimeric antigen receptor T cell (CAR-T) treatment in one individual]. We tested the 48 patients for their Ab response to SARS-CoV-2 mRNA vaccines. We found that 1 of the 43 patients did not have a known B cell deficiency but had an insufficient Ab response to the vaccine [defined as within 3 SDs from the mean of unvaccinated controls; Fig. 1A (arrow) and fig. S1A]. The other patients had levels of Ab response to the vaccine similar to those of vaccinated controls (*t* test, table S1). Three of the five patients with a known B cell deficiency had a normal Ab response (above 3 SDs; Fig. 1A). Overall, 42 patients had both no–B cell deficiency and a normal Ab response to the vaccine and thus were further investigated.

Auto-Abs against type I IFNs in 10 of 42 patients with normal Ab response to the vaccine

We next tested all the samples from the 42 patients without known B cell deficiency and with a normal Ab response to the mRNA vaccine for immunoglobulin G (IgG) auto-Ab to type I IFN levels using a radioligand binding assay (RLBA). Seven of the 42 patients tested had elevated titers of anti–IFN-α2 auto-Abs in RLBA (Fig. 1B). We then tested all of these samples for their neutralization activity against IFN-α2 and IFN-ω at 10 ng/ml and 100 pg/ml and IFN-β at 10 ng/ml. We identified 10 (24%) patients with IgG auto-Abs neutralizing IFN-α2 and/or IFN-ω, as did the APS-1–positive controls, whereas the healthy controls did not (Fig. 1, C and D). Patients with neutralizing auto-Abs had lower luciferase induction (below threshold in dotted lines). All of these patients had normal anti–SARS-CoV-2 Spike Ab response to the vaccine (fig. S1, D and E). In contrast, auto-Abs to type I IFN were not found in any of the six patients previously excluded because of a known B cell immunodeficiency ($n = 5$) or an insufficient Ab response to the vaccine ($n = 1$; fig. S1, B and C). Eight of these 10 individuals (80%) had circulating auto-Abs neutralizing both IFN-α2 and IFN-ω, whereas two neutralized IFN-ω only (20%), and none neutralized IFN-β (Fig. 1, C and D). In addition, plasma from seven patients (diluted 1/10) neutralized a high concentration (10 ng/ml) of type I IFNs (70%), whereas three neutralized only the lower, more physiological dose (100 pg/ml) of type I IFNs (including the two neutralizing IFN-ω only; 30%; Fig. 1, C and D). Overall, auto-Abs neutralizing IFN-α2 and/or IFN-ω were found at the onset of disease in 10 of the 42 patients (24%) with breakthrough COVID-19 who suffered from hypoxemic pneumonia despite having a normal Ab response to an mRNA vaccine.

Demographic, clinical, and virological features of the 10 patients with auto-Abs to type I IFNs

The patients with hypoxemic breakthrough COVID-19 pneumonia and auto-Abs neutralizing type I IFNs included three women and seven men. They were aged 43 to 86 years old (mean, 75 years old; Table 1). All were of European ancestry, except one Cambodian, and they originated from France ($n = 3$), Greece ($n = 5$), and the United States ($n = 2$). None of these individuals reported having previously suffered from other severe viral infections. All 10 patients were hospitalized during COVID-19 for oxygen supplementation, including five hospitalized in an intensive care unit (ICU) who received mechanical ventilation and one who received nasal oxygen high flow therapy but was recused of ICU because of age (P8). All of them survived. All presented with bilateral COVID-19 pneumonia and had a positive SARS-CoV-2 reverse transcription polymerase chain reaction (PCR) in the respiratory tract. The SARS-CoV-2 variants involved were unknown but most likely to be Delta variant, given the epidemiology at the location and time of sampling (i.e., before October 2021 for all samples tested). The patients had been vaccinated 2 to 16 weeks before the diagnosis of COVID-19. One individual (P2) had at least two autoimmune conditions (myasthenia gravis and

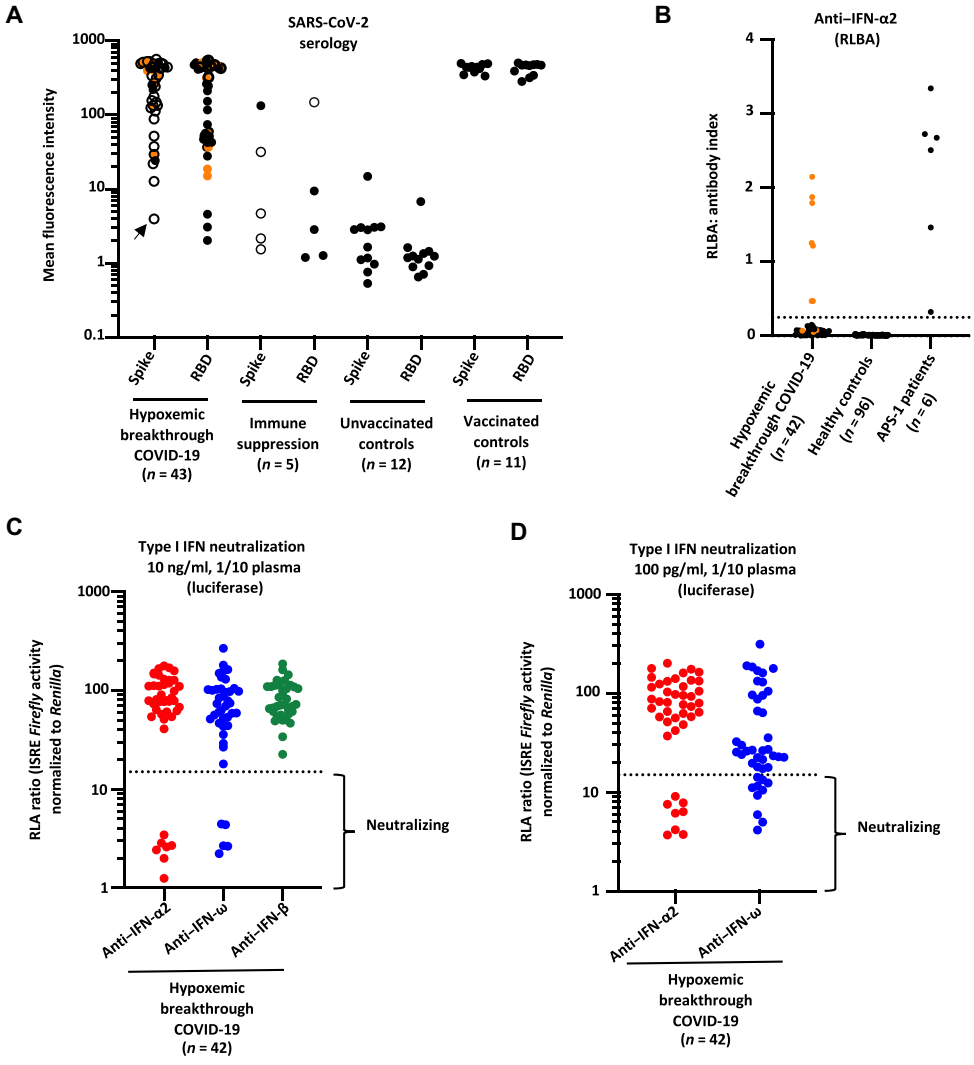

Fig. 1. Neutralizing auto-Abs against IFN-α2 and IFN-ω in patients with hypoxemic breakthrough COVID-19 despite a normal serological response to SARS-CoV-2 mRNA vaccine. (**A**) SARS-CoV-2 serology against spike (S) protein and RBD in hypoxemic breakthrough COVID-19 ($n = 43$), patients with immune suppression ($n = 5$), unvaccinated controls ($n = 12$), and vaccinated and uninfected healthy controls ($n = 11$). Mean fluorescence intensity is shown. The orange dots correspond to the 10 individuals with auto-Abs neutralizing type I IFNs. Empty circles represent either Spike or RBD serology to outline the highest value for one patient. The arrow indicates the patient without B cell deficiency but with an insufficient Ab response to the virus. (**B**) RLBA results for auto-Abs against IFN-α2 in patients with hypoxemic breakthrough COVID-19 pneumonia without immune suppression or low Ab response to the vaccine ($n = 42$), uninfected controls ($N = 96$), and uninfected APS-1 patients ($n = 6$). (**C**) Neutralization of IFN-α2, IFN-ω, or IFN-β (10 ng/ml) in the presence of plasma 1/10 from patients with hypoxemic breakthrough COVID-19 pneumonia with a good Ab response to the vaccine ($n = 42$). Relative luciferase activity is shown (ISRE dual luciferase activity, with normalization against *Renilla* luciferase activity) after stimulation with IFN-α2 or IFN-ω (10 ng/ml) in the presence of plasma 1/10. RLA, relative luciferase activity. (**D**) Neutralization of IFN-α2 or IFN-ω (100 pg/ml) in the presence of plasma 1/10 from patients with hypoxemic breakthrough COVID-19 pneumonia with a good Ab response to the vaccine ($n = 42$).

Hashimoto's thyroiditis), whereas another (P10) had APS-1. Myasthenia gravis and APS-1 are associated with auto-Abs to type I IFNs which had, however, not been measured before COVID-19 in these two individuals. Last, one individual (P1) belonged to a large family whose members had all been fully vaccinated, and many were infected at the same time as he was (*43*). He was, nevertheless, the only one to suffer from critical disease and also the only one to harbor neutralizing auto-Abs to type I IFNs. None of the 10 patients died of COVID-19, whereas more than 20% of unvaccinated individuals who died of COVID-19 harbored neutralizing auto-Abs (*34*) and 5 to 10% of unvaccinated patients with these auto-Abs died of COVID-19 (*35*), suggesting that, although insufficient to prevent hypoxemic pneumonia, vaccination may have protected these patients from a fatal outcome. Overall, auto-Abs to type I IFNs can underlie hypoxemic breakthrough COVID-19 infection in previously healthy individuals who developed normal Ab responses after SARS-CoV-2 mRNA vaccination.

Abs neutralizing SARS-CoV-2 in all 10 patients

To further test the hypothesis that the hypoxemic breakthrough cases were driven by the auto-Abs neutralizing type I IFNs and not by an insufficient Ab response to the vaccine, we assessed the neutralizing activity in all 10 patients' plasma against SARS-CoV-2 (Table 2). Although

Table 1. Clinical and demographic information of the 10 patients with hypoxemic breakthrough COVID-19 infection and auto-Abs neutralizing type I IFNs. 00HTN, hypertension; AF, atrial fibrillation.

Patient	Origin	Residence	Sex	Age	Comorbidities	Vaccine source	Dose number	Time of disease post vaccination (weeks)	ICU	Classification	Outcome
P1	American	United States	M	80	Diabetes, asthma	Pfizer	2	2	Yes	Critical	Alive
P2	Greek	Greece	F	82	HTN, myasthenia gravis, Hashimoto, dyslipidemia	Pfizer	2	4	Yes	Critical	Alive
P3	Greek	Greece	M	73	HTN, diabetes, dyslipidemia, glaucoma	Pfizer	2	2	Yes	Critical	Alive
P4	Greek	Greece	M	86	HTN, diabetes, dyslipidemia, AF, benign prostate hyperplasia, Parkinson's	Pfizer	2	12	Yes	Critical	Alive
P5	Greek	Greece	M	73	Diabetes, coronary heart disease	Pfizer	2	3	No	Severe	Alive
P6	Greek	Greece	F	77	HTN, diabetes, dyslipidemia	Pfizer	2	16	No	Severe	Alive
P7	Cambodian	France	M	71	HTN	Pfizer	2	15	Yes	Critical	Alive
P8	French	France	F	86	NA	Pfizer	2	6	No	Critical	Alive
P9	American	United States	M	80	NA	Pfizer	2	2	No	Critical	Alive
P10	French	France	M	43	APS-1	Pfizer	2	2	No	Severe	Alive

we did not collect blood samples before COVID-19 diagnosis, we collected them in the first 3 days of hospitalization. Because we did not determine with which viral strain the patients had been infected, we performed the neutralization assay with pseudoviruses representing both the previously globally dominant D614G strain and the Delta variant (B.1.617.2), which was dominant when and where the patients were infected. We compared the patients' results with the neutralization titers of healthy vaccinated donors 2 to 8 weeks after the second dose of the mRNA vaccine. All 10 individuals tested had a neutralization capacity when compared with the healthy vaccinated controls, although it was slightly reduced for two individuals (P4 and P6) for the D614G strain and for three individuals (P1, P4, and P6) for the Delta variant (Fig. 2, A and B, and fig. S1, D and E). Although P1 neutralized type I IFNs at 10 ng/ml, P4 and P6 only neutralized low concentrations of type I IFNs. Specifically, P4 neutralized both IFN-α2 and IFN-ω but only at 100 pg/ml, whereas P6 neutralized only IFN-ω at 100 pg/ml. This observation suggests that in patients whose auto-Abs neutralized only low concentrations of type I IFNs, suboptimal Ab response to the vaccine may have also contributed to hypoxemic pneumonia. Overall, this suggested that hypoxemic COVID-19 pneumonia can occur in individuals with a normal Ab response to two doses of mRNA vaccine (42 of 48 patients tested). Moreover, in about 20% of the breakthrough cases (10 of 42 cases), hypoxemic pneumonia was probably due to auto-Abs neutralizing IFN-α2 and/or IFN-ω (and typically at high concentration of both IFNs). Last, in 70% of the latter cases (7 of 10 cases), plasma neutralization of two viral strains was normal, whereas 1 had a lower neutralization against the Delta strain, and the remaining 2 had a subnormal neutralization of both viral strains (D614G and Delta).

