

## An international perspective on hospitalized patients with viral community-acquired pneumonia

Dejan Radovanovic<sup>hh</sup>, Giovanni Sotgiu<sup>hi</sup>, Mateja Jankovic<sup>hj</sup>, Padukudru Anand Mahesh<sup>hk</sup>, Pedro Jorge Marcos<sup>hl</sup>, Mohamed I. Abdalla<sup>hm</sup>, Marta Francesca Di Pasquale<sup>hn</sup>, Andrea Gramegna<sup>hn</sup>, Silvia Terraneo<sup>ho,hq</sup>, Francesco Blasi<sup>hn</sup>, Pierachille Santus<sup>hh</sup>, Stefano Aliberti<sup>hn,\*</sup>, Luis F. Reyes<sup>hp</sup>, Marcos I. Restrepo<sup>hm</sup>, the GLIMP Study Group<sup>1</sup> (Patricia Karina Aruj<sup>a</sup>, Silvia Attorri<sup>b</sup>, Enrique Barimboim<sup>c</sup>, Juan Pablo Caeiro<sup>d</sup>, María I. Garzón<sup>d</sup>, Victor Hugo Cambursano<sup>e</sup>, Adrian Ceccato<sup>f</sup>, Julio Chertcoff<sup>g</sup>, Ariel Cordon Díaz<sup>h</sup>, Lautaro de Vedia<sup>i</sup>, Maria Cristina Ganaha<sup>j</sup>, Sandra Lambert<sup>k</sup>, Gustavo Lopardo<sup>l</sup>, Carlos M. Luna<sup>m</sup>, Alessio Gerardo Malberti<sup>n</sup>, Nora Morcillo<sup>o</sup>, Silvina Tartara<sup>o</sup>, Claudia Pensotti<sup>p</sup>, Betiana Pereyra<sup>q</sup>, Pablo Gustavo Scapellato<sup>r</sup>, Juan Pablo Stagnaro<sup>s</sup>, Sonali Shah<sup>t</sup>, Felix Lötsch<sup>u</sup>, Florian Thalhammer<sup>u</sup>, Kurt Anseeuw<sup>v</sup>, Camille A. Francois<sup>w</sup>, Eva Van Braeckel<sup>x</sup>, Jean Louis Vincent<sup>y</sup>, Marcel Zannou Djimon<sup>z</sup>, Simone Aranha Nouér<sup>aa</sup>, Peter Chipev<sup>ab</sup>, Milena Encheva<sup>ab</sup>, Darina Miteva<sup>ac</sup>, Diana Petkova<sup>ad</sup>, Adamou Dodo Balkissou<sup>ae</sup>, Eric Walter Pefura Yone<sup>af</sup>, Bertrand Hugo Mbatchou Ngahane<sup>ag</sup>, Ning Shen<sup>ah</sup>, Jin-fu Xu<sup>ai</sup>, Carlos Andres Bustamante Rico<sup>aj</sup>, Ricardo Buitrago<sup>aj</sup>, Fernando Jose Pereira Paternina<sup>ak</sup>, Jean-Marie Kayembe Ntumba<sup>al</sup>, Vesna Vladic-Carevic<sup>am</sup>, Marko Jakopovic<sup>an</sup>, Zinka Matkovic<sup>ao</sup>, Ivan Mitrećic<sup>ap</sup>, Marie-Laure Bouchy Jacobsson<sup>aq</sup>, Anette Bro Christensen<sup>ar</sup>, Uffe Bødtger<sup>as</sup>, Christian Niels Meyer<sup>at</sup>, Andreas Vestergaard Jensen<sup>au</sup>, Ibrahim El-Said Abd El-Wahhab<sup>av</sup>, Nesreen Elsayed Morsy<sup>aw</sup>, Hanaa Shafiek<sup>ax</sup>, Eman Sobh<sup>ay</sup>, Kedir Abdella Abdulsemed<sup>az</sup>, Fabrice Bertrand<sup>ba</sup>, Christian Brun-Buisson<sup>bb</sup>, Etienne de Montmollin<sup>bc</sup>, Muriel Fartoukh<sup>bd</sup>, Jonathan Messika<sup>be</sup>, Pierre Tattevin<sup>bf</sup>, Abdo Khoury<sup>bg</sup>, Bernard Ebruke<sup>bh</sup>, Michael Dreher<sup>bi</sup>, Martin Kolditz<sup>bj</sup>, Matthias Meisinger<sup>bk</sup>, Mathias W. Pletz<sup>bl</sup>, Stefan Hagel<sup>bl</sup>, Jan Rupp<sup>bm</sup>, Tom Schaberg<sup>bn</sup>, Marc Spielmanns<sup>bo</sup>, Petra Creutz<sup>bp</sup>, Norton Suttorp<sup>bp</sup>, Beatrice Siaw-Lartey<sup>bq</sup>, Katerina Dimakou<sup>br</sup>, Dimosthenis Papapetrou<sup>bs</sup>, Evdoxia Tsigou<sup>bt</sup>, Dimitrios Ampazis<sup>bt</sup>, Evangelos Kaimakamis<sup>bu</sup>, Mohit Bhatia<sup>bv</sup>, Raja Dhar<sup>bw</sup>, George D'Souza<sup>bx</sup>, Rajiv Garg<sup>by</sup>, Parvaiz A. Koul<sup>bz</sup>, B.S. Jayaraj<sup>ca</sup>, Kiran Vishnu Narayan<sup>cc</sup>, Hirennappa B. Udnur<sup>cc</sup>, Shashi Bhaskara Krishnamurthy<sup>cc</sup>, Surya Kant<sup>cd</sup>, Rajesh Swarnakar<sup>ce</sup>, Sundeep Salvi<sup>cf</sup>, Sneha Limaye<sup>cf</sup>, Keihan Golshani<sup>cg</sup>, Vera M. Keatings<sup>ch</sup>, Ignacio Martin-Loeches<sup>ci</sup>, Yasmin Maor<sup>cj</sup>, Jacob Strahilevitz<sup>ck</sup>, Salvatore Battaglia<sup>cl</sup>, Maria Carrabba<sup>cm</sup>, Piero Ceriana<sup>cn</sup>,

