



Autoantibodies neutralizing type I IFNs are present in 4% of uninfected individuals over 70 years old and account for 20% of COVID-19 deaths

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CORONAVIRUS

Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

Paul Bastard^{1,2,3*}, Adrian Gervais^{1,2†}, Tom Le Voyer^{1,2†}, Jérémie Rosain^{1,2†}, Quentin Philippot^{1,2†},
 Jérémy Manry^{1,2‡}, Eleftherios Michailidis^{4‡}, Hans-Heinrich Hoffmann^{4‡}, Shohei Eto^{5§},
 Marina Garcia-Prat^{6§}, Lucy Bizien^{1,2§}, Alba Parra-Martínez^{6§}, Rui Yang^{3§}, Liis Haljasmägi^{7§},
 Mélanie Migaud^{1,2§}, Karita Särekannu^{7§}, Julia Maslovskaja^{7§}, Nicolas de Prost^{8,9},
 Yacine Tandjaoui-Lambiotte¹⁰, Charles-Edouard Luyt^{11,12}, Blanca Amador-Borrero¹³,
 Alexandre Gaudet^{14,15,16,17,18}, Julien Poissy^{14,15,16,17,18}, Pascal Morel^{19,20}, Pascale Richard¹⁹,
 Fabrice Cognasse^{21,22}, Jesus Troya²³, Sophie Trouillet-Assant^{24,25,26}, Alexandre Belot^{24,25,27,28},
 Kahina Saker^{24,25}, Pierre Garçon²⁹, Jacques G. Rivière⁶, Jean-Christophe Lagier^{30,31}, Stéphanie Gentile^{32,33},
 Lindsey B. Rosen³⁴, Elana Shaw³⁴, Tomohiro Morio³⁵, Junko Tanaka³⁶, David Dalmau³⁷,
 Pierre-Louis Tharaux³⁸, Damien Sene¹³, Alain Stepanian³⁹, Bruno Megarbane⁴⁰, Vasiliki Triantafyllia⁴¹,
 Arnaud Fekkar^{1,42}, James R. Heath⁴³, José Luis Franco⁴⁴, Juan-Manuel Anaya⁴⁵, Jordi Solé-Violán^{46,47},
 Luisa Imberti⁴⁸, Andrea Biondi⁴⁹, Paolo Bonfanti⁵⁰, Riccardo Castagnoli^{34,51}, Ottavia M. Delmonte³⁴,
 Yu Zhang^{34,52}, Andrew L. Snow⁵³, Steven M. Holland³⁴, Catherine M. Biggs⁵⁴, Marcela Moncada-Vélez³,
 Andrés Augusto Arias^{3,55,56}, Lazaro Lorenzo^{1,2}, Soraya Boucherit^{1,2}, Boubacar Coulibaly^{1,2},
 Dany Anglicheau^{57,58}, Anna M. Planas^{59,60}, Filomeen Haerynck⁶¹, Sotirija Duvlis^{62,63}, Robert L. Nussbaum⁶⁴,
 Tayfun Ozelik⁶⁵, Sevgi Keles⁶⁶, Ahmed A. Bousfiha⁶⁷, Jalila El Bakkouri⁶⁷, Carolina Ramirez-Santana^{44,45},
 Stéphane Paul⁶⁸, Qiang Pan-Hammarström⁶⁹, Lennart Hammarström⁶⁹, Annabelle Dupont⁷⁰,
 Alina Kurolap⁷¹, Christine N. Metz⁷², Alessandro Aiuti⁷³, Giorgio Casari⁷³, Vito Lampasona⁷⁴,
 Fabio Ciceri⁷⁵, Lucila A. Barreiros⁷⁶, Elena Dominguez-Garrido⁷⁷, Mateus Vidigal⁷⁸,
 Mayana Zatz⁷⁸, Diederik van de Beek⁷⁹, Sabina Sahanic⁸⁰, Ivan Tancevski⁸⁰, Yurii Stepanovskyy⁸¹,
 Oksana Boyarchuk⁸², Yoko Nukui⁸³, Miyuki Tsumura⁵, Loreto Vidaur^{84,85}, Stuart G. Tangye^{86,87},
 Sonia Burrell⁸⁸, Darragh Duffy⁸⁹, Lluís Quintana-Murci^{90,91}, Adam Klocperk⁹², Nelli Y. Kann⁹³,
 Anna Shcherbina⁹³, Yu-Lung Lau⁹⁴, Daniel Leung⁹⁴, Matthieu Coulangeat⁹⁵, Julien Marlet^{96,97},
 Rutger Koning⁷⁹, Luis Felipe Reyes^{98,99}, Angélique Chauvineau-Grenier¹⁰⁰, Fabienne Venet^{101,102,103},
 Guillaume Monneret^{101,103}, Michel C. Nussenzweig^{104,105}, Romain Arrestier^{8,9}, Idris Boudhabhay^{57,58},
 Hagit Baris-Feldman^{71,106}, David Hagin^{106,107}, Joost Wauters¹⁰⁸, Isabelle Meyts^{109,110}, Adam H. Dyer^{111,112},
 Sean P. Kennelly^{111,112}, Nollaig M. Bourke¹¹³, Rabih Halwani¹¹⁴, Narjes Saheb Sharif-Askari¹¹⁴,
 Karim Dorgham¹¹⁵, Jérôme Sallette¹¹⁶, Souad Mehlal Sedkaoui¹¹⁶, Suzan AlKhater^{117,118},
 Raúl Rigo-Bonnin¹¹⁹, Francisco Morandeira¹²⁰, Lucie Roussel^{121,122}, Donald C. Vinh^{121,122}, Sisse Rye Ostrowski¹²³,
 Antonio Condino-Neto⁷⁶, Carolina Prando¹²⁴, Anastasiia Bondarenko⁸¹, András N. Spaan^{3,125},
 Laurent Gilardin^{126,127}, Jacques Fellay^{128,129,130}, Stanislas Lyonnet¹³¹, Kaya Bilguvar^{132,133,134,135},
 Richard P. Lifton^{132,133,136}, Shrikant Mane¹³³, 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^{||}, The Milieu Intérieur Consortium^{||},
 CoV-Contact Cohort^{||}, Amsterdam UMC Covid-19 Biobank Investigators^{||}, COVID Human Genetic Effort^{||},
 CONSTANCES cohort^{||}, 3C-Dijon Study^{||}, Cerba HealthCare^{||}, Etablissement du Sang study group^{||},
 Mark S. Anderson¹³⁷, Bertrand Boisson^{1,2,3}, Vivien Béziat^{1,2,3}, Shen-Ying Zhang^{1,2,3},
 Evangelos Andreacos^{41¶}, Olivier Hermine^{2,138¶}, Aurora Pujol^{139¶}, Pärt Peterson^{7¶},
 Trine H. Mogensen^{140,141¶}, Lee Rowen^{43¶}, James Mond^{142¶}, Stéphanie Debette^{143,144¶},
 Xavier de Lamballerie^{145¶}, Xavier Duval^{146,147,148,149¶}, France Mentre^{146,147,148¶}, Marie Zins^{150¶},
 Pere Soler-Palacin^{6¶}, Roger Colobran^{151¶}, Guy Gorochov^{115,152¶}, Xavier Solanich^{153¶},
 Sophie Susen^{70¶}, Javier Martinez-Picado^{154,155,156¶}, Didier Raoult^{30,31¶}, Marc Vasse^{157¶},
 Peter K. Gregersen^{72¶}, Lorenzo Piemonti^{74¶}, Carlos Rodríguez-Gallego^{158,159¶},
 Luigi D. Notarangelo^{34#}, Helen C. Su^{34,160#}, Kai Kisand^{7#}, Satoshi Okada^{5#}, Anne Puel^{1,2,3#},
 Emmanuelle Jouanguy^{1,2,3#}, Charles M. Rice^{4#}, Pierre Tiberghien^{19,20#}, Qian Zhang^{1,2,3#},
 Aurélie Cobat^{1,2,3#}, Laurent Abel^{1,2,3**}, Jean-Laurent Casanova^{1,2,3,105*,**}

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Circulating autoantibodies (auto-Abs) neutralizing high concentrations (10 ng/ml; in plasma diluted 1:10) of IFN- α and/or IFN- ω are found in about 10% of patients with critical COVID-19 (coronavirus disease 2019) pneumonia but not in individuals with asymptomatic infections. We detect auto-Abs neutralizing 100-fold lower, more physiological, concentrations of IFN- α and/or IFN- ω (100 pg/ml; in 1:10 dilutions of plasma) in 13.6% of 3595 patients with critical COVID-19, including 21% of 374 patients >80 years, and 6.5% of 522 patients with severe COVID-19. These antibodies are also detected in 18% of the 1124 deceased patients (aged 20 days to 99 years; mean: 70 years). Moreover, another 1.3% of patients with critical COVID-19 and 0.9% of the deceased patients have auto-Abs neutralizing high concentrations of IFN- β . We also show, in a sample of 34,159 uninfected individuals from the general population, that auto-Abs neutralizing high concentrations of IFN- α and/or IFN- ω are present in 0.18% of individuals between 18 and 69 years, 1.1% between 70 and 79 years, and 3.4% >80 years. Moreover, the proportion of individuals carrying auto-Abs neutralizing lower concentrations is greater in a subsample of 10,778 uninfected individuals: 1% of individuals <70 years, 2.3% between 70 and 80 years, and 6.3% >80 years. By contrast, auto-Abs neutralizing IFN- β do not become more frequent with age. Auto-Abs neutralizing type I IFNs predate SARS-CoV-2 infection and sharply increase in prevalence after the age of 70 years. They account for about 20% of both critical COVID-19 cases in the over 80s and total fatal COVID-19 cases.

INTRODUCTION

Since the start of the coronavirus disease 2019 (COVID-19) pandemic in December 2019, more than 200 million people have been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulting in at least 4 million deaths and probably closer to 7 to 9 million deaths worldwide. Interindividual clinical variability in the course of acute infection is vast, extending from silent or mild infection in about 90% of individuals to pneumonia and respiratory failure, both requiring hospitalization, in less than 10 and 2% of cases, respectively. Age is the major epidemiological risk factor for hospitalization or death from pneumonia, the risk doubling with every 5 years of age (1, 2). The frequencies of critical disease and death from COVID-19 are higher in men than in women (3–5). With the COVID Human Genetic Effort (6), we previously reported that inborn errors of Toll-like receptor 3 (TLR3)– and interferon (IFN) regulatory factor 7 (IRF7)–dependent type I IFN

induction and amplification can underlie life-threatening COVID-19 pneumonia in a small subset of patients (7, 8). Autosomal dominant disorders were found in 19 patients, but our cohort also included four previously healthy unrelated adults aged 25 to 50 years with autosomal recessive, complete IRF7 ($N = 2$) or IFN- α/β receptor 1 (IFNAR1) ($N = 2$) deficiency. These findings indicated that type I IFN immunity is essential for protective immunity to respiratory infection with SARS-CoV-2 but unexpectedly redundant otherwise. We also reported that an autoimmune phenocopy of inborn errors of type I IFN–dependent immunity can underlie critical COVID-19 pneumonia (9). Autoantibodies (auto-Abs) neutralizing IFN- $\alpha 2$ and/or IFN- ω (10 ng/ml) were found in the blood of at least 10% of an international cohort of patients with life-threatening COVID-19 pneumonia but in none of the tested individuals with asymptomatic or paucisymptomatic infection (9). These auto-Abs were detected in serum or plasma diluted 1:10. The auto-Abs in the patients' undiluted

¹Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France. ²University of Paris, Imagine Institute, Paris, France. ³St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, Rockefeller University, New York, NY, USA. ⁴Laboratory of Virology and Infectious Disease, Rockefeller University, New York, NY, USA. ⁵Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ⁶Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain. ⁷Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu, Estonia. ⁸Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, France. ⁹Groupe de Recherche Clinique CARMAS, Faculté de santé de Créteil, Université Paris Est Créteil, 51 Avenue du Maréchal de Lattre de Tassigny, 94010 Créteil Cedex, France. ¹⁰Avicenne Hospital, AP-HP, Bobigny, INSERM U1272, Hypoxia and Lung, Bobigny, France. ¹¹Sorbonne Université, Hôpital Pitié Salpêtrière, Médecine Intensive Réanimation, AP-HP, Paris, France. ¹²INSERM UMRS 1166-ICAN, Institute of Cardiometabolism and Nutrition, Paris, France. ¹³Internal Medicine Department, Lariboisière Hospital AP-HP, Paris University, Paris, France. ¹⁴University of Lille, U1019-UMR9017, Center for Infection and Immunity of Lille, Lille, France. ¹⁵CNRS, UMR9017, Lille, France. ¹⁶INSERM U1019, Lille, France. ¹⁷Institut Pasteur de Lille, Lille, France. ¹⁸CHU de Lille, Pôle de Réanimation, Hôpital Roger Salengro Lille, Lille, France. ¹⁹Établissement Français Du Sang, La Plaine Saint-Denis, France. ²⁰UMR1098 RIGHT, INSERM, EFS, Université de Franche-Comté, Besançon, France. ²¹SAINBIOSE, INSERM U1059, University of Lyon, Université Jean Monnet Saint-Etienne, Saint-Etienne, France. ²²Établissement Français du Sang, Auvergne-Rhône-Alpes, Saint-Etienne, France. ²³Department of Internal Medicine, Infanta Leonor University Hospital, Madrid, Spain. ²⁴Hospices Civils de Lyon, Lyon, France. ²⁵International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France. ²⁶Joint Research Unit, Hospices Civils de Lyon-BioMérieux, Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France. ²⁷National Referee Centre for Rheumatic, and Autoimmune and Systemic Diseases in Children (RAISE), Lyon, France. ²⁸Immunopathology Federation LIFE, Hospices Civils de Lyon, Lyon, France. ²⁹Intensive Care Unit, Grand Hôpital de l'Est Francilien Site de Marne-La-Vallée, Jossigny, France. ³⁰Institut Hospitalo-Universitaire Méditerranée Infection, Marseille, France. ³¹Aix-Marseille Université, IRD, Assistance Publique Hôpitaux de Marseille (APHM), MEPIH, Marseille, France. ³²Service d'Évaluation Médicale, Hôpitaux Universitaires de Marseille APHM, Marseille, France. ³³Aix-Marseille University, School of Medicine, La Timone Medical Campus, EA 3279, CERES–Health Service Research and Quality of Life Center, Marseille, France. ³⁴Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, National Institutes of Health (NIH), Bethesda, MD, USA. ³⁵Department of Pediatrics and Developmental Biology, Graduate School of Medical and Dental Sciences, Tokyo Medical and Dental University (TMDU), Tokyo, Japan. ³⁶Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ³⁷Hospital Universitari MútuaTerrassa; Fundació Docència i Recerca MútuaTerrassa; Universitat de Barcelona. ³⁸Paris Cardiovascular Research Center, PARCC, INSERM, Université de Paris, Paris, France. ³⁹Service d'Hématologie Biologique, Hôpital Lariboisière, AP-HP and EA3518, Institut Universitaire d'Hématologie-Hôpital Saint Louis, Université Paris Diderot, Paris, France. ⁴⁰Réanimation Médicale et Toxicologique, Hôpital Lariboisière (AP-HP), Université Paris-Diderot, INSERM Unité Mixte de Recherche Scientifique (UMRS) 1144, Paris, France. ⁴¹Laboratory of Immunobiology, Center for Clinical, Experimental Surgery, and Translational Research, Biomedical Research Foundation of the Academy of Athens, 11527 Athens, Greece. ⁴²Service de Parasitologie-Mycologie, Groupe Hospitalier Pitié Salpêtrière, AP-HP, Paris, France. ⁴³Institute for Systems Biology, Seattle, WA, USA. ⁴⁴Primary Immunodeficiencies Group, Department of Microbiology and Parasitology, School of Medicine, University of Antioquia UdeA, Medellín, Colombia. ⁴⁵Center for Autoimmune Disease Research, School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia. ⁴⁶Intensive Care Medicine, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Canary Islands, Spain. ⁴⁷CIBER de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain. ⁴⁸CREA Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia,

Brescia, Italy.⁴⁹Pediatric Department and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN, University of Milano Bicocca, Fondazione MBM, Ospedale San Gerardo, Monza, Italy.⁵⁰Department of Infectious Diseases, San Gerardo Hospital, University of Milano Bicocca, Monza, Italy.⁵¹Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy.⁵²NIAID Clinical Genomics Program, NIH, Bethesda, USA.⁵³Department of Pharmacology and Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA.⁵⁴Department of Pediatrics, British Columbia Children's Hospital, University of British Columbia, Vancouver, BC, Canada.⁵⁵Primary Immunodeficiencies Group, University of Antioquia UdeA, Medellín, Colombia.⁵⁶School of Microbiology, University of Antioquia UdeA, Medellín, Colombia.⁵⁷Department of Nephrology and Transplantation, Neckar University Hospital, AHP, Paris, France.⁵⁸INEM, INSERM U1151-CNRS UMR 8253, Paris University, Paris, France.⁵⁹Institute for Biomedical Research (IIBB), Spanish National Research Council (CSIC), Barcelona, Spain.⁶⁰Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain.⁶¹Department of Paediatric Immunology and Pulmonology, Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Center, Ghent University Hospital, Ghent, Belgium.⁶²Faculty of Medical Sciences, University "Goce Delchev," Stip, Republic of Northern Macedonia.⁶³Institute of public health of the Republic of North Macedonia, Skopje, Republic of Northern Macedonia.⁶⁴Cancer Genetics and Prevention Program, University of California, San Francisco, San Francisco, CA, USA.⁶⁵Department of Molecular Biology and Genetics, Bilkent University, Bilkent, Ankara, Turkey.⁶⁶Meram Faculty of Medicine, Necmettin Erbakan University, Konya, Turkey.⁶⁷Clinical Immunology Unit, Department of Pediatric Infectious Disease, CHU Ibn Rushd and LICIA, Laboratoire d'Immunologie Clinique, Inflammation et Allergie, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco.⁶⁸Department of Immunology, CIC1408, GIMAP Centre International de Recherche en Infectiologie (CIRI) INSERM U1111, University Hospital of Saint-Étienne, Saint-Étienne, France.⁶⁹Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden.⁷⁰Université de Lille, INSERM, CHU de Lille, Institut Pasteur de Lille, U1011-EGID, F-59000 Lille, France.⁷¹Genetics Institute, Tel Aviv Sourasky Medical Center, Tel Aviv University, Tel Aviv, Israel.⁷²Feinstein Institutes for Medical Research, Northwell Health, Manhasset, NY, USA.⁷³Vita-Salute San Raffaele University, and Clinical Genomics, IRCCS Ospedale San Raffaele, Milan, Italy.⁷⁴Diabetes Research Institute, IRCCS San Raffaele Scientific Institute, Milan, Italy.⁷⁵Hematology and Bone Marrow Transplantation Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy.⁷⁶Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil.⁷⁷Fundación Rioja Salud, Centro de Investigación Biomédica de La Rioja, Logroño, Spain.⁷⁸University of São Paulo, São Paulo, Brazil.⁷⁹Department of Neurology, Amsterdam Neuroscience, Amsterdam, Netherlands.⁸⁰Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria.⁸¹Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine.⁸²Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine.⁸³Department of Infection Control and Prevention, Medical Hospital, TMDU, Tokyo, Japan.⁸⁴Intensive Care Medicine, Donostia University Hospital, Biodonostia Institute of Donostia, San Sebastián, Spain.⁸⁵CIBERES, Instituto de Salud Carlos III, Madrid, Spain.⁸⁶Garvan Institute of Medical Research, Sydney, Australia.⁸⁷St Vincent's Clinical School, Faculty of Medicine and Health, UNSW Sydney, New South Wales, Australia.⁸⁸Sorbonne Université, INSERM U1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP), AP-HP, Hôpital Pitié Salpêtrière, Service de Virologie, Paris, France.⁸⁹Translational Immunology Laboratory, Institut Pasteur, Paris, France.⁹⁰Human Evolutionary Genetics Unit, Institut Pasteur, CNRS UMR 2000, Paris, France.⁹¹Chair of Human Genomics and Evolution, Collège de France, Paris, France.⁹²Department of Immunology, 2nd Faculty of Medicine, Charles University and University Hospital in Motol, Prague, Czech Republic.⁹³Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia.⁹⁴Department of Paediatrics and Adolescent Medicine, University of Hong Kong, Hong Kong, China.⁹⁵Division of Geriatric Medicine, Tours University Medical Center, Tours, France.⁹⁶INSERM U1259, MAVIWH, Université de Tours, Tours, France.⁹⁷Service de Bactériologie, Virologie et Hygiène hospitalière, CHU de Tours, Tours, France.⁹⁸Department of Microbiology, Universidad de La Sabana, Chía, Colombia.⁹⁹Department of Critical Care Medicine, Clínica Universidad de La Sabana, Chía, Colombia.¹⁰⁰Service de Biologie Médicale, CHI Robert Ballanger, Aulnay-sous-Bois, France.¹⁰¹Laboratoire d'Immunologie, Hospices Civils de Lyon, Hôpital Edouard Herriot, Lyon, France.¹⁰²CIRI, INSERM U1111, CNRS, UMR5308, Ecole Normale Supérieure de Lyon, Université Claude Bernard Lyon 1, Lyon, France.¹⁰³EA 7426, Pathophysiology of Injury-Induced Immunosuppression, Université Claude Bernard Lyon 1, Hospices Civils de Lyon, Hôpital Edouard Herriot-BioMérieux, Lyon, France.¹⁰⁴Laboratory of Molecular Immunology, Rockefeller University, New York, NY, USA.¹⁰⁵Howard Hughes Medical Institute, New York, NY, USA.¹⁰⁶Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel.¹⁰⁷Allergy and Clinical Immunology Unit, Department of Medicine, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.¹⁰⁸Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium.¹⁰⁹Laboratory of Inborn Errors of Immunity, Department of Microbiology, Immunology and Transplantation, KU Leuven, Leuven, Belgium.¹¹⁰Department of Pediatrics, Jeffrey Modell Diagnostic and Research Network Center, University Hospitals Leuven, Leuven, Belgium.¹¹¹Department of Age-Related Healthcare, Tallaght University Hospital, Dublin, Ireland.¹¹²Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland.¹¹³Department of Medical Gerontology, School of Medicine, Trinity College Dublin, Dublin, Ireland.¹¹⁴Sharjah Institute for Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates.¹¹⁵Sorbonne Université, INSERM, Centre d'Immunologie et des Maladies Infectieuses, (CIMI-Paris), Paris, France.¹¹⁶Cerba HealthCare, Issy-les-Moulineaux, France.¹¹⁷Department of Pediatrics, King Fahad Hospital of the University, Al Khobar, Saudi Arabia.¹¹⁸College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia.¹¹⁹Department of Clinical Laboratory, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain.¹²⁰Department of Immunology, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain.¹²¹Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, QC, Canada.¹²²Infectious Disease Susceptibility Program, Research Institute of the McGill University Health Centre, Montréal, QC, Canada.¹²³Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.¹²⁴Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil.¹²⁵Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands.¹²⁶Service de Médecine Interne, Hôpital universitaire Jean-Verdier AP-HP, Bondy, France.¹²⁷INSERM U1138, Centre de Recherche des Cordeliers, Paris, France.¹²⁸School of Life Sciences, École Polytechnique Fédérale de Lausanne, Lausanne, Switzerland.¹²⁹Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland.¹³⁰Swiss Institute of Bioinformatics, Lausanne, Switzerland.¹³¹Imagine Institute, Université de Paris, INSERM UMR 1163, Paris, France.¹³²Yale Center for Genome Analysis, Yale School of Medicine, New Haven, CT, USA.¹³³Department of Genetics, Yale University School of Medicine, New Haven, CT, USA.¹³⁴Department of Neurosurgery, Yale University School of Medicine, New Haven, CT, USA.¹³⁵Department of Medical Genetics, Acibadem University School of Medicine, Istanbul, Turkey.¹³⁶Laboratory of Human Genetics and Genomics, Rockefeller University, New York, NY, USA.¹³⁷Diabetes Center, University of California San Francisco, San Francisco, CA, USA.¹³⁸Department of Hematology, Neckar Hospital, AP-HP, Paris, France.¹³⁹Neurometabolic Diseases Laboratory, IDIBELL, Hospital Duran i Reynals, CIBERER U759, and Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain.¹⁴⁰Department of Infectious Diseases, Aarhus University Hospital, Denmark.¹⁴¹Department of Biomedicine, Aarhus University, Aarhus, Denmark.¹⁴²ADMA Biologics Inc., Ramsey, NJ, USA.¹⁴³University of Bordeaux, INSERM, Bordeaux Population Health Center, UMR1219, F-33000 Bordeaux, France.¹⁴⁴Bordeaux University Hospital, Department of Neurodegenerative Diseases, F-33000 Bordeaux, France.¹⁴⁵IHU Méditerranée Infection, Unité des Virus Émergents, UVE: Aix-Marseille University, IRD 190, INSERM 1207, Marseille, France.¹⁴⁶INSERM CIC 1425, Paris, France.¹⁴⁷Université de Paris, IAME UMR-S 1137, INSERM, Paris, France.¹⁴⁸AP-HP, Département Epidémiologie, Biostatistiques et Recherche Clinique, Hôpital Bichat, Paris, France.¹⁴⁹AP-HP, Bichat Claude Bernard Hospital, Infectious and Tropical Diseases Department, Paris, France.¹⁵⁰Université de Paris, Université Paris-Saclay, UVSQ, INSERM UMS11, Villejuif, France.¹⁵¹Immunology Division, Genetics Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Research Institute, Vall d'Hebron Barcelona Hospital Campus, UAB, Barcelona, Catalonia, Spain.¹⁵²Département d'Immunologie, AP-HP, Hôpital Pitié-Salpêtrière, Paris, France.¹⁵³Department of Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain.¹⁵⁴IrsiCaixa AIDS Research Institute and Institute for Health Science Research Germans Trias i Pujol (IGTP), Badalona, Spain.¹⁵⁵Infectious 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.¹⁵⁶Catalan ICREA, Barcelona, Spain.¹⁵⁷Service de Biologie Clinique and UMR-S 1176, Hôpital Foch, Suresnes, France.¹⁵⁸Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain.¹⁵⁹Department of Clinical Sciences, Universidad Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain.¹⁶⁰Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

*Corresponding author. Email: jean-laurent.casanova@rockefeller.edu (J.-L.C.); paul.bastard@institutimagine.org (P.B.)