DISCUSSION

The pathogenesis of life-threatening COVID-19 pneumonia involves two steps, with a deficiency of respiratory type I IFN immunity in the first days of infection resulting in viral spread, which triggers excessive systemic and pulmonary inflammation (*13, 44, 45*). The vaccination of billions of individuals has efficiently reduced the number of critical cases. Nevertheless, breakthrough hypoxemic COVID-19 pneumonia can occur in previously healthy individuals who are vaccinated against SARS-CoV-2; this is assumed to be due to a poor Ab response to the vaccine (*42*). Our findings suggest that most breakthrough hypoxemic cases (42 of 48 tested) did not have a known B cell deficiency and also had a normal Ab response to the vaccine, although no samples were available before SARS-CoV-2 infection. Moreover, we showed that about 20% (10 of 42) of these breakthrough cases with normal Ab response to the vaccine also carried auto-Abs neutralizing IFN-α2 and/or IFN-ω (10 ng/ml for 7 patients and 100 pg/ml for 3 patients). In addition, the plasma of 7 of the 10 patients with auto-Abs to type I IFNs efficiently neutralized SARS-CoV-2 in vitro, whereas 1 had a lower neutralization against the Delta strain, and plasma from the remaining 2 neutralized the two viral strains tested suboptimally. Both patients had auto-Abs neutralizing only type I IFNs at 100 pg/ml. Plasma (diluted 1/10) from 7 of the 10 individuals with these auto-Abs neutralized a high concentration (10 ng/ml) of both IFN-α2 and IFN-ω, consistent with unvaccinated individuals carrying such auto-Abs being at the greatest risk of critical COVID-19 among individuals carrying any combinations of auto-Abs to type I IFNs (*13, 34, 35*). The proportion of individuals with hypoxemic COVID-19 due to neutralizing both IFN-α2 and IFN-ω at the high dose (10 ng/ml) is even higher in the breakthrough cohort reported here (7 of 42; 16%) than in the previously

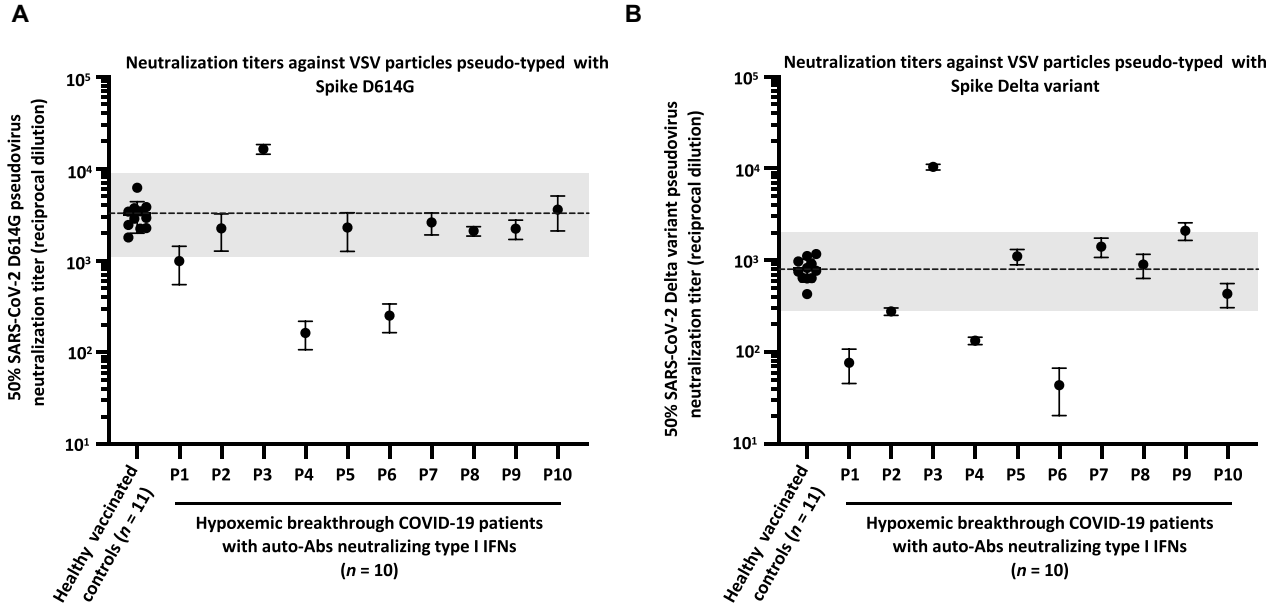

Fig. 2. Neutralization titers against SARS-CoV-2 in the patients with auto-Abs against type I IFNs. Neutralization titers against SARS-CoV-2 for healthy vaccinated donors 2 to 8 weeks after the second dose of mRNA vaccine ($n = 11$) and patients with hypoxemic breakthrough COVID-19 pneumonia and auto-Abs to type I IFNs ($n = 10$). The dashed line shows the geometric mean of healthy donor titers; the box shows interquartile range, and the shaded region is the full range. (**A**) Neutralization assay performed with pseudoviruses representing the D614G strain and (**B**) the Delta variant (B.1.617.2).

described unvaccinated cohort (175 of 3136; 7.1%; $P = 0.015$) (*34*). Two of the three patients neutralizing only type I IFNs at 100 pg/ml also had a slightly diminished neutralization capacity against SARS-CoV-2, suggesting in these individuals a combination of two factors: the presence of auto-Abs to low concentration of type I IFNs and a suboptimal Ab response to the vaccine.

Nevertheless, as we were not able to identify and study auto-Ab–positive individuals who were vaccinated and efficiently protected against severe infection, we cannot estimate the percentage of breakthrough cases with hypoxemic pneumonia in individuals with auto-Abs neutralizing type I IFNs infected with SARS-CoV-2. Until 70 years old, the proportion of individuals from the general population sampled before the pandemic that carry auto-Abs against both IFN-α2 and IFN-ω is 0.02 and 0.03% for the neutralization of 10 ng/ml and 100 pg/ml, respectively, whereas it reaches 0.6 and 1.6% for those over 70 years old. Because mRNA vaccines have high efficacy to prevent critical pneumonia, it is probable that most patients with auto-Abs against type I IFNs benefit from vaccination, although the protection might not be sufficient in individuals neutralizing high concentrations of multiple type I IFNs. It is also not unreasonable to speculate that, despite an infection with a vaccine-covered viral variant and a normal Ab response to the vaccine, a small proportion of the patients with such auto-Abs might not be fully protected by the vaccine, especially if they are infected with a high viral inoculum. By inference from previous studies, the auto-Abs of the eight patients neutralizing IFN-α2 also probably neutralize the 13 types of IFN-α (*14*, *24*, *34*, *46*). These findings suggest that a potent postvaccine humoral immunity can be insufficient to fight SARS-CoV-2 infection, especially in patients with auto-Abs neutralizing both IFN-α2 and IFN-ω and even more so at high concentration.

Our results here suggest that it may be beneficial to test for auto-Abs to type I IFN in vaccinated patients diagnosed with breakthrough COVID-19 pneumonia of varying severity and to treat if patients are auto-Ab positive. Testing uninfected people, including vaccinated individuals, may also be considered, especially in those over 70 years old given the high prevalence of auto-Abs to type I IFNs in this population (>4%) and their lower global type I IFN immunity (*13*). One of the 10 patients suffered from APS-1 and thus most likely harbored these auto-Abs since early childhood (*24*, *25*, *47*), whereas another patient had myasthenia gravis, which is also commonly associated with these auto-Abs (*48*). Testing patients with conditions known to be associated with these auto-Abs may benefit these patients. All individuals with auto-Abs to type I IFNs might benefit not only from vaccine boosters but perhaps also from recurrent vaccinations. Prospective studies assessing vaccine-induced immunity before infection

Table 2. Auto-Abs neutralized in the 10 patients. 1, neutralizing; 0, non-neutralizing.

Patient	Anti–IFN-α2 auto-Abs (10 ng/ml)	Anti–IFN-β auto-Abs (10 ng/ml)	Anti–IFN-ω, auto-Abs (10 ng/ml)	Anti–IFN-α2 auto-Abs (100 pg/ml)	Anti–IFN-ω, auto-Abs (100 pg/ml)
P1	1	0	1	1	1
P2	1	0	0	1	1
P3	1	0	0	1	1
P4	0	0	0	0	1
P5	1	0	1	1	1
P6	0	0	0	1	1
P7	0	0	0	0	1
P8	1	0	1	1	1
P9	1	0	1	1	1
P10	1	0	1	1	1

in patients with auto-Abs to type I IFNs would be informative, for example, in the setting of vaccine trials. Systematic screening at hospital admission for auto-Abs to type I IFNs would also be of help for the management of vaccinated or unvaccinated individuals with hypoxemic pneumonia. Monoclonal Abs neutralizing the virus could also be administered promptly (*49*), as shown for an IFN regulatory factor 9–deficient patient (*50*), especially in patients with the highest titers of auto-Abs to type I IFNs. Antiviral compounds, such as remdesivir (*51*, *52*), molnupiravir (*53*, *54*), or nirmatrelvir + rintonavir may also benefit these patients if administered early in the course of infection. Conversely, in ambulatory patients with these auto-Abs, early recombinant IFN-β therapy may also be considered to prevent the development of hypoxemic pneumonia (*55*). In sum, our findings indicate that auto-Abs to type I IFNs are a susceptibility factor for a severe clinical course of COVID-19, even in vaccinated individuals with a breakthrough infection.

MATERIALS AND METHODS

Study design

We enrolled 48 patients with proven hypoxemic COVID-19 pneumonia, 12 unvaccinated controls, and 11 vaccinated controls from six countries in this study. We collected plasma or serum samples from all of these individuals to test for the presence of IgG Abs against SARS-CoV-2 and auto-Abs to type I IFNs by immunoassay. All individuals were recruited according to protocols approved by local institutional review boards.

COVID-19 classification

The severity of COVID-19 was assessed for each patient as follows (*6*, *14*): "Critical COVID-19 pneumonia" was defined as pneumonia developing in patients with critical disease, whether pulmonary, with high-flow oxygen, mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, and intubation), septic shock, or with damage to any other organ requiring admission to the ICU. "Severe COVID-19" was defined as pneumonia developing in patients requiring low-flow oxygen (<6 liters/min). The controls were individuals infected with SARS-CoV-2 (as demonstrated by a positive PCR and/or serological test and/or displaying typical symptoms, such as anosmia/ageusia after exposure to a confirmed COVID-19 case) who remained asymptomatic or developed mild, self-healing, ambulatory disease with no evidence of pneumonia.

Statistics

For comparison of groups in Fig. 1A, a two-sided *t* test was performed using a Python library (SciPy) for both Spike and receptor binding domain (RBD). Briefly, all groups were compared with the unvaccinated control group ($n = 12$). In addition, the group of auto-Ab–positive breakthrough cases was compared with the group of auto-Ab–negative breakthrough cases.