*Abbreviation list:* CAD, coronary artery disease; CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum beta-lactamases; FEV<sub>1</sub>, forced expiratory volume in one second; GLIMP, global initiative for methicillin-resistant *Staphylococcus aureus* pneumonia; HIV, *Human Immunodeficiency virus*; HMPV, *human Metapneumovirus*; ICU, intensive care unit; LRTI, lower respiratory tract infection; MRSA, methicillin resistant *Staphylococcus aureus*; OR, odds ratio; PCV13, pneumococcal conjugate vaccine; PPSV23, pneumococcal polysaccharide vaccine; RIDT, rapid influenza diagnostic test; RSV, *Respiratory Syncytial virus*; RT-PCR, reverse transcriptase polymerase chain reaction

<sup>1</sup> Other investigators: Lorena Noriega; Ezequiel Alvarado; Mohamed Aman; Lucía Labra. We would like also to thank the Asociacion Latinoamericana de Torax, European Respiratory Society, World Federation of Societies of Intensive and Critical Care Medicine, and American College of Chest Physicians for their support of this project.

\* Corresponding author at: Department of Pathophysiology and Transplantation, University of Milan, Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Via Francesco Sforza 35, 20122 Milan, Italy.

E-mail address: [stefano.aliberti@unimi.it](mailto:stefano.aliberti@unimi.it) (S. Aliberti).

