Differentiation of COVID-19 signs and symptoms from allergic rhinitis and common cold : An ARIA-EAACI-GA(2)LEN consensus

Hagemann, Jan

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acceptedVersion

PROF. CEZMI AKDIS (Orcid ID : 0000-0001-8020-019X)

PROF. IOANA AGACHE (Orcid ID : 0000-0001-7994-364X)

PROF. TORSTEN ZUBERBIER (Orcid ID : 0000-0002-1466-8875)

PROF. CLAUS BACHERT (Orcid ID : 0000-0003-4742-1665)

DR. VICTORIA CARDONA (Orcid ID : 0000-0003-2197-9767)

PROF. THOMAS B CASALE (Orcid ID : 0000-0002-3149-7377)

DR. LORENZO CECCHI (Orcid ID : 0000-0002-0658-2449)

PROF. CEMAL CINGI (Orcid ID : 0000-0003-3934-5092)

PROF. JAIME CORREIA DE SOUSA (Orcid ID : 0000-0001-6459-7908)

PROF. MOTOHIRO EBISAWA (Orcid ID : 0000-0003-4117-558X)

DR. JEAN LUC FAUQUERT (Orcid ID : 0000-0002-6929-9819)

DR. ALESSANDRO FIOCCHI (Orcid ID : 0000-0002-2549-0523)

DR. TARI HAAHTELA (Orcid ID : 0000-0003-4757-2156)

PROF. ECKARD HAMELMANN (Orcid ID : 0000-0002-2996-8248)

DR. TOMOHISA IINUMA (Orcid ID : 0000-0002-9940-5520)

DR. MUSA KHAITOV (Orcid ID : 0000-0003-4961-9640)

DR. DÉSIRÉE ERLINDA LARENAS-LINNEMANN (Orcid ID : 0000-0002-5713-5331)

DR. JORGE F. MASPERO (Orcid ID : 0000-0001-9750-2346)

DR. MÁRIO MORAIS-ALMEIDA (Orcid ID : 0000-0003-1837-2980)

PROF. RALPH MOSGES (Orcid ID : 0000-0002-1928-810X)

PROF. MAREK NIEDOSZYTKO (Orcid ID : 0000-0003-1089-1911)

PROF. ROBYN O'HEHIR (Orcid ID : 0000-0002-3489-7595)

DR. KEN OHTA (Orcid ID : 0000-0001-9734-4579)

PROF. PETR PANZNER (Orcid ID : 0000-0002-1291-450X)

DR. NIKOLAOS G PAPADOPOULOS (Orcid ID : 0000-0002-4448-3468)

PROF. GIOVANNI PASSALACQUA (Orcid ID : 0000-0002-5139-3604)

DR. VINCENZO PATELLA (Orcid ID : 0000-0001-5640-6446)

PROF. OLIVER PFAAR (Orcid ID : 0000-0003-4374-9639)

DR. DERMOT RYAN (Orcid ID : 0000-0002-4115-7376)

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PROF. JOAQUIN SASTRE (Orcid ID : 0000-0003-4689-6837)
PROF. CRISTIANA STELLATO (Orcid ID : 0000-0002-1294-8355)
PROF. JEAN BOUSQUET (Orcid ID : 0000-0002-4061-4766)

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Differentiation of COVID-19 signs and symptoms from allergic rhinitis and common cold- An ARIA-EAACI-GA²LENconsensus

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Jan Hagemann [1], Gabrielle L. Onorato [2], Marek Jutel [3],Cezmi A Akdis [4], Ioana Agache [5], Torsten Zuberbier [6], Wienczyslawa Czarlewski [7], Joaquim Mullol [8], Anna Bedbrook [2,9], Claus Bachert [10], Kazi S Bennoor [11], Karl-Christian Bergmann [6], Fulvio Braido [12], Paulo Camargos[13], Luis Caraballo [14], Victoria Cardona [15], Thomas Casale [16], Lorenzo Cecchi [17], Tomas Chivato [18], Derek K Chu [19], Cemal Cingi [20], Jaime Correia-de-Sousa [21,92], Stefano del Giacco [22], Dejan Dokic [23], Mark Dykewicz [24], Motohiro Ebisawa [25], Yehia El-Gamal [26], Regina Emuzyte [27], Jean-Luc Fauquert [28], Alessandro Fiocchi [29], Wytske J Fokkens [30], Joao A Fonseca [31], Bilun Gemicioglu [32], Maximiliano Gomez [33], Maia Gotua [34], Tari Haahtela [35], Eckard Hamelmann[36], Tomohisa Iinuma [37], Juan Carlos Ivancevich [38], Ewa Jassem [39], Omer Kalayci [40], Przemyslaw Kardas [41], Musa Khaitov [42], Piotr Kuna [43], Violeta Kvedariene [44], Desiree E Larenas-Linnemann [45], Brian Lipworth [46], Michael Makris [47], Jorge F. Maspero [48], Neven Miculinic [49], Florin Mihaltan [50], Yousser Mohammad [51], Stephen Montefort [52], Mario Morais-Almeida [53], Ralph Mösges [54], Robert Naclerio [55], Hugo Neffen [56], Marek Niedoszytko [57], Robyn E O'Hehir [58], Ken Ohta [59], Yoshitaka Okamoto [37], Kimi Okubo [60], Petr Panzner [61], Nikolaos G Papadopoulos [62], Giovanni Passalacqua [63], Vincenzo Patella [64], Ana Pereira [65],Oliver Pfaar [66] , Davor Plavec [67], Todor A Popov [68], Emmanuel P. Prokopakis [69], Francesca Puggioni [70], Filip Raciborski [71], Jere Reijula [72], Frederico S Regateiro [73], Sietze Reitsma [74], Antonino Romano [75] , Nelson Rosario [76], Menachem Rottem [77], Dermot Ryan [78], Boleslaw Samolinski [71], Joaquin Sastre[79], Dirceu Solé [80], Milan Sova [81], Cristiana Stellato [82], Charlotte Suppli-Ulrik [83], Ioanna Tsiligianni [84], Antonio Valero [85], Arunas Valiulis [86], Erkka Valovirta [87], Tuula Vasankari [88], Maria Teresa Ventura [89], Dana Wallace [90], De Yun Wang [91],

Siân Williams [92], Arzu Yorgancioglu [93], Osman M Yusuf [94], Mario Zernotti [95], Jean Bousquet[2,6,96], Ludger Klimek [1,97]