Detection of anticytokine auto-Abs by a high-throughput automated enzyme-linked immunosorbent assay (Gyros)

Cytokines, either recombinant human (rh) IFN-α2 (Miltenyi Biotec, reference number 130-108-984) or rhIFN-ω (Merck, reference number SRP3061), were first biotinylated with EZ-Link Sulfo-NHS-LC-Biotin (Thermo Fisher Scientific, catalog number A39257), according to the manufacturer's instructions, with a biotin-to-protein molar ratio of 1:12. The detection reagent contained a secondary Ab Alexa Fluor 647 goat anti-human IgG (Thermo Fisher Scientific, reference number A21445) diluted in Rexip F (Gyros Protein Technologies, reference number P0004825; 1/500 dilution of the stock at 2 mg/ml to yield a final concentration of 4 μg/ml). Phosphate-buffered saline with tween (PBS-T) (0.01%) and Gyros Wash buffer (Gyros Protein Technologies, reference number P0020087) were prepared according to the manufacturer's instructions. Plasma or serum samples were then diluted 1/100 in 0.01% PBS-T and tested with the Bioaffy 1000 CD (Gyros Protein Technologies, reference number P0004253) and the Gyrolab xPand (Gyros Protein Technologies, reference number P0020520). Cleaning cycles were performed in 20% ethanol.

RLBA for anti–IFN-α2 auto-Ab detection

A DNA plasmid containing full-length cDNA sequence with a Flag-Myc tag (OriGene, #RC221091) was verified by Sanger sequencing and used as template in T7 promoter–based in vitro transcription/translation reactions (Promega, #L1170) using [^{35}S]-methionine (PerkinElmer, #NEG709A). IFN-α2 protein was column-purified using NAP-5 columns (GE Healthcare, #17-0853-01); incubated with 2.5 μl of serum, 2.5 μl of plasma, or 1 μl of anti-myc–positive control Ab (Cell Signaling Technology, #2272); and immunoprecipitated with Sephadex protein A/G beads (4:1 ratio; Sigma-Aldrich, #GE17-5280-02 and #GE17-0618-05) in 96-well polyvinylidene difluoride filtration plates (Corning, #EK-680860). The radioactive counts [counts per minute (cpm)] of immunoprecipitated protein were quantified using a 96-well MicroBeta TriLux liquid scintillation plate reader (PerkinElmer). The Ab index for each sample was calculated as follows: (sample cpm value − mean blank cpm value)/(positive control Ab cpm value − mean blank cpm value). A positive signal was defined as greater than 6 SDs above the mean of pre–COVID-19 blood bank noninflammatory controls.

Functional evaluation of anticytokine auto-Abs by luciferase reporter assays

The blocking activity of anti–IFN-α2 and anti–IFN-ω auto-Abs was determined with a reporter luciferase activity. Briefly, human embryonic kidney 293T cells were transfected with a plasmid containing the *Firefly* luciferase gene under the control of the human *ISRE* promoter in the pGL4.45 backbone and a plasmid constitutively expressing *Renilla* luciferase for normalization (pRL-SV40). Cells were transfected in the presence of the X-tremeGene9 transfection reagent (Sigma-Aldrich, reference number 6365779001) for 24 hours. Cells in Dulbecco's modified Eagle medium (DMEM; Thermo Fisher Scientific) supplemented with 2% fetal calf serum and 10% healthy control or patient serum/plasma (after inactivation at 56°C, for 20 min) were either left unstimulated or were stimulated for 16 hours at 37°C with IFN-α2 (Miltenyi Biotec, reference number 130-108-984) and IFN-ω (Merck, reference number SRP3061) at 10 ng/ml or 100 pg/ml or with IFN-β (Miltenyi Biotec, reference number: 130-107-888) at 10 ng/ml. Each sample was tested once for each cytokine and dose. Last, cells were lysed for 20 min at room temperature, and luciferase levels were measured with the Dual-Luciferase Reporter 1000 assay system (Promega, reference number E1980), according to the manufacturer's protocol. Luminescence intensity was measured with a VICTOR X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). *Firefly* luciferase activity values were normalized against *Renilla* luciferase activity values. These values were then normalized against the median induction level for non-neutralizing samples and expressed as a percentage. Samples were considered neutralizing if luciferase

induction, normalized against *Renilla* luciferase activity, was below 15% of the median values for controls tested the same day.

SARS-CoV-2 serological studies

Serum collection

Control serum was collected under informed consent from healthy recipients of BNT162b2 vaccine [vaccines based on the Wuhan spike protein sequence], who were confirmed to have no prior SARS-CoV-2 infection by anti–SARS-CoV-2 nucleocapsid (N protein) IgG assay (*56*). All serum samples were heat-inactivated at 56°C for 30 min before neutralization experiments.

Luminex assay

Luminex immunoassays for SARS-CoV-2 serology studies were performed as previously described using proteins from the Wuhan strain of the virus (*57*). Briefly, whole N protein, trimeric Spike ectodomain (residues 1 to 1213), and RBD (residues 328-533, all provided by J. Pak, Chan Zuckerberg Biohub) were each conjugated to a unique spectrally encoded bead using the manufacturer's instructions (Luminex Antibody Coupling Kit; #40-50016) with 5 μg of protein per 1 million beads. All beads were blocked overnight before use in PBS-T supplemented with 0.1% bovine serum albumin (BSA) and pooled on day of use. A total of 2000 to 2500 beads per ID were pooled per replicate. Patient serum or plasma was incubated with beads at a final dilution of 1:250 for 1 hour, washed twice in PBS-T, stained with an anti-IgG (human) preconjugated to phycoerythrin (Thermo Scientific, #12-4998-82) for 30 min at 1:2000, and then washed thrice in PBS-T. Primary incubations were done in PBS-T supplemented with 2% nonfat milk, and secondary incubations were done in PBS-T. Beads were processed in duplicate in 96-well format and analyzed on a Luminex LX 200 cytometer. Median fluorescence intensity from each set of beads within each bead ID was retrieved directly from the LX200 after normalizing to the intra-assay negative controls (BSA-conjugated beads).

Pseudovirus production

SARS-CoV-2 pseudoviruses were generated using a previously described recombinant vesicular stomatitis virus (VSV) expressing green fluorescent protein (GFP) in place of the VSV glycoprotein (rVSVΔG-GFP) (*58*). The SARS-CoV-2 spike gene bearing the D614G mutation or the set of mutations in the B.1.617.2/Delta variant (T19R, T95I, G142D, Δ157-158, L452R, T478K, P681R, D614G, and D950N) was cloned in a cytomegalovirus-driven expression vector and used to produce SARS-CoV-2 spike reporter pseudoviruses. Pseudoviruses were titered on Huh7.5.1 cells overexpressing angiotensin-converting enzyme 2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2; gift of A. Puschnik) using GFP expression to measure the concentration of focus-forming units (ffu).

Pseudovirus neutralization experiments

Huh7.5.1-ACE2-TMPRSS2 cells were seeded in 96-well plates at a density of 7000 cells per well 1 day before pseudovirus inoculation. Cells were verified to be free of mycoplasma contamination with the MycoAlert Mycoplasma detection kit (Lonza). Serum samples were diluted into complete culture media (DMEM with 10% fetal bovine serum, 10 mM Hepes, 1× penicillin-streptomycin-glutamine) using the LabCyte Echo 525 liquid handler, and 1500 ffu of SARS-CoV-2 pseudovirus was added to each well to reach final dilutions ranging from 1:20 to 1:10,240, including no-serum and no-pseudovirus controls. Serum/pseudovirus mixtures were incubated at 37°C for 1 hour before being added directly to cells. Cells inoculated with serum/pseudovirus mixtures were incubated at 37°C and 5% CO_2 for 24 hours and resuspended using 10× TrypLE Select (Gibco), and cell fluorescence was measured with the BD Celesta flow cytometer. All neutralization assays were repeated for a total of three independent experiments, with each experiment containing two technical replicates for each condition. Flow cytometry data were analyzed with FlowJo to determine the percentage of cells transduced with pseudovirus (GFP-positive). Percent neutralization for each serum dilution was calculated by normalizing GFP-positive cell percentage to no-serum control wells. Fifty percent neutralization titers were calculated from 10-point response curves generated in GraphPad Prism 7 using four-parameter logistic regression.

SUPPLEMENTARY MATERIALS

www.science.org/doi/10.1126/sciimmunol.abp8966
Materials and Methods
Table S1
Fig. S1
Data file S1

View/request a protocol for this paper from *Bio-protocol*.

REFERENCES AND NOTES

1. P. Zhou, X. L. Yang, X. G. Wang, B. Hu, L. Zhang, W. Zhang, H. R. Si, Y. Zhu, B. Li, C. L. Huang, H. D. Chen, J. Chen, Y. Luo, H. Guo, R. D. Jiang, M. Q. Liu, Y. Chen, X. R. Shen, X. Wang, X. S. Zheng, K. Zhao, Q. J. Chen, F. Deng, L. L. Liu, B. Yan, F. X. Zhan, Y. Y. Wang, G. F. Xiao, Z. L. Shi, A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* **579**, 270–273 (2020).
2. Worldometer (2021), vol. 2021.
3. A. T. Levin, W. P. Hanage, N. Owusu-Boaitey, K. B. Cochran, S. P. Walsh, G. Meyerowitz-Katz, Assessing the age specificity of infection fatality rates for COVID-19: Systematic review, meta-analysis, and public policy implications. *Eur. J. Epidemiol.* **35**, 1123–1138 (2020).
4. M. O'Driscoll, G. Ribeiro Dos Santos, L. Wang, D. A. T. Cummings, A. S. Azman, J. Paireau, A. Fontanet, S. Cauchemez, H. Salje, Age-specific mortality and immunity patterns of SARS-CoV-2. *Nature* **590**, 140–145 (2021).
5. D. Bogunovic, M. Merad, Children and SARS-CoV-2. *Cell Host Microbe* **29**, 1040–1042 (2021).
6. Q. Zhang, P. Bastard, Z. Liu, J. Le Pen, M. Moncada-Velez, J. Chen, M. Ogishi, I. K. D. Sabli, S. Hodeib, C. Korol, J. Rosain, K. Bilguvar, J. Ye, A. Bolze, B. Bigio, R. Yang, A. A. Arias, Q. Zhou, Y. Zhang, F. Onodi, S. Korniotis, L. Karpf, Q. Philippot, M. Chbihi, L. Bonnet-Madin, K. Dorgham, N. Smith, W. M. Schneider, B. S. Razooky, H. H. Hoffmann, E. Michailidis, L. Moens, J. E. Han, L. Lorenzo, L. Bizien, P. Meade, A. L. Neehus, A. C. Ugurbil, A. Corneau, G. Kerner, P. Zhang, F. Rapaport, Y. Seeleuthner, J. Manry, C. Masson, Y. Schmitt, A. Schluter, T. Le Voyer, T. Khan, J. Li, J. Fellay, L. Roussel, M. Shahrooei, M. F. Alosaimi, D. Mansouri, H. Al-Saud, F. Al-Mulla, F. Almourfi, S. Z. Al-Muhsen, F. Alsohime, S. Al Turki, R. Hasanato, D. van de Beek, A. Biondi, L. R. Bettini, M. D'Angio, P. Bonfanti, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, A. J. Oler, M. F. Tompkins, C. Alba, I. Vandernoot, J. C. Goffard, G. Smits, I. Migeotte, F. Haerynck, P. Soler-Palacin, A. Martin-Nalda, R. Colobran, P. E. Morange, S. Keles, F. Colkesen, T. Ozcelik, K. K. Yasar, S. Senoglu, S. N. Karabela, C. Rodriguez-Gallego, G. Novelli, S. Hraiech, Y. Tandjaoui-Lambiotte, X. Duval, C. Laouenan, COVID-STORM Clinicians, COVID Clinicians; Imagine COVID Group, French COVID Cohort Study Group, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, NIAID-USUHS/TAGC COVID Immunity Group, A. L. Snow, C. L. Dalgard, J. D. Milner, D. C. Vinh, T. H. Mogensen, N. Marr, A. N. Spaan, B. Boisson, S. Boisson-Dupuis, J. Bustamante, A. Puel, M. J. Ciancanelli, I. Meyts, T. Maniatis, V. Soumelis, A. Amara, M. Nussenzweig, A. Garcia-Sastre, F. Krammer, A. Pujol, D. Duffy, R. P. Lifton, S. Y. Zhang, G. Gorochov, V. Beziat, E. Jouanguy, V. Sancho-Shimizu, C. M. Rice, L. Abel, L. D. Notarangelo, A. Cobat, H. C. Su, J. L. Casanova, Inborn errors of type I IFN immunity in patients with life-threatening COVID-19. *Science* **370**, eabd4570 (2020).
7. T. Asano, B. Boisson, F. Onodi, D. Matuozzo, M. Moncada-Velez, M. R. L. Maglorius Renkilaraj, P. Zhang, L. Meertens, A. Bolze, A. Materna, S. Korniotis, A. Gervais, E. Talouarn, B. Bigio, Y. Seeleuthner, K. Bilguvar, Y. Zhang, A.-L. Neehus, M. Ogishi, S. J. Pelham, T. Le Voyer, J. Rosain, Q. Philippot, P. Soler-Palacín, R. Colobran, A. Martin-Nalda, J. G. Rivière, Y. Tandjaoui-Lambiotte, K. Chaïbi, M. Shahrooei, I. Alavi Darazam, N. Alipour Olyaei, D. Mansouri, N. Hatipoğlu, F. Palabiyik, T. Ozcelik, G. Novelli, A. Novelli, G. Casari, A. Aiuti, P. Carrera, S. Bondesan, F. Barzaghi, P. Rovere-Querini, C. Tresoldi, J. L. Franco, J. Rojas, L. F. Reyes, I. G. Bustos, A. A. Arias, G. Morelle, K. Christèle, J. Troya, L. Planas-Serra, A. Schlüter, M. Gut, A. Pujol, L. M. Allende, C. Rodriguez-Gallego, C. Flores, O. Cabrera-Marante, D. E. Pleguezuelo, R. Pérez de Diego, S. Keles, G. Aytekin, O. M. Akcan, Y. T. Bryceson, P. Bergman, P. Brodin, D. Smole,