Marco Confalonieri<sup>co</sup>, Antonella d'Arminio Monforte<sup>cp</sup>, Bruno Del Prato<sup>cq</sup>, Marino De Rosa<sup>cr</sup>, Riccardo Fantini<sup>cs</sup>, Giuseppe Fiorentino<sup>ct</sup>, Maria Antonia Gammino<sup>cu</sup>, Francesco Menzella<sup>cv</sup>, Giuseppe Milani<sup>cw</sup>, Stefano Nava<sup>cx</sup>, Gerardo Palmiero<sup>cy</sup>, Roberta Petrino<sup>cz</sup>, Barbra Gabrielli<sup>cz</sup>, Paolo Rossi<sup>da</sup>, Claudio Sorino<sup>db</sup>, Gundi Steinhilber<sup>dc</sup>, Alessandro Zanforlin<sup>dd</sup>, Fabio Franzetti<sup>de</sup>, Mauro Carone<sup>df</sup>, Vincenzo Patella<sup>dg</sup>, Simone Scarlata<sup>dh</sup>, Andrea Comel<sup>di</sup>, Kiyoyasu Kurahashi<sup>dj</sup>, Zeina Aoun Bacha<sup>dk</sup>, Daniel Barajas Ugalde<sup>dl</sup>, Omar Ceballos Zuñiga<sup>dm</sup>, José F. Villegas<sup>dn</sup>, Milic Medenica<sup>do</sup>, E.M.W. van de Garde<sup>dp</sup>, Deebya Raj Mihsra<sup>dq</sup>, Poojan Shrestha<sup>dr</sup>, Elliott Ridgeon<sup>ds</sup>, Babatunde Ishola Awokola<sup>dt</sup>, Ogonna N.O. Nwankwo<sup>du</sup>, Adefuye Bolanle Olufunlola<sup>dv</sup>, Segalolu Olumide<sup>dw</sup>, Kingsley N. Ukwaja<sup>dx</sup>, Muhammad Irfan<sup>dy</sup>, Lukasz Minarowski<sup>dz</sup>, Skoczynski Szymon<sup>ea</sup>, Felipe Froes<sup>eb</sup>, Pedro Leuschner<sup>ec</sup>, Mariana Meireles<sup>ed</sup>, Cláudia Ferrão<sup>ed</sup>, Pedro Leuschner<sup>ed</sup>, João Neves<sup>ed</sup>, Sofia B. Ravara<sup>ee</sup>, Victoria Brocovschii<sup>ef</sup>, Chesov Ion<sup>eg</sup>, Doina Rusu<sup>eh</sup>, Cristina Toma<sup>ei</sup>, Daniela Chirita<sup>ej</sup>, Carmen Mihaela Dorobat<sup>ek</sup>, Alexei Birkun<sup>el</sup>, Anna Kaluzhenina<sup>em</sup>, Abdullah Almotairi<sup>en</sup>, Zakeya Abdulbaqi Ali Bukhary<sup>eo</sup>, Jameela Edathodu<sup>ep</sup>, Amal Fathy<sup>eq</sup>, Abdullah Mushira Abdulaziz Enani<sup>er</sup>, Nazik Eltayeb Mohamed<sup>er</sup>, Jawed Ulhadi Memon<sup>es</sup>, Abdelhaleem Bella<sup>et</sup>, Nada Bogdanović<sup>eu</sup>, Branislava Milenkovic<sup>ev</sup>, Dragica Pesut<sup>ew</sup>, Luis Borderías<sup>ex</sup>, Noel Manuel Bordon Garcia<sup>ey</sup>, Hugo Cabello Alarcón<sup>ez</sup>, Catia Cilloniz<sup>fa</sup>, Antoni Torres<sup>fa</sup>, Vicens Diaz-Brito<sup>fa</sup>, Xavier Casas<sup>fa</sup>, Alicia Encabo González<sup>fb</sup>, Maria Luisa Fernández-Almira<sup>fc</sup>, Miguel Gallego<sup>fd,he</sup>, Inmaculada Gaspar-García<sup>fe</sup>, Juan González Del Castillo<sup>ff</sup>, Patricia Javaloyes Victoria<sup>fg</sup>, Elena Laserna Martínez<sup>fh</sup>, Rosa Malo de Molina<sup>fi</sup>, Rosario Menéndez<sup>fj</sup>, Ana Pando-Sandoval<sup>fk</sup>, Cristina Prat Aymerich<sup>fl,hf</sup>, Alicia Lacoma de la Torre<sup>fl,hf</sup>, Ignasi García-Olivé<sup>fl,hf</sup>, Jordi Rello<sup>fm</sup>, Silvia Moyano<sup>fm</sup>, Francisco Sanz<sup>fn</sup>, Oriol Sibila<sup>fo</sup>, Ana Rodrigo-Troyano<sup>fo</sup>, Jordi Solé-Violán<sup>fp</sup>, Ane Uranga<sup>fq</sup>, Job F.M. van Boven<sup>fr</sup>, Ester Vendrell Torra<sup>fs</sup>, Jordi Almirall Pujol<sup>fs</sup>, Charles Feldman<sup>ft</sup>, Ho Kee Yum<sup>fu</sup>, Arnauld Attannon Fiogbe<sup>fv</sup>, Ferdaous Yangui<sup>fw</sup>, Semra Bilaceroglu<sup>fx</sup>, Levent Dalar<sup>fy</sup>, Ufuk Yilmaz<sup>fz</sup>, Artemii Bogomolov<sup>ga</sup>, Naheed Elahi<sup>gb</sup>, Devesh J. Dhasmana<sup>gc</sup>, Andrew Feneley<sup>gd</sup>, Carole Hancock<sup>ge</sup>, Adam T. Hill<sup>gf</sup>, Banu Rudran<sup>gg</sup>, Silvia Ruiz-Buitrago<sup>gh</sup>, Marion Campbell<sup>gh</sup>, Paul Whitaker<sup>gi</sup>, Alexander Youzguin<sup>gj</sup>, Anika Singanayagam<sup>gk</sup>, Karen S. Allen<sup>gl</sup>, Veronica Brito<sup>gm</sup>, Jessica Dietz<sup>gn</sup>, Claire E. Dysart<sup>go,hg</sup>, Susan M. Kellie<sup>go,hg</sup>, Ricardo A. Franco-Sadud<sup>gp</sup>, Garnet Meier<sup>gp</sup>, Mina Gaga<sup>gq</sup>, Thomas L. Holland<sup>gr</sup>, Stephen P. Bergin<sup>gr</sup>, Fayez Kheir<sup>gs</sup>, Mark Landmeier<sup>gt</sup>, Manuel Lois<sup>gu</sup>, Girish B. Nair<sup>gv</sup>, Hemali Patel<sup>gw</sup>, Katherine Reyes<sup>gx</sup>, William Rodriguez-Cintron<sup>gy</sup>, Shigeki Saito<sup>gz</sup>, Nilam J. Soni<sup>ha</sup>, Julio Noda<sup>ha</sup>, Cecilia I. Hinojosa<sup>ha</sup>, Stephanie M. Levine<sup>ha</sup>, Luis F. Angel<sup>ha</sup>, Antonio Anzueto<sup>ha</sup>, K. Scott Whitlow<sup>hb</sup>, John Hipskind<sup>hb</sup>, Kunal Sukhija<sup>hb</sup>, Vicken Totten<sup>hb</sup>, Richard G. Wunderink<sup>hc</sup>, Ray D. Shah<sup>hc</sup>, Kondwelani John Mateyo<sup>hd</sup>, Manuela Carugati<sup>de</sup>, Manuela Morosi<sup>de</sup>, Elisa Monge<sup>de</sup>)