†These authors contributed equally to this work.

‡These authors contributed equally to this work.

§These authors contributed equally to this work.

||List of participants and their affiliations appear at the end of the paper.

¶These authors contributed equally to this work.

#These authors contributed equally to this work.

**These authors contributed equally to this work.

blood can therefore probably neutralize as much as IFN- α 2 and/or IFN- ω (100 ng/ml). The 17 subtypes of type I IFNs—including 13 IFN- α subtypes, IFN- ω , IFN- β , IFN- ϵ , and IFN- κ —bind to the same heterodimeric receptor (IFNAR1 and IFNAR2) (10). The 13 IFN- α subtypes and IFN- ω are closely related phylogenetically, whereas IFN- β , IFN- ϵ , and IFN- κ are more distant (9). The auto-Abs to IFN- α 2 and/or IFN- ω were mostly found in men (95%) and in the elderly (half the patients with antibodies being over the age of 65 years) (9). These findings were later replicated in independent cohorts from Amsterdam, Lyon, Madrid, New Haven, and San Francisco (11–16).

These auto-Abs against type I IFNs were found in about 0.3% of a general population sample of 1227 individuals collected before the pandemic and aged 20 to 69 years, suggesting that they predated SARS-CoV-2 infection and caused critical COVID-19 rather than being triggered by it (9). Moreover, production of these antibodies can be genetically driven and can begin during early childhood, as attested by their presence in almost all patients with autoimmune polyendocrine syndrome type-1 (APS-1) due to germline mutations of *AIRE* (17–19). Patients with APS-1 are at very high risk of developing severe or critical COVID-19 pneumonia (20, 21). These auto-Abs are also found in patients with combined immunodeficiency and hypomorphic mutations of *RAG1* or *RAG2* (22); in men with immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome and mutations of *FOXP3* (23); and in women with incontinentia pigmenti and heterozygous null mutations of X-linked *NEMO* (9). They are also seen in patients treated with IFN- α or IFN- β (24, 25) and in patients with systemic lupus erythematosus (26, 27), thymoma (28), or with myasthenia gravis (29, 30). Last, they underlie a third of adverse reactions to the 17D live-attenuated vaccine against yellow fever virus (YFV), further suggesting that they were present in these patients, as in patients with critical COVID-19, before viral infection (31). For all patients tested, the auto-Abs neutralized the protective effect of IFN- α 2 (~400 pg/ml) against SARS-CoV-2 or YFV-17D in vitro, even when the plasma was diluted by >1:1000 (9). Because blood IFN- α concentrations during acute asymptomatic or paucisymptomatic SARS-CoV-2 infection typically range from 1 to 100 pg/ml (32, 33) and IFN- α levels in the respiratory tract might be even lower yet protective, we hypothesized that auto-Abs neutralizing concentrations of type I IFNs below 10 ng/ml may underlie life-threatening COVID-19 pneumonia in more than 10% of cases. We also hypothesized that the prevalence of auto-Abs against type I IFNs in the general, uninfected population may increase with age and that these antibodies may be more common in men than in women.

RESULTS

High and intermediate levels of IgG auto-Abs against IFN- α 2 and/or IFN- ω in ~20% of patients with critical COVID-19

We recruited a cohort of 3595 patients hospitalized with critical COVID-19 pneumonia [hereafter referred to as “critical patients” and defined as pneumonia in patients with critical disease, including (i) pulmonary, with high-flow oxygen (>6 liters/min) or mechanical ventilation (continuous positive airway pressure, bilevel positive airway pressure, and intubation), (ii) cardiovascular shock, or (iii) any other organ failure requiring admission to an intensive care unit], including 566 patients of our previously described cohort of 987 patients with critical COVID-19 pneumonia for whom residual samples were available (9), 623 individuals with severe COVID-19 pneumonia (with less than 6 liters/min of oxygen supplementation,

hereafter referred to as “severe patients”), and 1639 individuals with asymptomatic or paucisymptomatic (mild) upper respiratory tract SARS-CoV-2 infection [the “controls,” infected with SARS-CoV-2 [as demonstrated by a positive polymerase chain reaction (PCR) and/or serological test and/or displaying typical manifestations, 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], including 427 samples from the initial control cohort of 663 individuals (9). The patients originated from 38 different countries, across all continents. We did not include patients with moderate pneumonia who did not receive oxygen therapy (7, 9). We searched for auto-Abs against IFN- α 2 and IFN- ω by establishing novel, sensitive, and robust assays for the detection of circulating immunoglobulin G (IgG) auto-Abs. We used Gyros Technology (34), a high-throughput automated enzyme-linked immunosorbent assay (ELISA)-like assay capable of detecting a large range of auto-Ab levels (fig. S1A). We confirmed that the Gyros technique was as sensitive as the techniques previously used (ELISA and Luminex) and that all tested patients with high levels of anti-IFN- α 2 and/or anti-IFN- ω auto-Abs on ELISA, as reported in our previous studies (defined as an optical density > 0.5), had high levels of auto-Abs when assessed with Gyros (defined as levels >100) (fig. S1B). We then screened newly recruited critical or severe patients and controls from our COVID-19 cohort (Fig. 1A). We found high levels of anti-IFN- α 2 and/or anti-IFN- ω auto-Abs in 6.9% of critical patients, 3.4% of patients with severe COVID-19, and only 0.6% of the asymptomatic or paucisymptomatic controls (Fig. 1A). We also found that another 12.7% of patients with critical COVID-19 had intermediate levels of anti-IFN- α 2 and/or anti-IFN- ω auto-Abs in Gyros assays (defined as levels >30 and <100, based on the distribution observed in healthy controls), whereas this was the case for 8.6% of patients with severe COVID-19 and 11% of the individuals in our control cohort. Collectively, these findings replicate and extend our previous results and those of other groups (9, 11–16) while suggesting that intermediate levels of auto-Abs against type I IFNs might be neutralizing and underlie critical disease.

Auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml) in almost 10% of the critical patients

We investigated the ability of these auto-Abs to neutralize high concentrations of type I IFNs, as defined in our previous reports [IFN- α 2 or IFN- ω (10 ng/ml) in medium containing 1:10 plasma or serum, the equivalent of IFN- α 2 or IFN- ω (100 ng/ml) in undiluted plasma]. We tested not only the patients with high levels of auto-Abs, as in our previous study (9), but also all the available patients with critical COVID-19 ($N = 3136$), or severe COVID-19 ($N = 623$), and controls ($N = 1076$) from our expanded cohort. We designed a high-throughput luciferase assay in which we transfected human embryonic kidney (HEK) 293 T cells with (i) a plasmid containing five IFN-stimulated response element (ISRE) repeats and a firefly luciferase reporter and (ii) a plasmid encoding the *Renilla* luciferase. We stimulated these cells with an individual recombinant type I IFN (IFN- α 2 or IFN- ω) in the presence of plasma diluted 1:10 (plasma 1:10) from patients or controls. We then measured firefly luciferase induction, normalized against *Renilla* luciferase activity (Fig. 1B). We confirmed the robustness of this assay by comparing the results with our previous phosphorylated signal transducer and activator of transcription 1 (pSTAT1) flow cytometry data (9). Consistent results were obtained for all 50 patients tested with both techniques

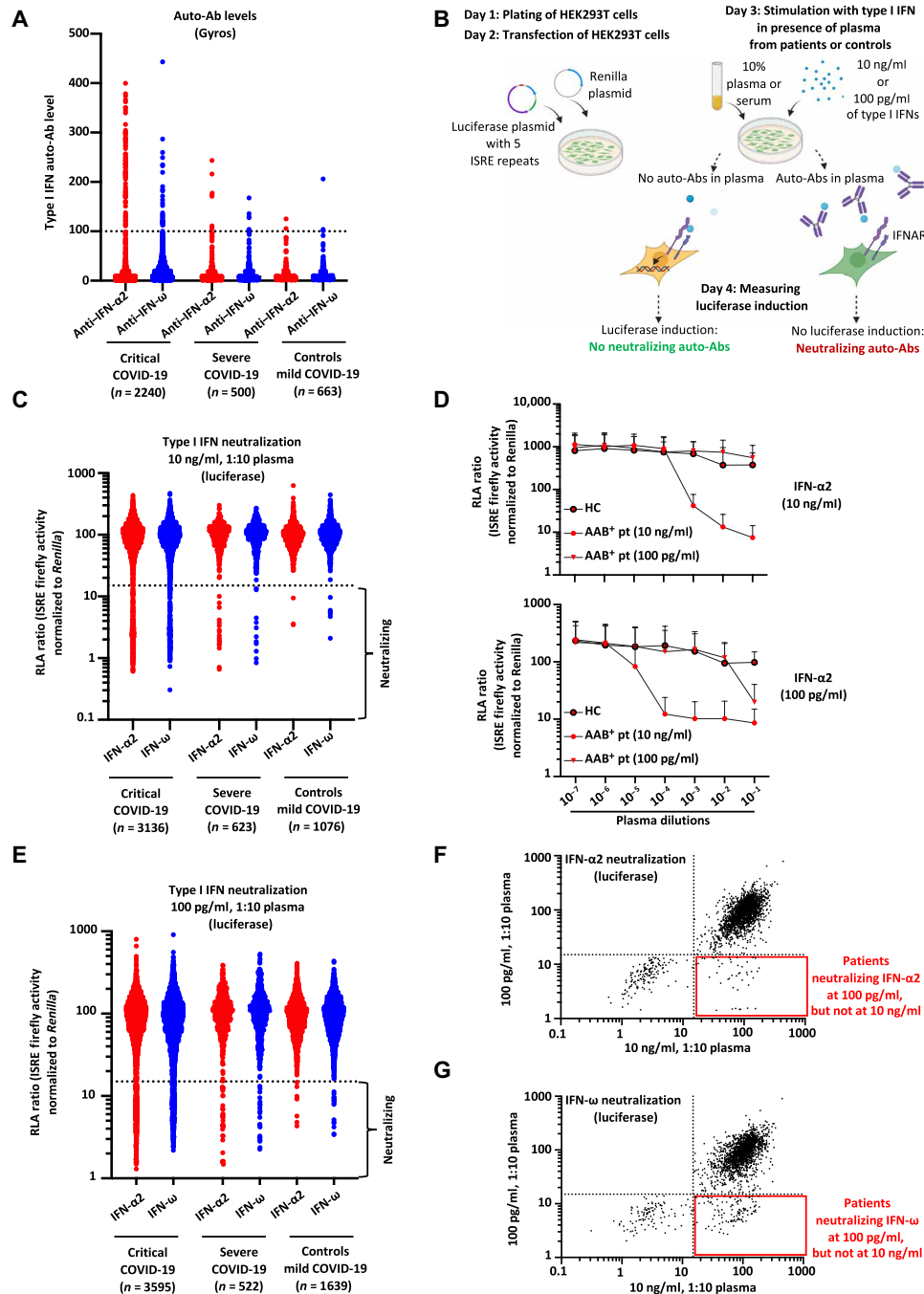


Fig. 1. Neutralizing auto-Abs against IFN-α2 and/or IFN-ω in patients with life-threatening COVID-19. (A) Gyros (high-throughput automated ELISA) results for auto-Abs against IFN-α2 and/or IFN-ω in patients with critical COVID-19 ($N = 2240$), severe COVID-19 ($N = 500$), or asymptomatic/mild SARS-CoV-2 infection ($N = 663$). (B) Schematic representation of the neutralization assay developed in HEK293T cells using a luciferase system. ISRE, interferon (IFN)-sensitive response elements. (C) Results for the neutralization of IFN-α2 or IFN-ω (10 ng/ml) in the presence of plasma 1:10 from patients with critical COVID-19 ($N = 3136$), severe COVID-19 ($N = 623$), or controls with mild/asymptomatic infection ($N = 1076$). 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) RLA after stimulation with IFN-α2 at a concentration of 10 ng/ml or 100 pg/ml, with various dilutions of plasma from a positive control (from 1:10 to 1:10⁷) neutralizing 10 ng/ml of type I IFNs (AAB⁺ pt, 10 ng/ml), a patient neutralizing type I IFNs (100 pg/ml) but not 10 ng/ml (AAB⁺ pt, 100 pg/ml), and a healthy control (HC). AAB, auto-Ab. Pt, patient. (E) Neutralization IFN-α2 or IFN-ω (100 pg/ml) in the presence of plasma 1:10 from patients with critical COVID-19 ($N = 3595$), severe COVID-19 ($N = 522$), or controls with asymptomatic/mild infection ($N = 1639$). (F) Plot showing luciferase induction after stimulation with IFN-α2 (10 ng/ml or 100 pg/ml), in the presence of plasma from patients with critical COVID-19. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Patients with auto-Abs neutralizing both IFN-α2 (10 ng/ml and 100 pg/ml) are shown in the bottom left corner, whereas the patients in the bottom right corner had auto-Abs capable of neutralizing only IFN-α2 (100 pg/ml). (G) Plot showing luciferase induction after stimulation with IFN-ω (10 ng/ml or 100 pg/ml) for patients with critical COVID-19.

(fig. S1, C and D). We then tested all patients and controls. Most plasma samples with high auto-Ab levels (>100) against IFN- α 2 according to the Gyros assay were neutralizing (fig. S1E). We found that 9.8% (307 of 3136) of the critical patients tested and that 3.53% (22 of 623) of the severe patients had auto-Abs neutralizing IFN- α 2 and/or IFN- ω versus only 0.37% (four of 1076) controls (Fig. 1C, Table 1, and table S1). In the patients with neutralizing auto-Abs, these auto-Abs were able to neutralize both IFN- α 2 and IFN- ω in 175 of the 307 critical patients (57%), six of the severe patients (27%), and none of the controls; IFN- α 2 alone in 106 critical patients (34.5%), 11 severe patients (50%), and only one of the controls (25%); and IFN- ω alone in 26 of critical patients (8.5%), five severe patients (22%), and three controls (75%) (table S1). None of the patients with these auto-Abs had inborn errors of TLR3- or TLR7-dependent type I IFN immunity (7, 35).

Auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml) in at least 13.6% of critical patients and 6.8% of severe patients

Because the amounts of circulating type I IFNs in infected individuals are 100 to 1000 times lower than the amounts tested previously (32, 33), we investigated the neutralization of more physiological

concentrations of type I IFNs by performing assays with type I IFN (100 pg/ml). We observed a robust response in our luciferase system in the presence of 1:10 dilutions of control plasma (fig. S1F). The plasma or serum was diluted 1:10, so the concentration neutralized corresponds to IFN (1 ng/ml) in circulating whole blood. With diluted plasma samples from a positive control, we gained at least two orders of magnitude of sensitivity in terms of neutralizing activity, providing proof of concept that these auto-Abs can neutralize lower, more physiological, amounts of type I IFNs (Fig. 1D and fig. S1G), lower than the concentrations previously tested by a factor of 100 (9). We then retested all available samples from our extended cohort. Overall, 13.6% of all critical patients tested ($N = 489$ of 3595), 6.5% ($N = 34$ of 522) of the severe patients, and 1% of the controls ($N = 17$ of 1639) had circulating auto-Abs that neutralized IFN- α 2 and/or IFN- ω (100 pg/ml) in plasma 1:10 (Fig. 1, E to G, Table 1, and table S1). In the patients with neutralizing auto-Abs, these auto-Abs were able to neutralize both IFN- α 2 and IFN- ω in 256 of the 489 positive critical patients (52%), 18 of the 34 severe patients (53%), and 1 of the 17 controls (6%); IFN- α 2 alone in 104 critical patients (21%), 14 severe patients (41%), and four of the controls (23.5%); and IFN- ω alone in 129 critical patients (26%), two severe

Table 1. Risk of critical COVID-19 pneumonia for individuals carrying auto-Abs to specific sets of type I IFNs, when compared with that of asymptomatic/mild infection, adjusted on age and sex. OR and P values were estimated by means of Firth's bias-corrected logistic regression. The numbers and proportions of individuals with critical COVID-19 pneumonia (patients) and asymptomatic or mild infection (controls) are shown in Figs. 1 to 3. Two combinations are not shown due to insufficient number of individuals: anti-IFN- β (10 ng/ml) and anti-IFN- α 2 (100 pg/ml) auto-Abs only and anti-IFN- β (10 ng/ml) and anti-IFN- ω (100 pg/ml) auto-Abs only.			
Anti-type I IFN auto-Ab positive (amount of type I IFN neutralized, in plasma diluted 1:10)	Proportion of critical patients with neutralizing auto-Abs	OR [95% CI]	P value
Anti-IFN- α 2 and anti-IFN- ω auto-Abs (10 ng/ml)	5.6%	67 [4–1109]	7.8×10^{-13}
Anti-IFN- α 2 and/or anti-IFN- ω auto-Abs (10 ng/ml)	9.8%	17 [7–45]	$<10^{-13}$
Anti-IFN- α 2 auto-Abs (10 ng/ml)	9%	45 [9–225]	$<10^{-13}$
Anti-IFN- α 2 auto-Abs only (10 ng/ml)	3.4%	21 [4–107]	1.8×10^{-09}
Anti-IFN- ω auto-Abs (10 ng/ml)	6.4%	13 [4–38]	1.4×10^{-12}
Anti-IFN- ω auto-Abs only (10 ng/ml)	0.8%	3 [0.9–10]	0.057
Anti-IFN- α 2 and anti-IFN- ω auto-Abs (100 pg/ml)	7.1%	54 [11–275]	$<10^{-13}$
Anti-IFN- α 2 and/or anti-IFN- ω auto-Abs (100 pg/ml)	13.6%	13 [8–21]	$<10^{-13}$
Anti-IFN- α 2 auto-Abs (100 pg/ml)	10%	23 [10–55]	$<10^{-13}$
Anti-IFN- α 2 auto-Abs only (100 pg/ml)	2.9%	10 [3–26]	2.8×10^{-09}
Anti-IFN- ω auto-Abs (100 pg/ml)	10.7%	13 [7–23]	$<10^{-13}$
Anti-IFN- ω auto-Abs only (100 pg/ml)	3.6%	6 [3–12]	3.9×10^{-10}
Anti-IFN- β auto-Abs (10 ng/ml)	1.3%	8 [2–36]	1.7×10^{-3}
Anti-IFN- β auto-Abs only (10 ng/ml)	0.96%	5 [1–25]	0.043
Anti-IFN- β auto-Abs (10 ng/ml) and anti-IFN- α 2 and/or anti-IFN- ω auto-Abs (100 pg/ml)	0.34%	16 [0.5–497]	0.018
Anti-IFN- β (10 ng/ml) and anti-IFN- α 2 and anti-IFN- ω auto-Abs (100 pg/ml)	0.28%	16 [0.5–502]	0.019

patients (6%), and 12 controls (70%) (table S1). Further dilution of a plasma sample from one patient neutralizing type I IFNs (100 pg/ml) led to a loss of neutralizing activity (Fig. 1D and fig. S1G). For four unrelated patients, all of whom suffered from critical COVID-19, including one who died, samples collected before COVID-19 were available and tested positive for neutralizing auto-Abs against type I IFNs. One neutralized IFN- α 2 and IFN- ω at a concentration of 10 ng/ml, two neutralized both cytokines at 100 pg/ml, and one neutralized IFN- ω only at 100 pg/ml (fig. S1H). The four patients tested therefore had auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml or 100 pg/ml) before infection with SARS-CoV-2. These four patients and another two reported in our previous study (9) all, therefore, had auto-Abs neutralizing type I IFNs before infection with SARS-CoV-2. We then assessed the risk, adjusted for age and sex, of having critical or severe disease for individuals carrying auto-Abs against each individual IFN and the different possible combinations. We found that all auto-Abs, except those neutralizing only IFN- ω at a concentration of 10 ng/ml, were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with controls (Table 1 and table S2). The strongest association was with auto-Abs against both IFN- α 2 and IFN- ω neutralizing concentrations at 10 ng/ml [odds ratio (OR) = 67, $P = 8 \times 10^{-13}$] and 100 pg/ml (OR = 54, $P < 10^{-13}$), followed by those against IFN- α 2 $\pm$ IFN- ω neutralizing concentrations at 10 ng/ml (OR = 45, $P < 10^{-13}$) and 100 pg/ml (OR = 23, $P < 10^{-13}$) (Table 1). Because the serum/plasma samples were diluted 1:10 in these assays, these findings suggest that more than 13.6% of patients with life-threatening COVID-19 have circulating auto-Abs neutralizing IFN- α 2 and/or IFN- ω (1 ng/ml) in vivo, a greater proportion than the 10% of patients with auto-Abs neutralizing 100 ng/ml reported in previous studies (9, 11–16).

Auto-Abs neutralize low concentrations of IFN- α 2 protective against SARS-CoV-2

We previously reported that plasma diluted 1:100 from patients with auto-Abs against type I IFNs neutralized the ability of IFN- α 2 (at a concentration of 20 pM, about 400 pg/ml) to block SARS-CoV-2 and YFV-17D replication in Huh-7.5 cells (9, 31). This neutralization was seen in all patients tested, even for a 1000-fold dilution, and, in most patients, it was more potent than the neutralizing effect of a commercially available neutralizing monoclonal Ab (mAb) against IFN- α 2. These auto-Abs against type I IFNs were, therefore, able to neutralize IFN- α 2 at concentrations well beyond physiological levels. We therefore hypothesized that patients with lower titers of auto-Abs against type I IFNs, which can neutralize 100 pg/ml but not 10 ng/ml in plasma diluted 1:10, would also neutralize the protective effect of IFN- α 2 against SARS-CoV-2. We therefore performed our SARS-CoV-2 assay with 5 pM (~100 pg/ml) or 20 pM (~400 pg/ml) IFN- α 2 on five samples from patients with life-threatening COVID-19 and two samples from uninfected elderly individuals with auto-Abs neutralizing IFN- α 2 (100 pg/ml but not 10 ng/ml). As controls, we tested a commercial mAb against IFN- α 2, a sample from a patient with auto-Abs neutralizing IFN- α 2 (10 ng/ml), samples from three patients with life-threatening COVID-19, and three healthy controls without detectable auto-Abs against type I IFNs. We found that the 1:100 dilutions of plasma from four of the five patients with critical COVID-19 and one of the two elderly individuals with auto-Abs neutralizing IFN- α 2 (100 pg/ml) were able to neutralize the protective effect of IFN- α 2 (~400 pg/ml) against SARS-CoV-2,

whereas samples from all these individuals fully or partially neutralized IFN- α 2 (~100 pg/ml) (Fig. 2A). No such neutralizing effect was observed for any of the auto-Ab-negative controls. Overall, our findings indicate that auto-Abs against type I IFNs capable of neutralizing IFN (100 pg/ml) in 1% plasma can block the protective effect of IFN- α 2 (~100 or ~400 pg/ml) against SARS-CoV-2. These findings raise the possibility that even 100-fold lower levels of auto-Abs against type I IFNs, capable of neutralizing lower, physiological concentrations of IFN- α 2 (10 pg/ml) may be present in an even larger proportion of patients. The testing of this hypothesis will require the development of new, more sensitive methods to screen for neutralization.

Neutralization of type I IFNs in the absence of detectable auto-Abs against IFN- α 2 or IFN- ω

The neutralization assays performed on all patients and controls revealed that some patients with neutralizing activity against IFN- α 2 and/or IFN- ω (10 ng/ml), as shown in luciferase assays, did not have high or even intermediate levels of IgG auto-Abs in Gyros assays (fig. S1E). We also observed that some patients with neutralizing auto-Abs had low or undetectable levels of auto-Abs in Luminex assays (fig. S1I). For these individuals, we assessed the prevalence of IgA and IgM auto-Abs against type I IFNs and found that none of the patients tested ($N = 12$) had detectable titers of IgA or IgM auto-Abs (fig. S1J). We then tested the alternative hypothesis that these auto-Abs were directed against the IFNAR1 or IFNAR2 chain of type I IFN receptors, assessing the ability of plasma samples from these patients to neutralize IFN- β . None of the samples from these patients neutralized IFN- β , suggesting that the auto-Abs in these patients were not directed against IFNAR1 or IFNAR2 (fig. S1K). An alternative plausible hypothesis is that the epitope recognized by the auto-Abs might be concealed by the binding of the cytokine to the plate (ELISA), biotinylation of the cytokine (Gyros), or covalent coupling of the cytokine to magnetic beads at lysine residues (Luminex) (19). This observation has important clinical implications, suggesting that a lack of detection of auto-Abs against type I IFNs does not rule out the possibility of such antibodies being present and having neutralization capacity.