C. I. E Smith, A.-C. Norlin, T. M. Campbell, L. E. Covill, L. Hammarström, Q. Pan-Hammarström, H. Abolhassani, S. Mane, N. Marr, M. Ata, F. Al Ali, T. Khan, A. N. Spaan, C. L. Dalgard, P. Bonfanti, A. Biondi, S. Tubiana, C. Burdet, R. Nussbaum, A. Kahn-Kirby, A. L. Snow; COVID Human Genetic Effort; COVID-STORM Clinicians; COVID Clinicians; Imagine COVID Group; French COVID Cohort Study Group; CoV-Contact Cohort; Amsterdam UMC Covid-; Biobank; NIAID-USUHS COVID Study Group; J. Bustamante, A Puel, S. Boisson-Dupuis, S.-Y. Zhang, V. Béziat, R. P. Lifton, P. Bastard, L. D. Notarangelo, L. Abel, H. C. Su, E. Jouanguy, A. Amara, V. Soumelis, A. Cobat, Q. Zhang, J.-L. Casanova, V. Soumelis, V. Soumelis, X-linked recessive TLR7 deficiency in ~1% of men under 60 years old with life-threatening COVID-19. *Sci. Immunol*. **6**, eabl4348 (2019).

8. H. Abolhassani, N. Landegren, P. Bastard, M. Matern, M. Modaresi, L. Du, M. Aranda-Guillén, F. Sardh, F. Zuo, P. Zhang, H. Marcotte, N. Marr, T. Khan, M. Ata, F. Al-Ali, R. Pescarmona, A. Belot, V. Béziat, Q. Zhang, J.-L. Casanova, O. Kämpe, S.-Y. Zhang, L. Hammarström, Q. Pan-Hammarström, Inherited IFNAR1 deficiency in a child with both critical COVID-19 pneumonia and multisystem inflammatory syndrome. *J. Clin. Immunol.* **42**, 471–483 (2022).
9. S. Khanmohammadi, N. Rezaei, M. Khazaei, A. Shirkani, A case of autosomal recessive interferon alpha/beta receptor alpha chain (IFNAR1) deficiency with severe COVID-19. *J. Clin. Immunol.* **42**, 19–24 (2022).
10. N. Hernandez, G. Bucciol, L. Moens, J. Le Pen, M. Shahrooei, E. Goudouris, A. Shirkani, M. Changi-Ashtiani, H. Rokni-Zadeh, E. Hazar Sayar, I. Reisli, A. Lefevre-Utile, D. Zijlmans, A. Jurado, R. Pholien, S. Drutman, S. Belkaya, A. Cobat, R. Boudewijns, D. Jochmans, J. Neyts, Y. Seeleuthner, L. Lorenzo-Diaz, C. Enemchukwu, I. Tietjen, H.-H. Hoffmann, M. Momenilandi, L. Pöyhönen, M. M. Siqueira, S. M. Barbosa de Lima, D. C. de Souza Matos, A. Homma, M. de Lourdes, S. Maia, T. Azamor da Costa Barros, P. Mouta Nunes de Oliveira, E. Ciclini Mesquita, R. Gijsbers, S.-Y. Zhang, S. J. Seligman, L. Abel, P. Hertzog, N. Marr, L. Pöyhönen, R. de Menezes Martins, I. Meyts, Q. Zhang, M. R. MacDonald, C.M. Rice, J.-L. Casanova, E. Jouanguy, X. Bossuyt, Inherited IFNAR1 deficiency in otherwise healthy patients with adverse reaction to measles and yellow fever live vaccines. *J. Exp. Med*. **216**, 2057–2070 (2019).
11. A. Schmidt, S. Peters, A. Knaus, H. Sabir, F. Hamsen, C. Maj, J. Fazaal, S. Sivalingam, O. Savchenko, A. Mantri, D. Holzinger, U. Neudorf, A. Müller, K. U. Ludwig, P. M. Krawitz, H. Engels, M. M. Nöthen, S. Bagc, TBK1 and TNFRSF13B mutations and an autoinflammatory disease in a child with lethal COVID-19. *NPJ Genom. Med*. **42**, 55 (2021).
12. R. Lévy, P. Zhang, P. Bastard, K. Dorgham, I. Melki, A. Hadchouel, G. C. Hartoularos, B. Neven, M. Castelle, C. Roy, T. Toin, L. Berteloot, L. Bizien, H. Abid, M. Burgard, N. Houhou-Fidouh, F. Rozenberg, E. Jouanguy, C. J. Ye, G. Gorochov, Q. Zhang, J.-L. Casanova, Monoclonal antibody-mediated neutralization of SARS-CoV-2 in an IRF9-deficient child. *Proc. Nat. Acad. Sci. U.S.A*. **118**, e2114390118 (2021).
13. Q. Zhang, P. Bastard, COVID Human Genetic Effort, A. Cobat, J. L. Casanova, Human genetic and immunological determinants of critical COVID-19 pneumonia. *Nature* **603**, 587–598 (2022).
14. P. Bastard, L. B. Rosen, Q. Zhang, E. Michailidis, H. H. Hoffmann, Y. Zhang, K. Dorgham, Q. Philippot, J. Rosain, V. Beziat, J. Manry, E. Shaw, L. Haljasmagi, P. Peterson, L. Lorenzo, L. Bizien, S. Trouillet-Assant, K. Dobbs, A. A. de Jesus, A. Belot, A. Kallaste, E. Catherinot, Y. Tandjaoui-Lambiotte, J. Le Pen, G. Kerner, B. Bigio, Y. Seeleuthner, R. Yang, A. Bolze, A. N. Spaan, O. M. Delmonte, M. S. Abers, A. Aiuti, G. Casari, V. Lampasona, L. Piemonti, F. Ciceri, K. Bilguvar, R. P. Lifton, M. Vasse, D. M. Smadja, M. Migaud, J. Hadjadj, B. Terrier, D. Duffy, L. Quintana-Murci, D. van de Beek, L. Roussel, D. C. Vinh, S. G. Tangye, F. Haerynck, D. Dalmau, J. Martinez-Picado, P. Brodin, M. C. Nussenzweig, S. Boisson-Dupuis, C. Rodriguez-Gallego, G. Vogt, T. H. Mogensen, A. J. Oler, J. Gu, P. D. Burbelo, J. I. Cohen, A. Biondi, L. R. Bettini, M. D'Angio, P. Bonfanti, P. Rossignol, J. Mayaux, F. Rieux-Laucat, E. S. Husebye, F. Fusco, M. V. Ursini, L. Imberti, A. Sottini, S. Paghera, E. Quiros-Roldan, C. Rossi, R. Castagnoli, D. Montagna, A. Licari, G. L. Marseglia, X. Duval, J. Ghosn, HGID Lab, NIAID-USUHS Immune Response to COVID Group, COVID Clinicians, COVID-STORM Clinicians, Imagine COVID Group, French COVID Cohort Study Group, Milieu Intérieur Consortium; CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank, COVID Human Genetic Effort, J. S. Tsang, R. Goldbach-Mansky, K. Kisand, M. S. Lionakis, A. Puel, S. Y. Zhang, S. M. Holland, G. Gorochov, E. Jouanguy, C. M. Rice, A. Cobat, L. D. Notarangelo, L. Abel, H. C. Su, J. L. Casanova, Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* **370**, eabd4585 (2020).
15. R. Koning, P. Bastard, J. L. Casanova, M. C. Brouwer, D. van de Beek, Amsterdam U.M.C. COVID-19 Biobank Investigators, Autoantibodies against type I interferons are associated with multi-organ failure in COVID-19 patients. *Intensive Care Med* **47**, 704–706 (2021).
16. J. Troya, P. Bastard, L. Planas-Serra, P. Ryan, M. Ruiz, M. de Carranza, J. Torres, A. Martinez, L. Abel, J. L. Casanova, A. Pujol, Neutralizing autoantibodies to type I IFNs in >10% of patients with severe COVID-19 pneumonia hospitalized in Madrid, Spain. *J. Clin. Immunol*. **41**, 914–922 (2021).
17. S. E. Vazquez, P. Bastard, K. Kelly, A. Gervais, P. J. Norris, L. J. Dumont, J. L. Casanova, M. S. Anderson, J. L. DeRisi, Neutralizing autoantibodies to type I interferons in COVID-19 convalescent donor plasma. *J. Clin. Immunol.* **41**, 1169–1171 (2021).
18. D. Goncalves, M. Mezidi, P. Bastard, M. Perret, K. Saker, N. Fabien, R. Pescarmona, R. Lombard, T. Walzer, J.-L. Casanova, A. Belot, J.-C. Richard, S. Trouillet-Assant, Antibodies against type-I interferon: Detection and association with severe clinical outcome in COVID-19 patients. *medRxiv* , 2021.04.02.21253262 (2021).
19. E. Y. Wang, T. Mao, J. Klein, Y. Dai, J. D. Huck, J. R. Jaycox, F. Liu, T. Zhou, B. Israelow, P. Wong, A. Coppi, C. Lucas, J. Silva, J. E. Oh, E. Song, E. S. Perotti, N. S. Zheng, S. Fischer, M. Campbell, J. B. Fournier, A. L. Wyllie, C. B. F. Vogels, I. M. Ott, C. C. Kalinich, M. E. Petrone, A. E. Watkins, I. T. Yale, C. Dela Cruz, S. F. Farhadian, W. L. Schulz, S. Ma, N. D. Grubaugh, A. I. Ko, A. Iwasaki, A. M. Ring, Diverse functional autoantibodies in patients with COVID-19. *Nature* **595**, 283–288 (2021).
20. M. G. P. van der Wijst, S. E. Vazquez, G. C. Hartoularos, P. Bastard, T. Grant, R. Bueno, D. S. Lee, J. R. Greenland, Y. Sun, R. Perez, A. Ogorodnikov, A. Ward, S. A. Mann, K. L. Lynch, C. Yun, D. V. Havlir, G. Chamie, C. Marquez, B. Greenhouse, M. S. Lionakis, P. J. Norris, L. J. Dumont, K. Kelly, P. Zhang, Q. Zhang, A. Gervais, T. Le Voyer, A. Whatley, Y. Si, A. Byrne, A. J. Combes, A. A. Rao, Y. S. Song, G. K. Fragiadakis, K. Kangelaris, C. S. Calfee, D. J. Erle, C. Hendrickson, M. F. Krummel, P. G. Woodruff, C. R. Langelier, J. L. Casanova, J. L. Derisi, M. S. Anderson, C. J. Ye, UCSF COMET consortium, Type I interferon autoantibodies are associated with systemic immune alterations in patients with COVID-19. *Sci. Transl. Med.* **13**, eabh2624 (2021).
21. Y. Acosta-Ampudia, D. M. Monsalve, M. Rojas, Y. Rodriguez, J. E. Gallo, J. C. Salazar-Uribe, M. J. Santander, M. P. Cala, W. Zapata, M. I. Zapata, R. Manrique, J. M. Pardo-Oviedo, B. Camacho, C. Ramirez-Santana, J.-M. Anaya, CP-COVID-19 group, COVID-19 convalescent plasma composition and immunological effects in severe patients. *J. Autoimmun.* **118**, 102598 (2021).
22. X. Solanich, R. Rigo-Bonnin, V. D. Gumucio, P. Bastard, J. Rosain, Q. Philippot, X. L. Perez-Fernandez, M. P. Fuset-Cabanes, M. A. Gordillo-Benitez, G. Suarez-Cuartin, E. Boza-Hernandez, A. Riera-Mestre, A. Parra-Martinez, R. Colobran, A. Antoli, S. Navarro, G. Rocamora-Blanch, M. Framil, L. Calatayud, X. Corbella, J. L. Casanova, F. Morandeira, J. Sabater-Riera, Pre-existing autoantibodies neutralizing high concentrations of type I interferons in almost 10% of COVID-19 patients admitted to intensive care in Barcelona. *J. Clin. Immunol.* **41**, 1733–1744 (2021).
23. A. Chauvineau-Grenier, P. Bastard, A. Servajean, A. Gervais, J. Rosain, E. Jouanguy, A. Cobat, J. L. Casanova, B. Rossi, Autoantibodies neutralizing type I interferons in 20% of COVID-19 deaths in a French hospital. *Res. Sq.* , rs.3.rs-915062 (2021).
24. P. Bastard, E. Orlova, L. Sozaeva, R. Levy, A. James, M. M. Schmitt, S. Ochoa, M. Kareva, Y. Rodina, A. Gervais, T. Le Voyer, J. Rosain, Q. Philippot, A.-L. Neehus, E. Shaw, M. Migaud, L. Bizien, O. Ekwall, S. Berg, G. Beccuti, L. Ghizzoni, G. Thiriez, A. Pavot, C. Goujard, M.-L. Fremond, E. Carter, A. Rothenbuhler, A. Linglart, B. Mignot, A. Comte, N. Cheikh, O. Hermine, L. Breivik, E. S. Husebye, S. Humbert, P. Rohrlich, A. Coaquette, F. Vuoto, K. Faure, N. Mahlaoui, P. Kotnik, T. Battelino, K. Trebusak Podkrajsek, K. Kisand, E. M. N. Ferre, T. DiMaggio, L. B. Rosen, P. D. Burbelo, M. McIntyre, N. Y. Kann, A. Shcherbina, M. Pavlova, A. Kolodkina, S. M. Holland, S.-Y. Zhang, Y. J. Crow, L. D. Notarangelo, H. C. Su, L. Abel, M. S. Anderson, E. Jouanguy, B. Neven, A. Puel, J.-L. Casanova, M. S. Lionakis, Preexisting autoantibodies to type I IFNs underlie critical COVID-19 pneumonia in patients with APS-1. *J. Exp. Med.* **218**, e20210554 (2021).
25. C. Meisel, B. Akbil, T. Meyer, E. Lankes, V. M. Corman, O. Staudacher, N. Unterwalder, U. Kolsch, C. Drosten, M. A. Mall, T. Kallinich, D. Schnabel, C. Goffinet, H. von Bernuth, Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1. *J. Clin. Invest.* **131**, e150867 (2021).
26. B. Akbil, T. Meyer, P. Stubbemann, C. Thibeault, O. Staudacher, D. Niemeyer, J. Jansen, B. Mühlemann, J. Doehn, C. Tabeling, C. Nusshag, C. Hirzel, D. Sökler Sanchez, A. Nieters, A. Lother, D. Duerschmied, N. Schallner, J. Nikolaus Lieberum, D. August, S. Rieg, V. Falcone, H. Hengel, U. Kölsch, N. Unterwalder, R.-H. Hübner, T. C. Jones, N. Suttorp, C. Drosten, K. Warnatz, T. Spinetti, J. C. Schefold, T. Dörner, L. E. Sander, V. M. Corman, U. Merle; Pa-COVID study Group, F. Kurth, H. von Bernuth, C. Meisel, C. Goffinet, Early and rapid identification of COVID-19 patients with neutralizing type I interferon auto-antibodies. *J. Clin. Immunol.* **42**, 1111–1129 (2022).
27. R. Carapito, R. Li, J. Helms, C. Carapito, S. Gujja, V. Rolli, R. Guimaraes, J. Malagon-Lopez, P. Spinnhirny, A. Lederle, R. Mohseninia, A. Hirschler, L. Muller, P. Bastard, A. Gervais, Q. Zhang, F. Danion, Y. Ruch, M. Schenck, O. Collange, T.-N. Chamaraux-Tran, A. Molitor, A. Pichot, A. Bernard, O. Tahar, S. Bibi-Triki, H. Wu, N. Paul, S. Mayeur, A. Larnicol, G. Laumond, J. Frappier, S. Schmidt, A. Hanauer, C. Macquin, T. Stemmelen, M. Simons, X. Mariette, O. Hermine, S. Fafi-Kremer, B. Goichot, B. Drenou, K. Kuteifan, J. Pottecher, P.-M. Mertes, S. Kailasan, M. Javad Aman, E. Pin, P. Nilsson, A. Thomas, A. Viari, D. Sanlaville, F. Schneider, J. Sibilia, P.-L. Tharaux, J.-L. Casanova, Y. Hansmann, D. Lidar, M. Radosavljevic, J. R. Gulcher, F. Meziani, C. Moog, T. W. Chittenden, S. Bahram, Identification of driver genes for critical forms of COVID-19 in a deeply phenotyped young patient cohort. *Sci. Transl. Med*. **14**, eabj7521 (2022).
28. F. Frasca, M. Scordio, L. Santinelli, L. Gabriele, O. Gandini, A. Criniti, A. Pierangeli, A. Angeloni, C. M. Mastroianni, G. d'Ettorre, R. P. Viscidi, G. Antonelli, C. Scagnola, Anti-IFN-α/-ω neutralizing antibodies from COVID-19 patients correlate with downregulation of