<sup>hh</sup> Department of Biomedical and Clinical Sciences (DIBIC), University of Milan, Section of Respiratory Diseases, Ospedale L. Sacco, ASST Fatebenefratelli-Sacco, Milan, Italy

<sup>hi</sup> Clinical Epidemiology and Medical Statistics Unit, Department of Medical, Surgical and Experimental Medicine, University of Sassari, Sassari, Italy

<sup>hj</sup> School of Medicine, University of Zagreb, Department for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Croatia

<sup>hk</sup> Department of Pulmonary Medicine, JSS Medical College, JSS Academy of Higher Education and Research, Mysore, India

<sup>hl</sup> Dirección de Procesos Asistenciales, Servicio de Neumología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complejo Hospitalario Universitario de A Coruña (CHUAC), Estructura Organizativa de Xestión Integrada (EOXI) de A Coruña, SERGAS, Universidade da Coruña (UDC), A Coruña, Spain

<sup>hm</sup> South Texas Veterans Health Care System and University of Texas Health, San Antonio, TX, USA

<sup>hn</sup> Department of Pathophysiology and Transplantation, University of Milan, Internal Medicine Department, Respiratory Unit and Cystic Fibrosis Adult Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

<sup>ho</sup> Department of Health Sciences, University of Milan, Milan, Italy

<sup>hp</sup> Department of Microbiology, Universidad de La Sabana, Chia, Colombia

<sup>hq</sup> Department of Health Sciences, University of Milan, Respiratory Unit, San Paolo Hospital, Milan, Italy

<sup>a</sup> Department of Internal Medicine, University Hospital Alfredo Lanari, Buenos Aires, Argentina

<sup>b</sup> Hospital Luis Lago maggiore, Mendoza, Argentina

<sup>c</sup> Hospital Central de Mendoza, Argentina

<sup>d</sup> Hospital Privado Universitario, Córdoba, Argentina

<sup>e</sup> V.H. Dr Cazaux A. Servicio de Neumología, Hospital Rawson, Córdoba, Argentina

<sup>f</sup> Hospital Nacional Prof Alejandro Posadas, Argentina

<sup>g</sup> Florencia Lascar and Fernando Di Tulio, Critical Care Unit and Respiratory Medicine, Buenos Aires British Hospital, Buenos Aires, Argentina