1. Department of Otolaryngology, Head and Neck Surgery, Universitätsmedizin Mainz, Mainz, Germany
2. MACVIA-France, Montpellier, France.
3. Department of Clinical Immunology, Wrocław Medical University, Poland.
4. Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland.
5. Transylvania University Brasov, Brasov, Romania.
6. Charité, Universitätsmedizin Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Comprehensive Allergy Center, Department of Dermatology and Allergy, Berlin, Germany.
7. Medical Consulting Czarlewski, Levallois, France.
8. Rhinology Unit & Smell Clinic, ENT Department, Hospital Clínic; Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, CIBERES, University of Barcelona, Spain.
9. MASK-air, Montpellier, France.
10. Upper Airways Research Laboratory, ENT Dept, Ghent University Hospital, Ghent, Belgium, and Sun Yat-sen University, International Airway Research Center, First Affiliated Hospital Guangzou, China, and Division of ENT Diseases, CLINTEC, Karolinska Institutet, Stockholm and Department of ENT Diseases, Karolinska University Hospital, Stockholm, Sweden.
11. Deptt of Respiratory Medicine, National Institute of Diseases of the Chest and Hospital, Dhaka, Bangladesh.
12. University of Genoa, Department of Internal Medicine (DiMI) and IRCCS Ospedale Policlinico San Martino, Genova, Italy.
13. Federal University of Minas Gerais, Medical School, Department of Pediatrics, Belo Horizonte, Brazil.
14. Institute for Immunological Research, University of Cartagena, Campus de Zaragocilla, Edificio Biblioteca Primer piso, Cartagena, Colombia, and Foundation for the Development of Medical and Biological Sciences (Fundemeb), Cartagena, Colombia.
15. Allergy Section, Department of Internal Medicine, Hospital Vall d'Hebron & ARADyAL research network, Barcelona, Spain.
16. Division of Allergy/immunology, University of South Florida, Tampa, Fla, USA.
17. SOS Allergology and Clinical Immunology, USL Toscana Centro, Prato, Italy.
18. School of Medicine, University CEU San Pablo, Madrid, Spain.
19. Departments of Medicine and Health Research Methods, Evidence & Impact, McMaster University, Hamilton, ON, Canada.
20. Eskisehir Osmangazi University, Medical Faculty, ENT Department, Eskisehir,Turkey.

21. Life and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, PT Government Associate Laboratory, Braga/Guimarães, Portugal.
22. Department of Medical Sciences and Public Health and Unit of Allergy and Clinical Immunology, University Hospital "Duilio Casula", University of Cagliari, Cagliari, Italy.
23. University Clinic of Pulmology and Allergy, Medical Faculty Skopje, Republic of Macedonia.
24. Section of Allergy and Immunology, Saint Louis University School of Medicine, Saint Louis, Missouri, USA.
25. Clinical Reserch Center for Allergy and Rheumatology, NHO Sagamihara National Hospital, Sagamihara, Japan. (ra N):atioanl
26. Pediatric Allergy and Immunology Unit, Children's hospital, Ain Shams University, Cairo, Egypt.
27. Clinic of Children's Diseases, Institute of Clinical Medicine, Faculty of Medicine, Vilnius University, Vilnius, Lithuania.
28. CHU Clermont-Ferrand, Unité d'Allergologie de l'Enfant, Pole pédiatrique, Hopital Estaing, Clermont-Ferrand , France.
29. Division of Allergy, Department of Pediatric Medicine - The Bambino Gesù Children's Research Hospital Holy see, IRCCS, Rome, Italy.
30. Department of Otorhinolaryngology, Academic Medical Centers, AMC, Amsterdam, The Netherland, and EUFOREA, Brussels, Belgiium.
31. CINTESIS, Center for HealthTechnology and Services Research, Faculdade de Medicina, Universidade do Porto, Porto, Portugal ; Allergy Unit, CUF Porto, Porto, Portugal.
32. Department of Pulmonary Diseases, Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Istanbul, Turkey.
33. Fundacion Ayre-Instituto Medico ALAS, Salta, Argentina.
34. Center of Allergy and Immunology, Georgian Association of Allergology and Clinical Immunology, Tbilisi, Georgia.
35. Skin and Allergy Hospital, Helsinki University Hospital, Helsinki, Finland.
36. University Hospital Bielefeld, Children's Center Bethel, EvKB, Bielefeld, Germany.
37. Dept of Otorhinolaryngology, Chiba University Hospital, Chiba, Japan.
38. Servicio de Alergia e Immunologia, Clinica Santa Isabel, Buenos Aires, Argentina.
39. Medical University of Gdańsk, Department of Allergology, Gdansk, Poland.
40. Pediatric Allergy and Asthma Unit, Hacettepe University School of Medicine, Ankara, Turkey.
41. Department of Family Medicine, Medical University of Lodz, Poland.
42. National Research Center, Institute of Immunology, Federal Medicobiological Agency, Laboratory of Molecular immunology, Moscow, Russian Federation
43. Division of Internal Medicine, Asthma and Allergy, Barlicki University Hospital, Medical University of Lodz, Poland.

44. Institute of Biomedical Sciences, Department of Pathology, Faculty of Medicine, Vilnius University and Institute of Clinical medicine, Clinic of Chest diseases and Allergology, faculty of Medicine, Vilnius University, Vilnius, Lithuania.
45. Center of Excellence in Asthma and Allergy, Médica Sur Clinical Foundation and Hospital, México City, Mexico.
46. Scottish Centre for Respiratory Research, Cardiovascular & Diabetes Medicine, Medical Research Institute, Ninewells Hospital, University of Dundee, UK.
47. Allergy Unit "D Kalogeromitros", 2nd Dpt of Dermatology and Venereology, National & Kapodistrian University of Athens, "Attikon" University Hospital, Greece.
48. Argentine Association of Allergy and Clinical Immunology, Buenos Aires, Argentina.
49. Croatian Pulmonary Society, Zagreb, Croatia.
50. National Institute of Pneumology M Nasta, Bucharest, Romania.
51. National Center for Research in Chronic Respiratory Diseases, Tishreen University School of Medicine, Latakia and Syrian Private University-Damascus, Syria.
52. Lead Respiratory Physician Mater Dei Hospital Malta, Academic Head of Dept and Professor of Medicine University of Malta, Deputy Dean Faculty of Medicine and Surgery University of Medicine, La Valette, Malta.
53. Allergy Center, CUF Descobertas Hospital, Lisbon, Portugal
54. CRI-Clinical Research International-Ltd, Hamburg, Germany.
55. Johns Hopkins School of Medicine, Baltimore, Maryland, USA.
56. Director of Center of Allergy, Immunology and Respiratory Diseases, Santa Fe, Argentina
57. Medical University of Gdańsk, Department of Allergology, Gdansk, Poland.
58. Department of Allergy, Immunology and Respiratory Medicine, Alfred Hospital and Central Clinical School, Monash University, Melbourne, Victoria, Australia; Department of Immunology, Monash University, Melbourne, Victoria, Australia.
59. National Hospital Organization, Tokyo National Hospital, Tokyo, Japan.
60. Dept of Otolaryngology, Nippon Medical School, Tokyo, Japan.
61. Department of Immunology and Allergology, Faculty of Medicine and Faculty Hospital in Pilsen, Charles University in Prague, Pilsen, Czech Republic.
62. Division of Infection, Immunity & Respiratory Medicine, Royal Manchester Children's Hospital, University of Manchester, Manchester, UK.
63. Allergy and Respiratory Diseases, Ospedale Policlino San Martino -University of Genoa, Italy
64. Division of Allergy and Clinical Immunology, Department of Medicine, Agency of Health ASL Salerno, "Santa Maria della Speranza" Hospital, Battipaglia, Salerno, Italy.
65. Center for research in health technologies and information systems- CINTESIS, University of Porto, Porto, Portugal ; Allergy Unit, Instituto CUF Porto and Hospital CUF Porto, Porto, Portugal ; Department of Community Medicine, Health Information and Decision - MEDCIDsS, Faculty of Medicina, UniversityofPorto, Porto, Portugal.