IFN response and laboratory biomarkers of disease severity. *Euro. J. Immunol.* 10.1002/eji.202249824 (2022).
29. M. P. Raadsen, A. Gharbharan, C. C. E. Jordans, A. Z. Mykytyn, M. M. Lamers, P. B. van den Doel, H. Endeman, J. P. C. van den Akker, C. H. GeurtsvanKessel, M. P. G. Koopmans, C. Rokx, M. Goeijenbier, E. C. M. van Gorp, B. J. A. Rijnders, B. L. Haagmans, Interferon-α2 auto-antibodies in convalescent plasma therapy for COVID-19. *J. Clin. Immunol.* **42**, 232–239 (2022).
30. C. Meisel, B. Akbil, T. Meyer, E. Lankes, V. M. Corman, O. Staudacher, N. Unterwalder, U. Kölsch, C. Drosten, M. A. Mall, T. Kallinich, D. Schnabel, C. Goffinet, H. von Bernuth, Mild COVID-19 despite autoantibodies against type I IFNs in autoimmune polyendocrine syndrome type 1. *J. Clin. Invest.* **131**, e150867 (2021).
31. G. Lamacchia, A. Mazzoni, M. Spinicci, A. Vanni, L. Salvati, B. Peruzzi, S. Bencini, M. Capone, A. Carnasciali, P. Farahvachi, A. Rocca, S. Tekle Kiros, L. Graziani, L. Zammarchi, J. Mencarini, M. Grazia Colao, R. Caporale, F. Liotta, L. Cosmi, G. M. Rossolini, A. Bartoloni, L. Maggi, F. Annunziato, Clinical and immunological features of SARS-CoV-2 breakthrough infections in vaccinated Individuals requiring hospitalization. *J. Clin. Immunol.* **42**, 1379–1391 (2022).
32. S. Eto, Y. Nukui, M. Tsumura, Y. Nakagama, K. Kashimada, Y. Mizoguchi, T. Utsumi, M. Taniguchi, F. Sakura, K. Noma, Y. Yoshida, S. Ohshimo, S. Nagashima, K. Okamoto, A. Endo, K. Imai, H. Kanegane, H. Ohnishi, S. Hirata, E. Sugiyama, N. Shime, M. Ito, H. Ohge, Y. Kido, P. Bastard, J.-L. Casanova, O. Ohara, J. Tanaka, T. Morio, S. Okada, Neutralizing type I Interferon autoantibodies in Japanese patients with severe COVID-19. *J. Clin. Immunol.* **42**, 1360–1370 (2022).
33. E. Savvateeva, M. Filippova, V. Valuev-Elliston, N. Nuralieva, M. Yukina, E. Troshina, V. Baklaushev, A. Ivanov, D. Gryadunov, Microarray-based detection of antibodies against SARS-CoV-2 proteins, common respiratory viruses and type I interferons. *Viruses* **13**, 2553 (2021).
34. P. Bastard, A. Gervais, T. Le Voyer, J. Rosain, Q. Philippot, J. Manry, E. Michailidis, H. H. Hoffmann, S. Eto, M. Garcia-Prat, L. Bizien, A. Parra-Martinez, R. Yang, L. Haljasmagi, M. Migaud, K. Sarekannu, J. Maslovskaja, N. de Prost, Y. Tandjaoui-Lambiotte, C. E. Luyt, B. Amador-Borrero, A. Gaudet, J. Poissy, P. Morel, P. Richard, F. Cognasse, J. Troya, S. Trouillet-Assant, A. Belot, K. Saker, P. Garcon, J. G. Riviere, J. C. Lagier, S. Gentile, L. B. Rosen, E. Shaw, T. Morio, J. Tanaka, D. Dalmau, P. L. Tharaux, D. Sene, A. Stepanian, B. Megarbane, V. Triantafyllia, A. Fekkar, J. R. Heath, J. L. Franco, J. M. Anaya, J. Sole-Violan, L. Imberti, A. Biondi, P. Bonfanti, R. Castagnoli, O. M. Delmonte, Y. Zhang, A. L. Snow, S. M. Holland, C. Biggs, M. Moncada-Velez, A. A. Arias, L. Lorenzo, S. Boucherit, B. Coulibaly, D. Anglicheau, A. M. Planas, F. Haerynck, S. Duvlis, R. L. Nussbaum, T. Ozcelik, S. Keles, A. A. Bousfiha, J. El Bakkouri, C. Ramirez-Santana, S. Paul, Q. Pan-Hammarstrom, L. Hammarstrom, A. Dupont, A. Kurolap, C. N. Metz, A. Aiuti, G. Casari, V. Lampasona, F. Ciceri, L. A. Barreiros, E. Dominguez-Garrido, M. Vidigal, M. Zatz, D. van de Beek, S. Sahanic, I. Tancevski, Y. Stepanovskyy, O. Boyarchuk, Y. Nukui, M. Tsumura, L. Vidaur, S. G. Tangye, S. Burrel, D. Duffy, L. Quintana-Murci, A. Klocperk, N. Y. Kann, A. Shcherbina, Y. L. Lau, D. Leung, M. Coulongeat, J. Marlet, R. Koning, L. F. Reyes, A. Chauvineau-Grenier, F. Venet, G. Monneret, M. C. Nussenzweig, R. Arrestier, I. Boudhabhay, H. Baris-Feldman, D. Hagin, J. Wauters, I. Meyts, A. H. Dyer, S. P. Kennelly, N. M. Bourke, R. Halwani, N. S. Sharif-Askari, K. Dorgham, J. Sallette, S. M. Sedkaoui, S. AlKhater, R. Rigo-Bonnin, F. Morandeira, L. Roussel, D. C. Vinh, S. R. Ostrowski, A. Condino-Neto, C. Prando, A. Bonradenko, A. N. Spaan, L. Gilardin, J. Fellay, S. Lyonnet, K. Bilguvar, R. P. Lifton, S. Mane, HGID Lab, COVID Clinicians, COVID-STORM Clinicians, NIAID Immune Response to COVID Group, NH-COVAIR Study Group, Danish CHGE, Danish Blood Donor Study, St. James's Hospital, SARS CoV2 Interest group, French COVID Cohort Study Group, Imagine COVID-Group, Milieu Intérieur Consortium, CoV-Contact Cohort, Amsterdam UMC Covid-19, Biobank Investigators, COVID Human Genetic Effort, CONSTANCES cohort, 3C-Dijon Study, Cerba Health-Care, Etablissement du Sang study group, M. S. Anderson, B. Boisson, V. Beziat, S. Y. Zhang, E. Vandreakos, O. Hermine, A. Pujol, P. Peterson, T. H. Mogensen, L. Rowen, J. Mond, S. Debette, X. de Lamballerie, X. Duval, F. Mentre, M. Zins, P. Soler-Palacin, R. Colobran, G. Gorochov, X. Solanich, S. Susen, J. Martinez-Picado, D. Raoult, M. Vasse, P. K. Gregersen, L. Piemonti, C. Rodriguez-Gallego, L. D. Notarangelo, H. C. Su, K. Kisand, S. Okada, A. Puel, E. Jouanguy, C. M. Rice, P. Tiberghien, Q. Zhang, A. Cobat, L. Abel, J. L. Casanova, Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths. *Sci. Immunol.* **6**, eabl4340 (2021).
35. J. Manry, P. Bastard, A. Gervais, T. L. Voyer, J. Rosain, Q. Philippot, E. Michailidis, H.-H. Hoffmann, S. Eto, M. Garcia-Prat, L. Bizien, A. Parra-Martinez, R. Yang, L. Haljasmagi, M. Migaud, K. Sarekannu, J. Maslovskaja, N. de Prost, Y. Tandjaoui-Lambiotte, C.-E. Luyt, B. Amador-Borrero, A. Gaudet, J. Poissy, P. Morel, P. Richard, F. Cognasse, J. Troya, S. Trouillet-Assant, A. Belot, K. Saker, P. Garcon, J. G. Riviere, J.-C. Lagier, S. Gentile, L. Rosen, E. Shaw, T. Morio, J. Tanaka, D. Dalmau, P.-L. Tharaux, D. Sene, A. Stepanian, B. Megarbane, V. Triantafyllia, A. Fekkar, J. Heath, J. Franco, J.-M. Anaya, J. Sole-Violan, L. Imberti, A. Biondi, P. Bonfanti, R. Castagnoli, O. Delmonte, Y. Zhang, A. Snow, S. Holland, C. Biggs, M. Moncada-Velez, A. Arias, L. Lorenzo, S. Boucherit, D. Anglicheau, A. Planas, F. Haerynck, S. Duvlis, R. Nussbaum, T. Ozcelik, S. Keles, A. Bousfiha, J. E. Bakkouri, C. Ramirez-Santana, S. Paul, Q. Pan-Hammarstrom, L. Hammarstrom, A. Dupont, A. Kurolap, C. Metz, A. Aiuti, G. Casari, V. Lampasona, F. Ciceri, L. Barreiros, E. Dominguez-Garrido, M. Vidigal, M. Zatz, D. van de Beek, S. Sahanic, I. Tancevski, Y. Stepanovskyy, O. Boyarchuk, Y. Nukui, M. Tsumura, L. Vidaur, S. Tangye, S. Burrel, D. Duffy, L. Quintana-Murci, A. Klocperk, N. Kann, A. Shcherbina, Y.-L. Lau, D. Leung, M. Coulongeat, J. Marlet, R. Koning, L. Reyes, A. Chauvineau-Grenier, F. Venet, G. Monneret, M. Nussenzweig, R. Arrestier, I. Boudhabhay, H. Baris-Feldman, D. Hagin, J. Wauters, I. Meyts, A. Dyer, S. Kennelly, N. Bourke, R. Halwani, F. Sharif-Askari, K. Dorgham, J. Sallette, S. Mehlal-Sedkaoui, S. AlKhater, R. Rigo-Bonnin, F. Morandeira, L. Roussel, D. Vinh, C. Erikstrup, A. Condino-Neto, C. Prando, A. Bondarenko, A. Spaan, L. Gilardin, J. Fellay, S. Lyonnet, K. Bilguvar, R. Lifton, S. Mane, M. Anderson, B. Boisson, V. Beziat, S.-Y. Zhang, E. Andreakos, O. Hermine, A. Pujol, P. Peterson, T. H. Mogensen, L. Rowen, J. Mond, S. Debette, X. deLamballerie, C. Burdet, L. Bouadma, M. Zins, P. Soler-Palacin, R. Colobran, G. Gorochov, X. Solanich, S. Susen, J. Martinez-Picado, D. Raoult, M. Vasse, P. Gregersen, C. Rodriguez-Gallego, L. Piemonti, L. Notarangelo, H. Su, K. Kisand, S. Okada, A. Puel, E. Jouanguy, C. Rice, P. Tiberghien, Q. Zhang, J.-L. Casanova, L. Abel, A. Cobat, The risk of COVID-19 death is much greater and age-dependent with type I IFN autoantibodies. *Proc. Natl. Acad. Sci.* **119**, e2200413119 (2022).
36. F. P. Polack, S. J. Thomas, N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J. L. Perez, G. Perez Marc, E. D. Moreira, C. Zerbini, R. Bailey, K. A. Swanson, S. Roychoudhury, K. Koury, P. Li, W. V. Kalina, D. Cooper, R. W. Frenck Jr., L. L. Hammitt, O. Tureci, H. Nell, A. Schaefer, S. Unal, D. B. Tresnan, S. Mather, P. R. Dormitzer, U. Sahin, K. U. Jansen, W. C. Gruber, C4591001 Clinical Trial Group, Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine. *N. Engl. J. Med.* **383**, 2603–2615 (2020).
37. S. J. Thomas, E. D. Moreira Jr., N. Kitchin, J. Absalon, A. Gurtman, S. Lockhart, J. L. Perez, G. Perez Marc, F. P. Polack, C. Zerbini, R. Bailey, K. A. Swanson, X. Xu, S. Roychoudhury, K. Koury, S. Bouguermouh, W. V. Kalina, D. Cooper, R. W. Frenck Jr., L. L. Hammitt, Ö. Tureci, H. Nell, A. Schaefer, S. Ünal, Q. Yang, P. Liberator, D. B. Tresnan, S. Mather, P. R. Dormitzer, U. Sahin, W. C. Gruber, K. U. Jansen, C4591001 Clinical Trial Group, Safety and efficacy of the BNT162b2 mRNA Covid-19 vaccine through 6 months. *N. Engl. J. Med.* **385**, 1761–1773 (2021).
38. M. Bergwerk, T. Gonen, Y. Lustig, S. Amit, M. Lipsitch, C. Cohen, M. Mandelboim, E. G. Levin, C. Rubin, V. Indenbaum, I. Tal, M. Zavitan, N. Zuckerman, A. Bar-Chaim, Y. Kreiss, G. Regev-Yochay, Covid-19 breakthrough infections in vaccinated health care workers. *N. Engl. J. Med.* **385**, 1474–1484 (2021).
39. C. Kuhlmann, C. K. Mayer, M. Claassen, T. Maponga, W. A. Burgers, R. Keeton, C. Riou, A. D. Sutherland, T. Suliman, M. L. Shaw, W. Preiser, Breakthrough infections with SARS-CoV-2 omicron despite mRNA vaccine booster dose. *Lancet* **399**, 625–626 (2022).
40. M. W. Tenforde, W. H. Self, K. Adams, M. Gaglani, A. A. Ginde, T. McNeal, S. Ghamande, D. J. Douin, H. K. Talbot, J. D. Casey, N. M. Mohr, A. Zepeski, N. I. Shapiro, K. W. Gibbs, D. C. Files, D. N. Hager, A. Shehu, M. E. Prekker, H. L. Erickson, M. C. Exline, M. N. Gong, A. Mohamed, D. J. Henning, J. S. Steingrub, I. D. Peltan, S. M. Brown, E. T. Martin, A. S. Monto, A. Khan, C. L. Hough, L. W. Busse, C. C. Ten Lohuis, A. Duggal, J. G. Wilson, A. J. Gordon, N. Qadir, S. Y. Chang, C. Mallow, C. Rivas, H. M. Babcock, J. H. Kwon, N. Halasa, J. D. Chappell, A. S. Lauring, C. G. Grijalva, T. W. Rice, I. D. Jones, W. B. Stubblefield, A. Baughman, K. N. Womack, J. P. Rhoads, C. J. Lindsell, K. W. Hart, Y. Zhu, S. M. Olson, M. Kobayashi, J. R. Verani, M. M. Patel, Influenza and Other Viruses in the Acutely Ill (IVY) Network, Association between mRNA vaccination and COVID-19 hospitalization and disease severity. *JAMA* **326**, 2043–2054 (2021).
41. E. Leshem, K. Nelson, B. A. Lopman, Severe breakthrough COVID-19 infections in Scotland-implications for immunisation programmes. *Lancet. Respir. Med.* **9**, 1354–1356 (2021).
42. M. Lipsitch, F. Krammer, G. Regev-Yochay, Y. Lustig, R. D. Balicer, SARS-CoV-2 breakthrough infections in vaccinated individuals: Measurement, causes and impact. *Nat. Rev. Immunol.* **22**, 57–65 (2022).
43. J. Liu, M. T. Laurie, L. Rubio, S. E. Vazquez, S. Sunshine, A. M. Mitchell, M. Hapte-Selassie, S. A. Mann, G. Pilarowski, D. Black, C. Marquez, S. Rojas, M. S. Lionakis, M. Petersen, J. D. Whitman, V. Jain, M. Anderson, D. Havlir, J. DeRisi, SARS-CoV-2 transmission dynamics and immune responses in a household of vaccinated persons. *Clin. Infect. Dis.* ciac029 (2022).
44. T. Carvalho, F. Krammer, A. Iwasaki, The first 12 months of COVID-19: A timeline of immunological insights. *Nat. Rev. Immunol.* **21**, 245–256 (2021).
45. S. Stertz, B. G. Hale, Interferon system deficiencies exacerbating severe pandemic virus infections. *Trends Microbiol.* **29**, 973–982 (2021).
46. P. Bastard, E. Michailidis, H.-H. Hoffmann, M. Chbihi, T. Le Voyer, J. Rosain, Q. Philippot, Y. Seeleuthner, A. Gervais, M. Materna, P. M. N. de Oliveira, M. L. S. Maia, A. P. Dinis Ano Bom, T. Azamor, D. Araujo da Conceicao, E. Goudouris, A. Homma, G. Slesak, J. Schafer, B. Pulendran, J. D. Miller, R. Huits, R. Yang, L. B. Rosen, L. Bizien, L. Lorenzo, M. Chrabieh, L. V. Erazo, F. Rozenberg, M. M. Jeljeli, V. Beziat, S. M. Holland, A. Cobat, L. D. Notarangelo, H. C. Su, R. Ahmed, A. Puel, S.-Y. Zhang, L. Abel, S. J. Seligman,