Auto-Abs typically neutralize the 13 IFN- α subtypes and/or IFN- ω

In six patients with auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml but not 10 ng/ml), we tested the reactivity of the antibodies against the 17 type I IFNs (the 13 IFN- α forms, IFN- ω , IFN- β , IFN- ϵ , and IFN- κ). Similar to patients with auto-Abs neutralizing type I IFNs (10 ng/ml) (9), those capable of neutralizing only 100 pg/ml had detectable auto-Abs against most of the 13 IFN- α forms and/or IFN- ω , albeit at lower levels (Fig. 2B). Of the six patients with auto-Abs against IFN- α and/or IFN- ω tested, only one also had auto-Abs against IFN- β , and none had detectable auto-Abs against IFN- ϵ or IFN- κ . Overall, the patients with auto-Abs against IFN- α 2 and/or IFN- ω capable of neutralizing IFN (100 pg/ml) displayed patterns of reactivity to the 17 type I IFNs similar to those reported in previously described patients with auto-Abs neutralizing 10 ng/ml (9). We then set up an assay for assessing neutralization of the 13 IFN- α forms using our luciferase-based assay. We tested two patients with auto-Abs neutralizing IFN- α 2 and IFN- ω , two patients with auto-Abs neutralizing only IFN- α 2, and two patients with auto-Abs neutralizing only IFN- ω . We found that the patient

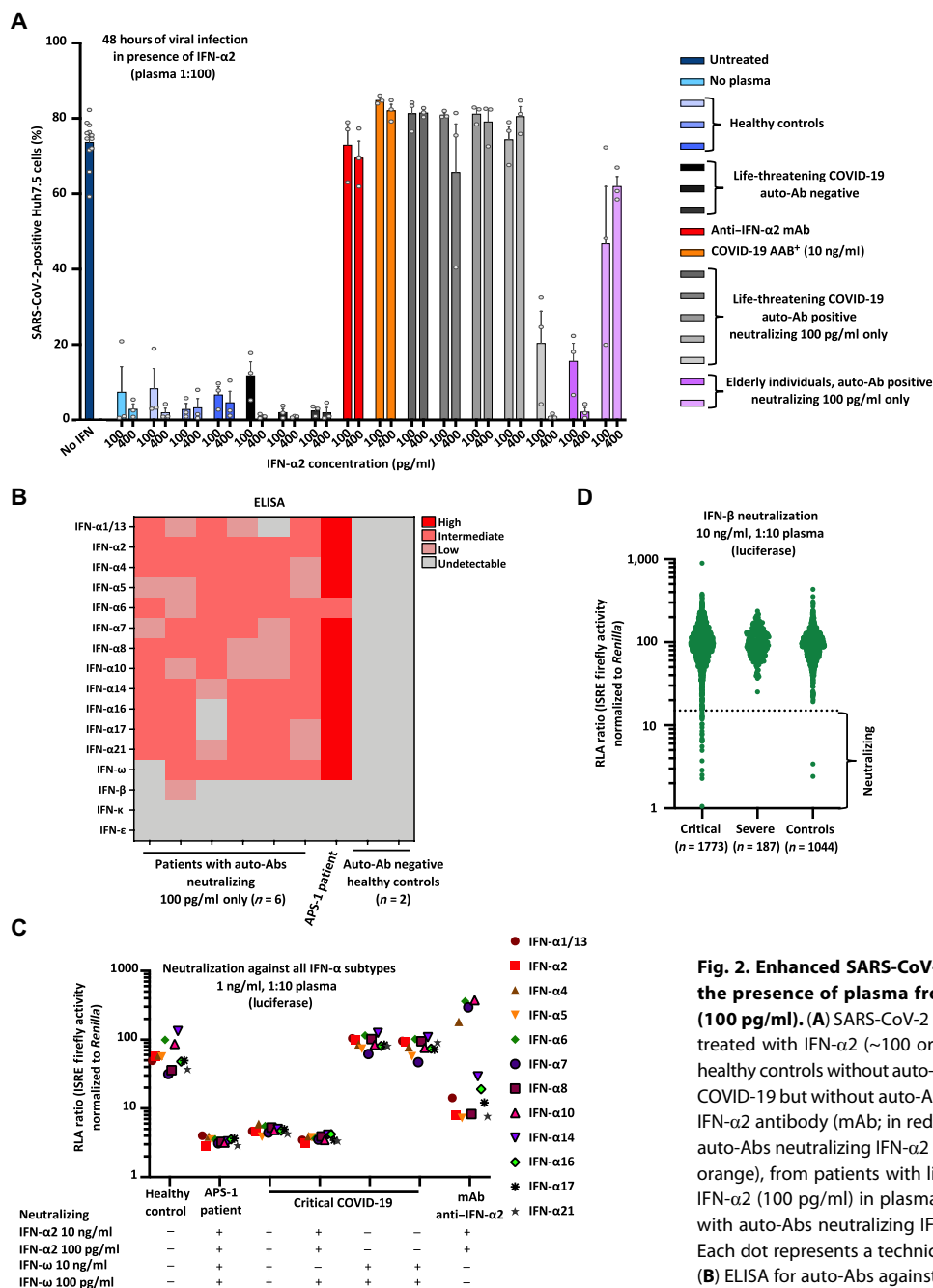


Fig. 2. Enhanced SARS-CoV-2 replication, despite the presence of IFN- α 2, in the presence of plasma from patients with auto-Abs neutralizing IFN- α 2 (100 pg/ml). (A) SARS-CoV-2 replication in Huh-7.5 cells untreated (in dark blue) or treated with IFN- α 2 (~100 or ~400 pg/ml) in the presence of 1:100 plasma from healthy controls without auto-Abs (N = 3, in blue), from patients with life-threatening COVID-19 but without auto-Abs against IFN- α 2 (N = 3, in black), a commercial anti-IFN- α 2 antibody (mAb; in red); from a patient with life-threatening COVID-19 and auto-Abs neutralizing IFN- α 2 (10 ng/ml) in plasma 1:100 (COVID-19 AAB⁺; N = 1, in orange), from patients with life-threatening COVID-19 and auto-Abs neutralizing IFN- α 2 (100 pg/ml) in plasma 1:100 (N = 5, in gray); and from elderly individuals with auto-Abs neutralizing IFN- α 2 (100 pg/ml) in plasma 1:100 (N = 2, in purple). Each dot represents a technical replicate. All experiments were done in triplicate. (B) ELISA for auto-Abs against the 13 IFN- α forms, IFN- ω , IFN- β , IFN- ϵ , and IFN- κ in patients with life-threatening COVID-19 and auto-Abs neutralizing IFN- α 2 (100 pg/ml) (N = 6), patient with APS-1 with life-threatening COVID-19 and auto-Abs neutralizing IFN- α 2 and IFN- ω (10 ng/ml) (N = 1), and healthy controls (N = 2). (C) RLA after stimulation with the all individual IFN- α at a concentration of 1 ng/ml, with 1:10 plasma from a healthy control (negative control), a patient with APS-1 (positive control), and patients with life-threatening COVID-19 and neutralizing IFN- α 2 and/or IFN- ω or a mAb anti-IFN- α 2. (D) Neutralization of IFN- β (10 ng/ml) in the presence of plasma 1:10 from patients with critical COVID-19 (N = 1773), severe COVID-19 (N = 187), or asymptomatic/mild controls (N = 1044).

with APS-1 and the two patients with auto-Abs neutralizing IFN- α 2 and IFN- ω (10 ng/ml) were able to neutralize all 13 IFN- α subtypes, as were the two patients with neutralizing auto-Abs against IFN- α 2. Conversely, in the conditions tested, the two patients with auto-Abs neutralizing IFN- ω only, but not IFN- α 2, were not able to neutralize any of the 13 IFN- α subtypes (Fig. 2C). In addition, to confirm that the IgG auto-Abs detected were the cause of the neutralization

activity observed, we performed an IgG depletion experiment and found that the removal of the IgG fraction abolished the neutralizing activity, whereas the purified IgG fraction had full neutralizing activity (fig. S2A). Thus, patients with neutralizing auto-Abs against only IFN- ω do not seem to neutralize any of the 13 IFN- α subtypes, whereas patients with auto-Abs neutralizing IFN- α 2 neutralize all these subtypes.

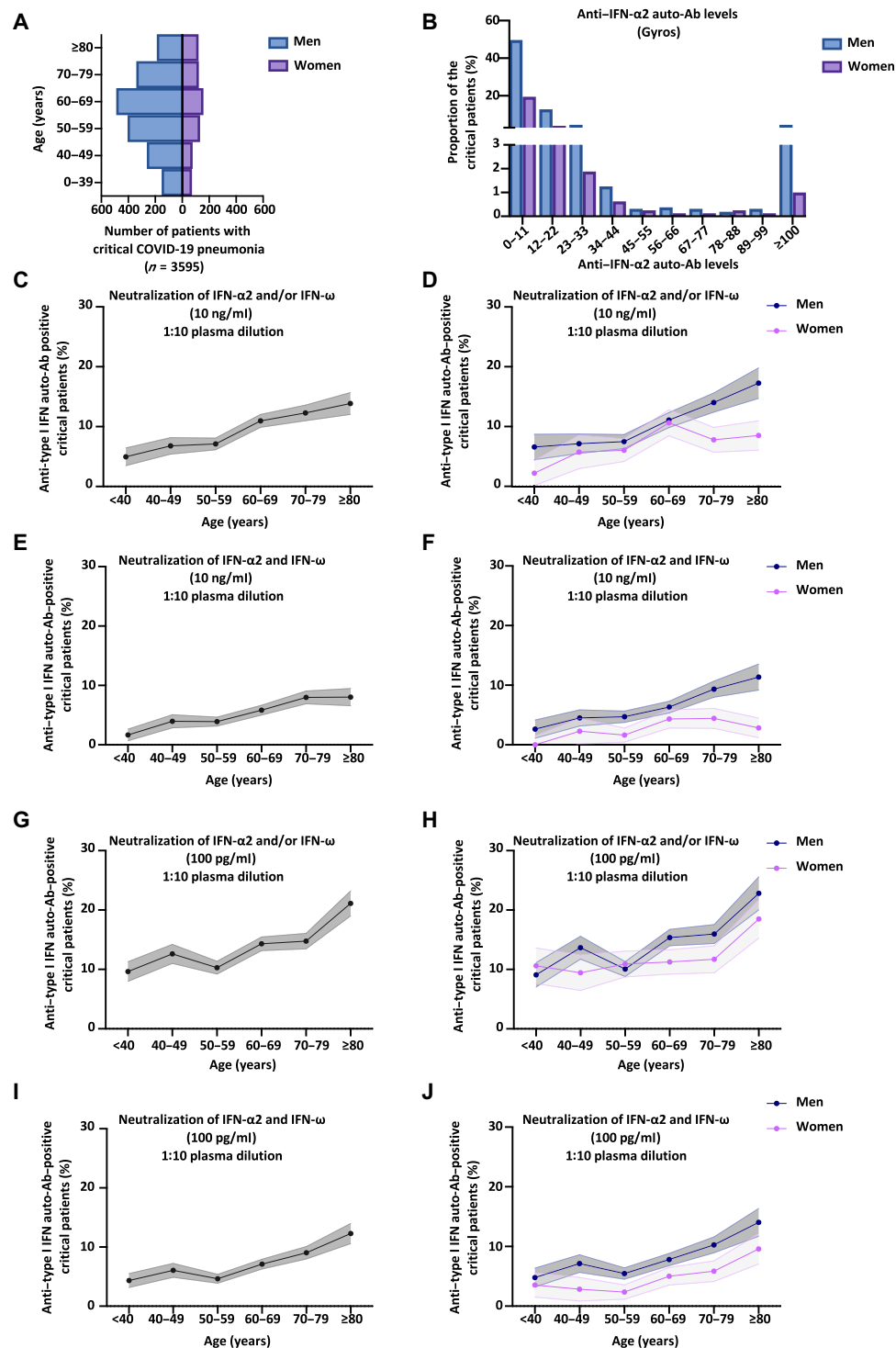


Fig. 3. Higher prevalence of neutralizing auto-Abs against type I IFNs in elderly patients with critical COVID-19. (A) Bar plot of the age and sex distribution of the patients with life-threatening COVID-19 included in our expanded cohort ($N = 3595$). (B) Graph showing the anti-IFN-α2 auto-Ab levels, assessed by Gyros, in patients with life-threatening COVID-19. Men and women are shown separately. The upper section of the y axis starts at 3%. (C to J) Proportion by decade of patients with critical COVID-19 and positive for neutralizing auto-Abs (in plasma 1:10) against (C) IFN-α2 and/or IFN-ω, at 10 ng/ml, for both sexes. (D) IFN-α2 and/or IFN-ω, at 10 ng/ml, for men or women. (E) IFN-α2 and IFN-ω, at 10 ng/ml, for both sexes. (F) IFN-α2 and IFN-ω, at 10 ng/ml, for men or women. (G) IFN-α2 and/or IFN-ω, at 100 pg/ml, for both sexes. (H) IFN-α2 and/or IFN-ω, at 100 pg/ml, for men or women. (I) IFN-α2 and IFN-ω, at 100 pg/ml, for both sexes. (J) IFN-α2 and IFN-ω, at 100 pg/ml, for men or women.

Auto-Abs neutralizing IFN- β in 1.3% of critical patients

We previously reported that auto-Abs neutralizing IFN- β were detected in only two of 101 critical patients with auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml) (9). Given the potential therapeutic use of IFN- β (36, 37) and the absence of IFN- β neutralization data for patients with COVID-19, we tested a larger number of patients and controls, including patients without auto-Abs against IFN- α or IFN- ω , for auto-Abs against IFN- β , assessing the levels and neutralizing activity of auto-Abs against IFN- β (10 ng/ml). We screened 1773 patients with critical COVID-19 pneumonia and found that 1.3% ($N = 23$) had neutralizing auto-Abs against IFN- β ; by contrast, such antibodies were present in none of the 187 severe patients tested and in only two of the 1044 controls tested (0.18%) (Fig. 2D, fig. S2B, and table S3). Only 6 of the 23 (21.7%) critical patients also had auto-Abs neutralizing IFN- α 2 and/or IFN- ω at 100 pg/ml, and none of the controls had such antibodies. Five of these six patients had auto-Abs neutralizing all three cytokines. All the other critical patients and controls had only neutralizing auto-Abs against IFN- β . The presence of neutralizing auto-Abs against IFN- β was significantly associated with critical, but not severe, disease relative to the controls (Table 1 and tables S2 and S3). Gyros did not appear to be able to detect auto-Abs against IFN- β , perhaps because of the biotinylation of the cytokine hiding the epitope recognized by the auto-Abs. Because most (78.3%) of the patients with neutralizing auto-Abs against IFN- β did not have neutralizing auto-Abs against IFN- α 2 or IFN- ω , this suggests that auto-Abs against IFN- β alone may also underlie life-threatening COVID-19 (Table 1).

Neutralizing auto-Abs against type I IFNs in at least 20% of critical patients over 80 years of age

We further assessed the percentage of patients with critical COVID-19 positive for neutralizing auto-Abs per decade of life and by sex (Fig. 3, A to J; fig. S3, A to W; and tables S1 to S4). In our previous report, we found that patients with critical COVID-19 with auto-Abs neutralizing IFN- α 2 or IFN- ω at 10 ng/ml were older (more than half the patients with auto-Abs were over the age of 65 years) and more likely to be male (95% of the antibody carriers were men) (9). These results have been confirmed by other groups, albeit with a smaller proportion of men (11–14, 16). In our expanded cohort of patients with critical COVID-19 pneumonia ($N = 3595$), the mean age was 61 years, and 73% of the patients were men (Fig. 3A and table S4). We confirmed that critical patients with auto-Abs neutralizing IFN- α and/or IFN- ω at 10 ng/ml were significantly older than those not carrying auto-Abs (mean age [SD], 65.8 years [14.1] versus 61.6 years [15.5], Firth's multivariable logistic regression, $P = 3 \times 10^{-6}$) and more likely to be male (78.5 versus 71%, Firth's multivariable logistic regression, $P = 0.003$). The proportion of patients with critical COVID-19 with auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml) increased continuously, with auto-Abs detected in 5% of patients under the age of 40 years, 6.8% of those between 40 and 49 years of age, 7.1% of those between 50 and 59 years of age, 10.7% of those between 60 and 69 years of age, 12.3% of those between 70 and 79 years of age, and almost 14% in those over 80 years of age (Fig. 3, C to F, and fig. S3, B to I). In severe patients, the proportion of auto-Abs was much more stable with age (Firth's multivariable logistic regression, $P = 0.16$; fig. S3, T to W) and sex (Firth's multivariable logistic regression, $P = 0.44$). Similar results were obtained for patients with critical COVID-19 with auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml) but with even higher

proportions (Fig. 3, G to J, and fig. S3, L to S) (table S1). The proportion of patients with auto-Abs ranged from 9.6% of patients below the age of 40 years to more than 21% of those over 80 (Fig. 3, G to J, and fig. S3, L to S). In men, the proportion of patients with critical COVID-19 carrying auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml) increased up to 23% over 80 years of age. A very different pattern was seen for auto-Abs neutralizing IFN- β (10 ng/ml), with a more stable proportion of auto-Abs carriers according to age (Firth's multivariable logistic regression, $P = 0.68$; fig. S3, J and K) (table S3). Overall, the prevalence of auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml and/or 100 pg/ml) increased sharply with age in critical patients. A notable enrichment in patients with neutralizing auto-Abs against IFN- α 2 and/or IFN- ω was observed in the elderly, with more than 20% of patients and 23% of men, over the age of 80 years with critical COVID-19 having neutralizing auto-Abs against these type I IFNs.

Neutralizing auto-Abs against type I IFNs in at least 18% of deceased patients

The prevalence of auto-Abs against type I IFNs in patients dying from COVID-19 pneumonia is unknown. For the 3595 patients with critical COVID-19, we analyzed data for the 1124 who died. These patients were aged 20 days to 99 years (mean age: 71 years), 73% were male, and all had confirmed SARS-CoV-2 infection and critical COVID-19 pneumonia before death (Fig. 4A). In these patients, we analyzed the presence of neutralizing auto-Abs against type I IFNs at concentrations of 10 ng/ml and 100 pg/ml for IFN- α 2 and IFN- ω , respectively, and at 10 ng/ml for IFN- β (Fig. 4, B to J, and fig. S4, A to K). We found that 13.3% of the deceased patients carried auto-Abs neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml) (Fig. 4, B to F, and fig. S4, A to E). A total of 18.5% carried auto-Abs neutralizing 100 pg/ml of either or both cytokines (Fig. 4, G to J, and fig. S4, F to I). In addition, 0.9% had auto-Abs neutralizing IFN- β (fig. S4, J and K). An analysis of the prevalence of neutralizing auto-Abs against type I IFNs in these patients who died of COVID-19 by decade of age revealed a moderate increase with age for auto-Abs neutralizing 10 ng/ml (Firth's multivariable logistic regression, $P = 0.03$) or 100 pg/ml (Firth's multivariable logistic regression, $P = 0.01$) (tables S1 and S2). For a type I IFN concentration (100 pg/ml), the prevalence of auto-Abs neutralizing IFN- α 2 and/or IFN- ω was 20% below the age of 40 years, 14% for individuals between 40 and 49 years old, 12.5% for those between 50 and 60 years old, 16.3% for those between 60 and 69 years old, 17.9% for those between 70 and 79 years old, and greater than 23% for those over the age of 80 years. Overall, at least 18% of patients dying from COVID-19 pneumonia have auto-Abs capable of neutralizing type I IFNs (100 pg/ml) in plasma 1:10.

Auto-Abs capable of neutralizing IFN- α 2 and/or IFN- ω at 10 ng/ml in 0.53% and at 100 pg/ml in 2.3% of individuals from the general population

We previously tested a sample of 1227 individuals aged 20 to 65 years from the general population collected in 2015–2017. This sample had an equal sex distribution, and we identified four individuals with auto-Abs against type I IFNs among the 1227 tested (0.3%), suggesting that the auto-Abs predated COVID-19 (9). These findings were replicated at the University of California, San Francisco in a sample of 4041 individuals aged 4 to 90 years (0.32%) (16). In the current study, we tested a much larger cohort of 34,159 individuals

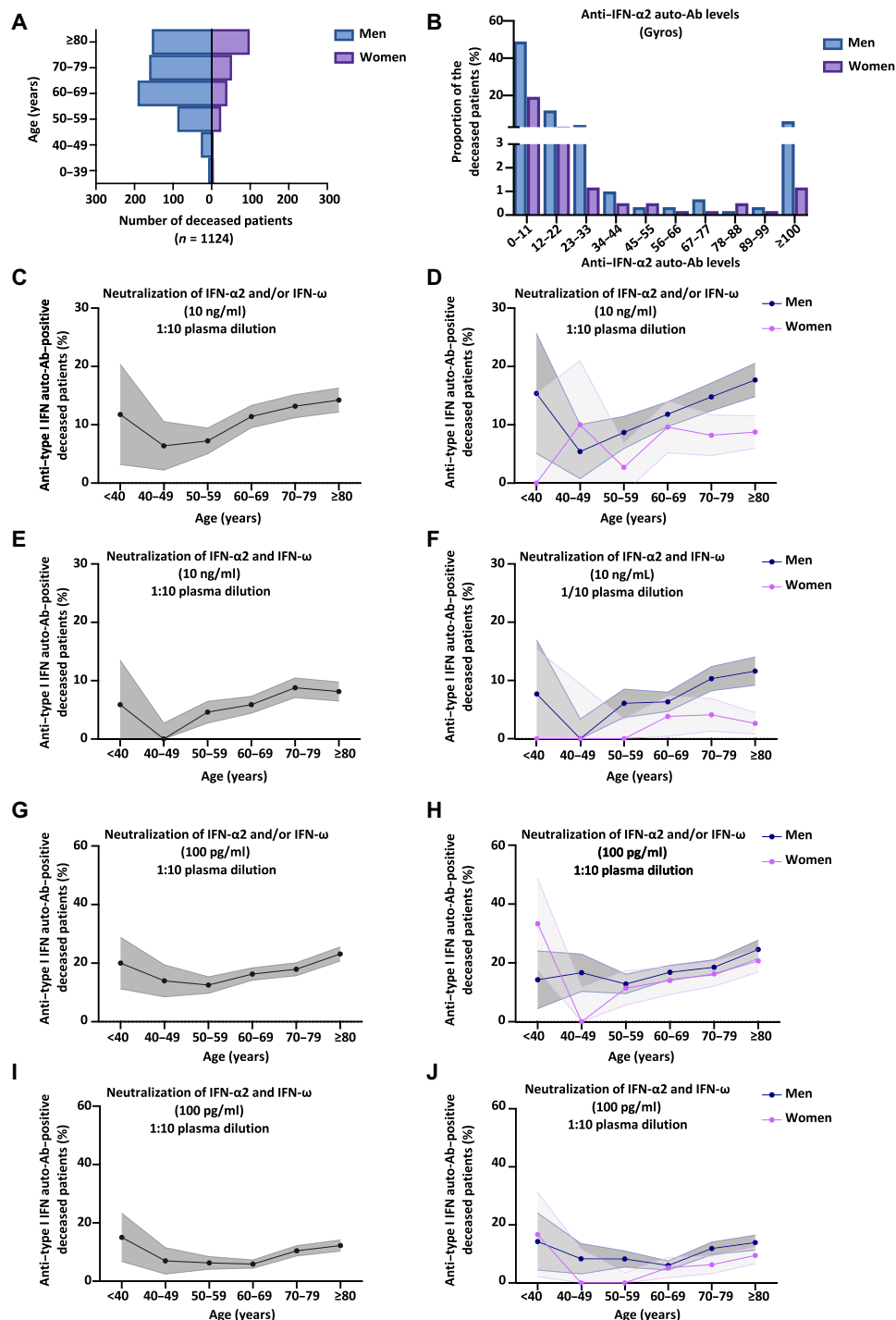


Fig. 4. Higher prevalence of neutralizing auto-Abs against type I IFNs in patients who died of COVID-19. (A) Bar plot of the age and sex distribution of the patients who died of COVID-19 included in our cohort ($N = 1124$). (B) Graph showing the anti-IFN- $\alpha 2$ auto-Ab levels, assessed by Gyros, in patients who died of COVID-19. Men or women are shown separately. The upper section of the y axis starts at 3%. (C to J) Proportion by decade of patients who died of COVID-19 and positive for neutralizing auto-Abs (in plasma 1:10) against (C) IFN- $\alpha 2$ and/or IFN- ω , at 10 ng/ml, for both sexes. (D) IFN- $\alpha 2$ and/or IFN- ω , at 10 ng/ml, for men or women. (E) IFN- $\alpha 2$ and IFN- ω , at 10 ng/ml, for both sexes. (F) IFN- $\alpha 2$ and IFN- ω , at 10 ng/ml, for men or women. (G) IFN- $\alpha 2$ and/or IFN- ω , at 100 pg/ml, for both sexes. (H) IFN- $\alpha 2$ and/or IFN- ω , at 100 pg/ml, for men or women. (I) IFN- $\alpha 2$ and IFN- ω , at 100 pg/ml, for both sexes. (J) IFN- $\alpha 2$ and IFN- ω , at 100 pg/ml, for men or women.

aged 20 to 100 years from the general population, with an equal distribution between the sexes (Fig. 5A). Samples were collected before 2018 for blood donors at the French Blood Bank (19,966

individuals) and the Three-City (3C) cohort (801) and in 2019 for participants in the French CONSTANCES cohort (8850) and Cerba HealthCare (4542). We performed serological tests for SARS-CoV-2