<sup>h</sup> Hospital General Alvear, Ciudad, Mendoza, Argentina

<sup>i</sup> Respiratory Intensive Care Unit, Hospital Muñiz, Buenos Aires, Argentina

<sup>j</sup> Infectious Diseases Ward, Hospital Interzonal General de Agudos "Vicente Lopez y Planes" from General Rodriguez, Buenos Aires, Argentina

<sup>k</sup> Hospital El Cruce - Alta Complejidad en Red, Argentina

<sup>l</sup> Hospital Bernardo Houssay, Vicente López, Argentina

<sup>m</sup> Pulmonary Medicine Division, Department of Medicine, Hospital de Clínicas, Universidad de Buenos Aires, Argentina

<sup>n</sup> Hospital Nuestra Señora del Carmen, Argentina

<sup>o</sup> Hospital Zonal Especializado de Agudos y Crónicos Dr. Antonio A. Cetrangolo, Argentina

<sup>p</sup> Infectious Diseases and Infection Control Department, Buenos Aires, Clínica Privada Monte Grande, Argentina

<sup>q</sup> Hospital San Roque, Córdoba, Argentina

<sup>r</sup> Infectious Diseases Department, Hospital D.F. Santojanni, Argentina

<sup>s</sup> HZGA Mi Pueblo, Florencio Varela, Argentina

<sup>t</sup> Department of General medicine, Austin hospital, Heidelberg, Australia

<sup>u</sup> Division of Infectious Diseases and Tropical Medicine, Department of Medicine I, Medical University of Vienna, Austria

<sup>v</sup> ZNA Campus Stuivenberg, Antwerp, Belgium

<sup>w</sup> Anesthesia and critical care department, Erasme university hospital, Brussels, Belgium

<sup>x</sup> Department of Respiratory Medicine, Ghent University Hospital, Belgium

<sup>y</sup> Department of Intensive Care, Erasme University Hospital, Université Libre de Bruxelles, Brussels, Belgium

<sup>z</sup> Jules Bashi and Roger Dodo, Centre Hospitalier Universitaire HKM of Cotonou, Benin

<sup>aa</sup> Federal University of Rio de Janeiro, Brazil

<sup>ab</sup> Clinic of Pulmonary Diseases, Military Medical Academy, Sofia, Bulgaria

<sup>ac</sup> UMHAT "St. Marina", Varna, Bulgaria

<sup>ad</sup> University Hospital Varna, Bulgaria

<sup>ae</sup> Yaounde Jamot Hospital, Yaounde, Cameroon

<sup>af</sup> Département de Médecine Interne, University of Yaounde, Yaoundé, Cameroon

<sup>ag</sup> Douala General Hospital, Douala, Cameroon

<sup>ah</sup> Respiratory Medicine, Peking University Third Hospital, Beijing, China

<sup>ai</sup> Department of Respiratory Medicine, Shanghai Pulmonary Hospital, Tongji University, China

<sup>aj</sup> Clínica Shaio, Bogota, Colombia

<sup>ak</sup> Las Americas Clinic, Medellín, Colombia

<sup>al</sup> Cliniques Universitaires de Kinshasa, DR, Congo

<sup>am</sup> Interne Medicine, Dubrovnik, Croatia

<sup>an</sup> Medical School, University of Zagreb, Department for Respiratory Diseases Jordanovac, University Hospital Centre Zagreb, Zagreb, Croatia

<sup>ao</sup> University Hospital Dubrava, Zagreb, Croatia

<sup>ap</sup> Karlovac general hospital, Karlovac, Croatia

<sup>aq</sup> Emergency Department in North Zealand's Hospital -, Hillerød, Denmark

<sup>ar</sup> Department of Anaesthesiology, Viborg Region Hospital, Denmark

<sup>as</sup> Department of Pulmonology, Naestved Hospital, Denmark

<sup>at</sup> Department of Internal Medicine, Roskilde Hospital, Copenhagen University Hospital, Roskilde, Denmark

<sup>au</sup> Gertrud Baumbaek-knudsen, Pelle Trier Petersen and Stine Andersen, Department of Lung- and Infectious Diseases, Nordsjællands Hospital-Hillerød, Denmark

<sup>av</sup> Thoracic Medicine, Faculty of Medicine, Mansoura University, Egypt

<sup>aw</sup> Pulmonary, Critical Care and Sleep Medicine, Mansoura University, Mansoura, Egypt