Q. Zhang, M. R. MacDonald, E. Jouanguy, C. M. Rice, J.-L. Casanova, Auto-antibodies to type I IFNs can underlie adverse reactions to yellow fever live attenuated vaccine. *J. Exp. Med.* **218**, e20202486 (2021).
47. A. Meager, K. Visvalingam, P. Peterson, K. Moll, A. Murumagi, K. Krohn, P. Eskelin, J. Perheentupa, E. Husebye, Y. Kadota, N. Willcox, Anti-interferon autoantibodies in autoimmune polyendocrinopathy syndrome type 1. *PLOS Med.* **3**, e289 (2006).
48. A. Meager, M. Wadhwa, P. Dilger, C. Bird, R. Thorpe, J. Newsom-Davis, N. Willcox, Anti-cytokine autoantibodies in autoimmunity: Preponderance of neutralizing autoantibodies against interferon-alpha, interferon-omega and interleukin-12 in patients with thymoma and/or myasthenia gravis. *Clin. Exp. Immunol.* **132**, 128–136 (2003).
49. A. Gupta, Y. Gonzalez-Rojas, E. Juarez, M. Crespo Casal, J. Moya, D. R. Falci, E. Sarkis, J. Solis, H. Zheng, N. Scott, A. L. Cathcart, C. M. Hebner, J. Sager, E. Mogalian, C. Tipple, A. Peppercorn, E. Alexander, P. S. Pang, A. Free, C. Brinson, M. Aldinger, A. E. Shapiro, COMET-ICE Investigators, Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. *N. Engl. J. Med.* **385**, 1941–1950 (2021).
50. R. Levy, P. Zhang, P. Bastard, K. Dorgham, I. Melki, A. Hadchouel, G. C. Hartoularos, B. Neven, M. Castelle, C. Roy, T. Toin, L. Berteloot, L. Bizien, H. Abid, M. Burgard, N. Houhou-Fidouh, F. Rozenberg, E. Jouanguy, C. J. Ye, G. Gorochov, Q. Zhang, J.-L. Casanova, Monoclonal antibody-mediated neutralization of SARS-CoV-2 in an IRF9-deficient child. *Proc. Natl. Acad. Sci. U.S.A.* **118**, e2114390118 (2021).
51. J. H. Beigel, K. M. Tomashek, L. E. Dodd, A. K. Mehta, B. S. Zingman, A. C. Kalil, E. Hohmann, H. Y. Chu, A. Luetkemeyer, S. Kline, D. L. de Castilla, R. W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T. F. Patterson, R. Paredes, D. A. Sweeney, W. R. Short, G. Touloumi, D. C. Lye, N. Ohmagari, M. D. Oh, G. M. Ruiz-Palacios, T. Benfield, G. Fatkenheuer, M. G. Kortepeter, R. L. Atmar, C. B. Creech, J. Lundgren, A. G. Babiker, S. Pett, J. D. Neaton, T. H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, H. C. Lane, ACTT-1 Study Group Members, Remdesivir for the treatment of Covid-19—Final report. *N. Engl. J. Med.* **383**, 1813–1826 (2020).
52. R. L. Gottlieb, C. E. Vaca, R. Paredes, J. Mera, B. J. Webb, G. Perez, G. Oguchi, P. Ryan, B. U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R. H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F. M. Marty, M. J. Katz, A. A. Ginde, S. M. Brown, J. T. Schiffer, J. A. Hill, G.-U.-. Investigators, Early remdesivir to prevent progression to severe Covid-19 in outpatients. *N. Engl. J.Med.* **386**, 305–315 (2021).
53. A. Jayk Bernal, M. M. Gomes da Silva, D. B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martin-Quiros, Y. Caraco, A. Williams-Diaz, M. L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J. A. Grobler, H. H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J. R. Butterton, M. G. Johnson, C. De Anda, MOVe-OUT Study Group, Molnupiravir for oral treatment of Covid-19 in nonhospitalized patients. *N. Engl. J. Med.* **386**, 509–520 (2022).
54. J. Hammond, H. Leister-Tebbe, A. Gardner, P. Abreu, W. Bao, W. Wisemandle, M. Baniecki, V. M. Hendrick, B. Damle, A. Simón-Campos, R. Pypstra, J. M. Rusnak; EPIC-HR Investigators, Oral nirmatrelvir for high-risk, nonhospitalized adults with COVID-19. *N. Engl. J. Med.* **386**, 1397–1408 (2022).
55. P. D. Monk, R. J. Marsden, V. J. Tear, J. Brookes, T. N. Batten, M. Mankowski, F. J. Gabbay, D. E. Davies, S. T. Holgate, L. P. Ho, T. Clark, R. Djukanovic, T. M. A. Wilkinson, Inhaled Interferon Beta COVID-19 Study Group, Safety and efficacy of inhaled nebulised interferon beta-1a (SNG001) for treatment of SARS-CoV-2 infection: A randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Respir. Med.* **9**, 196–206 (2021).
56. S. K. Elledge, X. X. Zhou, J. R. Byrnes, A. J. Martinko, I. Lui, K. Pance, S. A. Lim, J. E. Glasgow, A. A. Glasgow, K. Turcios, N. S. Iyer, L. Torres, M. J. Peluso, T. J. Henrich, T. T. Wang, C. M. Tato, K. K. Leung, B. Greenhouse, J. A. Wells, Engineering luminescent biosensors for point-of-care SARS-CoV-2 antibody detection. *Nat. Biotechnol.* **39**, 928–935 (2021).
57. C. R. Zamecnik, J. V. Rajan, K. A. Yamauchi, S. A. Mann, R. P. Loudermilk, G. M. Sowa, K. C. Zorn, B. D. Alvarenga, C. Gaebler, M. Caskey, M. Stone, P. J. Norris, W. Gu, C. Y. Chiu, D. Ng, J. R. Byrnes, X. X. Zhou, J. A. Wells, D. F. Robbiani, M. C. Nussenzweig, J. L. DeRisi, M. R. Wilson, ReScan, a multiplex diagnostic pipeline, pans human sera for SARS-CoV-2 antigens. *Cell Rep. Med.* **1**, 100123 (2020).
58. M. Hoffmann, H. Kleine-Weber, S. Pöhlmann, A multibasic cleavage site in the spike protein of SARS-CoV-2 is essential for infection of human lung cells. *Mol. Cell* **78**, 779–784.e5 (2020).