66. Department of Otorhinolaryngology, Head and Neck Surgery, Section of Rhinology and Allergy, University Hospital Marburg, Philipps-Universität Marburg , Germany.
67. Children's Hospital Srebrnjak, Zagreb, School of Medicine, University J.J. Strossmayer, Osijek, Croatia.
68. University Hospital 'Sv Ivan Rilski'", Sofia, Bulgaria.
69. Department of Otorhinolaryngology University of Crete School of Medicine, Heraklion, Greece.
70. Personalized Medicine Clinic Asthma & Allergy, Humanitas Clinical and Research Center IRCCS, Rozzano, and Department of Biomedical Sciences, Humanitas University Pieve Emanuele, MI, Italy.
71. Department of Prevention of Envinronmental Hazards and Allergology, Medical University of Warsaw, Poland.
72. Dept of Pulmonology, Helsinki University Central Hospital, Helsinki, Dept of Public Health, University of Helsinki, Helsinki, Finland.
73. Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra and Institute of Immunology, Faculty of Medicine, University of Coimbra, Coimbra, Portugal.
74. Department of Otorhinolaryngology, Amsterdam University Medical Centres, AMC, Amsterdam, the Netherlands.
75. Oasi Research Institute-IRCCS, Troina, Italy; bFondazione Mediterranea GB Morgagni, Catania, Italy.
76. Hospital de Clinicas, University of Parana, Brazil.
77. Division of Allergy Asthma and Clinical Immunology, Emek Medical Center, Afula, Israel.
78. Usher Institute, University of Edinburgh, Edinburgh, UK
79. Fundacion Jimenez Diaz, CIBERES, Faculty of Medicine, Autonoma University of Madrid, Spain.
80. Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Federal University of São Paulo, São Paulo, Brazil
81. Department of Respiratory Medicine, University Hospital Olomouc, Czech Republic.
82. Department of Medicine, Surgery and Dentistry "Scuola Medica Salernitana", University of Salerno, Salerno, Italy.
83. Department of Respiratory Medicine, Copenhagen University Hospital-Hvidovre, and Institute of Clinical Medicine, University of Copenhagen, Denmark.
84. Health Planning Unit, Department of Social Medicine, Faculty of Medicine, University of Crete, Greece and International Primary Care Respiratory Group IPCRG, Aberdeen, Scotland.
85. Pneumology and Allergy Department CIBERES and Clinical & Experimental Respiratory Immunoallergy, IDIBAPS, University of Barcelona, Spain.
86. Vilnius University Faculty of Medicine, Institute of Clinical Medicine & Institute of Health Sciences, Vilnius, Lithuania; European Academy of Paediatrics (EAP/UEMS-SP), Brussels, Belgium.
87. Department of Lung Diseases and Clinical Immunology, University of Turku and Terveystalo allergy clinic, Turku, Finland.
88. Filha, Finnish Lung Health Association, Helsinki, and University of Turku, Turku, Finland.
89. University of Bari Medical School, Unit of Geriatric Immunoallergology, Bari, Italy.

90. Nova Southeastern University, Fort Lauderdale, Florida, USA.
91. Department of Otolaryngology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore.
92. International Primary Care Respiratory Group IPCRG, London, UK.
93. Celal Bayar University Department of Pulmonology, Manisa, Turkey.
94. The Allergy and Asthma Institute, Pakistan.
95. Universidad Católica de Córdoba, Universidad Nacional de Villa Maria, Argentina.
96. University Hospital Montpellier, France.
97. Center for Rhinology and Allergology, Wiesbaden, Germany.

Short title: rhinitis, cold and COVID

Author's for correspondence: Professor Jean Bousquet

273 avenue d'Occitanie, 34090 Montpellier, France Tel +33 611 42 88 47, Fax +33 467 41 67 01

jean.bousquet@orange.fr

ARIA member list:

Amir Hamzah Abdul Latiff, Baharudin Abdullah, Werner Aberer, Nancy Abusada, Ian Adcock, Alejandro Afani, Ioana Agache, Xenofon Aggelidis, Jenifer Agustin, Cezmi A Akdis, Mübeccel Akdis, Mona Al-Ahmad, Abou Al-Zahab Bassam, Hussam Alburdan, Oscar Aldrey-Palacios, Emilio Alvarez Cuesta, Hiba Alwan Salman, Ashraf Alzaabi, Salma Amade, Gene Ambrocio, Rosana Angles, Isabella Annesi-Maesano, Ignacio J Ansotegui, Josep Anto, Paula Ara Bardajo, Stefania Arasi, Margarete Arrais, Hasan Arshad, Maria-Cristina Artesani, Estrella Asayag, Francesca Avolio, Khuzama Azhari, Claus Bachert, Diego Bagnasco, Ilaria Baiardini, Nissera Bajrović, Petros Bakakos, Sergio Bakeyala Mongono, Christine Balotro-Torres, Sergio Barba, Cristina Barbara, Elsa Barbosa, Bruno Barreto, Joan Bartra, Xavier Basagana, Eric D. Bateman, Lkhagvaa Battur, Anna Bedbrook, Martín Bedolla Barajas, Bianca Beghé, Antra Bekere, Elizabeth Bel, Ali Ben Kheder, Mikael Benson, Elena-Camelia Berghea, Karl-Christian Bergmann, Roberto Bernardini, David Bernstein, Mike Bewick, Slawomir Bialek, Artur Białoszewski, Thomas Bieber, Nils E. Billo, Maria-Beatrice Bilo, Carsten Bindslev-Jensen, Leif Bjermer, Hubert Blain, Irina Bobolea, Malgorzata Bochenska Marciniak, Christine Bond, Attilio Boner, Matteo Bonini, Sergio Bonini, Sinthia Bosnic-Anticevich, Isabelle Bosse, Sofia Botskariova, Jacques Bouchard, Louis-Philippe Boulet, Rodolphe Bourret, Philippe Bousquet, Fulvio Braido, Andrew Briggs, Christopher E Brightling, Jan Brozek, Luisa Brussino, Roland Buhl, Roxana Bumbacea, Rosalva Buquicchio, María-Teresa Burguete Cabañas, Andrew Bush, William W Busse, Jeroen Buters, Fernan Caballero-Fonseca, Moïses A Calderon, Mario Calvo, Paulo Camargos, Thierry Camuzat, FR Canevari, Antonio Cano, G Walter Canonica, Arnaldo Capriles-Hulett, Luis Caraballo, Vicky Cardona, Kai-Hakon Carlsen, Jonas Carmona Pirez, Jorge Caro, Warner Carr, Pedro Carreiro-Martins, Fredelita Carreon-Asuncion, Ana-Maria Carriazo, Carme Carrion-Ribas, Thomas Casale, Mary-Ann Castor, Elizabeth Castro, A.G. Caviglia, Lorenzo Cecchi, Alfonso Cepeda Sarabia, Maciej Chalubinski, Ramanathan Chandrasekharan, Yoon-Seok Chang, Victoria Chato-Andeza, Lida Chatzi, Christina Chatzidaki, Niels H. Chavannes, Claudia Chaves Loureiro, Aurora-Alejandra Chavez Garcia, Marta Chelninska, Yuzhi Chen, Lei Cheng, Sharon Chinthrajah, Tomas Chivato, Ekaterine Chkhartishvili, George Christoff, Henry Chrystyn, Derek K Chu, Antonio Chua, Alexander Chuchalin, Kian Fan Chung, Alberto Cicerán, Cemal Cingi, Giorgio Ciprandi, Ieva Cirule, Ana-Carla Coelho, Enrico Compalati, Jannis Constantinidis, Jaime Correia de Sousa, Elisio Manuel Costa, David Costa, María del Carmen Costa Domínguez, André Coste, M. Cottini, Linda Cox, Carlos Crisci, Maria Angiola Crivellaro, Alvaro A Cruz, John Cullen, Adnan Custovic, Biljana Cvetkovski, Wienczyslawa Czarlewski, Gennaro D'Amato, Jane da Silva, Ronald Dahl, Sven-Erik Dahlen, Vasilis Daniilidis, Louei Darjazini Nahhas, Ulf Darsow, Janet Davies, Frédéric de Blay, Giulia De Feo, Eloisa De Guia, José-Ricardo de la Torre Navarrete, Chato de los Santos, Esteban De Manuel Keenoy, Govert De Vries, Diana Deleanu, Pascal Demoly, Judah Denburg, Philippe Devillier, Alain Didier, Sanja Dimic Janjic, Maria Dimou, Anh Tuan Dinh-Xuan, Ratko Djukanovic, Maria Do Ceu Texeira, Dejan Dokic, Margarita Gabriela Domínguez Silva, Habib Douagui, Nikolaos Douladiris, Maria Doulaptsi, Gérard Dray, Ruta Dubakiene, Eve Dupas, Stephen Durham, Marzia Duse, Mark Dykewicz, Didier Ebo, Natalija Edelbaher, Thomas Eiwegger, Patrik Eklund, Yehia El-Gamal, Zeinab A. El-Sayed, Shereen S. El-Sayed, Magda El-Seify, Regina Emuzyte, Lourdes Enecilla, Marina Erhola, Heidilita Espinoza, Jesús Guillermo Espinoza Contreras, John Farrell, Lenora Fernandez, Paola Fimbres Jimenez, Antje Fink Wagner, Alessandro Fiocchi, Wytske J Fokkens, Lenia Folletti, Joao A Fonseca, Jean-François Fontaine, Francesco Forastiere, Jose Miguel Fuentes Pèrez, Emily Gaerlan-Resureccion, Mina Gaga, José Luis Gálvez Romero, Amiran Gamkrelidze, Alexis Garcia, Cecilia Yvonne García Cobas, María de la Luz Hortensia García Cruz, Valeria Garcia Ortiz, Jacques Gayraud, Matteo Gelardi, Bilun Gemicioglu, Dimitra Gennimata, Sonya Genova, José Gereda, Roy Gerth van Wijk, Antonio Giuliano, René-Maximiliano Gomez, Miguel-Ange Gonzalez Ballester, Sandra González Diaz, Maia Gotua, Christos Grigoreas, Ineta Grisle, Marta Guidacci, Nick Guldemond, Zdenek Gutter, Antonieta Guzmán, Tari Haahtela, Ramsa Halloum, David Halpin, Eckard Hamelmann, Suleiman Hammadi, Richard Harvey, Enrico Heffler, Joachim Heinrich, Adnan Hejjaoui, Birthe Hellquist-Dahl, Luiana Hernández Velázquez, Mark Hew, Elham Hossny, Peter Howarth, Martin Hrubiško, Yunuen Rocío Huerta Villalobos, Marc Humbert, Salina Husain, Michael Hyland, Guido Iaccarino, Moustafa Ibrahim, Natalia Ilina, Maddalena Illario, Cristoforo Incorvaia, Antonio Infantino, Carla Irani, Zhanat Ispayeva, Juan-Carlos Ivancevich, Edgardo EJ Jares, Deborah Jarvis, Ewa Jassem, Klemen Jenko, Rubén Darío Jiméneracruz Uscanga, Sebastian L Johnston, Guy Joos, Maja Jošt, Kaja Julge, Ki-Suck Jung, Jocelyne Just, Marek Jutel, Igor Kaidashev, Omer Kalayci, Fuat Kalyoncu, Jeni Kapsali, Przemyslaw Kardas, Jussi Karjalainen, Carmela A. Kasala, Michael Katotomichelakis, Loreta Kavaliukaite, Bennoor S Kazi, Thomas Keil, Paul Keith, Musa Khaitov, Nikolai Khaltaev, You-Young Kim, Bruce Kirenga, Jorg Kleine-Tebbe, Ludger Klimek, Fanny Ko, Bernard Koffi N'Goran, Evangelia Kompoti, Peter Kopač, Gerard Koppelman, Anja Koren Jeverica, Seppo Koskinen, Mitja Košnik, Tomasz Kostka, Kosta V. Kostov, Marek L Kowalski, Tanya Kralimarkova, Karmen Kramer Vrščaj, Helga Kraxner, Samo Kreft, Vicky Kritikos, Dmitry Kudlay, Mikael Kuitunen, Inger Kull, Piotr Kuna, Maciej Kupczyk, Violeta Kvedariene, Marialena Kyriakakou, Nika Lalek, Massimo Landi, Stephen Lane, Désiree Larenas-Linnemann, Susanne Lau, Daniel Laune, Jorge Lavrut, Lan Le, Martina Lenzenhuber, Gualtiero Leo, Marcus Lessa, Michael Levin,