<sup>ax</sup> Chest diseases department, Alexandria University, Egypt

<sup>ay</sup> Chest Diseases Department, Al-Azhar University, Cairo, Egypt

<sup>az</sup> Department of Medical Laboratory Science and Pathology, College of Health sciences, Mycobacteriology Research Centre, Institute of Biotechnology Research, Jimma University, Jimma, Ethiopia

<sup>ba</sup> Critical care Unit, Robert Ballanger Hospital, Aulnay sous Bois, France

<sup>bb</sup> Univ Hospital Henri Mondor, 94000 Créteil, France

<sup>bc</sup> Intensive care unit, Hôpital Delafontaine, Centre hospitalier de Saint-Denis, Saint-Denis, France

<sup>bd</sup> Unité de réanimation médico-chirurgicale, Pôle Thorax Voies aériennes, Hôpital Tenon, Groupe Hospitalier Est Parisien, France

<sup>be</sup> Publique-Hôpital de Paris, Service de Réanimation Médico-chirurgicale, Hôpital Louis Mourier, Colombes, France, and Université Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, Paris, France

<sup>bf</sup> Infectious Diseases & ICU, Pontchaillou University Hospital, Rennes, France

<sup>bg</sup> Department of Emergency Medicine & Critical Care, University of Franche - Comté, Medical Center, France

<sup>bh</sup> Medical Research Council Unit, Gambia

<sup>bi</sup> Department of Cardiology, Pneumology, Vascular Medicine and Intensive Care Medicine, University Hospital Aachen, Aachen, Germany

<sup>bj</sup> Division of Pulmonology, Medical Department I, University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany

<sup>bk</sup> Klinikum Niederlausitz GmbH, Klinik für Innere Medizin und Intensivmedizin, Senftenberg, Germany

<sup>bl</sup> Center for Infectious Diseases and Infection Control, Jena University Hospital, Germany

<sup>bm</sup> Department of Molecular and Infectious Diseases, University of Lübeck, Lübeck, Germany

<sup>bn</sup> Zentrum für Pneumologie, Agaplesion Diakonieklinikum Rotenburg, Germany

<sup>bo</sup> Internal Medicine Department, Pulmonary rehabilitation and Department of Health, School of Medicine, University Witten-Herdecke, St.Remigius-Hospital, Leverkusen, Germany

<sup>bp</sup> Department of Infectious Disease and Respiratory Medicine, Charité - University Medicine, Berlin, Germany

<sup>bq</sup> Komfo-Anokye Teaching Hospital, Kumasi, Ghana

<sup>br</sup> 5th Respiratory Medicine Dpt, "SOTIRIA" Chest Hospital, Athens 11527, Greece

<sup>bs</sup> Medical Group of Athens (Paleo Faliro Clinic), Athens, Greece

<sup>bt</sup> Agioi Anargiroi Hospital, Kifissia, Athens, Greece

<sup>bv</sup> Intensive Care Unit, "G. Papanikolaou" General Hospital of Thessaloniki, Greece

<sup>bw</sup> S.S. Hospital IMS BHU, Varanasi, India

<sup>bx</sup> Fortis Hospitals, Kolkata, India

<sup>by</sup> Department of Pulmonary Medicine, St. John's Medical College Hospital, Bangalore 560034, India

<sup>bz</sup> Department of Respiratory Medicine, King George's Medical University UP, Lucknow, India

<sup>ca</sup> Department of Internal & Pulmonary Medicine, SheriKashmir Institute of Medical Sciences, Srinagar, India

<sup>cb</sup> Department of Pulmonary Medicine, JSS Medical College, JSS University, Mysore, India

<sup>cc</sup> Pulmonary Medicine, Government Medical College Kozhikode, Kerala, India

<sup>cd</sup> Columbia Asia Hospital, Hebbal, Bengaluru, Karnataka, India

<sup>ce</sup> Department of Respiratory Medicine, King George's Medical University, Chowk, Lucknow 226003, Uttar Pradesh, India

<sup>cf</sup> Getwell Hospital & Research Institute, Dhantoli, Nagpur, India

<sup>cg</sup> on behalf of the Respiratory Research Network of India (RRNI) from the Chest Research Foundation in Pune, India

<sup>ch</sup> Isfahan University of Medical Sciences, Iran

<sup>ci</sup> Letterkenny General Hospital, Co. Donegal, Ireland

<sup>cj</sup> Multidisciplinary Intensive Care Research Organization (MICRO), St James's University Hospital, Trinity Centre for Health Sciences Dublin, Ireland