Acknowledgments: We thank the patients and the patients' families for placing trust in us; the members of both branches of the Laboratory of Human Genetics of Infectious Diseases; Y. Nemirovskaya, M. Woollett, D. Liu, S. Boucherit, C. Rivalain, M. Chrabieh, and L. Lorenzo for administrative assistance; H. C. Su for fruitful discussions; and Y. Muyshondt and S. Sandmeyer for assistance. **Funding:** The Laboratory of Human Genetics of Infectious Diseases is supported by the Howard Hughes Medical Institute; The Rockefeller University; the St. Giles Foundation; the NIH (R01AI088364 and R01AI163029); the National Center for Advancing Translational Sciences (NCATS); NIH Clinical and Translational Science Award (CTSA) program (UL1 TR001866); a Fast Grant from Emergent Ventures, Mercatus Center at George Mason University; the Fisher Center for Alzheimer's Research Foundation; the Meyer Foundation; the JPB Foundation; the program "Investissement d'Avenir" launched by the French Government and implemented by the Agence Nationale de la Recherche (ANR) with references ANR-21-RHUS-08 and ANR-10-IAHU-01; the Integrative Biology of Emerging Infectious Diseases Laboratory of Excellence (ANR-10-LABX-62-IBEID); the French Foundation for Medical Research (FRM; EQU201903007798); the ANRS-COV05, ANR GENVIR (ANR-20-CE93-003), ANR AABIFNCOV (ANR-20-CO11-0001), and ANR GenMISC (ANR-21-COVR-0039) projects; the European Union's Horizon 2020 research and innovation programme under grant agreement no. 824110 (EASI-genomics); the Square Foundation; Grandir–Fonds de solidarité pour l'enfance; the Fondation du Souffle; the SCOR Corporate Foundation for Science; the French Ministry of Higher Education, Research, and Innovation (MESRI-COVID-19); Institut National de la Santé et de la Recherche Médicale (INSERM); REACTing-INSERM; and the University of Paris. C.R.-G., R.P.D., and C.F. were funded by Instituto de Salud Carlos III (COV20_01333 and COV20_01334), the Spanish Ministry of Science and Innovation (RTC-2017-6471-1; AEI/FEDER, UE), the Fundación Canaria Instituto de Investigación Sanitaria de Canarias (FIISC19/43), Grupo DISA (OA18/017), Fundación MAPFRE Guanarteme (OA21/131), and Cabildo Insular de Tenerife (CGIEU0000219140 and "Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19"). E.A. is supported by the Hellenic Foundation for Research and Innovation (INTERFLU, no. 1574) and the European Commission's Horizon 2020 research and innovation programme (CURE, grant no. 767015; IMMUNAID, grant no. 779295). L.R. and L.F.P.N. were supported by Singapore National Medical Research Council COVID-19 Research Fund (COVID19RF-001, COVID19RF-007, COVID19RF-0008, and COVID19RF-060) and A*STAR COVID-19 Research funding (H/20/04/g1/006). The UCSF COMET Consortium is supported by the Clinical and Translational Science Institute University of California, San Francisco and the NIH (U19AI077439). A.A., G.R.-B., and X.S. are funded by the 202115-31 project, funded by La Marató de TV3. L.D.N. was supported by the intramural Research Program of the NIAID, NIH. J.L.D. is supported by the Chan Zuckerberg Biohub. We acknowledge the support of the Chao Family Comprehensive Cancer Center Experimental Tissue Shared Resource, supported by the National Cancer Institute of the NIH under award number P30CA062203. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH. P.B. was supported by the FRM (EA20170638020). P.B. and T.L.V. were supported by the MD-PhD program of the Imagine Institute (with the support of the Fondation Bettencourt-Schueller). **Author contributions:** P.B. and J.-L.C. wrote the manuscript, with the assistance of S.V., Q.Z., S.-Y.Z., E.J., M.S.A., and J.L.D. who edited the manuscript, tables, and figures. P.B., S.V., J.L., L.M., A.Ge., T.L.V., J.R., Q.P., L.B., J.M., A.Pu., E.Jo., C.J.Y., A.C., and L.M.T. performed the experiments and generated and analyzed the data. P.B., S.D., L.Re., D.C.V., E.C., L.F.R., C.M., V.E., C.Z., A.W., A.M.M., G.W., R.B., A.F., S.S., I.T., P.G., Y.Z., S.D., D.A.-S., E.P.A., L.R., M.G., N.H., D.B., Y.T.-L., R.He., N.S.S.-A., J.D., S.B., Y.S., O.B., C.M., M.N., B.N., K.S., O.A., A.An., E.J., G.R.-B., C.T., M.L., P.L.T., A.V., A.N., C.R.-G., C.Y.W., C.D., C.P., E.S., F.V., G.P., G.N., G.M., H.A., H.K., I.C., L.A., L.N., L.I., M.S., M.T.L., M.R.W., M.B., Q.P.-H., V.Q., X.S., T.B., K.D., G.G., G.R.G., A.Bo., L.F.P.N., L.R., A.P., A.Ba., A.Bo., F.R., T.O., S.K., J.M.-P., L.D.N., J.T., X.S.M., S.T.-A., L.M.A., and E.A. treated and recruited the patients. Y.A.J., S.A., S.B., S.A.C., S.C., Z.C., G.K.F., R.G., A.J., K.N.K., T.L., D.L., A.L., C.L., R.L., M.M., V.N., R.P., L.P., P.P., A.A.R., A.R., N.R., B.S., C.S., A.S., K.T., L.T.A., A.W., and M.R.W. recruited patients and collected and managed samples and data. C.S.C., D.J.E., C.M.H., M.F.K., C.R.L., and P.G.W. founded and led the COMET Consortium. Q.Z., S.-Y.Z., E.J., M.S.A., J.-L.C., and J.L.D. supervised the study. **Competing interests:** J.-L.C. reports being an inventor on patent application PCT/US2021/042741, filed 22 July 2021, submitted by the Rockefeller University, which covers the diagnosis of, susceptibility to, and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. C.S.C., D.J.E., C.M.H., M.F.K., C.R.L., and P.G.W. report funding from Genentech. C.S.C. reports funding from the National Heart, Lung, and Blood Institute (NHLBI), the U.S. Food and Drug Administration (FDA), U.S. Department of Defense (DOD), and Quantum Leap Healthcare Collaborative and serves on consulting and advisory boards for Vasomune, Gen1e Life Sciences, Janssen, and Cellenkos. C.M.H. reports funding from NHLBI and consulting fees for clinical trial design with Spring Discovery. The other authors declare that they have no competing interests. **Data and materials availability:** All data needed to evaluate the conclusions in the paper are present in the paper or the Supplementary Materials.