Jing Li, Philip Lieberman, Giuseppe Liotta, Brian Lipworth, Xuandao Liu, Rommel Lobo, Karin C Lodrup Carlsen, Carlo Lombardi, Renaud Louis, Stelios Loukidis, Olga Lourenço, Jorge A. Luna Pech, Bojan Madjar, Enrico Maggi, Antoine Magnan, Bassam Mahboub, Alpana Mair, Anke-Hilse Maitland van der Zee, Mika Makela, Michael Makris, Hans-Jorgen Malling, Mariana Mandajieva, Patrick Manning, Manolis Manousakis, Pavlos Maragoudakis, Gianluigi Marseglia, Gailen Marshall, Mohammad Reza Masjedi, Jorge F. Máspero, Juan José Matta Campos, Marcus Maurer, Sandra Mavale-Manuel, Cem Meço, Erik Melén, Giovanni Melioli, Elisabete Melo-Gomes, Eli O Meltzer, Enrica Menditto, Andrew Menzies-Gow, Hans Merk, Jean-Pierre Michel, Yann Micheli, Neven Miculinic, Luís Midão, Florin Mihaltan, Nikolaos Mikos, Manlio Milanese, Branislava Milenkovic, Dimitrios Mitsias, Bassem Moalla, Giuliana Moda, María Dolores Mogica Martínez, Yousser Mohammad, Frances-Montserrat Moharra, Mostafa Moin, Mathieu Molimard, Isabelle Momas, Monique Mommers, Alessandro Monaco, Steve Montefort, Lucia-Elvira Montenegro, Riccardo Monti, Dory Mora, Mario Morais-Almeida, Ralph Mösges, Badr Eldin Mostafa, Joaquim Mullol, Lars Münter, Antonella Muraro, Ruth Murray, Antonio Musarra, Tihomir Mustakov, Robert Naclerio, Kari C. Nadeau, Rachel Nadif, Alla Nakonechna, Leyla Namazova-Baranova, Gretchen Navarro-Locsin, Hugo Neffen, Kristof Nekam, Angelos Neou, Eustachio Nettis, Daniel Neuberger, Laurent Nicod, Stefania Nicola, Verena Niederberger-Leppin, Marek Niedoszytko, Antonio Nieto, Ettore Novellino, Elizabete Nunes, Dieudonné Nyembue, Robyn O'Hehir, Cvetanka Odjakova, Ken Ohta, Yoshitaka Okamoto, Kimi Okubo, Brian Oliver, Gabrielle L Onorato, Maria Pia Orru, Solange Ouédraogo, Kampadilemba Ouoba, Francisco-Javier Padilla, Pier Luigi Paggiaro, Aris Pagkalos, Giovanni Pajno, Gianni Pala, SP Palaniappan, Isabella Pali-Schöll, Susanna Palkonen, Stephen Palmer, Carmen Panaitescu Bunu, Petr Panzner, Nikos G Papadopoulos, Vasilis Papanikolaou, Alberto Papi, Bojidar Paralchev, Giannis Paraskevopoulos, Hae-Sim Park, Giovanni Passalacqua, Vincenzo Patella, Ian Pavord, Ruby Pawankar, Soren Pedersen, Susete Peleve, Simona Pellegino, Ana Pereira, Mariana Pereira, Tamara Pérez, Andrea Perna, Diego Peroni, Oliver Pfaar, Nhân Pham-Thi, Bernard Pigearias, Isabelle Pin, Konstantina Piskou, Constantinos Pitsios, Davor Plavec, Dagmar Poethig, Wolfgang Pohl, Antonija Poplas Susic, Todor A. Popov, Fabienne Portejoie, Paul Potter, Lars Poulsen, Alexandra Prados-Torres, Fotis Prarros, David Price, Emmanuel Prokopakis, Francesca Puggioni, Elisa Puig-Domenech, Robert Puy, Klaus Rabe, Silvia Rabotti, Filip Raciborski, Josephine Ramos, Cristina Recalcati, Marysia T. Recto, Shereen M. Reda, Frederico S Regateiro, Norbert Reider, Sietze Reitsma, Susana Repka-Ramirez, Erminia Ridolo, Janet Rimmer, Daniela Rivero Yeverino, José Angelo Rizzo, Carlos Robalo-Cordeiro, Graham Roberts, Karen Robles, Nicolas Roche, Mónica Rodríguez González, Eréndira Rodríguez Zagal, Giovanni Rolla, Christine Rolland, Regina Roller-Wirnsberger, Miguel Roman Rodriguez, Antonino Romano, Jan Romantowski, Philippe Rombaux, Joel Romualdez, Jose Rosado-Pinto, Nelson Rosario, Lanny Rosenwasser, Oliviero Rossi, Menachem Rottem, Philip Rouadi, Nikoleta Rovina, Irma Rozman Sinur, Mauricio Ruiz, Lucy Tania Ruiz Segura, Dermot Ryan, Hironori Sagara, Daiki Sakai, Daiju Sakurai, Wafaa Saleh, Johanna Salimaki, Konstantinos Samitas, Boleslaw Samolinski, María Guadalupe Sánchez Coronel, Mario Sanchez-Borges, Jaime Sanchez-Lopez, Melissa Sansonna, Codrut Sarafoleanu, Faradiba Sarquis Serpa, Joaquin Sastre-Dominguez, Eleonora Savi, Agne Savonyte, Bisher Sawaf, Glenis K Scadding, Sophie Scheire, Peter Schmid-Grendelmeier, Juan Francisco Schuhl, Holger Schunemann, Maria Schvalbová, Jorgen Schwarze, Nicola Scichilone, Gianenrico Senna, Cecilia Sepúlveda, Elie Serrano, Sara Shamai, Aziz Sheikh, Mike Shields, Vasil Shishkov, Nikos Siafakas, Alexander Simeonov, Estelle FER Simons, Juan Carlos Sisul, Brigita Sitkauskiene, Ingelbjorg Skrindo, Tanja Soklič Košak, Dirceu Solé, Martin Sondermann, Talant Sooronbaev, Manuel Soto-Martinez, Manuel Soto-Quiros, Barnaro Sousa Pinto, Milan Sova, Michael Soyka, Krzysztof Specjalski, Annette Sperl, Otto Spranger, Sofia Stamataki, Lina Stefanaki, Cristiana Stellato, Rafael Stelmach, Timo Strandberg, Petra Stute, Abirami Subramaniam, Charlotte Suppli Ulrik, Michael Sutherland, Silvia Sylvestre, Aikaterini Syrigou, Luis Taborda Barata, Nadejda Takovska, Rachel Tan, Frances Tan, Vincent Tan, Ing Ping Tang, Masami Taniguchi, Line Tannert, Pongsakorn Tantilipikorn, Jessica Tattersall, Filippo Tesi, Uta Thieme, Carel Thijs, Mike Thomas, Teresa To, Ana Maria Todo-Bom, Alkis Togias, Peter-Valentin Tomazic, Vesna Tomic-Spiric, Sanna Toppila-Salmi, Maria-José Torres Jaen, Elina Toskala, Massimo Triggiani, Nadja Triller, Katja Triller, Ioanna Tsiligianni, M. Uberti, Ruxandra Ulmeanu, Jure Urbancic, Marilyn Urrutia Pereira, Martina Vachova, Felipe Valdés, Rudolf Valenta, Marylin Valentin Rostan, Antonio Valero, Arunas Valiulis, Mina Vallianatou, Erkka Valovirta, Michiel Van Eerd, Eric Van Ganse, Marianne van Hage, Olivier Vandenplas, Tuula Vasankari, Dafina Vassileva, Cesar Velasco Munoz, Maria Teresa Ventura, Cécilia Vera-Munoz, Frédéric Viart, Dilyana Vicheva, Pakit Vichyanond, Petra Vidgren, Giovanni Viegi, Claus Vogelmeier, Leena Von Hertzen, Theodoros Vontetsianos, Dimitris Vourdas, Vu Tran Thien Quan, Martin Wagenmann, Samantha Walker, Dana Wallace, De Yun Wang, Susan Waserman, Katrin Wehner, Magnus Wickman, Sian Williams, Dennis Williams, Nicola Wilson, Gary Wong, Kent Woo, Lucyna Wozniak, John Wright, Piotr Wroczynski, Paraskevi Xepapadaki, Plamen Yakovliev, Masao Yamaguchi, Kwok Yan, Yoke Yeow Yap, Mais Yassin, Barbara Yawn, Panayiotis Yiallouros, Arzu Yorgancioglu, Shigemi Yoshihara, Ian Young, Osman B Yusuf, Asghar Zaidi, Fares Zaitoun, Petra Zalud, Heather Zar, M.T. Zedda, Mario E Zernotti, Luo Zhang, Nanshan Zhong, Mihaela Zidarn, Torsten Zuberbier, Celia Zubrinich.