<sup>ck</sup> Infectious Disease Unit, Affiliated to Tel Aviv University, Wolfson Medical Center, Holon, Israel

<sup>cl</sup> Department of Clinical Microbiology & Infectious Diseases, Hadassah-Hebrew University, Jerusalem, Israel

<sup>c1</sup> University of Palermo, Pneumologia DiBiMIS, Palermo, Italy

<sup>cm</sup> Internal Medicine Department, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milano, Italy

<sup>cn</sup> Pulmonary rehabilitation, IRCCS Fondazione Maugeri, 27100 Pavia, Italy

<sup>co</sup> Department of Pulmunology, University Hospital, Trieste, Italy

<sup>cp</sup> Department of Health Sciences, Clinic of Infectious Disease, San Paolo Hospital, University of Milan, Italy

<sup>cq</sup> Interventional Pneumology, Hospital Antonio Cardarelli, Naples, Italy

<sup>cr</sup> UOC Pneumologia P.O. San Filippo Neri ASL RM E Roma, Italy

<sup>cs</sup> Respiratory Diseases clinic, Policlinico di Modena, 41124 Modena, Italy

<sup>ct</sup> UOC Fisiopatologia e Riabilitazione Respiratoria AO Ospedali dei Colli PO Monaldi, Italy

<sup>cw</sup> Pulmonary Medicine Unit, San Martino Hospital, ASL 5 Oristano, Sardegna, Italy

<sup>cx</sup> Department of Cardiac-Thoracic-Vascular and Intensive Care Medicine, Pneumology Unit, IRCCS- Arcispedale Santa Maria Nuova, Reggio Emilia, Italy

<sup>cw</sup> Azienda Ospedaliera Sant Anna di Como, Presidio Ospedale S. Anna Nuovo, Unità Operativa di Pneumologia, Como, Italy

<sup>cx</sup> Alma Mater University of Bologna, DIMES, Respiratory and Critical Care Unit Sant'Orsola Malpighi Hospital, Italy

<sup>cy</sup> Respiratory Unit, Versilia Hospital, Azienda USL 12 Viareggio, Lido di Camaione, Lucca, Italy

<sup>cz</sup> Emergency Medicine Unit, S. Andrea Hospital, Vercelli, Italy

<sup>da</sup> Internal Medicine Department, Azienda Ospedaliero-Universitaria S. Maria della Misericordia, Udine, Italy

<sup>db</sup> Pulmonology Unit, A.O. Sant'Anna di Como, Italy

<sup>dc</sup> Spedali Civili Brescia, U.O. Pneumologia e Fisiopatologia Respiratoria, Brescia, Italy

<sup>dd</sup> ULSS 18 Rovigo, Ospedale San Luca, 45027 Trecenta (RO), Italy

<sup>de</sup> Department of Biomedical and Clinical Sciences, Division of Infectious Diseases, Luigi Sacco Hospital, Università degli Studi di Milano, Milan, Italy

<sup>df</sup> Fondazione Salvatore Maugeri, IRCCS, Cassano Murge, Italy

<sup>dg</sup> Allergology and Clinical Immunology Unit, Department of Medical Sciences, Battipaglia Hospital, Battipaglia, Salerno, Italy

<sup>dh</sup> Geriatrics, Unit of Respiratory Pathophysiology and Thoracic Endoscopy, Campus Bio Medico University and Teaching Hospital, Rome, Italy

<sup>di</sup> UO Pneumologia, Ospedale Pederzoli, Peschiera del Garda, Italy

<sup>dj</sup> Yokohama City University Medical Center, Japan

<sup>dk</sup> Medicine school, St Joseph University, Beyrouth, Lebanon

<sup>dl</sup> National Institute of Respiratory Diseases, Mexico

<sup>dln</sup> Hospital General de Mexicali, Mexicali, Baja California, Mexico

<sup>dm</sup> Hospital Universitario Monterrey, n. l. México CP 64030, Mexico

<sup>do</sup> Hospital for Lung Diseases - Brezovik, Niksic, Montenegro

<sup>dp</sup> Dept. Clinical Pharmacy, St. Antonius Hospital, Utrecht/Nieuwegein, The Netherlands