Appendix: List of COVID HGE consortium authors

Laurent Abel[1], Cristian Achille[2], Alessandro Aiuti[3], Saleh Al-Muhsen[4], Fahd Al-Mulla[5], Mark S. Anderson[6], Evangelos Andreakos[7], Micol Angelini[2], Andrés A. Arias[8], Gokhan Aytekin[9], Fausto Baldanti[10,14], Aggelos Banos[11], Hagit Baris Feldman[12], Alexandre Belot[13], Federica Bergami[14], Catherine M. Biggs[15], Dusan Bogunovic[16], Alexandre Bolze[17], Anastasiia Bondarenko[18], Ahmed A. Bousfiha[19], Petter Brodin[20],

Yenan Bryceson[21], Carlos D. Bustamante[22], Manish J. Butte[23], Giorgio Casari[24], John Christodoulou[25], Bénédicte Clément[26], Antonio Condino-Neto[27], Stefan N. Constantinescu[28], Francesca Conti[29], Megan A. Cooper[30] , Maria Daganou[31], Clifton L. Dalgard[32], Murkesh Desai[33], Beth A. Drolet[34], Jamila El Baghdadi[35], Recai Ergun[36], Dilek Ergun[36], Sara Espinosa-Padilla[37], Jacques Fellay[38], Carlos Flores[39], José Luis Franco[40], Antoine Froidure[41], Stefano Ghirardello[2], Peter K. Gregersen[42], Bodo Grimbacher[43], Filomeen Haerynck[44], David Hagin[45], Rabih Halwani[46], Lennart Hammarström[47], James R. Heath[48], Sarah E. Henrickson[49], Elena W. Y. Hsieh[50], Eystein Husebye[51], Kohsuke Imai[52], Yuval Itan[53], Erich D. Jarvis[54], Fikret Kanat[36], Timokratis Karamitros[55], Kai Kisand[56], Vasyl Kopcha[57], Mykhaylo Korda[57], Cheng-Lung Ku[58], Vicky Lampropoulou[7], Yu-Lung Lau[59], Yun Ling[60], Carrie L. Lucas[61], Tom Maniatis[62], Davood Mansouri[63], László Maródi[64], Isabelle Meyts[65], Joshua D. Milner[66], Kristina Mironska[67], Trine H. Mogensen[68], Francesco Mojoli[69], Francisco Morandeira[70], Tomohiro Morio[71], Lisa F.P. Ng[72], Luigi D. Notarangelo[73], Giuseppe Novelli[74], Antonio Novelli[75], Cliona O'Farrelly[76], Satoshi Okada[77], Keisuke Okamoto[78], Tayfun Ozcelik[79], Michele Pagani[69], Qiang Pan-Hammarström[47], Maria Papadaki[7], Jean W. Pape[80], Rebeca Perez de Diego[81], David S. Perlin[82], Graziano Pesole[83], Andrea Pession[29], Antonio Piralla[14], Maria Pirounaki[11], Anna M. Planas[84], Carolina Prando[85], Aurora Pujol[86], Lluis Quintana-Murci[87], Sathishkumar Ramaswamy[88], Vasiliki Rapti[89], Laurent Renia[72], Igor Resnick[90], Raúl Rigo-Bonnin[70], Carlos Rodríguez-Gallego[91], Vanessa Sancho-Shimizu[92], Anna Sediva[93], Mikko R.J. Seppänen[94], Mohammed Shahrooei[95], Anna Shcherbina[96], Ondrej Slaby[97], Andrew L. Snow[98], Pere Soler-Palacín[99], András N. Spaan[100], Konstantinos Syrigos[89], Ivan Tancevski[101], Stuart G. Tangye[102], Ahmad Abou Tayoun[88], Vasiliki Triantafyllia[7], Sotirios Tsiodras[103], Baykal Tulek[36], Stuart E. Turvey[104], K. M. Furkan Uddin[105], Mohammed J. Uddin[106], Diederik van de Beek[107], Hulya Vatansev[108], Donald C. Vinh[109], Horst von Bernuth[110], Joost Wauters[111], Mayana Zatz[112], Pawel Zawadzki[113], Funda Gok[114], Melike Emiroglu[115], Gulsum Alkan[116], Burcu Yormaz[117], Jean-Laurent Casanova[118]

[1]Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France; University of Paris Cité, Imagine Institute, Paris, France.

[2]Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

[3]San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, and Vita Salute San Raffaele University, Milan, Italy.

[4]Immunology Research Lab, Department of Pediatrics, College of Medicine, King Saud University, Riyadh, Saudi Arabia.

[5]Dasman Diabetes Institute, Department of Genetics and Bioinformatics, Dasman, Kuwait.

[6]Diabetes Center, University of California, San Francisco, San Francisco, CA, USA.

[7]Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece.

[8]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA; Primary Immunodeficiencies Group, Department of Microbiology and Parasitology, School of Medicine, University of Antioquia, Medellín, Colombia; and School of Microbiology, University of Antioquia UdeA, Medellín, Colombia.

[9]Department of Immunology and Allergy, Konya City Hospital, Konya, Turkey.

[10]Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy.

[11]2nd Department of Internal Medicine and Research Laboratory, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Athens, Greece.

[12]Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.

[13]Pediatric Nephrology, Rheumatology, Dermatology, HFME, Hospices Civils de Lyon, National Referee Centre RAISE, and INSERM U1111, Université de Lyon, Lyon, France.

[14]Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

[15]Department of Pediatrics, BC Children's and St. Paul's Hospitals, University of British Columbia, Vancouver, British Columbia, Canada.

[16]Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[17]Helix, San Mateo, CA, USA.

[18]Shupyk National Medical Academy for Postgraduate Education, Kyiv, Ukraine.

[19]Clinical Immunology Unit, Department of Pediatric Infectious Disease, CHU Ibn Rushd and Laboratoire d'Immunologie Clinique, Inflammation et Allergie (LICIA), Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco.

[20]SciLifeLab, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden.

[21]Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden.

[22]Stanford University, Stanford, CA, USA.

[23]Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics and the Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA, USA.

[24]Clinical Genomics, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy.

[25]Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Melbourne, Victoria, Australia.

[26]Service des Urgences, Groupement Hospitalier Nord, Hospices Civils de Lyon, Lyon, France.

[27]Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil.

[28]de Duve Institute and Ludwig Cancer Research, Brussels, Belgium.

[29]Pediatric Unit, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna, Italy.

[30]Washington University School of Medicine, St. Louis, MO, USA.

[31]ICU, "Sotiria" General Hospital of Chest Diseases, Athens, Greece.

[32]Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.

[33]Bai Jerbai Wadia Hospital for Children, Mumbai, India.

[34]School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA.

[35]Genetics Unit, Military Hospital Mohamed V, Rabat, Morocco.

[36]Selcuk University, Department of Pulmonology, Konya, Turkey.

[37]Instituto Nacional de Pediatria (National Institute of Pediatrics), Mexico City, Mexico.

[38]School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; and Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.

[39]Research Unit, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid; and Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife; and Faculty of Health Sciences, University of Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain.
[40]Group of Primary Immunodeficiencies, University of Antioquia UDEA, Medellin, Colombia.
[41]Pulmonology Department, Cliniques Universitaires Saint-Luc; and Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium.
[42]Feinstein Institute for Medical Research, Northwell Health, Manhasset, NY, USA.
[43]Center for Chronic Immunodeficiency and Institute for Immunodeficiency, Medical Center, Faculty of Medicine, University of Freiburg, Freiburg, Germany.
[44]Department of Paediatric Immunology and Pulmonology, Centre for Primary Immunodeficiency Ghent (CPIG), PID Research Laboratory, Jeffrey Modell Diagnosis and Research Centre, Ghent University Hospital, Ghent, Belgium.
[45]Genetics Institute Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.
[46]Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates.
[47]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden.
[48]Institute for Systems Biology, Seattle, WA, USA.
[49]Department of Pediatrics, Division of Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; and Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.
[50]Departments of Pediatrics, Immunology and Microbiology, University of Colorado, School of Medicine, Aurora, CO, USA.
[51]Department of Medicine, Haukeland University Hospital, Bergen, Norway.
[52]Department of Community Pediatrics, Perinatal and Maternal Medicine, Tokyo Medical and Dental University (TMDU), Tokyo, Japan.
[53]Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; and Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA.
[54]Laboratory of Neurogenetics of Language and Howard Hughes Medical Institute, Rockefeller University, New York, NY, USA.
[55]Bioinformatics and Applied Genomics Unit, Hellenic Pasteur Institute, Athens, Greece.
[56]Molecular Pathology, Department of Biomedicine, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia.
[57]Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.
[58]Chang Gung University, Taoyuan County, Taiwan.
[59]Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong, China.
[60]Shanghai Public Health Clinical Center, Fudan University, Shanghai, China.
[61]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA.
[62]Zukerman Mind Brain Behavior Institute, Columbia University, New York, NY, USA.
[63]Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Masih Daneshvari Hospital, Shahid Beheshti, University of Medical Sciences, Tehran, Iran.
[64]Primary Immunodeficiency Clinical Unit and Laboratory, Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary.
[65]Department of Pediatrics, University Hospitals Leuven; KU Leuven, Department of Microbiology, Immunology and Transplantation; and Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium.
[66]Department of Pediatrics, Columbia University Irving Medical Center, New York, NY, USA.
[67]University Clinic for Children's Diseases, Department of Pediatric Immunology, Medical Faculty, University "St. Cyril and Methodij" Skopje, North Macedonia.
[68]Department of Biomedicine, Aarhus University, Aarhus, Denmark.
[69]Anesthesia and Intensive Care, Rianimazione I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.
[70]Department of Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain.
[71]Tokyo Medical and Dental University Hospital, Tokyo, Japan.
[72]A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore, Singapore; and Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore, Singapore.
[73]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA.
[74]Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy.
[75]Laboratory of Medical Genetics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy.
[76]Comparative Immunology Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland.
[77]Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan.
[78]Tokyo Medical and Dental University, Tokyo, Japan.
[79]Department of Molecular Biology and Genetics, Bilkent University, Bilkent-Ankara, Turkey.
[80]Haitian Study Group for Kaposi's Sarcoma and Opportunistic Infections (GHESKIO), Port-au-Prince, Haiti.
[81]Institute of Biomedical Research of IdiPAZ, University Hospital "La Paz", Madrid, Spain.
[82]Center for Discovery and Innovation, Hackensack Meridian Health, Nutley, NJ, USA.
[83]Department of Biosciences, Biotechnology and Biopharmaceutics, University of Bari A. Moro, Bari, Italy.
[84]IIBB-CSIC, IDIBAPS, Barcelona, Spain.
[85]Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil.
[86]Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; Catalan Institution of Research and Advanced Studies

(ICREA), Barcelona, Spain; and Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Barcelona, Spain.
[87]Human Evolutionary Genetics Unit, CNRS U2000, Institut Pasteur, Paris, France; and Human Genomics and Evolution, Collège de France, Paris, France.
[88]Al Jalila Children's Hospital, Dubai, United Arab Emirates.
[89]3rd Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, "Sotiria" General Hospital of Chest Diseases, Athens, Greece.
[90]University Hospital St. Marina, Varna, Bulgaria.
[91]Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; and Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain.
[92]Department of Paediatric Infectious Diseases and Virology, Imperial College London, London, UK; and Centre for Paediatrics and Child Health, Faculty of Medicine, Imperial College London, London, UK.
[93]Department of Immunology, Second Faculty of Medicine Charles University, V Uvalu, University Hospital in Motol, Prague, Czech Republic.
[94]Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; and Rare Diseases Center and Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland.
[95]Specialized Immunology Laboratory of Dr. Shahrooei, Ahvaz, Iran; and Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium.
[96]Department of Immunology, Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia.
[97]Central European Institute of Technology and Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czech Republic.
[98]Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.
[99]Pediatric Infectious Diseases and Immunodeficiencies Unit, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain.
[100]St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA; and Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands.
[101]Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria.
[10] Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia; and St. Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, Kensington, New South Wales, Australia.
[103]4th Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, "Attikon" University General Hospital, Athens, Greece.
[104]BC Children's Hospital, University of British Columbia, Vancouver, Canada.
[105]Centre for Precision Therapeutics, Genetics and Genomic Medicine Centre, NeuroGen Children's Healthcare and Lecturer, Holy Family Red Crescent Medical College Dhaka, Bangladesh.
[106]College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, United Arab Emirates; and Cellular Intelligence (Ci) Lab, GenomeArc Inc., Toronto, Ontario, Canada.
[107]Department of Neurology, Amsterdam Neuroscience, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands.
[108]Necmettin Erbakan University, Department of Pulmonology, Konya, Turkey.
[109]Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, Québec, Canada; and Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, Québec, Canada.
[110]Department of Pediatric Pneumology, Immunology and Intensive Care, Charité Universitätsmedizin, Berlin University Hospital Center, Berlin, Germany; and Labor Berlin GmbH, Department of Immunology, Berlin, Germany; and Berlin Institutes of Health (BIH), Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany.
[111]Department of General Internal Medicine, Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium.
[112]Biosciences Institute, University of São Paulo, São Paulo, Brazil.
[113]Molecular Biophysics Division, Faculty of Physics, A. Mickiewicz University, Poznań, Poland.
[114]Necmettin Erbakan University, Division of Intensive Care Unit, Konya, Turkey.
[115]Selcuk University, Division of Pediatric Infectious Disease, Konya, Turkey.
[116]Division of Pediatric Infectious Disease, Konya, Turkey.
[117]Selcuk University, Department of Pulmonology, Konya, Turkey.
[118]Rockefeller University and Howard Hughes Medical Institute, New York, NY, USA; and Necker Hospital for Sick Children and INSERM, Paris, France.

Submitted 4 March 2022
Accepted 26 May 2022
Published First Release 14 June 2022
Final published 22 December 2023
10.1126/sciimmunol.abp8966