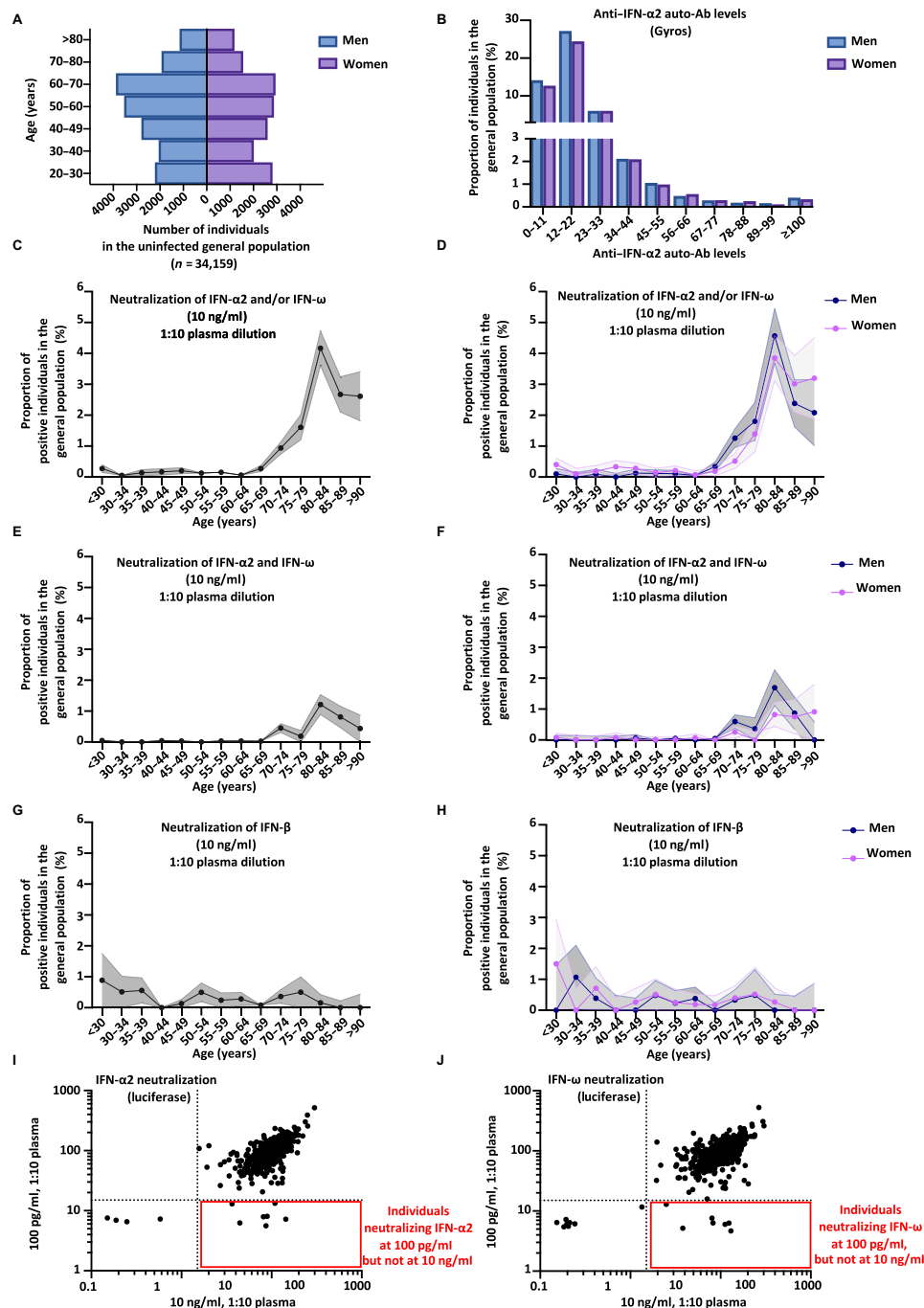


Fig. 5. Neutralizing auto-Abs against IFN- $\alpha 2$ and/or IFN- ω at 10 ng/ml are more prevalent in the elderly, in the general population. (A) Bar plot of the age and sex distribution of individuals from the general population ($N = 34,159$). (B) Graph showing the IFN- $\alpha 2$ auto-Ab levels, assessed by Gyros, in individuals from the general population. Men or women are shown separately. The upper section of the y axis starts at 3%. (C to H) Proportion by 5 years of individuals from the general population and positive for neutralizing auto-Abs (in plasma 1:10) against (C) IFN- $\alpha 2$ and/or IFN- ω , at 10 ng/ml, for both sexes. (D) IFN- $\alpha 2$ and/or IFN- ω , at 10 ng/ml, for men or women. (E) IFN- $\alpha 2$ and IFN- ω , at 10 ng/ml, for both sexes. (F) IFN- $\alpha 2$ and IFN- ω , at 10 ng/ml, for men or women. (G) IFN- β , at 10 ng/ml, for both sexes. (H) IFN- β , at 10 ng/ml, for men or women. (I) Plot showing luciferase induction after stimulation with IFN- $\alpha 2$ (10 ng/ml or 100 pg/ml) in the presence of plasma from individuals from the general population. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Individuals with antibodies neutralizing both IFN- $\alpha 2$ (10 ng/ml and 100 pg/ml) are shown in the bottom left corner, whereas the individuals in the bottom right corner had antibodies capable of neutralizing only IFN- $\alpha 2$ (100 pg/ml). (J) Plot showing luciferase induction after stimulation with IFN- ω (10 ng/ml or 100 pg/ml) for individuals from the general population. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Individuals with antibodies neutralizing both IFN- ω (10 ng/ml and 100 pg/ml) are shown in the bottom left corner, whereas the individuals in the bottom right corner had antibodies capable of neutralizing only IFN- ω (100 pg/ml).

on the samples collected in 2019 and included only the individuals who had not been infected with SARS-CoV-2 in the sample. We used Gyros to screen this whole cohort for IgG auto-Abs against IFN- α 2 and IFN- ω (Fig. 5B and fig. S5A). We did not measure auto-Abs against IFN- β by Gyros. We found that only 0.05 and 4.2% had anti-IFN- α 2 and/or anti-IFN- ω auto-Abs above the thresholds of 100 and 30, respectively (Fig. 5B and fig. S5A). We then assessed the ability of these antibodies to neutralize IFN- α 2 or IFN- ω (10 ng/ml) for all individuals with a high or intermediate level of IgG auto-Abs against IFN- α 2 or IFN- ω . We found 181 individuals with neutralizing auto-Abs, for whom 1:10 dilutions of plasma neutralized IFN- α 2

and/or IFN- ω (10 ng/ml), giving an overall prevalence of 0.53% (Fig. 5, C to F, and fig. S5, B to I) (table S5 and S6), consistent with our two previous reports (9, 16). We may have slightly underestimated the number of positive individuals, because some may have had neutralizing auto-Abs at too low a titer for detection. Next, we assessed the prevalence of auto-Abs neutralizing IFN- β (10 ng/ml) in 9583 individuals and found an overall prevalence of 0.26% (Fig. 5, G and H and table S5 and S6). Last, for a subset of 10,778 samples, we further assessed the ability of serum/plasma samples (diluted 1:10) to neutralize IFN- α 2 and/or IFN- ω (100 pg/ml) in the luciferase assay (Figs. 5, I and J, and 6, A to H). The prevalence of

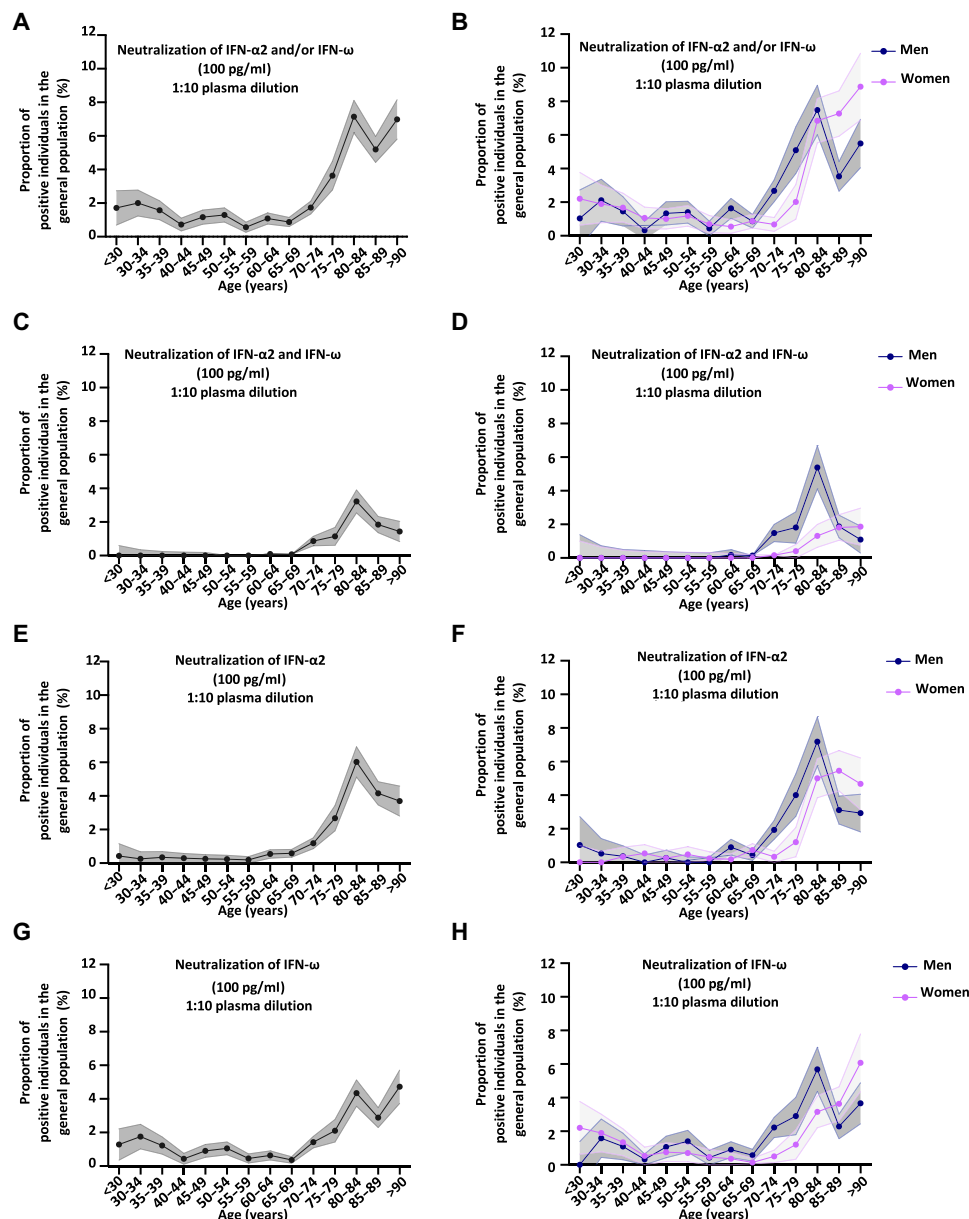


Fig. 6. Neutralizing auto-Abs against IFN- α 2 and/or IFN- ω at 100 pg/ml are more prevalent in the elderly, in the general population. (A to H) Proportion, binned every 5 years, of individuals from the general population and positive for neutralizing auto-Abs (in plasma 1:10) against (A) IFN- α 2 and/or IFN- ω , at 100 pg/ml, for both sexes. (B) IFN- α 2 and/or IFN- ω , at 100 pg/ml, for men or women. (C) IFN- α 2 and IFN- ω , at 100 pg/ml, for both sexes. (D) IFN- α 2 and IFN- ω , at 100 pg/ml, for men or women. (E) IFN- α 2, at 100 pg/ml, for both sexes. (F) IFN- α 2, at 100 pg/ml, for men or women. (G) IFN- ω , at 100 pg/ml, for both sexes. (H) IFN- ω , at 100 pg/ml, for men or women.

auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml) was 2.3% (table S1).

Sharp increase in the prevalence of auto-Abs against IFN- α 2 and/or IFN- ω after the age of 70 years in the general population

We then assessed the percentage of individuals from the general population positive for neutralizing auto-Abs per decade of life and by sex. We noted that the prevalence of auto-Abs neutralizing type I IFN (10 ng/ml) was more than 10 times higher in individuals over the age of 70 years than in those below this age (Firth's multivariable logistic regression, $P < 10^{-13}$) (Fig. 5, C to F; fig. S5, B to I; and tables S5 and S6). The prevalence of auto-Abs capable of neutralizing IFN- α 2 and/or IFN- ω (10 ng/ml) was 0.17% in individuals below 70 years of age, 0.9% in individuals between 70 and 75 years of age, 1.6% between the ages of 75 and 80 years, and more than 4% between the ages of 80 and 85 years. After 85 years, the prevalence of these antibodies decreased to about 2.6%. These findings were replicated independently in two cohorts of 703 and 376 elderly individuals from Estonia and Japan, tested with luciferase-based immunoprecipitation (IP) assay (LIPS) and ELISA assays, respectively (fig. S5, J and K). A strong increase in the prevalence of auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml) was observed with age (Fig. 6, A to H, and fig. S6, A to D), with the prevalence almost doubling with every 5 years from 65 to 85 years of age. A total of 0.87% of individuals between the ages of 65 and 70 years, 1.73% of those between 70 and 75 years, and 7.1% of those between 75 and 80 years were positive for auto-Abs. There was an overall decrease in the prevalence of auto-Abs after 85 years of age, especially in men. By contrast, the prevalence of auto-Abs neutralizing IFN- β did not vary significantly with age (Fig. 5, G and H, and table S4). We then assessed the risk, adjusted for age and sex, of having critical or severe disease, for individuals carrying auto-Abs against each individual IFN and the different possible combinations, relative to the general population. We also found that all auto-Abs were highly significant risk factors in comparisons of patients with critical or severe COVID-19 with the general population (Table 1 and table S2). The strongest association was again that for auto-Abs neutralizing both IFN- α 2 and IFN- ω at 10 ng/ml (OR = 30, $P < 1 \times 10^{-13}$), followed by those neutralizing IFN- α 2 $\pm$ IFN- ω at 10 ng/ml (OR = 20, $P < 10^{-13}$) and IFN- ω $\pm$ IFN- α 2 at 10 ng/ml (OR = 15, $P < 10^{-13}$) (Table 1). Auto-Abs neutralizing both IFN- α 2 and IFN- ω at 100 pg/ml were also highly significant risk factors (OR [95% confidence interval (CI)] = 12 [9 to 16], $P < 10^{-13}$) (Table 1). Overall, these findings indicate that there is a sharp increase in the prevalence of auto-Abs neutralizing type I IFNs with age in elderly uninfected individuals, with at least 4% of those over the age of 70 years positive for auto-Abs against IFN- α 2 and/or IFN- ω , and that these auto-Abs pre-date COVID-19.

DISCUSSION

We report that at least 20% of patients over 80 years of age with life-threatening COVID-19 pneumonia carry circulating auto-Abs neutralizing IFN- α 2 and/or IFN- ω (100 pg/ml) and that such antibodies are present in more than 13.6% of patients of all ages with this condition. Some of these auto-Abs are not identified by immunoassays and are only detectable by a neutralization assay. In addition, at least 18% of deceased individuals in most age groups were found

to have such auto-Abs. We also report that auto-Abs against IFN- β are found in about 1.3 and 0.9% of critical and deceased patients, most of whom do not have auto-Abs against IFN- α 2 and/or IFN- ω . In all four patients tested for whom pre-COVID-19 samples were also available, the auto-Abs against IFN- α 2 and/or IFN- ω were clearly present before SARS-CoV-2 infection, as in patients with APS-1 (9, 20) and in two other previously described patients (9). Auto-Abs capable of neutralizing high concentrations of type I IFNs have been found in patients without inborn errors of TLR3- or TLR7-dependent type I IFN immunity (7, 35), suggesting that both inborn errors and auto-Abs are independently causal of critical disease. It is also notable that inborn errors are more common in patients under the age of 60 years, whereas auto-Abs are more common in patients over the age of 70 years. We also report that the prevalence of auto-Abs neutralizing (10 ng/ml and 100 pg/ml) type I IFNs, except for IFN- β , increases significantly with age in the general population, with 0.17% (1.1%) of individuals positive for these antibodies before the age of 70 years and more than 1.4% (4.4%) positive after the age of 70 years, with a prevalence of 4.2% (7.1%) between the ages of 80 and 85 years.

These auto-Abs provide an explanation for the major increase in the risk of critical COVID-19 in the elderly. This increase with age is consistent with studies of various auto-Abs since the 1960s (38–42). These auto-Abs appear to have remained clinically silent in these individuals until SARS-CoV-2 infection. Our results also suggest that the neutralization of only one type I IFN (IFN- α 2, IFN- ω , or IFN- β) can underlie life-threatening COVID-19 (Table 1 and tables S1 to S3). Auto-Abs neutralizing IFN- β (10 ng/ml) have a frequency only about one-tenth that of auto-Abs neutralizing the same concentrations of IFN- α 2 and/or IFN- ω (Table 1 and table S3). We have shown that auto-Abs neutralizing type I IFN (100 pg/ml) in plasma diluted 1:10, corresponding to the neutralization of IFN (1 ng/ml) in vivo, can account for at least 18% of deaths and more than 20% of critical cases in the elderly >80 years of age. It is tempting to speculate that an even greater proportion of life-threatening COVID-19 cases are due to auto-Abs neutralizing lower, physiological concentrations of type I IFNs. In vitro, concentrations of type I IFN as low as 100 pg/ml can impair SARS-CoV-2 replication in epithelial cells (Fig. 2A). Moreover, the levels of type I IFN detected in the blood of patients with acute and benign SARS-CoV-2 infections are in the range of 1 to 100 pg/ml (32, 33).

Our findings have immediate clinical applications. First, it is quick and easy to test for auto-Abs against type I IFNs in patients infected with SARS-CoV-2. Screening for these antibodies is even possible in the general population before infection. The type I IFN-neutralizing activity of these antibodies is a better readout than their mere detection, which can be falsely negative. Tests should be performed for auto-Abs against at least three individual IFNs: IFN- α 2, IFN- ω , and IFN- β . Particular attention should be paid to elderly individuals and patients with known autoimmune or genetic conditions associated with auto-Abs against type I IFNs (17–20, 22, 23, 26–29). Second, patients with auto-Abs against type I IFN should be vaccinated against COVID-19 as a priority. Third, live-attenuated vaccines, including YFV-17D and vaccines using the YFV-17D backbone against SARS-CoV-2, should not be given to patients with auto-Abs (31, 43). Fourth, these patients appeared to be healthy before SARS-CoV-2 infection, but they should also be carefully followed for other viral illnesses as exemplified by adverse reactions to YFV-17D (31). Fifth, in cases of SARS-CoV-2 infection in unvaccinated individuals with auto-Abs

against type I IFNs, the patients should be hospitalized for prompt management. Early treatment with mAbs (44, 45) can be administered in patients without symptoms of severe COVID-19 pneumonia, and IFN- β can be administered in the absence of both pneumonia and auto-Abs against IFN- β (36, 37). Rescue treatment by plasma exchange is another therapeutic option in patients who already have pneumonia (46).

Sixth, blood products, especially plasma, should be screened for anti-IFN auto-Abs and any products containing such antibodies should be excluded from donation (13). Plasma from donors convalescing from COVID-19 should be tested for such auto-Abs (13). Seventh, given the documented innocuity and potential efficacy of a single injection, early therapy with IFN- β may be considered for the contacts of contagious individuals or during the first week after infection, even in the absence of, or before the documentation of auto-Abs against type I IFNs in elderly patients who have a higher risk of critical pneumonia and auto-Abs against IFN- α 2 and IFN- ω but not IFN- β (47). Another possibility would be the administration of mAbs that can neutralize SARS-CoV-2 (44, 45). Last, it will be important to decipher the mechanism underlying the development of these auto-Abs, which may differ in patients over and under 65 years of age. Overall, our findings show that auto-Abs neutralizing concentrations of type I IFN lower than previously reported (9, 11–16), but still higher than physiological concentrations, are common in the elderly population. Their prevalence increases with age in the uninfected general population, reaching more than 4% of individuals after the age of 70 years. They underlie about 20% of cases of critical COVID-19 pneumonia in patients over the age of 80 years and about 20% of total COVID-19 deaths. We previously reported that they can underlie severe adverse reactions to the live-attenuated vaccine against YFV (31). It is tempting to speculate that they may also underlie other severe viral diseases, especially in the elderly.

MATERIALS AND METHODS

Study design

We enrolled, from 38 countries across all continents, 3595 patients with proven critical COVID-19, 623 patients with severe COVID-19, 1639 asymptomatic or paucisymptomatic individuals with proven COVID-19, and 34,159 healthy controls in this study. We collected plasma or serum samples for all these individuals to test by immunoassay for the presence of IgG auto-Abs to type I IFNs. All individuals were recruited according to protocols approved by local Institutional Review Boards (IRBs).

COVID-19 classification

The severity of COVID-19 was assessed for each patient as follows (7, 9): “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 intensive care unit. “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.

Detection of anti-cytokine auto-Abs

Gyros

Cytokines, recombinant human (rh)IFN- α 2 (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 antibody [Alexa Fluor 647 goat anti-human IgG (Thermo Fisher Scientific, reference number A21445)] diluted in Rextip F (Gyros Protein Technologies, reference number P0004825; 1:500 dilution of the 2 mg/ml stock to yield a final concentration of 4 μ g/ml). Buffer phosphate-buffered saline, 0.01% Tween 20 (PBS-T) 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.

Multiplex particle-based assay

Serum/plasma samples were screened for auto-Abs against IFN- α 2 and IFN- ω in a multiplex particle-based assay in which magnetic beads with differential fluorescence were covalently coupled to recombinant human proteins (2.5 μ g per reaction). Beads were combined and incubated with 1:100 diluted serum/plasma samples for 30 min. Each sample was tested once. The beads were then washed and incubated with phycoerythrin (PE)-labeled goat anti-human IgG (1 μ g/ml) for an additional 30 min. They were then washed again and used for a multiplex assay on a Bio-Plex X200 instrument.

Enzyme-linked immunosorbent assays

ELISA was performed as previously described. Briefly, 96-well ELISA plates (MaxiSorp, Thermo Fisher Scientific) were coated by incubation overnight at 4°C with rhIFN- α 2 (2 μ g/ml; Miltenyi Biotec, reference number 130-108-984) and rhIFN- ω (Merck, reference number SRP3061). Plates were then washed (PBS, 0.005% Tween 20), blocked by incubation with 5% nonfat milk powder in the same buffer, washed, and incubated with 1:50 dilutions of plasma from the patients or controls for 2 hours at room temperature (or with specific mAbs as positive controls). Each sample was tested once. Plates were thoroughly washed. Horseradish peroxidase-conjugated Fc-specific IgG fractions from polyclonal goat antiserum against human IgG, IgM, or IgA (Nordic Immunological Laboratories) were added to a final concentration of 2 μ g/ml. Plates were incubated for 1 hour at room temperature and washed. Substrate was added, and the optical density was measured. A similar protocol was used to test for antibodies against 12 subtypes of IFN- α , except that the plates were coated with cytokines from PBL Assay Science (catalog no. 11002-1), or IFN- β (Miltenyi Biotec, reference number 130-107-888).

Functional evaluation of anti-cytokine auto-Abs

Luciferase reporter assays

The blocking activity of anti-IFN- α 2 and anti-IFN- ω auto-Abs was determined with a reporter luciferase activity. Briefly, HEK293T 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 with IFN- α 2 (Miltenyi Biotec, reference number 130-108-984) and IFN- ω (Merck, reference number SRP3061) at 10 ng/ml or 100 pg/ml or IFN- β (Miltenyi Biotec, reference number 130-107-888) at 10 ng/ml for 16 hours at 37°C. 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. A similar protocol was used to test for auto-Abs against 12 subtypes of IFN- α , except that we used cytokines from PBL Assay Science (catalog no. 11002-1) at 1 ng/ml for stimulation.

pSTAT1 induction in PBMC

The blocking activity of anti-IFN- α 2 and anti-IFN- ω auto-Abs was determined by assessing STAT1 phosphorylation in healthy control cells after stimulation with the appropriate cytokines in the presence of 10% healthy control or patient serum/plasma. Surface-stained healthy control peripheral blood mononuclear cells (PBMCs) (350,000 per reaction) were cultured in serum-free RPMI 1640 medium with 10% healthy control or patient serum/plasma and were either left unstimulated or were stimulated with IFN- α 2 or IFN- ω (10 ng/ml) for 15 min at 37°C. Each sample was tested once. Cells were fixed, permeabilized, and stained for intranuclear pSTAT1 (Y701). Cells were acquired on a BD LSRFortessa cytometer with gating on CD14⁺ monocytes, and the data were analyzed with FlowJo software.

Luciferase-based immunoprecipitation assay

Levels of auto-Abs against IFN- α subtypes were measured in LIPS, as previously described (9). IFNA1, IFNA2, IFNA8, and IFNA21 sequences were inserted into a modified pPK-CMV-F4 fusion vector (PromoCell GmbH, Germany), in which the firefly luciferase replaced the NanoLuc luciferase (Promega, USA). The resulting constructs were used to transfect HEK293 cells, and the IFNA-luciferase fusion proteins were collected in the tissue culture supernatant. For auto-Ab screening, we combined 2×10^6 luminescence units (LU) of IFNA1, IFNA2, IFNA8, and IFNA21 in a single IP reaction mixture (pool 1) and IFNA4, IFNA5, IFNA6, and IFNA7 in another IP reaction mixture (pool 2). Serum samples were incubated with Protein G agarose beads (Exalpha Biologicals, USA) at room temperature for 1 hour in a 96-well microfilter plate (Merck Millipore, Germany), and we then added 2×10^6 LU of antigen and incubated for another hour. Each sample was tested once. The plate was washed with a vacuum system, and Nano-Glo Luciferase Assay Reagent (Promega, USA) was added. Luminescence intensity was measured with a VICTOR X Multilabel Plate Reader (PerkinElmer Life Sciences, USA). The results are expressed in arbitrary units as a fold-difference relative to the mean of the negative control samples.