Abstract

Background: Although there are many asymptomatic patients, one of the problems of COVID-19 is early recognition of the disease. COVID-19 symptoms are polymorphic and may include upper respiratory symptoms. However, COVID-19 symptoms may be mistaken withthe common cold or allergic rhinitis. An ARIA-EAACI study group attempted to differentiate upper respiratory symptoms betweenthe three diseases.

Methods: A modified Delphi process was used and ARIA members who were seeing COVID-19 patients were asked to fill in a questionnaire on the upper airway symptoms of COVID-19, common cold andallergic rhinitis.

Results: Among the 192 ARIA members who were invited to respond to the questionnaire, 89 responded. 87 questionnaires were analysed. The consensus was then reported.A two-way ANOVA analysis revealed significant differences inthe symptom intensity between the three diseases ($p<0.001$).

Conclusions: This modified Delphi approach enabled thedifferentiationof upper respiratory symptoms betweenCOVID-19, common cold and allergic rhinitis. An electronic algorithm will be devised using the questionnaire.

Key words: COVID-19, allergic rhinitis, common cold, smell, taste, cough, Delphi

Introduction

Although there are many asymptomatic patients, one of the problems of COVID-19 is early recognition of the disease. Pre-medical visit screening and symptom evaluation have to be implemented quickly to minimize the risk of seeing COVID-19 patients unprepared. Furthermore, testing for coronavirus is still widely restricted due to the shortage of available PCR tests in many countries [1]. Testing capacities have improved dramatically since the beginning of the pandemic, with the recent addition of antigen-based testing.Some of these tests are home-based and have only just obtained FDA approval.However, they still represent a bottleneck [2],with the subsequent waiting periods leading to large groups of people at risk of infection requiring quarantine. To prevent unnecessary closure of critical facilities, e.g. schools and public services, triage requires further improvement in terms of speed and accuracy.

COVID-19 symptoms are polymorphic. Typically, COVID-19 induces shortness of breath, cough, fever, nasal congestion, and general malaise [3]. However, SARS-coronavirus-2 (SARS-CoV-2) infection has been linked to a number of other symptoms afflicting several organ systems, including muscle and joint pain, sore throat, headache, nausea, vomiting and diarrhoea, as well as coagulopathy [4]. Impaired sense of smell and taste has emerged as an alarming symptom of SARS-CoV-2 infection in the West, but not so much in Asia [5-9]. The presentation in the upper respiratory tract has also been described as extremely variable across age groups [10], making it difficult to distinguish COVID-19 from common upper respiratory infections (e.g., croup in children [10]).

Therefore, besides the management of severe COVID-19, one of the major problems of the infection is how to screen citizens with possible COVID-19 and distinguish them from patients with similar symptoms caused by allergic rhinitis[11,12] or other common viral infections of the respiratory tract. A digital tool enabling a rapid distinction is needed for this approach and may be of great importance during the winter with the co-existence of COVID-19, flu, common cold or other respiratory viral infections and house dust mite-induced rhinitis.

Although systematic reviews and meta-analyses have been produced for many COVID-19 symptoms including differentiation between flu and COVID-19 [13], there is insufficient knowledge on consensus across the international medical community regarding nasal symptoms that may enable differentiation between COVID-19, common cold and allergic rhinitis. An ARIA (Allergic Rhinitis and its Impact on Asthma)-EAACI (European Academy of Allergy and Clinical Immunology)-GA^{2}LEN (Global Allergy and Asthma European Network) initiative was carried out to establish consensus on a set of questions aimed at distinguishing these diseases. From this consensus, an algorithm will be proposed and digitalised using a method already validated in MASK [14-16]. The current paper presents the results of the consensus.

This is a new paper of the series of ARIA-EAACI papers in COVID-19 [17-21].

Methods

A modified Delphi was carried out [22]. A questionnaire developed by JB, WC, LK and JM was sent to all ARIA members by GLO. Those seeing COVID-19 patients were requested to answer within a week.

The questionnaire included items related to upper and lower airway symptoms for COVID-19, common cold and allergic rhinitis (Table 1). In the questionnaire, the respondents were asked to assess 5 nasal symptoms, 3 ocular symptoms, taste, smell, cough, wheezing and sore throat. For each question, there was a statement on frequency and severity. For this, participants were asked to grade the severity from 0 to 10. Then, they gave a global assessment from 0 to 10 according to whether they agreed on the suggested severity grading for the 3 diseases. A level of 6 or higher was considered as agreement. Suggestions for questions / statements were able to be added to the questionnaire.

A total of 87 answer sheets were included in this analysis. Any written comments were transformed into numeric changes where possible. To determine whether the participants agreed that the symptom/item was to be included in the tool, we collected the total number of participants agreeing as well as the total percentages. The same procedure was used for disagreement and missing / invalid data, respectively.

Results

Among the 192 questionnaires sent, 89 (46.3%) were received within 7 days. The average monthly number of COVID-19 consultations among the participants was 16.8 ± 20. The participants were from 37 different countries (Figure 1).

There was a high proportion of agreeing participants, with an average of 76.3% (range 69-83). The overall data quality was acceptable,and missing values for some of the questions were below 20 % (Table 2).

Participants were able to grade the maximum expected severity for each disease and the average final VAS severity data is shown in Figure 3. A two-way ANOVA analysis revealed significant differences of the symptom intensity between the three diseases ($p<0.001$).

Eye symptoms (7, 8) were among the most discussed statements, and the corresponding statements had relatively low levels of approval (Figure 1). Nasal pain (5) was regarded as impractical by 6 participants, which was also reflected by a relatively low level of agreement (8.21 ± 2.2; Figure 2). This was possibly

caused by different interpretations of the item's description, which needs to be approached in further developments of the algorithm.

Additional COVID-19 symptoms common in COVID-19 will be considered for integration in the future algorithm development process (Table 3).

Discussion

This paper presents the results of a consensus initiative across the ARIA network of health professionals. The aim was to develop a set of questions on symptoms and their intensity in order to discriminate between classical rhinologic disorders and COVID-19. The presentation of COVID-19 is highly variable, ranging from a complete absence of symptoms to severe illness and critical organ dysfunction. The underlying mechanisms for this polymorphic behaviour are yet to be defined.

Within the ARIA network of specialists in upper and lower respiratory diseases, we asked 193 to respond to our consensus initiative, of whom 89 did. The response rate was under 50% but many physicians were not seeing COVID-19 patients. The strength of this paper is that the involved participants represented different medical specialties and many different countries, suggesting a generalization of the study.