IgG purification

We demonstrated that the IFN- α 2- or IFN- ω -neutralizing activity observed was due to auto-Abs and not another plasma factor by depleting IgG from the plasma with a protein G buffer (Pierce Protein G IgG Binding Buffer, 21011) and column (NAB Protein G Spin Columns, 89953). All buffers were homemade: 0.1 M glycine (pH 2.7) and 1.5 M tris (pH 8). Total plasma was loaded onto the column. Each sample was tested once. Purified IgG were then concentrated [Pierce Protein Concentrators polyethersulfone (PES), 50K molecular weight cut-off (MWCO), 88504]. Without eluting the IgG, the flow-through fraction (IgG depleted) was then collected and compared to total plasma in the luciferase neutralization assay.

Statistical analysis

OR and *P* values for the effect of auto-Abs neutralizing each type I IFN on critical or severe COVID-19, using asymptomatic/mild patients or the general population as controls and adjusted on age in years and sex, were estimated by means of Firth's bias-corrected logistic regression (48, 49) as implemented in the "logistf" R package (<https://rdrr.io/cran/logistf/>). Effect of age (quantitative in years or binary ± 65 years) and sex on the presence of neutralizing auto-Abs in each cohort (critical, severe, deceased, and general population) was tested by multivariable Firth's bias-corrected logistic regression. The SE of the prevalence of neutralizing auto-Abs to each type I IFN per age groups and sex was estimated using the Agresti-Coull approximation (50).

Schematic representation

Schematic representations (Fig. 1B) were created with BioRender.com.

SARS-CoV-2 experiment

SARS-CoV-2 strain USA-WA1/2020 was obtained from BEI Resources and amplified in Caco-2 cells at 37°C. Viral titers were measured on Huh-7.5 hepatoma cells in a standard plaque assay. Caco-2 (*Homo sapiens*, sex: male, colon epithelial) and Huh-7.5 cells (*H. sapiens*, sex: male, liver epithelial) were cultured in DMEM supplemented with 1% nonessential amino acids and 10% fetal bovine serum at 37°C under an atmosphere containing 5% CO₂. Both cell lines have been tested negative for contamination with mycoplasma. SARS-CoV-2 experiments were performed as follows: Huh-7.5 cells were used to seed 96-well plates at a density of 7.5×10^3 cells per well. The following day, plasma samples or a commercial anti-IFN- α 2 antibody (catalog number 21100-1; R&D Systems) was diluted to 1% and incubated with 5 pM (~100 pg/ml) or 20 pM (~400 pg/ml) recombinant IFN- α 2 (catalog number 11101-2, R&D systems) for 1 hour at 37°C (dilutions: plasma samples = 1:100 and anti-IFN- α 2 antibody = 1:1000). Molar ratio was calculated according to the manufacturer's datasheet and with http://molbiol.ru/eng/scripts/01_04.html. After this incubation period, the cell culture medium was removed from the 96-well plates by aspiration and replaced with the plasma/anti-IFN- α 2 antibody and IFN- α 2 mixture. Each sample was tested once in triplicate. The plates were incubated overnight, and the plasma/anti-IFN- α 2 antibody plus IFN- α 2 mixture was removed by aspiration. The cells were washed once with PBS to remove potential anti-SARS-CoV-2-neutralizing antibodies, and fresh medium was then added. Cells were then infected with SARS-CoV-2 by directly adding the virus to the wells. Cells infected at a multiplicity of infection of 0.05 plaque-forming units per cell and incubated at 33°C for 48 hours. The cells were fixed with 7% formaldehyde, stained

for SARS-CoV-2 with an anti-N antibody (catalog no. GTX135357, GeneTex), imaged, and analyzed as previously described (9).

SUPPLEMENTARY MATERIALS

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Materials and Methods

Figs. S1 to S6

Tables S1 to S6

[View/request a protocol for this paper from Bio-protocol.](#)

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Members of the HGID Lab: Benedetta Bigio¹, Soraya Boucherit^{2,3}, Aliénor de la Chapelle², Jie Chen¹, Maya Chrabieh^{2,3}, Boubacar Coulibaly^{2,3}, Dana Liu¹, Yelena Nemirowskaya¹, Inés Marín Cruz², Marie Materna^{2,3}, Sophie Pelet², Yoann Seelouthner^{2,3}, Chloé Thibault^{2,3}, Zhiyong Liu¹
¹St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA. ²Laboratory of Human Genetics of Infectious Diseases, Necker Branch, INSERM U1163, Necker Hospital for Sick Children, Paris, France. ³University of Paris, Imagine Institute, Paris, France.

Members of the COVID Clinicians: Jorge Abad¹, Giulia Accordini², Cristian Achille³, Sergio Aguilera-Albisa⁴, Aina Aguiló-Cucurull⁵, Alessandro AIUTI⁶, Esra Akyüz Özkan⁷, Ilad Alavi Darazam⁸, Jonathan Antonio Roblero Albisures⁹, Juan C. Aldave¹⁰, Miquel Alfonso Ramos¹¹, Taj Ali Khan¹², Anna Aliberti¹³, Seyed Alireza Nadjli¹⁴, Gulsum Alkan¹⁵, Suzan A. Alkhatir¹⁶, Jerome Allardet-Servent¹⁷, Luis M. Allende¹⁸, Rebecca ALONSO-ARIAS¹⁹, Mohammed S. Alshahrani²⁰, Laia Alsina²¹, Marie-Alexandra Alyanaki²², Blanca Amador Borrero²³, Zahir Amoura²⁴, Arnau Antolí²⁵, Romain Arrestier²⁶, Mélodie Aubart²⁷, Teresa August²⁸, Iryna Avramenko²⁹, Gökhan Aytekin³⁰, Axelle Azot³¹, Seiamak Bahram³², Fanny Bajolle³³, Fausto Baldanti³⁴, Aurélie Baldolli³⁵, Maite Ballester³⁶, Hagit Baris Feldman³⁷, Benoit Barrou³⁸, Federica BARZAGHI³⁹, Sabrina Basso³⁹, Gulsum Iclal BAYHAN⁴⁰, Alexandre Belot⁴¹, Liliana BEZRODNIK⁴², Agurtzane Bilbao⁴³, Geraldine Blanchard-Rohner⁴⁴, Ignacio Blanco⁴⁵, Adeline Bandinieres⁴⁶, Daniel Blázquez-Gamero⁴⁷, Alexandre Bleibtreu⁴⁸, Marketa Bloomfield⁴⁹, Mireia Bolívar-Prados⁵⁰, Anastasia Bondarenko⁵¹, Alessandro Borghesi⁵², Raphael Borie⁵², Elisabeth Botdhu-Nevers⁵³, Ahmed A. Bousfiha⁵⁴, Aurore Bousquet⁵⁵, David Boutolleau⁵⁶, Claire Bouvattier⁵⁷, Oksana Boyarchuk⁵⁸, Juliette Bravais⁵⁹, M. Luisa Briones⁶⁰, Marie-Eve Brunne⁶¹, Raffaele Bruno⁶², Maria Rita P. Bueno⁶³, Huda Bukhari⁶⁴, Jacinta Bustamante³³, Juan José Cáceres Agra⁶⁵, Ruggero Capra⁶⁶, Raphael Carapito⁶⁷, Maria Carrabba⁶⁸, Giorgio CASARÉ⁶⁹, Carlos Casanovas⁶⁹, Marion Caseris⁷⁰, Irene Cassaniti³⁴, Martin Castelle⁷¹, Francesco Castelli⁷², Martín Castillo de Vera⁷³, Mateus V. Castro⁶³, Emilie Catherinot⁷⁴, Jale Bengi Celik⁷⁵, Alessandro Ceschi⁷⁶, Martin Chalumeau⁷⁷, Bruno Charbit⁷⁸, Matthew P. Cheng⁷⁹, Père Clavé⁵⁰, Bonaventura Clotet⁸⁰, Anna Codina⁸¹, Yves Cohen⁸², Roger Colobran⁸³, Cléo Comarmond⁸⁴, Alain Combes⁸⁵, Patrizia Comoli³⁹, Angelo G. Corsico², Taner Coşkun⁸⁶, Aleksandar Cvetkovski⁸⁷, Cyril Cyrus⁸⁸, David Dalmau⁸⁹, François Danion⁹⁰, David Ross Darley⁹¹, Vincent Das⁹², Nicolas Dauby⁹³, Stéphane Dauger⁹⁴, Paul De Munter⁹⁵, Loïc de Pontual⁹⁶, Amin Dehban⁹⁷, Geoffroy Delplancq⁹⁸, Alexandre Demoule⁹⁹, Isabelle Desguerre¹⁰⁰, Antonio Di Sabatino¹⁰¹, Jean-Luc Diehl¹⁰², Stephanie Dobbela¹⁰³, Elena Dominguez-Garrido¹⁰⁴, Clément Dubost¹⁰⁵, Olov EKWALL¹⁰⁶, Şefika Elmas Bozdemir¹⁰⁷, Marwa H. Elnagdy¹⁰⁸, Melike Emiroglu¹⁵, Akifumi Endo¹⁰⁹, Emine Hafize Erdeniz¹¹⁰, Selma Erol Aytekin¹¹¹, Maria Pilar ETXART LASA¹¹², Romain Euvrard¹¹³, Giovanna Fabio⁶⁸, Laurence Faivre¹¹⁴, Antonin Falck¹¹⁵, Muriel Fartoukh¹¹⁶, Morgane Faure¹¹⁷, Miguel Fernandez Arquer¹¹⁸, Ricard Ferrer¹¹⁹, Jose Ferreres¹²⁰, Carlos Flores¹²¹, Bruno Francois¹²², Victoria Fumadó¹²³, Kitty S. C. Fung¹²⁴, Francesca Fusco¹²⁵, Alenka Gagro¹²⁶, Blanca Garcia Solis¹²⁷, Pascale Gaussem¹²⁸, Zeynep GAYRETLI¹²⁹, Juana Gil-Herrera¹³⁰, Laurent Gilardin¹³¹, Audrey Giraud Gatineau¹³², Mònica Girona-Alarcón¹³³, Karen Alejandra Cifuentes Godínez¹³⁴, Jean-Christophe Goffard¹³⁵, Nacho Gonzales¹³⁵, Luis I. Gonzalez-Granado¹³⁷, Rafaela González-Montelongo¹³⁸, Antoine Guerder¹³⁹, Belgün Gülhan¹⁴⁰, Victor Daniel Gumucio¹⁴¹, Leif Gunnar Hanitsch¹⁴², Jan Gunst¹⁴³, Marta Gut¹⁴⁴, Jérôme Hadjadj¹⁴⁵, Filomena Haerynck¹⁴⁶, Rabih Halwani¹⁴⁷, Lennart Hammarström¹⁴⁸, Selda HANCERLI¹⁴⁹, Tetyana Hariyan¹⁵⁰, Nevlin Hatipoglu¹⁵¹, Deniz Heppke¹⁵², Elisa Hernandez-Brito¹⁵³, Po-ki Ho¹⁵⁴, María Soledad Holanda-Peña¹⁵⁵, Juan P. Horcajada¹⁵⁶, Sami Hraiech¹⁵⁷, Linda Humbert¹⁵⁸, Ivan F. N. Hung¹⁵⁹, Alejandro D. Iglesias¹⁶⁰, Antonio Iñigo-Campos¹³⁸, Matthieu Jamme¹⁶¹, María Jesús Arranz⁸⁹, Marie-Thérèse Jimeno¹⁶², Iolanda Jordan¹³³, Saliha Kanik-Yüksek¹⁶³, Yalcin Burak Kara¹⁶⁴, Aydin Karahan¹⁶⁵, Adem Karbuz¹⁶⁶, Kadriye Kart Yasar¹⁶⁷, Ozgur Kasapcopur¹⁶⁸, Kenichi Kashimada¹⁶⁹, Sevgi Keles¹¹¹, Yasemin Kendir Demirkol¹⁷⁰, Yasutoshi Kido¹⁷¹, Can Kizil¹⁷², Ahmet Osman Kiliç¹⁷³, Adam Klocperk¹⁷⁴, Antonia Koutsoukou¹⁷⁵, Zbigniew J. Król¹⁷⁶, Hatem Ksouri¹⁷⁷, Paul Kuentz¹⁷⁸, Arthur M. C. Kwan¹⁷⁹, Yat Wah M. Kwan¹⁸⁰, Janette S. Y. Kwok¹⁸¹, Jean-Christophe Lagier¹⁸², David S. Y. Lam¹⁸³, Vicky Lampropoulou³¹⁰, Fanny Lanternier¹⁸⁵, Yu-Lung Lai¹⁸⁶, Fleur Le Bourgeois⁹⁴, Yee-Sin Leo¹⁸⁷, Rafael Leon Lopez¹⁸⁸, Daniel Leung¹⁸⁶, Michael Levin¹⁸⁹, Michael Levy⁹⁴, Romain Lévy³³, Zhi Li⁷⁸, Daniele Lilleri³⁴, Edson Jose Adrian Bolanos Lima¹⁹⁰, Agnes Linglart¹⁹¹, Eduardo López-Collazo¹⁹², José M. Lorenzo-Salazar¹³⁸, Céline Louapre¹⁹³, Catherine Lubetzki¹⁹³, Kwok-Cheung Lung¹⁹⁴, Charles-Edouard Luyt¹⁹⁵, David C. Lye¹⁹⁶, Cinthia Magnone¹⁹⁷, Davood Mansouri¹⁹⁸, Enrico Marchioni¹⁹⁹, Carola Marioli²⁰⁰, Majid Marjani²⁰⁰, Laura Marques²⁰¹, Jesus Marquez Pereira²⁰², Andrea Martin-Nalda²⁰³, David Martinez Pueyo²⁰⁴, Javier Martinez-Picado²⁰⁵, Iciar Marzán²⁰⁶, Carmen Mata-Martínez²⁰⁷, Alexis Mathian²⁴, Larissa RB Matos⁶³, Gail V. Matthews²⁰⁸, Julien Mayaux²⁰⁹, Raquel McLaughlin-García²¹⁰, Philippe Merseman²¹¹, Jean-Louis Mège²¹², Armand Mekontso-Dessap²¹³, Isabelle Melki¹¹⁵, Federica Meloni², Jean-François Meritet²¹⁴, Paolo Merlani²¹⁵, Özge Metin Akan²¹⁶, Isabelle Meyts²¹⁷, Mehdi Mezidi²¹⁸, Isabelle Migeotte²¹⁹, Maude Millereux²²⁰, Matthieu Million²²¹, Tristan Mirault²²², Clotilde Mircher²²³, Mehdi Mirsaedi²²⁴, Yoko Mizoguchi²²⁵, Bhavi P. Modi²²⁶, Francesco Mojoli¹³, Elsa Moncomble²²⁷, Abián Montesdeoca Melián²²⁸, Antonio Morales Martinez²²⁹, Francisco Morandeira²³⁰, Pierre-Emmanuel Morange²³¹, Clémence Mordacq¹⁵⁸, Guillaume Morelle²³²,

Stéphane J. Mouly²³³, Adrián Muñoz-Barrera¹³⁸, Cyril Nafati²³⁴, Shintaro Nagashima²³⁵, Yu Nakagama¹⁷¹, Bénédicte Neven²³⁶, João Farel Neves²³⁷, Lisa F. P. Ng²³⁸, Yuk-Yung Ng²³⁹, Hubert Nielly¹⁰⁵, Yeray Novoa Medina²¹⁰, Esmeralda Nuñez Cuadros²⁴⁰, J. Gonzalo Ocejio-Vinyals²⁴¹, Keisuke Okamoto¹⁰⁹, Mehdi Oualha³³, Amani Ouedrani²², Tayfun Özçelik²⁴², Aslinur Ozkaya-Parlakay¹⁴⁰, Michele Pagani¹¹³, Qiang Pan-Hammarström¹⁴⁸, Maria Papadaki³¹⁰, Christophe Parizot²⁰⁹, Philippe Parola²⁴⁴, Tiffany Pascreau²⁴⁵, Stéphane Paul²⁴⁶, Estela Paz-Artal²⁴⁷, Sigifredo Pedraza²⁴⁸, Nancy Carolina González Pellicer¹³⁴, Silvia Pellegrini²⁴⁹, Rebeca Pérez de Diego¹²⁷, Xosé Luis Pérez-Fernández¹⁴¹, Aurélien Pelletier²⁵⁰, Quentin Philippot¹¹⁶, Adrien Picod²⁵¹, Marc Pineton de Chambrun⁸⁵, Antonio Piralla³⁴, Laura Planas-Serra²⁵², Dominique Ploin²⁵³, Julien Poissy²⁵⁴, Géraldine Poncet⁷⁰, Garyphalia Poulakou¹⁷⁵, Marie S. Pouletty²⁵⁵, Persia Pourshahnazari²⁵⁶, Jia Li Qiu-Chen²⁵⁷, Paul Quentric²⁰⁹, Thomas Rambaud²⁵⁸, Didier Raoult²¹², Violette Raoult²⁵⁹, Anne-Sophie Rebillat²²³, Claire Redin²⁶⁰, Léa Resmini²⁶¹, Pilar Ricart²⁶², Jean-Christophe Richard²⁶³, Raúl Rigo-Bonnin²⁶⁴, Nadia rivet⁴⁶, Jacques G. Rivière²⁶⁵, Gemma Rocamora-Blanch²⁵, Mathieu P. Rodero²⁶⁶, Carlos Rodrigo²⁶⁷, Luis Antonio Rodriguez¹⁹⁰, Carlos Rodriguez-Gallego²⁶⁸, Agustí Rodríguez-Palmero²⁶⁹, Carolina Soledad Romero²⁷⁰, Anya Rothenbuhler²⁷¹, Damien Roux²⁷², Nikoleta Rovina¹⁷⁵, Flore Rozenberg²⁷³, Yvon Ruch⁹⁰, Montse Ruiz²⁷⁴, María Yolanda Ruiz del Prado²⁷⁵, Juan Carlos Ruiz-Rodríguez¹¹⁹, Joan Sabater-Riera¹⁴¹, Kai Saks²⁷⁶, Maria Salagianni¹⁸⁴, Oliver Sanchez²⁷⁷, Adrián Sánchez-Montalvá²⁷⁸, Silvia Sánchez-Ramón²⁷⁹, Laire Schidlowski²⁸⁰, Agatha Schluter²⁵², Julien Schmidt²⁸¹, Mathieu Schmidt²⁸², Catharina Schuetz²⁸³, Cyril E. Schweitzer²⁸⁴, Francesco Scolari²⁸⁵, Anna Sediva²⁸⁶, Luis Seijo²⁸⁷, Analia Gisela Seminario⁴², Damien Sene²³, Piseth Seng²²¹, Senvat Senoglu¹⁶⁷, Mikko Seppänen²⁸⁸, Alex Serra Llovich²⁸⁹, Mohammad Shahrooei⁹⁷, Anna Shcherbina²⁹⁰, Virginie Siguret²⁹¹, Eleni Siouti³¹⁰, David M. Smadja²⁹³, Nikaia Smith⁷⁸, Ali Sobh²⁹⁴, Xavier Solanich²⁵, Jordi Solé-Violán²⁹⁵, Catherine Soler²⁹⁶, Pere Soler-Palacin²⁹⁷, Betül Sözen⁸⁶, Giulia Maria Stella², Yuriy Stepanovskiy²⁹⁸, Annabelle Stoclin²⁹⁹, Fabio Taccone²¹⁹, Yacine Tandjaoui-Lambiotte³⁰⁰, Jean-Luc Taupin³⁰¹, Simon J. Tavernier³⁰², Loreto Vidaur¹¹², Benjamin Terrier³⁰³, Guillaume Thiery³⁰⁴, Christian Thorball²⁶⁰, Karolina Thörn³⁰⁵, Caroline Thumerelle¹⁵⁸, Imran Tipu³⁰⁶, Martin Tolstrup³⁰⁷, Gabriele Tomasoni³⁰⁸, Julie Toubiana⁷⁷, Josep Trenado Alvarez³⁰⁹, Sophie Trouillet-Assant³¹¹, Jesús Troya³¹², Owen T. Y. Tsang³¹³, Liina Tserel³¹⁴, Eugene Y. K. Tso³¹⁵, Alessandra Tucci³¹⁶, Şadiye Kübra Tüter Öz¹⁵, Matilde Valeria Ursini¹²⁵, Takanori Utsumi²²⁵, Yurdagül Uzunhan³¹⁷, Pierre Vabres³¹⁸, Juan Valencia-Ramos³¹⁹, Ana Maria Van Den Rym¹²⁷, Isabelle Vandernoot³²⁰, Valentina Velez-Santamaria³²¹, Silvia Patricia Zuniga Veliz¹³⁴, Mateus C. Vidigal³²², Sébastien Viel²⁵³, Cédric Vilain³²³, Marie E. Vilaire-Meunier²²³, Judit Villar-García³²⁴, Audrey Vincent⁵⁷, Guillaume Vogt³²⁵, Guillaume Voiriot³²⁶, Alla Volokha³²⁷, Fanny Vuotto¹⁵⁸, Els Wauters³²⁸, Joost Wauters³²⁹, Alan K. L. Wu³³⁰, Tak-Chiu Wu³³¹, Aysun Yahşi³³², Osman Yasilbas³³³, Mehmet Yildiz¹⁶⁸, Barnaby E. Young¹⁸⁷, Ufuk Yükseliş³³⁴, Mayana Zatz⁶³, Marco Zecca³⁹, Valentina Zuccaro⁶², Jens Van Praet³³⁵, Bart N. Lambrecht³³⁶, Eva Van Braeckel³³⁶, Cédric Bosteels³³⁶, Levi Hoste³³⁷, Eric Hoste³³⁸, Fré Bauters³³⁶, Jozefien De Clercq³³⁶, Cathérine Heijmans³³⁹, Hans Slabbynck³⁴⁰, Leslie Naesens³⁴¹, Benoit Florkin³⁴², Cécile Boulanger³⁴³, Dimitri Vanderlinden³⁴⁴

¹Germans Trias i Pujol University Hospital and Research Institute, Badalona, Barcelona, Spain.

²Respiratory Diseases Division, IRCCS Policlinico San Matteo Foundation, University of Pavia, Pavia, Italy.

³Neonatal Intensive Care Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

⁴Navarra Health Service Hospital, Pamplona, Spain.

⁵Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain; Immunology Division, Genetics Department, Vall d'Hebron University Hospital (HUVH), Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain.

⁶Immunohematology Unit, San Raffaele Hospital, Milan, Italy.

⁷Ondokuz Mayıs University Medical Faculty Pediatrics, Samsun, Turkey.

⁸Department of Infectious Diseases, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

⁹Hospital Regional de Huehuetenango, "Dr. Jorge Vides de Molina," Guatemala.

¹⁰Hospital Nacional Edgardo Rebagliati Martins, Lima, Peru.

¹¹Parc Sanitari Sant Joan de Déu, Sant Boi de Llobregat Spain.

¹²Khyber Medical University, Khyber Pakhtunkhwa, Pakistan.

¹³Anesthesia and Intensive Care, Rianimazione I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

¹⁴Virology Research Center, National Research Institute of Tuberculosis and lung diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

¹⁵Department of Pediatrics, Division of Pediatric Infectious Diseases, Selçuk University Faculty of Medicine, Konya, Turkey.

¹⁶College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia; Department of Pediatrics, King Fahad Hospital of the University, Al-Khobar, Saudi Arabia.

¹⁷Intensive care unit, Hôpital Européen, Marseille, France.

¹⁸Immunology Department, Hospital 12 de Octubre, Research Institute imas12, Complutense University, Madrid, Spain.

¹⁹Immunology Department, Asturias Central University Hospital, Biosanitary Research Institute of the Principality of Asturias (ISPA), Oviedo, Spain.

²⁰Emergency and Critical Care Medicine Departments, College of Medicine, Imam Abdulrahman Ben Faisal University, Dammam, Saudi Arabia.

²¹Clinical Immunology and Primary Immunodeficiencies Unit, Hospital Sant Joan de Déu, Institut de Recerca Sant Joan de Déu, Barcelona; Universitat de Barcelona, Barcelona, Spain.

²²Department of Biological Immunology, Necker Hospital for Sick Children, APHP and INEM, Paris, France.

²³Internal medicine department, Hôpital Lariboisière, APHP; Université de Paris, Paris, France.

²⁴Internal medicine department, Pitié-Salpêtrière Hospital, Paris, France.

²⁵Department of Internal Medicine, Hospital

Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²⁶Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, Assistance Publique - Hôpitaux de Paris (AP-HP); Groupe de Recherche Clinique CARMAS, Faculté de Santé de Créteil, Université Paris Est Créteil, Créteil, France. ²⁷INSERM U1163, University of Paris, Imagine Institute, Paris, France & Pediatric Neurology Department, Necker-Enfants malades Hospital, APHP, Paris, France. ²⁸Hospital U. de Tarragona Joan XXIII. Universitat Rovira i Virgili (URV). IISPV, Tarragona, Spain. ²⁹Department of Propedeutics of Pediatrics and Medical Genetics, Danylo Halatsky Lviv National Medical University, Lviv, Ukraine. ³⁰Department of Immunology and Allergy, Konya City Hospital, Konya, Turkey. ³¹Private practice, Paris, France. ³²INSERM U1109, University of Strasbourg, Strasbourg, France. ³³Necker Hospital for Sick Children, AP-HP, Paris, France. ³⁴Molecular Virology Unit, Microbiology and Virology Department, Fondazione IRCCS Policlinico San Matteo and Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy. ³⁵Department of Infectious Diseases, CHU de Caen, Caen, France. ³⁶Consorcio Hospital General Universitario, Valencia, Spain. ³⁷The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ³⁸Department Urology, Nephrology, Transplantation, APHP-SU, Sorbonne Université, INSERM U 1082, Paris, France. ³⁹Cell Factory and Pediatric Hematology-Oncology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ⁴⁰Yildirim Beyazit University, Faculty of Medicine, Ankara City Hospital, Children's Hospital, Ankara, Turkey. ⁴¹University of Lyon, CIRI, INSERM U1111, National referee centre RAISE, Pediatric Rheumatology, HFME, Hospices Civils de Lyon, Lyon, France. ⁴²Center for Clinical Immunology, CABA, Buenos Aires, Argentina. ⁴³Cruces University Hospital, Bizkaia, Spain. ⁴⁴Paediatric Immunology and Vaccinology Unit, Geneva University Hospitals and Faculty of Medicine, Geneva, Switzerland. ⁴⁵University Hospital and Research Institute "Germans Trias i Pujol," Badalona, Spain. ⁴⁶Hematology, Georges Pompidou Hospital, APHP, Paris, France. ⁴⁷Pediatric Infectious Diseases Unit, Instituto de Investigación Hospital 12 de Octubre (imas12), Hospital Universitario 12 de Octubre, Universidad Complutense, Madrid, Spain. ⁴⁸Infectious disease Unit, Pitié-Salpêtrière Hospital, AP-AP, Paris, France. ⁴⁹Department of Pediatrics, 1st Faculty of Medicine, Charles University and Thomayer University Hospital, Prague, Czech Republic; Department of Immunology, Motol University Hospital, 2nd Faculty of Medicine, Charles University, Prague, Czech Republic. ⁵⁰Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (Ciberehd). Hospital de Mataró, Consorci Sanitari del Maresme, Mataró, Spain. ⁵¹Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. ⁵²Service de Pneumologie, Hôpital Bichat, APHP, Paris, France. ⁵³Department of infectious diseases, CIC1408, GIMAP CIRI INSERM U1111, University Hospital of Saint-Étienne, Saint-Étienne, France. ⁵⁴Clinical immunology unit, pediatric infectious disease departement, Faculty of Medicine and Pharmacy, Averroes University Hospital. LICIA Laboratoire d'immunologie clinique, d'inflammation et d'allergie, Hassani II University., Casablanca, Morocco. ⁵⁵Bégin Military Hospital, Saint-Mandé, France. ⁵⁶Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique (IPLESP), AP-HP, Hôpital Pitié Salpêtrière, Service de Virologie, Paris, France. ⁵⁷Endocrinology unit, APHP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ⁵⁸Department of Children's Diseases and Pediatric Surgery, I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. ⁵⁹Pneumology Unit, Tenon Hospital, AP-HP, Paris, France. ⁶⁰Department of Respiratory Diseases, Hospital Clínico y Universitario de Valencia, Valencia, Spain. ⁶¹Intensive care unit, Réseau Hospitalier Neuchâtelais, Neuchâtel, Switzerland. ⁶²Infectious Diseases Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. ⁶³Human Genome and Stem Cell Research Center, University of São Paulo, São Paulo, Brazil. ⁶⁴Department of Internal Medicine, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. ⁶⁵Hospital Insular, Las Palmas de Gran Canaria, Spain. ⁶⁶MS Center, Spedali Civili di Brescia, Italy. ⁶⁷Laboratoire d'Immunorhumatologie Moléculaire, plateforme GENOMAX, INSERM UMR_S 1109, Faculté de Médecine, ITI TRANSPLANTEX NG, Université de Strasbourg, Strasbourg, France. ⁶⁸Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy. ⁶⁹Neuromuscular Unit, Neurology Department, Hospital Universitari de Bellvitge, IDIBELL and CIBERER, Barcelona, Spain. ⁷⁰Hôpital Robert Debré, Paris, France. ⁷¹Pediatric Immuno-Hematology Unit, Necker Enfants Malades Hospital, AP-HP, Paris, France. ⁷²Department of Infectious and Tropical Diseases, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ⁷³Doctoral Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ⁷⁴Hôpital Foch, Suresnes, France. ⁷⁵Selcuk University Faculty of Medicine, Department of Anesthesiology and Reanimation, Intensive Care Medicine Unit, Konya, Turkey. ⁷⁶Division of Clinical Pharmacology and Toxicology, Institute of Pharmacological Sciences of Southern Switzerland, Ente Ospedaliero Cantonale and Faculty of Biomedical Sciences, Università della Svizzera italiana, Lugano, Switzerland. ⁷⁷Necker Hospital for Sick Children, Paris University, AP-HP, Paris, France. ⁷⁸Pasteur Institute, Paris, France. ⁷⁹McGill University Health Centre, Montreal, Canada. ⁸⁰University Hospital and Research Institute Germans Trias i Pujol, IrsiCaixa AIDS Research Institute, UVic-UCC, Badalona, Spain. ⁸¹Clinical Biochemistry, Pathology, Paediatric Neurology and Molecular Medicine Departments and Biobank, Institut de Recerca Sant Joan de Déu and CIBERER-ISCIII, Esplugues, Spain. ⁸²AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; University Sorbonne Paris Nord, Bobigny, France; INSERM, U942, F-75010, Paris, France. ⁸³Hospital Universitari Vall d'Hebron, Barcelona, Spain. ⁸⁴Pitié-Salpêtrière Hospital, Paris, France. ⁸⁵Service de médecine Intensive Réanimation, Groupe Hospitalier Pitié-Salpêtrière, Sorbonne Université, France. ⁸⁶Umraniye Training and Research Hospital, Istanbul, Turkey. ⁸⁷Faculty of Medical Sciences at University "Goce Delcev", Shtip, North Macedonia. ⁸⁸Department of Biochemistry, College of Medicine, Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia. ⁸⁹Fundació Docència i Recerca Mutua Terrassa, Barcelona, Spain. ⁹⁰Maladies Infectieuses et Tropicales, Nouvel Hôpital Civil, CHU Strasbourg, Strasbourg, France. ⁹¹UNSW Medicine, St Vincent's Clinical School; Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst, Sydney, Australia. ⁹²Intensive Care Unit, Montreuil Hospital, Montreuil, France. ⁹³CHU Saint-Pierre, Université Libre de Bruxelles (ULB), Brussels, Belgium. ⁹⁴Pediatric Intensive Care Unit, Robert-Debré University Hospital, APHP, Paris, France. ⁹⁵General Internal Medicine, University Hospitals Leuven, Belgium. ⁹⁶Hôpital Jean Verdier, APHP, Bondy, France. ⁹⁷Specialized Immunology Laboratory of Dr. Shahrooei, Sina Medical Complex, Ahvaz, Iran. ⁹⁸Centre de génétique humaine, CHU Besançon, Besançon, France. ⁹⁹Sorbonne Université Médecine and APHP Sorbonne Université site Pitié-Salpêtrière, Paris, France. ¹⁰⁰Pediatric Neurology Department, Necker-Enfants Malades Hospital, APHP, Paris, France. ¹⁰¹Department of Internal Medicine, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. ¹⁰²Intensive Care Unit, Georges Pompidou Hospital, APHP, Paris, France. ¹⁰³Department of Pneumology, AZ Delta, Roesselaer, Belgium. ¹⁰⁴Molecular Diagnostic Unit, Fundación Rioja Salud, Logroño, La Rioja, Spain. ¹⁰⁵Bégin Military Hospital, Saint-Mandé, France. ¹⁰⁶Department of Pediatrics, Institute of Clinical Sciences, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ¹⁰⁷Bursa City Hospital, Bursa, Turkey. ¹⁰⁸Department of Medical Biochemistry and Molecular Biology, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ¹⁰⁹Tokyo Medical and Dental University, Tokyo, Japan. ¹¹⁰Ondokuz Mayıs University Faculty of Medicine, Samsun, Turkey. ¹¹¹Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Allergy and Immunology, Konya, Turkey. ¹¹²Intensive Care Medicine, Donostia University Hospital, Biodonostia Institute of Donostia, CIBER Enfermedades Respiratorias ISCIII, Donostia, Spain. ¹¹³Internal Medicine, University Hospital Edouard Herriot, Hospices Civils de Lyon, Lyon, France. ¹¹⁴Centre de Génétique, CHU Dijon, Dijon, France. ¹¹⁵Robert Debré Hospital, Paris, France. ¹¹⁶APHP Tenon Hospital, Paris, France. ¹¹⁷Sorbonne Universités, UPMC University of Paris, Paris, France. ¹¹⁸Department of Clinical Immunology, Hospital Clínico San Carlos, Madrid, Spain. ¹¹⁹Intensive Care Department, HUVH, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain; Shock, Organ Dysfunction and Resuscitation Research Group, Vall d'Hebron Research Institute (VHIR), Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ¹²⁰Intensive Care Unit, Hospital Clínico y Universitario de Valencia, Valencia, Spain. ¹²¹Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristóbal de La Laguna, Spain, Santa Cruz de Tenerife, Spain. ¹²²CHU Limoges and INSERM CIC 1435 and UMR 1092, Limoges, France. ¹²³Infectious Diseases Unit, Department of Pediatrics, Hospital Sant Joan de Déu, Barcelona, Spain; Institut de Recerca Sant Joan de Déu, Spain; Universitat de Barcelona (UB), Barcelona, Spain. ¹²⁴Department of Pathology, United Christian Hospital, Hong Kong. ¹²⁵Institute of Genetics and Biophysics "Adriano Buzzati-Traverso", IGB-CNR, Naples, Italy. ¹²⁶Department of Pediatrics, Children's Hospital Zagreb, University of Zagreb School of Medicine, Zagreb, Josip Juraj Strossmayer University of Osijek, Medical Faculty Osijek, Osijek, Croatia. ¹²⁷Laboratory of Immunogenetics of Human Diseases, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ¹²⁸Hematology, APHP, Hôpital Européen Georges Pompidou and INSERM UMR-S1140, Paris, France. ¹²⁹Faculty of Medicine, Department of Pediatrics, Division of Pediatric Infectious Diseases, Karadeniz Technical University, Trabzon, Turkey. ¹³⁰Division of Immunology, Hospital General Universitario and Instituto de Investigación Sanitaria "Gregorio Marañón", Madrid, Spain. ¹³¹Bégin military Hospital, Saint-Mandé, France. ¹³²Aix-Marseille University, IRD, AP-HM, SSA, VITROME, IHU Méditerranée Infection, Marseille, France, French Armed Forces Center for Epidemiology and Public Health (CESPA), Marseille, France. ¹³³Pediatric Intensive Care Unit, Hospital Sant Joan de Déu, Barcelona, Spain. ¹³⁴Gestión Integral en Salud, San José Pinula, Guatemala. ¹³⁵Department of Internal Medicine, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ¹³⁶Immunodeficiencias Unit, Research Institute Hospital, Madrid, Spain. ¹³⁷Primary Immunodeficiencies Unit, Pediatrics, University Hospital 12 octubre, Madrid, Spain; School of Medicine Complutense University of Madrid, Madrid, Spain. ¹³⁸Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain. ¹³⁹Assistance Publique Hôpitaux de Paris, Paris, France. ¹⁴⁰Ankara City Hospital, Ankara, Turkey. ¹⁴¹Department of Intensive Care, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ¹⁴²Immunodeficiency Outpatient Clinic, Institute for Medical Immunology, FOCIS Center of Excellence, Charité Universitätsmedizin Berlin, Germany. ¹⁴³Surgical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. ¹⁴⁴CNAG-CRG, Barcelona Institute of Science and Technology, Barcelona, Spain. ¹⁴⁵Department of Internal Medicine, National Reference Center for Rare Systemic Autoimmune Diseases, AP-HP, APHP-CUP, Hôpital Cochin, Paris, France. ¹⁴⁶Department of Paediatric Immunology and Pulmonology, Center for Primary Immunodeficiency Ghent, Jeffrey Modell Diagnosis and Research Center, PID Research Lab, Ghent University Hospital, Ghent, Belgium. ¹⁴⁷Sharjah Institute of Medical Research, College of Medicine, University of

Sharjah, Sharjah, UAE, Sharjah, UAE. ¹⁴⁸Department of Biosciences and Nutrition, SE14183, Huddinge, Karolinska Institutet, Stockholm, Sweden. ¹⁴⁹Department of Pediatrics (Infectious Diseases), Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey. ¹⁵⁰I. Horbachevsky Ternopil National Medical University, Ternopil, Ukraine. ¹⁵¹Pediatric Infectious Diseases Unit, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹⁵²Health Sciences University, Darica Farabi Education and Research Hospital, Kocaeli, Turkey. ¹⁵³Department of Immunology, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ¹⁵⁴Department of Paediatrics, Queen Elizabeth Hospital, Hong Kong. ¹⁵⁵IntensiveCare Unit, Marqués de Valdecilla Hospital, Santander, Spain. ¹⁵⁶Hospital del Mar, Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), UAB, UPF, Barcelona. ¹⁵⁷Intensive care unit, APHM, Marseille, France. ¹⁵⁸CHU Lille, unité de pneumologie et allergologie pédiatriques, Lille, France. ¹⁵⁹Department of Medicine, The University of Hong Kong, Hong Kong. ¹⁶⁰Department of Pediatrics, Columbia University, New York, NY, USA. ¹⁶¹Centre hospitalier intercommunal Poissy Saint Germain en Laye, Poissy, France. ¹⁶²IHU Méditerranée Infection, Service de l'Information Médicale, Hôpital de la Timone, Marseille, France. ¹⁶³Health Science University Ankara City Hospital, Ankara, Turkey. ¹⁶⁴School of Medicine, General Surgery Department Fevzi Çakmak Mah, Marmara University, Istanbul, Turkey. ¹⁶⁵Mersin City Education and Research Hospital, Mersin, Turkey. ¹⁶⁶Division of Pediatric Infectious Diseases, Prof. Dr. Cemil Tascioglu City Hospital, Istanbul, Turkey. ¹⁶⁷Departments of Infectious Diseases and Clinical Microbiology, Bakirkoy Dr. Sadi Konuk Training and Research Hospital, University of Health Sciences, Istanbul, Turkey. ¹⁶⁸Department of Pediatric Rheumatology, Istanbul University-Cerrahpasa, Istanbul, Turkey. ¹⁶⁹Department of Pediatrics, Tokyo Medical and Dental University, Tokyo, Japan. ¹⁷⁰Health Sciences University, Umraniye Education and Research Hospital, Istanbul, Turkey. ¹⁷¹Department of Parasitology and Research Center for Infectious Disease Sciences, Graduate School of Medicine, Osaka City University, Osaka, Japan. ¹⁷²Pediatric Infectious Diseases Unit of Osman Gazi University Medical School in Eskişehir, Turkey. ¹⁷³Meram Medical Faculty, Necmettin Erbakan University, Konya, Turkey. ¹⁷⁴Department of Immunology, 2nd Faculty of Medicine, Charles University and University Hospital in Motol, Prague, Czech Republic. ¹⁷⁵3rd Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, "Sotiria" General Hospital of Chest Diseases, Athens, Greece. ¹⁷⁶Central Clinical Hospital of the Ministry of Interior and Administration, Warsaw, Poland. ¹⁷⁷Clinique des soins intensifs, HFR Fribourg, Fribourg, Switzerland. ¹⁷⁸Oncobiologie Génétique Bioinformatique, PC Bio, CHU Besançon, Besançon, France. ¹⁷⁹Department of Intensive Care, Tuen Mun Hospital, Hong Kong. ¹⁸⁰Paediatric Infectious Disease Unit, Hospital Authority Infectious Disease Center, Princess Margaret Hospital, Hong Kong (Special Administrative Region), China. ¹⁸¹Department of Pathology, Queen Mary Hospital, Hong Kong. ¹⁸²Aix-Marseille Univ, IRD, MEPHI, IHU Méditerranée Infection, Marseille, France. ¹⁸³Department of Paediatrics, Tuen Mun Hospital, Hong Kong. ¹⁸⁵Necker hospital, Paris, France. ¹⁸⁶Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, China. ¹⁸⁷National Centre for Infectious Diseases, Singapore. ¹⁸⁸Hospital Universitario Reina Sofia, Cordoba, Spain. ¹⁸⁹Imperial College, London, England. ¹⁹⁰Hospital General San Juan de Dios, Ciudad de Guatemala, Guatemala. ¹⁹¹Endocrinology and Diabetes for Children, AP-HP, Bicêtre Paris-Saclay Hospital, Le Kremlin-Bicêtre, France. ¹⁹²Innate Immunity group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ¹⁹³Neurology unit, APHP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹⁹⁴Department of Medicine, Pamela Youde Nethersole Eastern Hospital, Hong Kong. ¹⁹⁵Intensive care unit, APHP Pitié-Salpêtrière Hospital, Paris University, Paris, France. ¹⁹⁶National Centre for Infectious Diseases; Tan Tock Seng Hospital; Yong Loo Lin School of Medicine; Lee Kong Chian School of Medicine, Singapore. ¹⁹⁷Hospital de Niños Dr. Ricardo Gutierrez, Buenos Aires, Argentina. ¹⁹⁸Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran. ¹⁹⁹Neurooncology and Neuroinflammation Unit, IRCCS Mondino Foundation, Pavia, Italy. ²⁰⁰Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran. ²⁰¹Coordenadora da Unidade de Infecçologia e Imunodeficiências do Serviço de Pediatria, Centro Materno-Infantil do Norte, Porto, Portugal. ²⁰²Hospital Sant Joan de Déu and University of Barcelona, Barcelona, Spain. ²⁰³Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, VHIR, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain. ²⁰⁴Hospital Universitari Mutua de Terrassa, Universitat de Barcelona, Barcelona, Spain. ²⁰⁵IrsiCaixa AIDS Research Institute, ICREA, UVic-UCC, Research Institute Germans Trias i Pujol, Badalona, Spain. ²⁰⁶Department of Laboratory, Cruces University Hospital, Barakaldo, Bizkaia, Spain, Bizkaia, Spain. ²⁰⁷Intensive Care Unit, Hospital General Universitario Gregorio Marañón, Madrid, Spain. ²⁰⁸Department of Infectious Diseases, Kirby Institute, UNSW Sydney, Sydney, NSW 2052, Australia; St Vincent's Hospital Sydney, Darlinghurst, NSW, Australia. ²⁰⁹APHP Pitié-Salpêtrière Hospital, Paris, France. ²¹⁰Department of Pediatrics, Complejo Hospitalario Universitario Insular-Materno Infantil, Canarian Health System, Las Palmas de Gran Canaria, Spain. ²¹¹Medical Intensive Care Unit, University Hospitals Leuven, Leuven, Belgium. ²¹²Aix-Marseille University, APHM, Marseille, France. ²¹³Service de Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor,

AP-HP, Groupe de Recherche Clinique CARMAS, Faculté de Santé de Créteil, Université Paris Est Créteil, France. ²¹⁴APHP Cohin Hospital, Paris, France. ²¹⁵Department of Critical Care Medicine, Ente Ospedaliero Cantonale, Bellinzona, Switzerland. ²¹⁶Necmettin Erbakan University, Meram Medical Faculty, Division of Pediatric Infectious Diseases, Konya, Turkey. ²¹⁷Department of Pediatrics, University Hospitals Leuven; KU Leuven, Department of Microbiology, Immunology and Transplantation; Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium. ²¹⁸Hospices Civils de Lyon, Hôpital de la Croix-Rousse, Lyon, France. ²¹⁹Center of Human Genetics, Hôpital Erasme, Brussels, Belgium. ²²⁰Centre hospitalier de Gonesse, Gonesse, France. ²²¹Aix-Marseille University, IRD, AP-HM, MEPHI, IHU Méditerranée Infection, Marseille, France. ²²²Vascular Medicine, Georges Pompidou Hospital, APHP, Paris, France. ²²³Institut Jérôme Lejeune, Paris, France. ²²⁴Division of Pulmonary and Critical Care, College of Medicine-Jacksonville, University of Florida, Jacksonville, FL, USA. ²²⁵Department of Pediatrics, Hiroshima University Graduate School of Biomedical and Health Sciences, Hiroshima, Japan. ²²⁶BC Children's Hospital Research Institute, University of British Columbia, Vancouver, Canada. ²²⁷Médecine Intensive Réanimation, Hôpitaux Universitaires Henri Mondor, AP-HP, Créteil, France. ²²⁸Guanarteme Health Care Center, Canarian Health System, Las Palmas de Gran Canaria, Spain. ²²⁹Regional University Hospital of Malaga, Malaga, Spain. ²³⁰Department of Immunology, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²³¹Aix-Marseille University, INSERM, INRAE, C2VN, Marseille, France. ²³²Department of General Paediatrics, Hôpital Bicêtre, AP-HP, University of Paris-Saclay, Le Kremlin-Bicêtre, France. ²³³INSERM U1144, Université de Paris, DMU INVICTUS, APHP-Nord, Département de Médecine Interne, Lariboisière Hospital, Paris, France. ²³⁴CHU de La Timone, Marseille, France. ²³⁵Department of Epidemiology, Infectious Disease Control and Prevention, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ²³⁶Pediatric Immunology and rheumatology Department, Necker Hospital, AP-HP, Paris, France. ²³⁷Centro Hospitalar Universitário de Lisboa Central, Lisbon, Portugal. ²³⁸Infectious Diseases Horizontal Technology Centre, A*STAR; Singapore Immunology Network, A*STAR, Singapore. ²³⁹Department of Medicine and Geriatrics, Tuen Mun Hospital, Hong Kong. ²⁴⁰Regional University Hospital of Malaga, Málaga, Spain. ²⁴¹Department of Immunology, Hospital Universitario Marqués de Valdecilla, Santander, Spain. ²⁴²Bilkent University, Department of Molecular Biology and Genetics, Ankara, Turkey. ²⁴⁴IHU Méditerranée Infection, Aix-Marseille Univ, IRD, AP-HM, SSA, VITROME, IHU Méditerranée Infection, Marseille, France. ²⁴⁵L'Hôpital Foch, Suresnes, France. ²⁴⁶Department of Immunology, CICI1408, GIMAP CIRI INSERM U1111, University Hospital of Saint-Étienne, Saint-Étienne, France. ²⁴⁷Department of Immunology, Hospital Universitario 12 de Octubre, Instituto de Investigación Sanitaria Hospital 12 de Octubre (imas12), Madrid, Spain. ²⁴⁸Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico. ²⁴⁹Diabetes Research Institute, IRCCS San Raffaele Hospital, Milan, Italy. ²⁵⁰APHP Hôpitaux Universitaires Paris-Sud, Le Kremlin-Bicêtre, France. ²⁵¹AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; INSERM UMR-S 942, Cardiovascular Markers in Stress Conditions (MASCOT), University of Paris, Paris, France. ²⁵²Neurometabolic Diseases Laboratory, IDIBELL-Hospital Duran i Reynals, Barcelona; CIBERER U759, ISCIII Madrid, Spain. ²⁵³Hospices Civils de Lyon, Lyon, France. ²⁵⁴Univ. Lille, INSERM U1285, CHU Lille, Pôle de médecine intensive-réanimation, CNRS, UMR 8576-Unité de Glycobiologie Structurale et Fonctionnelle, Lille, France. ²⁵⁵Department of General pediatrics, Robert Debre Hospital, Paris, France. ²⁵⁶University of British Columbia, Vancouver, Canada. ²⁵⁷Jeffrey Modell Diagnostic and Research Center for Primary Immunodeficiencies, Barcelona, Catalonia, Spain, Diagnostic Immunology Research Group, VHIR, HUVH, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Catalonia, Spain. ²⁵⁸AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France; University Sorbonne Paris Nord, Bobigny, France. ²⁵⁹Centre Hospitalier de Saint-Denis, Saint-Denis, France. ²⁶⁰Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ²⁶¹Paris Cardiovascular Center, PARCC, INSERM, Université de Paris, Paris, France. ²⁶²Germans Trias i Pujol Hospital, Badalona, Spain. ²⁶³Medical intensive care unit. Hospital de la Croix-Rousse. Hospices Civils de Lyon, Lyon, France. ²⁶⁴Department of Clinical Laboratory, Hospital Universitari de Bellvitge, IDIBELL, Barcelona, Spain. ²⁶⁵Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, VHIR, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. ²⁶⁶Université de Paris, CNRS UMR-8601: Team Chemistry & Biology, Modeling & Immunology for Therapy, CBMIT, Paris, France. ²⁶⁷Germans Trias i Pujol University Hospital and Research Institute, Badalona, Badalona, Spain. ²⁶⁸Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ²⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), 08908 L'Hospitalet de Llobregat; University Hospital Germans Trias i Pujol, Badalona, Barcelona, Catalonia, Spain. ²⁷⁰Consorcio Hospital General Universitario, Valencia, Spain. ²⁷¹APHP Hôpitaux Universitaires Paris-Sud, Paris, France. ²⁷²Intensive Care Unit, Louis-Mourier Hospital, Colombes, France. ²⁷³Virology unit, Université de Paris, Cohin Hospital, APHP, Paris, France. ²⁷⁴Neurometabolic Diseases Laboratory and CIBERER U759, Barcelona, Spain. ²⁷⁵Hospital San Pedro, Logroño, Spain. ²⁷⁶University of Tartu, Institute of Biomedicine and Translational Medicine, Tartu, Estonia. ²⁷⁷Respiratory medicine, Georges Pompidou Hospital, APHP, Paris, France. ²⁷⁸Infectious Diseases Department, International Health Program of the Catalan Institute of Health (PROSICS), HUVH, Vall d'Hebron Barcelona Hospital Campus,