We found high levels of consensus among this community, with over 76% of participants agreeing to the symptoms presented in our questionnaire. VAS was found to be a useful and simple tool for discussing questions of symptom intensity in this large group of health professionals. Statistical analysis revealed a significantly different expected maximum VAS of the three diseases (two-way ANOVA, $p<0.001$). Hence, there are potential symptom constellations that allow discrimination between the three diseases.

The triage of patients with newly developed symptoms – any individual under suspicion of being at risk of SARS-CoV-2 infection– remains a challenge during this pandemic. Digital application-based symptom reporting and triage have been evaluated in prospective trials in the UK, China and the US. [23-25]. The improvement of triage will also (i) enhance pre-test probability for SARS-CoV-2 PCR swabs or alternative test methods, (ii) increase the availability of tests in general to make current infection numbers more accurate, (iii) ease unnecessary quarantine and (iv) reduce the closure of schools, child day care and public services.

ARIA-MASK includes a decision-making tool for allergic rhinitis [14]. With a broad user base of 39,670, there is the opportunity to provide newly developed tools for a large group of patients. The questionnaire, along with the participants' comments, has to be transferred to a validation process. This process can be

enhanced by already-developed artificial intelligence (AI) in order to fine-tune and improve symptom VAS thresholds. A final questionnaire and algorithm are open for use across the medical community, focussing on specialists treating upper and lower airway diseases and allergy, hence confronted with similar rhinologic, pneumologic and ophthalmologic symptoms. For allergy and respiratory tract specialists, undoubtedly at high risk of infection during examinations, recommendations for treatment and handling of the field of allergic diseases have been suggested by the European Academy of Allergy and Clinical Immunology (EAACI) in alliance with the global initiative "Allergic Rhinitis and its Impact on Asthma" (ARIA) [17,19-21,26]. It has been shown that digital decision-making tools and app-based algorithms can improve patient-doctor communication and therapy adherence for both patients and physicians [27,28].

In summary, our future COVID-19 symptom tool may be a helpful device for improving active patient reporting and triage of patients when integrated in the ARIA MASK-air App. We have asked the networks to circulate the tool to their members for testing, and we hope to be able to present the results and create more robust evidence in its practicality. This article presents a substantial consensus effort in COVID-19-treating physicians across the globe. Limitations arise from missing or inappropriate data in the returned questionnaires. However, the development process is followed by AI-supported validation, and future studies have to show the power of such questionnaires.

Figures & Tables

Table 1: The original survey with 15 items

	Question	COVID-19				Common Cold				Allergic rhinitis				Level Agreement MEAN	SD
		Occurrence	Characteristics	Max VAS (mean)	SD	Occurrence	Characteristics	Max VAS (mean)	SD	Occurrence	Characteristics	Max VAS (mean)	SD		
1	**Runny nose (anterior rhinorrhea)**	Rare	if present mild symptoms (VAS<5/10)	**3,98**	**0,15**	Always	Anterior and posterior rhinorrhea	**9,93**	**0,54**	Often	Profuse anterior rhinorrhea	**5,41**	**1,22**	**8,50**	**1,90**
2	**Sneezing**	Rare	Not in burst	**3,99**	**0,11**	Common	Not in burst	**5,02**	**0,21**	Very common	In burst	**9,99**	**0,11**	**9,37**	**1,09**
3	**Stuffy nose**	Not uncommon	if present mild symptoms (VAS<5/10)	**4,10**	**0,68**	Always	Often severe	**10,00**	**0,00**	Very common	May be severe	**8,07**	**0,36**	**8,86**	**1,51**
4	**Nasal pruritus**	Not uncommon		**0,00**	**0,00**	NO		**0,08**	**0,53**	Very common	Variable in intensity	**8,02**	**0,21**	**9,22**	**1,38**
5	**Nasal pain**	Possible		**2,99**	**0,11**	Sometimes		**3,00**	**0,00**	NO		**0,00**	**0,00**	**8,21**	**2,22**
6	**Ocular itch**	NO		**2,94**	**0,38**	NO		**3,00**	**0,00**	Common		**10,00**	**0,00**	**9,31**	**1,41**
7	**Ocular pain**	Possible		**3,09**	**0,78**			**3,00**	**0,00**	NO		**0,06**	**0,53**	**8,14**	**2,43**
8	**Ocular redness**	Possible		**3,07**	**0,54**	NO		**3,05**	**0,30**	Common		**9,98**	**0,21**	**8,36**	**2,29**
9	**≥3 nasal symptoms**	NO		**N/A**		YES		**N/A**		YES		**N/A**		**8,92**	**1,82**
10	**Smell dysfunction**	Common	Usually anosmia whereas in other diseases it is hyposmia. Associated with other COVID-19 symptoms, it is likely to be significant diagnostic criterion	**10,00**	**0,00**	Sometimes		**6,98**	**0,21**	Rare	Anosmia very seldor	**6,95**	**0,30**	**8,88**	**1,88**
11	**Taste dysfunction**	Common	Dysgeusia rather than loss of taste. Associated with other COVID-19 symptoms, it is likely to be significant diagnostic criterion	**10,00**	**0,00**	Rare		**3,00**	**0,00**	Very rare		**2,00**	**0,00**	**9,24**	**1,34**
12	**Dyspnea**	Relatively common	May start by isolated mild symptoms but may rapidly becomes severe with respiratory rate >24/min	**10,00**	**0,00**	Rare		**5,00**	**2,92**	Sometimes if asthma		**10,00**	**0,00**	**9,08**	**1,35**
13	**Cough**	Common	May start by isolated mild symptoms (2-4 episodes of dry cough per hour) but may rapidly becomes severe	**10,00**	**0,00**	Common	Follows the nasal symptoms	**7,60**	**2,06**	Sometimes if asthma		**10,00**	**0,00**	**9,22**	**1,22**
14	**Wheezing**	Not uncommon	Rarely isolated, not severe in contradistinction to asthma	**4,99**	**0,11**	Rare		**3,50**	**1,12**	Sometimes if asthma		**10,00**	**0,00**	**8,77**	**1,73**
15	**Sore throat**	Not uncommon		**5,09**	**0,62**	Common		**8,25**	**1,09**	Rare		**4,33**	**2,87**	**8,84**	**1,66**

Table 2: Participants' agreement to the questionnaire items

No	Symptom	Disagree (<=6)		Agree (>6) *n*=87		Missing / invalid answer	
		n	**%**	***n***	**%**	***n***	**%**
1	Runny nose (anterior rhinorrhea)	12	13,8	62	71,3	13	14,9
2	Sneezing	3	3,4	72	82,8	12	13,8
3	Stuffy nose	8	9,2	68	78,2	11	12,6
4	Nasal pruritus	7	8,0	69	79,3	11	12,6
5	Nasal pain	14	16,1	61	70,1	12	13,8
6	Ocular itch	5	5,7	70	80,5	12	13,8
7	Ocular pain	16	18,4	60	69,0	11	12,6
8	Ocular redness	13	14,9	62	71,3	12	13,8
9	≥ 3 nasal symptoms	7	8,0	65	74,7	15	17,2
10	Smell dysfunction	8	9,2	67	77,0	12	13,8
11	Taste dysfunction	2	2,3	73	83,9	12	13,8
12	Dyspnea	5	5,7	67	77,0	15	17,2
13	Cough	4	4,6	69	79,3	14	16,1
14	Wheezing	7	8,0	64	73,6	16	18,4
15	Sore throat	8	9,2	67	77,0	12	13,8

Table 3: Additional items to be integrated in the algorithm

Stenuous fatigue
Fever
COVID-19 comorbidities
Contact with COVID patient
Travel to "high-risk" region
Gastrointestinal symptoms
Muscle/body ache
Profound sweating

Figure 1: Countries involved in the questionnaire

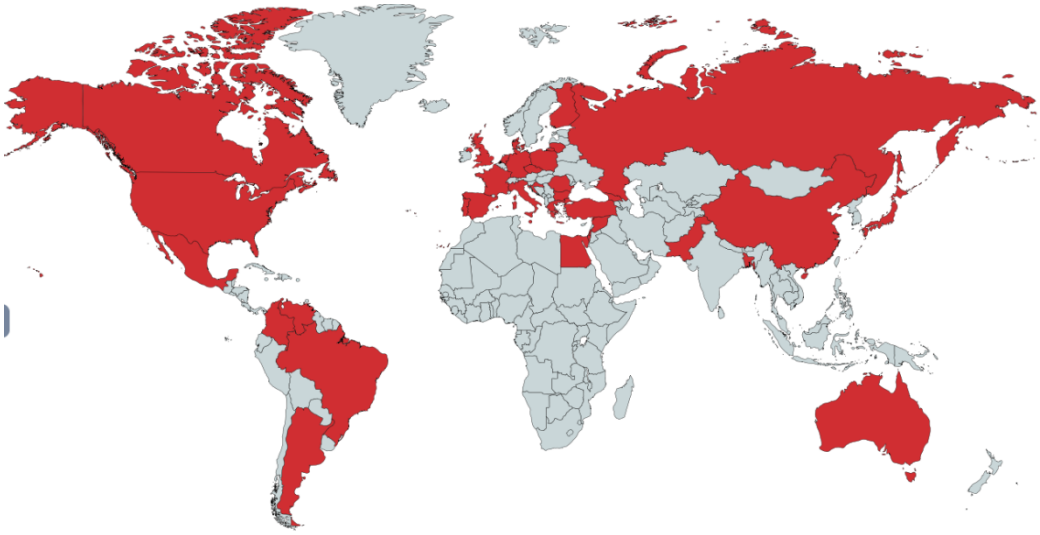


Figure 2: Mean level of agreement to suggested symptom severity. Analogue scale rating with range from 0 (disagreement) to 10 (complete agreement). A level of 6 or higher was considered as "agreement". Means ±SD are shown.

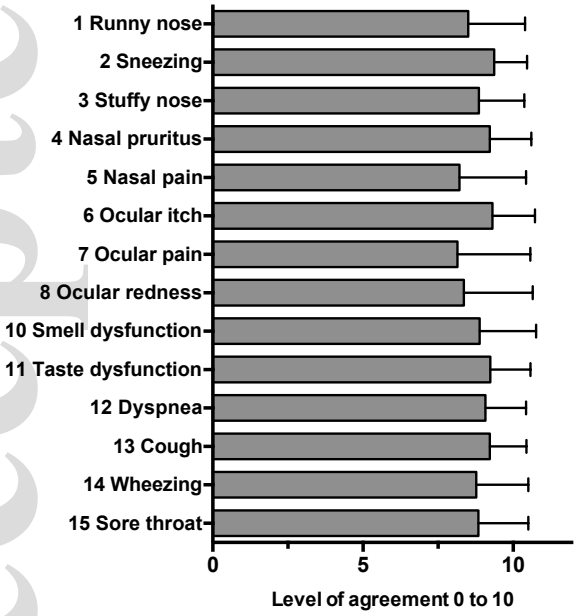
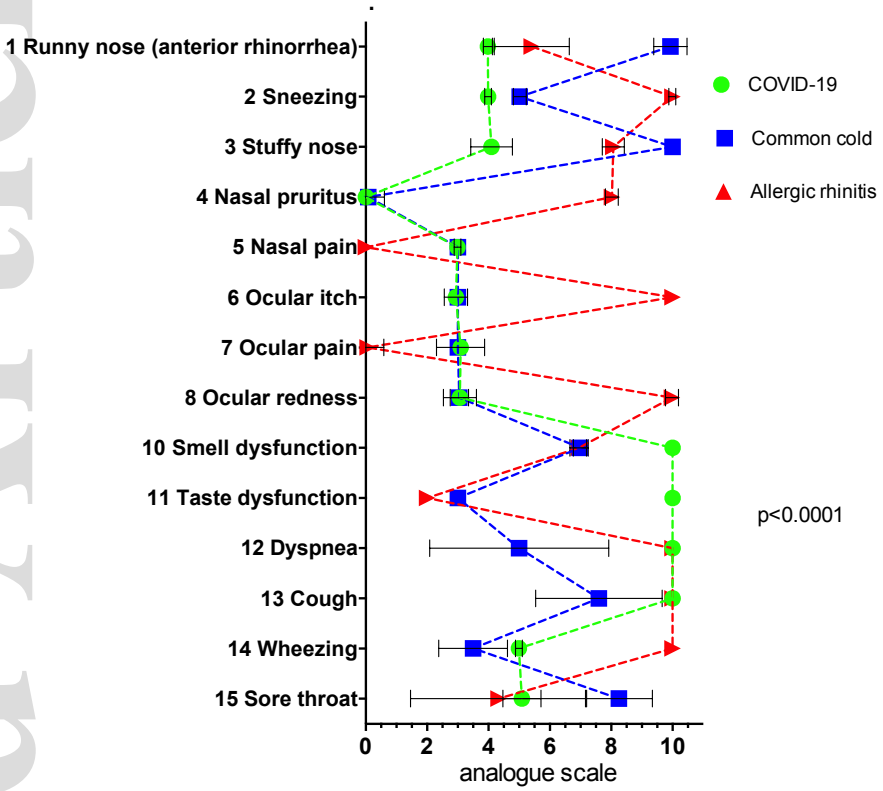


Figure 3: Maximum expected symptom severity. Analogue scale from 0 (not present) to 10 (maximum severity). Means ±SD are shown.A two-way ANOVA revealed significant differences in VAS between diseases (p<0.001).



Conflict of interest

CA reports grants from Allergopharma, Idorsia, Swiss National Science Foundation, Christine Kühne-Center for Allergy Research and Education, European Commission's Horison's 2020 Framework Programme, Cure, Novartis Research Institutes, Astra Zeneca, Scibase, advisory role in Sanofi/Regeneron, grants from Glakso Smith-Kline, advisory role in Scibase.

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NR reports and Advisory Board: Sanofi,Mylan, AstraZeneca,

Speaker: Sanofi, Mylan, Chiesi.

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