Universitat Autònoma de Barcelona, Barcelona, Spain. ²⁷⁹Hospital Clínico San Carlos and IdSSC, Madrid, Spain. ²⁸⁰Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ²⁸¹AP-HP, Avicenne Hospital, Intensive Care Unit, Bobigny, France. ²⁸²Service de Médecine Intensive Réanimation, Institut de Cardiologie, Hôpital Pitié-Salpêtrière, Paris, France. ²⁸³Department of Pediatrics, Medizinische Fakultät Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany. ²⁸⁴CHRU de Nancy, Hôpital d'Enfants, Vandoeuvre, France. ²⁸⁵Chair of Nephrology, University of Brescia, Brescia, Italy. ²⁸⁶Department of Immunology, 2nd Faculty of Medicine, Charles University and Motol University Hospital, Prague, Czech Republic. ²⁸⁷Clinica Universidad de Navarra and Ciberes, Madrid, Spain. ²⁸⁸HUS Helsinki University Hospital, Children and Adolescents, Rare Disease Center, and Inflammation Center, Adult Immunodeficiency Unit, Majakka, Helsinki, Finland. ²⁸⁹Fundació Docència i Recerca Mutua Terrassa, Terrassa, Spain. ²⁹⁰D. Rogachev National Medical and Research Center of Pediatric Hematology, Oncology, Immunology, Moscow, Russia. ²⁹¹Haematology Laboratory, Lariboisière Hospital, University of Paris, Paris, France. ²⁹²INSERM U1140, University of Paris, European Georges Pompidou Hospital, Paris, France. ²⁹³Department of Pediatrics, Faculty of Medicine, Mansoura University, Mansoura, Egypt. ²⁹⁴Intensive Care Medicine, Hospital Universitario de Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain. ²⁹⁵CHU de Saint Etienne, Saint-Priest-en-Jarez, France. ²⁹⁶Pediatric Infectious Diseases and Immunodeficiencies Unit, Hospital Universitari Vall d'Hebron, VHIR, Vall d'Hebron Barcelona Hospital Campus, Universitat Autònoma de Barcelona (UAB), Barcelona, Catalonia, Spain, EU, Barcelona, Spain. ²⁹⁷Department of pediatric infectious diseases and pediatric immunology, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. ²⁹⁸Gustave Roussy Cancer Campus, Villejuif, France. ²⁹⁹Intensive Care Unit, Avicenne Hospital, APHP, Bobigny, France. ³⁰⁰Laboratory of Immunology and Histocompatibility, Saint-Louis Hospital, Paris University, Paris, France. ³⁰¹Center for Inflammation Research, Laboratory of Molecular Signal Transduction in Inflammation, VIB, Ghent, Belgium. ³⁰²Department of Internal Medicine, Université de Paris, INSERM, U970, PARCC, F-75015, Paris, France. ³⁰³Service de médecine intensive réanimation, CHU de Saint-Étienne, France. ³⁰⁴Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden. ³⁰⁵University of Management and Technology, Lahore, Pakistan. ³⁰⁶Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark. ³⁰⁷First Division of Anesthesiology and Critical Care Medicine, University of Brescia, ASST Spedali Civili di Brescia, Brescia, Italy. ³⁰⁸Intensive Care Department, Hospital Universitari MutuaTerrassa, Universitat Barcelona, Terrassa, Spain. ³⁰⁹Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ³¹⁰International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS UMR 5308, ENS, UCBL, Lyon, France; Hospices Civils de Lyon, Lyon Sud Hospital, Pierre-Bénite, France. ³¹¹Infanta Leonor University Hospital, Madrid, Spain. ³¹²Department of Medicine and Geriatrics, Princess Margaret Hospital, Hong Kong. ³¹³University of Tartu, Institute of Clinical Medicine, Tartu, Estonia. ³¹⁴Department of Medicine, United Christian Hospital, Hong Kong. ³¹⁵Hematology Department, ASST Spedali Civili di Brescia, Brescia, Italy. ³¹⁶Pneumologie, Hôpital Avicenne, APHP, INSERM U1272, Université Sorbonne Paris Nord, Bobigny, France. ³¹⁷Dermatology unit, Laboratoire GAD, INSERM UMR1231 LNC, Université de Bourgogne, Dijon, France. ³¹⁸University Hospital of Burgos, Burgos, Spain. ³¹⁹Center of Human Genetics, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium. ³²⁰Bellvitge University Hospital, L'Hospitalet de Llobregat, Barcelona, Spain. ³²¹University of São Paulo, São Paulo, Brazil. ³²²CHU de Caen, Caen, France. ³²³Hospital del Mar-IMIM Biomedical Research Institute, Barcelona, Catalonia, Spain. ³²⁴Neglected Human Genetics Laboratory, INSERM, University of Paris, Paris, France. ³²⁵Sorbonne Université, Service de Médecine Intensive Réanimation, Hôpital Tenon, AP-HP, Paris, France. ³²⁶Pediatric Infectious Disease and Pediatric Immunology Department, Shupyk National Healthcare University of Ukraine, Kyiv, Ukraine. ³²⁷Department of Pneumology, University Hospitals Leuven, Leuven, Belgium. ³²⁸Laboratory for Clinical Infectious and Inflammatory Disorders, Department of Microbiology, Immunology and Transplantation, Leuven, Belgium. ³²⁹Department of Clinical Pathology, Pamela Youde Nethersole Eastern Hospital, Hong Kong. ³³⁰Department of Medicine, Queen Elizabeth Hospital, Hong Kong. ³³¹Ankara City Hospital, Children's Hospital, Ankara, Turkey. ³³²Division of Pediatric Infectious Disease, Department of Pediatrics, Faculty of Medicine, Karadeniz Technical University, Department of Pediatrics, Division of Pediatric Critical Care Medicine, Trabzon, Turkey. ³³³Health Sciences University, Lütfi Kırdar Kartal Education and Research Hospital, Istanbul, Turkey. ³³⁴Department of Nephrology and Infectiology, AZ Sint-Jan, Bruges, Belgium. ³³⁵Department of Pulmonology, Ghent University Hospital, Belgium. ³³⁶Department of Pediatric Pulmonology and Immunology, Ghent University Hospital, Belgium. ³³⁷Department of Intensive Care Unit, Ghent University Hospital, Belgium. ³³⁸Department of Pediatric Hemato-Oncology, Jolimont Hospital; Department of Pediatric Hemato-Oncology, Huderf, La Louvière, Belgium. ³³⁹Department of Pulmonology, ZNA Middelheim, Antwerp, Belgium. ³⁴⁰Department of Internal Medicine, Ghent University Hospital, Belgium. ³⁴¹Department of Pediatric Immuno-Hemato-Rheumatology, CHR Citadelle, Liège, Belgium. ³⁴²Department of Pediatric Hemato-Oncology, UCL Louvain, Brussels, Belgium. ³⁴³Department of Pediatrics, Saint Luc, UCL Louvain, Brussels, Belgium.

Members of the COVID-STORM Clinicians: Giuseppe Foti¹, Giacomo Bellani¹, Giuseppe Citerio¹, Ernesto Contro¹, Alberto Pesci², Maria Grazia Valsecchi³, Marina Cazzaniga⁴

¹Department of Emergency, Anesthesia and Intensive Care, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ²Department of Pneumology, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ³Center of Bioinformatics, Biostatistics and Bioimaging, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ⁴Phase I Research Center, School of Medicine and Surgery, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy.

Members of the NIAID Immune Response to COVID Group: Jeffrey J. Danielson¹, Kerry Dobbs¹, Anuj Kashyap¹, Li Ding¹, Clifton L. Dalgard², Alessandra Sottini³, Virginia Quaresima³, Eugenia Quiros-Roldan⁴, Camillo Rossi⁵, Laura Rachele Bettini⁶, Mariella D'Angio⁶, Ilaria Beretta⁷, Daniela Montagna⁸, Amelia Licari⁹, Gian Luigi Marsegli¹⁰
¹Laboratory of Clinical Immunology and Microbiology, Division of Intramural Research, NIAID, NIH, Bethesda, MD, USA. ²Department of Anatomy, Physiology and Genetics, Uniformed Services University of the Health Sciences; The American Genome Center, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ³CREA Laboratory, Diagnostic Department, ASST Spedali Civili di Brescia, Brescia, Italy. ⁴Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili di Brescia, Brescia, Italy. ⁵Chief Medical Officer, ASST Spedali Civili di Brescia, Brescia, Italy. ⁶Pediatric Department and Centro Tettamanti-European Reference Network PaedCan, EuroBloodNet, MetabERN-University of Milano-Bicocca-Fondazione MBBM-Ospedale, San Gerardo, Monza, Italy. ⁷Department of Infectious Diseases, University of Milano-Bicocca, San Gerardo Hospital, Monza, Italy. ⁸Laboratory of Immunology and Transplantation, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy. ⁹Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy. ¹⁰Department of Pediatrics, Fondazione IRCCS Policlinico San Matteo and Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy.

Members of the NH-COVAIR Study Group: Isabella Batten¹, Conor Reddy¹, Matt McElheron¹, Claire Noonan¹, Emma Connolly¹, Aoife Fallon¹

¹Department of Age-Related Healthcare, Tallaght University Hospital and Department of Medical Gerontology, School of Medicine, Trinity College Dublin.

Members of the Danish CHGE: Merete Storgaard¹, Sofie Jørgensen¹, Martin Tolstrup¹

¹Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark.

Members of the The Danish Blood Donor Study (DBDS): Christian Erikstrup¹, Ole Birger Pedersen², Erik Sørensen³, Susan Mikkelsen¹, Khoa Manh Dinh¹, Margit Anita Hørup Larsen³, Isabella Worlewenut Paulsen², Jakob Hjorth Von Stemmann³, Morten Bagge Hansen³, Sisse Rye Ostrowski³

¹Department of Clinical Immunology, Aarhus University Hospital, Aarhus, Denmark.

²Department of Clinical Immunology, Zealand University Hospital, Køge, Denmark.

³Department of Clinical Immunology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark.

Members of the St James's Hospital, SARS CoV2 Interest group: Liam Townsend¹, Cliona Ni Cheallaigh¹, Colm Bergin¹, Ignacio Martin-Loeches², Jean Dunne³, Niall Conlon³, Nollaig Bourke⁴, Cliona O'Farrelly⁵

¹Department of Infectious Diseases, St James's Hospital; Department of Clinical Medicine, School of Medicine, Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland. ²Department of Intensive Care Medicine, St James's Hospital, Dublin, Ireland.

³Department of Immunology, St James's Hospital; Department of Immunology, School of Medicine, Trinity College Dublin, Ireland. ⁴Department of Medical Gerontology, School of Medicine, Trinity Translational Medicine Institute, Trinity College Dublin, Dublin, Ireland.

⁵School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin; School of Medicine, Trinity College Dublin, Dublin, Ireland.

Members of the French COVID Cohort Study Group: Laurent Abel¹, Clotilde Allavena², Claire Andrejak³, François Angoulvant⁴, Cecile Azoulay⁵, Delphine Bachelet⁶, Marie Bartoli⁷, Romain Basmaci⁸, Sylvie Behillil⁹, Marine Beluze¹⁰, Nicolas Benech¹¹, Dehbia Benkerrou¹², Krishna Bhavsar⁶, Laurent Bitker¹¹, Lila Bouadma⁶, Maude Bouscambert-Duchamp¹³, Pauline Caraux Paz¹⁴, Minerva Cervantes-Gonzalez⁶, Anissa Chair⁶, Catherine Chirouze¹⁵, Alexandra Coelho¹⁶, Hugues Cordel¹⁷, Camille Couffignal⁶, Sandrine Couffin-Cadiergues¹⁸, Eric d'Ortenzio⁷, Etienne De Montmollin⁶, Alexa Debard¹⁹, Marie-Pierre Debray⁶, Dominique Deplagne²⁰, Diane Descamps⁶, Mathilde Desvallée²¹, Alpha Diallo⁶, Jean-Luc Diehl²², Alphonsine Diouf¹⁶, Céline Dorival¹², François Dubos²³, Xavier Duval⁶, Philippine Eloy⁶,

Vincent Enouf⁹, Olivier Epaulard²⁴, Hélène Esperou¹⁸, Marina Esposito-Farase⁶, Manuel Etienne²⁵, Denis Garot²⁶, Nathalie Gault⁶, Alexandre Gaymard¹³, Jade Ghosn⁶, Tristan Gigante²⁷, Morgane Gilg²⁷, François Goehringer²⁸, Jérémie Guedj²⁹, Alexandre Hocht¹⁶, Isabelle Hoffmann⁶, Ikram Houas¹⁸, Jean-Sébastien Hulot²², Salma Jaafoura¹⁸, Oufiyya Kafif⁶, Florentia Kaguelidou³⁰, Sabrina Kali⁶, Younes Kerroumi³¹, Antoine Khalil⁶, Coralie Khan²¹, Antoine Kimmoun³², Fabrice Laine³³, Cédric Laouénan⁶, Samira Laribi⁶, Minh Le⁶, Cyril Le Bris³⁴, Sylvie Le Gac⁶, Quentin Le Hingrat⁶, Soizic Le Mestre⁷, Hervé Le Nagard³⁵, Adrien Lemaiguen²⁶, Véronique Lemee²⁵, François-Xavier Lescure⁶, Sophie Letrou⁶, Yves Levy⁶, Bruno Lina¹³, Guillaume Lingas³⁵, Jean Christophe Lucet⁶, Moïse Machado³⁷, Denis Malvy³⁸, Marina Mambert¹⁶, Aldric Manuel³⁹, France Mentré⁶, Amina Meziane¹², Hugo Mouquet⁹, Jimmy Mullaert⁶, Nadège Neant³⁵, Duc Nguyen³⁸, Marion Noret⁴⁰, Aurélie Papadopoulos¹⁸, Christelle Pauli⁷, Nathan Peiffer-Smadja⁶, Vincent Peigne⁴¹, Ventsislava Petrov-Sanchez⁷, Gilles Peytavin⁶, Huong Pham⁶, Olivier Picone⁸, Valentine Piquard⁶, Julien Poissy²³, Oriane Puéchal⁴², Manuel Rosa-Calatrava¹³, Bénédicte Rossignol²⁷, Patrick Rossignol²⁸, Carine Roy⁶, Marion Schneider⁶, Richa Su⁶, Coralie Tardivon⁶, Marie-Capucine Tellier⁶, François Téoulé¹², Olivier Terrier¹³, Jean-François Timsit⁶, Christelle Tual⁴³, Sarah Tubiana⁶, Sylvie Van Der Werf⁹, Noémie Vanel⁴⁴, Aurélie Veislinger⁴³, Benoit Visseaux⁶, Aurélie Wiedemann⁴⁵, Yazdan Yazdanpanah⁶

¹INSERM UMR 1163, Paris, France. ²CHU Nantes, France. ³CHU Amiens, France. ⁴Hôpital Necker, Paris, France. ⁵Hôpital Cochin, Paris, France. ⁶Hôpital Bichat, Paris, France. ⁷ANRS, Paris, France. ⁸Hôpital Louis Mourier, Colombes, France. ⁹Pasteur Institute, Paris, France. ¹⁰F-CRIN Partners Platform, Paris, France. ¹¹CHU Lyon, France. ¹²INSERM UMR 1136, Paris, France. ¹³INSERM UMR 1111, Lyon, France. ¹⁴CH Villeneuve Saint Georges, France. ¹⁵CHRU Jean Minjoz, Besançon, France. ¹⁶INSERM UMR 1018, Paris, France. ¹⁷Hôpital Avicenne, Bobigny, France. ¹⁸INSERM Pôle Recherche Clinique, Paris, France. ¹⁹CHU Toulouse, France. ²⁰Hôpital Calmette, Lille, France. ²¹INSERM UMR 1219, Bordeaux, France. ²²Hôpital Européen Georges Pompidou, Paris, France. ²³CHU Lille, France. ²⁴CHU Grenoble, France. ²⁵CHU Rouen, France. ²⁶CHU Tours, France. ²⁷F-CRIN INI-CRCT, Nancy, France. ²⁸CHU Nancy, France. ²⁹Université de Paris, INSERM, IAME, F-75018 Paris, France. ³⁰Hôpital Robert Debré, Paris, France. ³¹GH Diaconesses, Paris, France. ³²Université de Lorraine, CHRU de Nancy, Service de Médecine Intensive et Réanimation Brabois, INSERM U116, Nancy, France. ³³CHU Rennes, France. ³⁴CH Beziers, France. ³⁵INSERM UMR 1137, Paris, France. ³⁶Vaccine Research Institute (VRI), INSERM U955, Créteil, France. ³⁷Grand Hôpital de l'Est Francilien, Marne-la-Vallée, France. ³⁸CHU Bordeaux, France. ³⁹CH Annecy, France. ⁴⁰RENARCI, Annecy, France. ⁴¹CH Métropole Savoie, Cambery, France. ⁴²REACTing, Paris, France. ⁴³INSERM CIC-1414, Rennes, France. ⁴⁴Hôpital la Timone, Marseille, France. ⁴⁵Vaccine Research Institute (VRI), INSERM UMR 955, Créteil, France.

Members of the Imagine COVID-Group: Jean-Philippe Annereau¹, Luis Briseño-Roa¹, Olivier Gribouval², Anna Pelet²

¹Medetia Pharmaceuticals, Paris, France. ²Imagine Institute, Université de Paris, INSERM UMR 1163, Paris, France.

Members of the The Milieu Intérieur Consortium: Laurent Abel¹, Andres Alcover², Hugues Aschard², Philippe Bousso², Nollaig Bourke³, Petter Brodin⁴, Pierre Bruhns², Nadine Cerf-Bensussan⁵, Ana Cumano², Christophe D'Enfert², Ludovic Deriano², Marie-Agnès Dillies², James Di Santo², Françoise Dromer², Gérard Eberl², Jost Enninga², Jacques Fellay⁶, Ivo Gomperts-Boneca², Milena Hasan², Gunilla Karlsson Hedestam⁴, Serge Hercberg⁷, Molly A. Ingersoll⁸, Olivier Lant⁸, Rose Anne Kenny⁹, Mickaël Ménager⁵, Frédérique Michel², Hugo Mouquet², Cliona O'Farrelly³, Etienne Patin², Sandra Pellegrini², Antonio Rausell², Frédéric Rieux-Laucat¹, Lars Rogge², Magnus Fontes⁹, Anavaj Sakuntabhai², Olivier Schwartz², Benno Schwikowski², Spencer Shorte², Frédéric Tangy², Antoine Toubert¹⁰, Mathilde Touvier¹², Marie-Noëlle Ungeheuer², Christophe Zimmer², Matthew L. Albert¹¹, Darragh Duffy², Lluis Quintana-Murci²

¹Hôpital Necker, Paris, France. ²Institut Pasteur, Paris, France. ³Trinity College, Dublin, Ireland. ⁴Karolinska Institutet, Stockholm, Sweden. ⁵INSERM U1163, Institut Imagine, Paris, France. ⁶EPFL, Lausanne, Switzerland. ⁷Université Paris 13, Paris, France. ⁸Institut Curie, Paris, France. ⁹Institut Roche, Paris, France. ¹⁰Hôpital Saint-Louis, Paris, France. ¹¹In Situ, San Francisco, USA. ¹²Sorbonne Paris Nord University, INSERM U1153, INRAE U1125, CNAM, Nutritional Epidemiology Research Team (EREN), Epidemiology and Statistics Research Center – University of Paris (CRESS), Bobigny, France.

Members of the CoV-Contact Cohort: Loubna Alavoine¹, Sylvie Behillil², Charles Burdet³, Charlotte Charpentier^{3,4}, Aline Dechanet⁵, Diane Descamps^{3,6}, Xavier Duval^{1,3}, Jean-Luc Ecobichon¹, Vincent Enouf⁶, Wahiba Frezouls¹, Nadhira Houhou⁵, Oufiyya Kafif⁶, Jonathan Lehacaut¹, Sophie Letrou¹, Bruno Lina⁹, Jean-Christophe Lucet¹⁰, Pauline Manchon⁵, Mariama Nourouline¹, Valentine Piquard⁹, Caroline Quintin¹, Michael Thy¹¹, Sarah Tubiana¹, Sylvie van der Werf⁹, Valérie Vignali¹, Benoit Visseaux^{3,10}, Yazdan Yazdanpanah^{3,10}, Abir Chahine¹², Nawal Waucquier¹², Maria-Claire Migaud¹², Dominique Deplanque¹², Félix Djossou¹³, Mayka Mergeay-Fabre¹⁴, Aude Lucarelli¹⁵, Magalie Demar¹³, Léa Bruneau¹⁶,

Patrick Gérardin¹⁷, Adrien Maillot¹⁶, Christine Payet¹⁸, Bruno Laviolle¹⁹, Fabrice Laine¹⁹, Christophe Paris¹⁹, Mireille Desille-Dugast¹⁹, Julie Fouchard¹⁹, Denis Malvy²⁰, Duc Nguyen²⁰, Thierry Pistone²⁰, Pauline Perreau²⁰, Valérie Gissot²¹, Carole Le Goas²¹, Samatha Montagne²², Lucie Richard²³, Catherine Chirouze²⁴, Kévin Bouiller²⁴, Maxime Desmaret²⁵, Alexandre Meunier²⁶, Benjamin Lefèvre²⁷, Hélène Jeulin²⁸, Karine Legrand²⁹, Sandra Lomazzi³⁰, Bernard Tardy³¹, Amandine Gagneux-Brunon³², Frédérique Bertholon³³, Elisabeth Botelho-Nevers³², Kouakam Christelle³⁴, Leturque Nicolas³⁴, Layidé Roufai³⁴, Karine Amat³⁵, Sandrine Couffin-Cadiergues³⁴, Hélène Espérou³⁶, Samia Hendou³⁴.

¹Centre d'Investigation Clinique, INSERM CIC 1425, Hôpital Bichat Claude Bernard, APHP, Paris, France. ²Institut Pasteur, Paris, France. ³Université de Paris, IAME, INSERM U1137, Paris, France, Hôpital Bichat Claude Bernard, APHP, Paris, France. ⁴Service de Virologie, Université de Paris, INSERM, IAME, UMR 1137, AP-HP, Hôpital Bichat-Claude Bernard, F-75018 Paris, France. ⁵IAME INSERM U1140, Hôpital Bichat Claude Bernard, APHP, Paris, France. ⁶Centre d'Investigation Clinique, INSERM CIC 1425, APHP, IAME, Paris University, Paris, France. ⁸Institut Pasteur, U3569 CNRS, Université de Paris, Paris, France. ⁹Virpath Laboratory, International Center of Research in Infectiology, Lyon University, INSERM U1111, CNRS U5308, ENS, UCBL, Lyon, France. ¹⁰IAME INSERM U1138, Hôpital Bichat Claude Bernard, APHP, Paris, France. ¹¹Center for Clinical Investigation, Assistance Publique-Hôpitaux de Paris, Bichat-Claude Bernard University Hospital, Paris, France. ¹²Centre d'Investigation Clinique, INSERM CIC 1403, Centre Hospitalo Universitaire de Lille, Lille, France. ¹³Center of Biological Resource (CRB Amazonie), Centre Hospitalier de Cayenne André Rosemon, Guiana, France. ¹⁴Centre d'Investigation Clinique, INSERM CIC 1424, Centre Hospitalier de Cayenne, Cayenne, Guyane Française. ¹⁵Service Hôpital de jour Adulte, Centre Hospitalier de Cayenne, Guyane, France. ¹⁶Centre d'Investigation Clinique, INSERM CIC 1410, Centre Hospitalo universitaire de la Réunion, La Réunion, France. ¹⁷Centre d'Investigation Clinique, INSERM CIC 1410, CHU Reunion, Saint-Pierre, Reunion island. ¹⁸Centre de Ressources Biologiques, Centre Hospitalo universitaire de la Réunion, La Réunion, France. ¹⁹CRB Santé, INSERM U1241, Université de Rennes 1, Centre hospitalier universitaire de Rennes, Rennes, France. ²⁰Service des maladies infectieuses, Centre Hospitalo universitaire de Bordeaux, Bordeaux, France. ²¹Centre d'Investigation Clinique, INSERM CIC 1415, CHRU Tours, Tours, France. ²²CRBT, Centre Hospitalo universitaire de Tours, Tours, France. ²³Pole de Biologie Médicale, Centre Hospitalo universitaire de Tours, Tours, France. ²⁴Service des maladies infectieuses, Centre Hospitalo universitaire de Besançon, Besançon, France. ²⁵Service des maladies infectieuses, Centre d'Investigation Clinique, INSERM CIC1431, Centre Hospitalier Universitaire de Besançon, Besançon, France. ²⁶Centre de Ressources Biologiques - Filière Microbiologique de Besançon, Centre Hospitalier Universitaire, Besançon, France. ²⁷Université de Lorraine, CHRU-Nancy and APEMAC, Infectious and tropical diseases, Nancy, France. ²⁸Laboratoire de Virologie, CHRU de Nancy Brabois, Vandoeuvre-lès-Nancy, France. ²⁹INSERM CIC-EC 1433, Centre Hospitalo universitaire de Nancy, Nancy, France. ³⁰Centre de ressources Biologiques, Centre Hospitalo universitaire de Nancy, Nancy, France. ³¹Centre d'Investigation Clinique, INSERM CIC 1408, Centre Hospitalo universitaire de Saint-Étienne, Saint-Étienne, France. ³²Service des maladies infectieuses, Centre Hospitalo universitaire de Saint-Étienne, Saint-Étienne, France. ³³Service des maladies infectieuses, CRB⁴²-BTK, Centre Hospitalo Universitaire de Saint-Étienne, Saint-Étienne, France. ³⁴Pole Recherche Clinique, INSERM, Paris France. ³⁵IMEA Fondation Léon M'Ba, Paris, France. ³⁶INSERM Pôle Recherche Clinique, Paris, France.

Members of the Amsterdam UMC Covid-19 Biobank: Michiel van Agtmael², Anne Geke Algera¹, Brent Appelman², Frank van Baarle¹, Diane Bax³, Martijn Beudel⁴, Harm Jan Bogaard⁵, Marije Bomers², Peter Bonta⁵, Lieuwe Bos¹, Michela Botta¹, Justin de Brabander², Godelieve de Bree², Sanne de Bruin¹, David T. P. Buis¹, Marianna Bugiani⁵, Esther Bulle¹, Osoul Chouchane², Alex Cloherty³, Mirjam Dijkstra¹², Dave A. Dongelmans¹, Romein W. G. Dujardin¹, Paul Elbers¹, Lucas Fleuren¹, Suzanne Geerlings², Theo Geijtenbeek³, Armand Girbes¹, Bram Goorhuis², Martin P. Grobusch², Florianne Hafkamp³, Laura Hagens¹, Jorg Hamann⁷, Vanessa Harris², Robert Hemke⁸, Sabine M. Hermans², Leo Heunks¹, Markus Hollmann⁶, Janneke Horn¹, Joppe W. Hovius², Menno D. de Jong⁹, Rutger Koning⁴, Endry H. T. Lim¹, Niels van Mourik¹, Jeaninne Nellen², Esther J. Nossent⁵, Frederique Paulus¹, Edgar Peters², Dan A. I. Pina-Fuentes⁴, Tom van der Pol¹², Benedikt Preckel⁶, Jan M. Prins², Jorinde Raasveld¹, Tom Reijnders⁵, Maurits C. F. J. de Rotte¹², Michiel Schinkel², Marcus J. Schultz¹, Femke A. P. Schrauwen¹², Alex Schuurman¹⁰, Jaap Schuurmans¹, Kim Sigaloff¹, Marleen A. Slim^{1,2}, Patrick Smeele⁵, Marry Smit¹, Cornelis S. Stijnis⁵, Willemke Stilma¹, Charlotte Teunissen¹¹, Patrick Thorat¹, Anissa M. Tsonas¹, Pieter R. Tuinman², Marc van der Valk², Denise Veelo⁶, Carolien Volleman¹, Heder de Vries¹, Lonneke A. Vught^{1,2}, Michèle van Vugt², Dorien Wouters¹², A. H. (Koo) Zwiderman¹³, Matthijs C. Brouwer⁴, W. Joost Wiersinga², Alexander P. J. Vlaar¹, Diederik van de Beek⁴

¹Department of Intensive Care, Amsterdam UMC, Amsterdam, Netherlands. ²Department of Infectious Diseases, Amsterdam UMC, Amsterdam, Netherlands. ³Experimental Immunology, Amsterdam UMC, Amsterdam, Netherlands. ⁴Department of Neurology, Amsterdam UMC, Amsterdam Neuroscience, Amsterdam, Netherlands. ⁵Department of Pulmonology,

Amsterdam UMC, Amsterdam, Netherlands. ⁶Department of Anesthesiology, Amsterdam UMC, Amsterdam, Netherlands. ⁷Amsterdam UMC Biobank Core Facility, Amsterdam UMC, Amsterdam, Netherlands. ⁸Department of Radiology, Amsterdam UMC, Amsterdam, Netherlands. ⁹Department of Medical Microbiology, Amsterdam UMC, Amsterdam, Netherlands. ¹⁰Department of Internal Medicine, Amsterdam UMC, Amsterdam, Netherlands. ¹¹Neurochemical Laboratory, Amsterdam UMC, Amsterdam, Netherlands. ¹²Department of Clinical Chemistry, Amsterdam UMC, Amsterdam, Netherlands. ¹³Department of Clinical Epidemiology, Biostatistics and Bioinformatics, Amsterdam UMC, Amsterdam, Netherlands.

Members of the COVID Human Genetic Effort: Laurent Abel¹, Alessandro Aiuti²,

Saleh Al-Muhsen³, Fahd Al-Mulla⁴, Mark S. Anderson⁵, Evangelos Andreaskos⁶, Andrés A. Arias⁷, Hagit Baris Feldman⁸, Alexandre Belot⁹, Catherine M. Biggs¹⁰, Dusan Bogunovic¹¹, Alexandre Bolze¹², Anastasiia Bondarenko¹³, Ahmed A. Bousfiha¹⁴, Petter Brodin¹⁵, Yenan Bryceson¹⁶, Carlos D. Bustamante¹⁷, Manish J. Butte¹⁸, Giorgio Casari¹⁹, Samya Chakravorty²⁰, John Christodoulou²¹, Antonio Condino-Neto²², Stefan N. Constantinescu²³, Megan A. Cooper²⁴, Clifton L. Dalgard²⁵, Murkesh Desai²⁶, Beth A. Drole²⁷, Jamila El Baghdadi²⁸, Sara Espinosa-Padilla²⁹, Jacques Fellay³⁰, Carlos Flores³¹, José Luis Franco⁷, Antoine Froidure³², Peter K. Gregeresen³³, Filomeen Haerynck³⁴, David Hagin³⁵, Rabih Halwani³⁶, Lennart Hammarström³⁷, James R. Heath³⁸, Sarah E. Henriksson³⁹, Elena W. Y. Hsieh⁴⁰, Eystein S. Husebye⁴¹, Kohsuke Imai⁴², Yuval Itan⁴³, Erich D. Jarvis⁴⁴, Timokratits Karamitros⁴⁵, Kai Kisand⁴⁶, Cheng-Lung Ku⁴⁷, Yu-Lung Lau⁴⁸, Yun Ling⁴⁹, Carrie L. Lucas⁵⁰, Tom Maniatis⁵¹, Davood Mansouri⁵², László Maródi⁵³, Isabelle Meyts⁵⁴, Joshua D. Milner⁵⁵, Kristina Mironska⁵⁶, Trine H. Mogensen⁵⁷, Tomohiro Morio⁵⁸, Lisa F. P. Ng⁵⁹, Luigi D. Notarangelo⁶⁰, Antonio Novelli⁶¹, Giuseppe Novelli⁶², Cliona A. Snow⁷⁹, Pere Soler-Palacin⁸⁰, Andrés N. Spaan⁸¹, Ivan Tancevski⁸², Stuart G. Tangye⁸³, Ahmad Abou Tayoun⁸⁴, Sathishkumar Ramaswamy⁸⁴, Stuart E. Turvey⁸⁵, K. M. Furkan Uddin⁸⁶, Mohammed J. Uddin⁸⁷, Diederik van de Beek⁸⁸, Donald C. Vinh⁸⁹, Horst von Bernuth⁹⁰, Mayana Zatz⁹¹, Pawel Zawadzki⁹², Helen C. Su⁶⁰, Jean-Laurent Casanova⁹³

¹INSERM U1163, University of Paris, Imagine Institute, Paris, France. ²San Raffaele Telethon Institute for Gene Therapy, IRCCS Ospedale San Raffaele, and Vita Salute San Raffaele University, Milan, Italy. ³Immunology Research Laboratory, Department of Pediatrics, College of Medicine and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia. ⁴Dasman Diabetes Institute, Department of Genetics and Bioinformatics, Dasman, Kuwait. ⁵Diabetes Center, University of California San Francisco, San Francisco, CA, USA. ⁶Laboratory of Immunobiology, Center for Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, Greece. ⁷Group of Primary Immunodeficiencies, University of Antioquia UdeA, Medellín, Colombia. ⁸The Genetics Institute, Tel Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel. ⁹Pediatric Nephrology, Rheumatology, Dermatology, HFME, Hospices Civils de Lyon, National Referee Centre RAISE, and INSERM U1111, Université de Lyon, Lyon, France. ¹⁰Department of Pediatrics, British Columbia Children's Hospital, The University of British Columbia, Vancouver, BC, Canada. ¹¹Icahn School of Medicine at Mount Sinai, New York, NY, USA. ¹²Helix, San Mateo, CA, USA. ¹³Shupyk National Medical Academy for Postgraduate Education, Kiev, Ukraine. ¹⁴Clinical Immunology Unit, Department of Pediatric Infectious Disease, CHU Ibn Rushd and LICIA, Laboratoire d'Immunologie Clinique, Inflammation et Allergie, Faculty of Medicine and Pharmacy, Hassan II University, Casablanca, Morocco. ¹⁵SciLifeLab, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden. ¹⁶Department of Medicine, Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden. ¹⁷Stanford University, Stanford, CA, USA. ¹⁸Division of Immunology, Allergy, and Rheumatology, Department of Pediatrics and the Department of Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA, USA. ¹⁹Clinical Genomics, IRCCS San Raffaele Scientific Institute and Vita-Salute San Raffaele University, Milan, Italy. ²⁰Department of Pediatrics and Children's Healthcare of Atlanta, Emory University, Atlanta, GA, USA. ²¹Murdoch Children's Research Institute and Department of Paediatrics, University of Melbourne, Australia. ²²Department of Immunology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil. ²³de Duve Institute and Ludwig Cancer Research, Brussels, Belgium. ²⁴Washington University School of Medicine, St. Louis, MO, USA. ²⁵Department of Anatomy, Physiology & Genetics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ²⁶Bai Jerbai Wadia Hospital for Children, Mumbai, India. ²⁷School of Medicine and Public Health, University of Wisconsin, Madison, WI, USA. ²⁸Genetics Unit, Military Hospital Mohamed V, Rabat, Morocco. ²⁹Instituto Nacional de Pediatría (National Institute of Pediatrics), Mexico City, Mexico. ³⁰School of Life Sciences, Ecole Polytechnique Fédérale de Lausanne, Lausanne, Switzerland; Precision Medicine Unit, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland. ³¹Genomics Division, Instituto Tecnológico y de Energías Renovables (ITER), Santa Cruz de Tenerife, Spain; Research Unit, Hospital Universitario N.S. de Candelaria, Santa Cruz de Tenerife, Spain; Instituto de Tecnologías Biomédicas (ITB), Universidad de La Laguna, San Cristóbal de La Laguna, Spain;

CIBER de Enfermedades Respiratorias, Instituto de Salud Carlos III, Madrid, Spain.

³²Pulmonology Department, Cliniques Universitaires Saint-Luc; Institut de Recherche Expérimentale et Clinique (IREC), Université Catholique de Louvain, Brussels, Belgium.

³³Feinstein Institute for Medical Research, Northwell Health USA, Manhasset, NY, USA.

³⁴Department 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. ³⁵The Genetics Institute Tel Aviv Sourasky Medical Center, Tel Aviv, Israel. ³⁶Sharjah Institute of Medical Research, College of Medicine, University of Sharjah, Sharjah, United Arab Emirates. ³⁷Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden. ³⁸Institute for Systems Biology, Seattle, WA, USA. ³⁹Department of Pediatrics, Division of Allergy Immunology, Children's Hospital of Philadelphia, Philadelphia, PA, USA; Department of Microbiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. ⁴⁰Departments of Pediatrics, Immunology and Microbiology, University of Colorado, School of Medicine, Aurora, Colorado, USA. ⁴¹Department of Clinical Science and K.G. Jebsen Center for Autoimmune Diseases, University of Bergen, Bergen, Norway. ⁴²Department of Community Pediatrics, Perinatal and Maternal Medicine, Tokyo Medical and Dental University (TMDU). ⁴³Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA; Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA. ⁴⁴Laboratory of Neurogenetics of Language and Howard Hughes Medical Institute, The Rockefeller University, New York, NY, USA. ⁴⁵Bioinformatics and Applied Genomics Unit, Hellenic Pasteur Institute, Athens, Greece. ⁴⁶Molecular Pathology, Department of Biomedicine, Institute of Biomedicine and Translational Medicine, University of Tartu, Tartu Estonia. ⁴⁷Chang Gung University, Taoyuan County, Taiwan. ⁴⁸Department of Paediatrics & Adolescent Medicine, The University of Hong Kong, Hong Kong, China. ⁴⁹Shanghai Public Health Clinical Center, Fudan University, Shanghai, China. ⁵⁰Department of Immunobiology, Yale University School of Medicine, New Haven, CT, USA. ⁵¹Columbia University Zuckerman Institute, New York, NY, USA. ⁵²Department of Clinical Immunology and Infectious Diseases, National Research Institute of Tuberculosis and Lung Diseases, The 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. ⁵³Primary Immunodeficiency Clinical Unit and Laboratory, Department of Dermatology, Venereology and Dermatooncology, Semmelweis University, Budapest, Hungary. ⁵⁴Department of Pediatrics, University Hospitals Leuven, Department of Microbiology, Immunology and Transplantation, and Laboratory for Inborn Errors of Immunity, KU Leuven, Leuven, Belgium. ⁵⁵Department of Pediatrics, Columbia University Irving Medical Center, New York, NY, USA. ⁵⁶University Clinic for Children's Diseases, Department of Pediatric Immunology, Medical Faculty, University "St. Cyril and Methodij" Skopje, North Macedonia. ⁵⁷Department of Biomedicine, Aarhus University, Aarhus, Denmark. ⁵⁸Tokyo Medical & Dental University Hospital, Tokyo, Japan. ⁵⁹A*STAR Infectious Disease Labs, Agency for Science, Technology and Research, Singapore; Lee Kong Chian School of Medicine, Nanyang Technology University, Singapore. ⁶⁰National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, USA. ⁶¹Laboratory of Medical Genetics, IRCCS Bambino Gesù Children's Hospital, Rome, Italy. ⁶²Department of Biomedicine and Prevention, Tor Vergata University of Rome, Rome, Italy. ⁶³Comparative Immunology Group, School of Biochemistry and Immunology, Trinity Biomedical Sciences Institute, Trinity College Dublin, Ireland. ⁶⁴Department of Pediatrics, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan. ⁶⁵Department of Molecular Biology and Genetics, Bilkent University, Bilkent, Ankara, Turkey. ⁶⁶Laboratory of Immunogenetics of Human Diseases, Innate Immunity Group, IdiPAZ Institute for Health Research, La Paz Hospital, Madrid, Spain. ⁶⁷IBB-CSIC, IDIBAPS, Barcelona, Spain. ⁶⁸Faculdades Pequeno Príncipe, Instituto de Pesquisa Pelé Pequeno Príncipe, Curitiba, Brazil. ⁶⁹Neurometabolic Diseases Laboratory, Bellvitge Biomedical Research Institute (IDIBELL), L'Hospitalet de Llobregat, Barcelona, Spain; Catalan Institution of Research and Advanced Studies (ICREA), Barcelona, Spain; Center for Biomedical Research on Rare Diseases (CIBERER), ISCIII, Barcelona, Spain. ⁷⁰Human Evolutionary Genetics Unit, CNRS U2000, Institut Pasteur, Paris, France; Human Genomics and Evolution, Collège de France, Paris, France. ⁷¹Department of Medical Genetics, Medical University, Varna and Department Hematology and BMT, University Hospital St. Marina, Bulgaria. ⁷²Department of Immunology, University Hospital of Gran Canaria Dr. Negrín, Canarian Health System, Las Palmas de Gran Canaria, Spain; Department of Clinical Sciences, University Fernando Pessoa Canarias, Las Palmas de Gran Canaria, Spain. ⁷³Department of Paediatric Infectious Diseases and Virology, Imperial College London, London, UK; Centre for Paediatrics and Child Health, Faculty of Medicine, Imperial College London, London, UK. ⁷⁴Department of Immunology, Second Faculty of Medicine Charles University, V Uvalu, University Hospital in Motol, Prague, Czech Republic. ⁷⁵Adult Immunodeficiency Unit, Infectious Diseases, Inflammation Center, University of Helsinki and Helsinki University Hospital, Helsinki, Finland; Rare Diseases Center and Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland. ⁷⁶Saeed Pathobiology and Genetics Lab, Tehran, Iran; Department of Microbiology and Immunology, Clinical and Diagnostic Immunology, KU Leuven, Leuven, Belgium. ⁷⁷Department of Immunology, Dmitry Rogachev National

Medical Research Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russia. ⁷⁸Central European Institute of Technology & Department of Biology, Faculty of Medicine, Masaryk University, Brno, Czech Republic. ⁷⁹Department of Pharmacology & Molecular Therapeutics, Uniformed Services University of the Health Sciences, Bethesda, MD, USA. ⁸⁰Pediatric Infectious Diseases and Immunodeficiencies Unit, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain. ⁸¹St. Giles Laboratory of Human Genetics of Infectious Diseases, Rockefeller Branch, The Rockefeller University, New York, NY, USA; Department of Medical Microbiology, University Medical Center Utrecht, Utrecht, Netherlands ⁸²Department of Internal Medicine II, Medical University of Innsbruck, Innsbruck, Austria. ⁸³Garvan Institute of Medical Research, Darlinghurst, NSW, Australia; St Vincent's Clinical School, Faculty of Medicine, UNSW Sydney, NSW, Australia. ⁸⁴Al Jalila Children's Hospital, Dubai, UAE ⁸⁵BC Children's Hospital, The University of British Columbia, Vancouver, Canada ⁸⁶Centre for Precision Therapeutics, Genetic and Genomic Medicine Centre, NeuroGen Children Healthcare, Dhaka, Bangladesh; Holy Family Red Crescent Medical College, Dhaka, Bangladesh. ⁸⁷College of Medicine, Mohammed Bin Rashid University of Medicine and Health Sciences, Dubai, UAE; Cellular Intelligence (CI) Lab, GenomeArc Inc., Toronto, ON, Canada ⁸⁸Department of Neurology, Amsterdam Neuroscience, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, The Netherlands. ⁸⁹Department of Medicine, Division of Infectious Diseases, McGill University Health Centre, Montréal, Québec, Canada; Infectious Disease Susceptibility Program, Research Institute, McGill University Health Centre, Montréal, Québec, Canada. ⁹⁰Department of Pediatric Pneumology, Immunology and Intensive Care, Charité Universitätsmedizin, Berlin University Hospital Center, Berlin, Germany; Labor Berlin GmbH, Department of Immunology, Berlin, Germany; Berlin Institutes of Health (BIH), Berlin-Brandenburg Center for Regenerative Therapies, Berlin, Germany. ⁹¹Biosciences Institute, University of São Paulo, São Paulo, Brazil. ⁹²Molecular Biophysics Division, Faculty of Physics, A. Mickiewicz University, Poznań, Poland. ⁹³The Rockefeller University & Howard Hughes Medical Institute, New York, NY, USA; Necker Hospital for Sick Children & INSERM, Paris, France.

Members of the CONSTANCES cohort: Rachel Nadif¹, Marcel Goldberg², Anna Ozguler², Joseph Henny², Sylvie Lemonnier², Mireille Coeuret-Pellicier³, Stéphane Le Got², Marie Zins²

¹Université de Paris-Saclay, UVSQ, Université Paris-Sud, Inserm, Equipe d'Epidémiologie Respiratoire Intégrative, Inserm CESP, Villejuif, France. ²Université de Paris, Université Paris-Saclay, UVSQ, Inserm UMS11, Villejuif, France. ³Inserm U011 Constances cohort, Villejuif, France.

Members of the 3C-Dijon Study: Christophe Tzourio¹, Stéphanie Debette², Carole Dufouil¹, Aïcha Soumaré¹, Morgane Lachaize², Nathalie Fievet³, Amandine Flaig³

¹University of Bordeaux; Bordeaux Population Health Center, INSERM U1219, Bordeaux, France. ²University of Bordeaux; Bordeaux Population Health Center, INSERM U1219; Bordeaux University Hospital, Department of Neurology, Institute of Neurodegenerative Diseases, Bordeaux, France. ³Laboratoire d'Analyses Génomiques - Centre de Ressources Biologiques; Institut Pasteur de Lille, Lille, France.

Member of the Cerba HealthCare: Fernando Martin¹

¹Cerba HealthCare, Issy-les-Moulineaux, France.

Members of the Etablissement du Sang study group: Brigitte Bonneadeau¹, Fabrice Cognasse^{5,6}, Dorothée Cannet², Pierre Gallian³, Michel Jeanne⁴, Pascal Morel¹, Magali Perroquin⁴, Pascale Richard¹, Pierre Tiberghien¹, Hind Hamzeh-Cognasse^{5,6}

¹Etablissement Français du sang, La Plaine St-Denis, France. ²Etablissement Français du sang, Dijon, France. ³Etablissement Français du sang, Marseille, France. ⁴Etablissement Français du sang, Bordeaux, France. ⁵Etablissement Français du sang, Saint-Étienne, France. ⁶SAINBIOSE, INSERM, U1059, University of Lyon, Université Jean-Monnet Saint-Étienne.

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Autoantibodies neutralizing type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths

Paul BastardAdrian GervaisTom Le VoyerJérémie RosainQuentin PhilippotJérémy ManryEleftherios MichailidisHans-Heinrich HoffmannShohei EtoMarina Garcia-PratLucy BizienAlba Parra-MartínezRui YangLiis HaljasmägiMélanie MigaudKarita SärekannuJulia MaslovskajaNicolas de ProstYacine Tandjaoui-LambiotteCharles-Edouard LuytBlanca Amador-BorreroAlexandre GaudetJulien PoissyPascal MorelPascale RichardFabrice CognasseJesus TroyaSophie Trouillet-AssantAlexandre BelotKahina SakerPierre GarçonJacques G. RivièreJean-Christophe LagierStéphanie GentileLindsey B. RosenElana ShawTomohiro MorioJunko TanakaDavid DalmauPierre-Louis TharauxDamien SeneAlain StepanianBruno MegarbaneVasiliki TriantafylliaArnaud FekkarJames R. HeathJosé Luis FrancoJuan-Manuel AnayaJordi Solé-ViolánLuisa ImbertiAndrea BiondiPaolo BonfantiRiccardo CastagnoliOttavia M. DelmonteYu ZhangAndrew L. SnowSteven M. HollandCatherine M. BiggsMarcela Moncada-VélezAndrés Augusto AriasLazaro LorenzoSoraya BoucheritBoubacar CoulibalyDany AnglicheauAnna M. PlanasFilomeen HaerynckSotirija DuvlisRobert L. NussbaumTayfun OzelikSevgi KelesAhmed A. BousfihaJaïla El BakkouriCarolina Ramirez-SantanaStéphane PaulQiang Pan-HammarströmLennart HammarströmAnnabelle DupontAlina KurolapChristine N. MetzAlessandro AiutiGiorgio CasariVito LampasonaFabio CiceriLucila A. BarreirosElena Dominguez-GarridoMateus VidigalMayana ZatzDiederik van de BeekSabina SahanicIvan TancevskiYurii StepanovskyyOksana BoyarchukYoko NukuiMiyuki TsumuraLoreto VidaurStuart G. TangyeSonia BurrelDarragh DuffyLluís Quintana-MurciAdam KlocperkNelli Y. KannAnna ShcherbinaYu-Lung LauDaniel LeungMatthieu CoulongeatJulien MarletRutger KoningLuis Felipe ReyesAngélique Chauvineau-GrenierFabienne VenetGuillaume MonneretMichel C. NussenzweigRomain ArrestierIdris BoudhabhayHagit Baris-FeldmanDavid HaginJoost WautersIsabelle MeytsAdam H. DyerSean P. KennellyNollaig M. BourkeRabih HalwaniNarjes Saheb Sharif-AskariKarim DorghamJérôme SallatteSouad Mehlaï SedkaouiSuzan AlKhaterRaúl Rigo-BonninFrancisco MorandeiraLucie RousselDonald C. VinhSisse Rye OstrowskiAntonio Condino-NetoCarolina PrandoAnastasiia BondarenkoAndrés N. SpaanLaurent GilardinJacques FellayStanislas LyonnetKaya BilguvarRichard P. LiftonShrikant ManeMark S. AndersonBertrand BoissonVivien BéziatShen-Ying ZhangEvangelos AndreacosOlivier HermineAurora PujolPärt PetersonTrine H. MogensenLee RowenJames MondStéphanie DebetteXavier de LamballerieXavier DuvalFrance MentréMarie ZinsPere Soler-PalacinRoger ColobranGuy GorochoyXavier SolanichSophie SusenJavier Martinez-PicadoDidier RaoultMarc VassePeter K. GregersenLorenzo PiemontiCarlos Rodríguez-GallegoLuigi D. NotarangeloHelen C. SuKai KisandSatoshi OkadaAnne PuelEmmanuelle JouanguyCharles M. RicePierre TiberghienQian ZhangAurélié CobatLaurent AbelJean-Laurent Casanova

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COVID-19 vulnerability via autoantibodies

Type I interferons are potent antiviral cytokines induced promptly after human respiratory exposure to SARS-CoV-2 virus. Either genetic or acquired defects in type I interferon signaling can increase host vulnerability to developing severe COVID-19 (coronavirus disease 2019) disease. Bastard *et al.* used sensitive immunoassays and neutralization testing to detect presence of autoantibodies to α , β , or γ type I interferons in plasma samples from a large cohort of patients with COVID-19 and prepandemic controls. The incidence of neutralizing autoantibodies to type I interferon increased with age in the control cohort, increasing sharply after the age of 70. These findings indicate that autoantibodies targeting type I IFNs represent a not uncommon type of acquired immunodeficiency that contributes to about 20% of all COVID-19 fatalities.

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