<sup>dq</sup> Internal Medicine, BP Koirala Institute of Health Sciences, Nepal

<sup>dr</sup> Oxford University Clinical Research Unit, Patan Hospital, Nepal

<sup>ds</sup> Medical Research Institute of New Zealand, New Zealand

<sup>dt</sup> Department of Family Medicine & Primary Care, Lily Hospitals Limited, Warri, Nigeria

<sup>du</sup> University of Calabar Teaching Hospital, Calabar, Nigeria

<sup>dv</sup> Olabisi Onabanjo University teaching hospital, Sagamu, Ogun State, Nigeria

<sup>dw</sup> Department of Medicine (Pulmonary Unit), University College Hospital, Ibadan, Nigeria

<sup>dx</sup> Department of Medicine, Federal Teaching Hospital Abakaliki, Ebonyi State, Nigeria

<sup>dy</sup> Section of Pulmonary and Critical Care Medicine, Department of Medicine, Aga Khan University, Karachi 74800, Pakistan

<sup>dz</sup> Department of Lung Diseases and Tuberculosis, Medical University of Białystok, Poland

<sup>ea</sup> Department of Pneumology, School of Medicine in Katowice, Medical University of Silesia, Katowice, Institute of Occupational Medicine and Environmental Health, Sosnowiec, Poland

<sup>eb</sup> Hospital Pulido Valente - CHLN, Lisboa, Portugal

<sup>ec</sup> Centro Hospitalar do Porto, Porto, Portugal

<sup>ed</sup> Serviço de Medicina, Centro Hospitalar do Porto, Largo Prof. Abel Salazar, 4099-001 Porto, Portugal

<sup>ee</sup> Faculty of Health Sciences, University of Beira Interior; Cova da Beira Hospital Center, 6200-251 Covilhã, Portugal

<sup>ef</sup> Department of Pneumology & Allergology, State University of Medicine and Pharmacy "Nicolae Testemitanu", Moldavia

<sup>eg</sup> Clinic of Anesthesia and Intensive Care "Valeriu Gherg", Institute of Emergency Medicine, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Moldavia

<sup>eh</sup> SMFU "N.Testemitanu", Chisinau, Moldavia

<sup>ei</sup> Department of Pneumology & Allergology, State University of Medicine and Pharmacy "Nicolae Testemitanu", Chisinau, Moldavia

<sup>ej</sup> Hospital Sfantul Stefan, Bucharest, Romania

<sup>ek</sup> Universitatea de Medicină și Farmacie "Gr. T. Popa" I a și Facultatea de Medicină Stomatologică, Spitalul Clinic de Boli Infecțioase "Sfânta Parascheva" I a și str. Octav Botez, nr. 2, 700116 Iași, Romania

<sup>el</sup> Department of Anesthesiology, Critical Care and Emergency Medicine, Medical Academy named after S. I. Georgievsky, Russia

<sup>em</sup> Volgograd State Medical University, Russia

<sup>en</sup> King Fahad medical City (KFMC), Riyadh, Saudi Arabia

<sup>eo</sup> College of Medicine, Taibah University, Medina, Saudi Arabia

<sup>ep</sup> Al Faisal University, King Faisal Specialist Hospital, Riyadh, Saudi Arabia

<sup>eq</sup> Pulmonary and respiratory critical care Medicine, Mansoura University Egypt, Affiliate at Taibah University, Saudi Arabia

<sup>er</sup> Infectious Diseases Section, Medical Specialties Department, King Fahad Medical City, Riyadh, Saudi Arabia

<sup>es</sup> Pulmonology Division, Department of Internal Medicine, King Fahad Hospital, Hofuf, Al Ahasa, 31982, Saudi Arabia

<sup>et</sup> Dammam University-Saudi Arabia and King Fahad Hospital, Saudi Arabia

<sup>eu</sup> Pulmonary department of KHC Dr.Dragiša Mišović, Belgrade, Serbia

<sup>ev</sup> Clinic for Pulmonary Diseases, Clinical Centre of Serbia, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

<sup>ew</sup> University of Belgrade School of Medicine, Teaching Hospital of Pulmonology, Clinical Centre of Serbia, Belgrade, Serbia

<sup>ex</sup> Respiratory and Sleep Unit, Hospital San Jorge, Huesca, Spain

<sup>ey</sup> Barcelona Policlinic and Moises Broggi Hospital at sant Joan Despí, Spain

<sup>ez</sup> Sant Hospital Seu de Urgell, Catalonia, Spain

<sup>fa</sup> Department of Pneumology, Institut Clinic del Tórax, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona (UB), Spain

<sup>fb</sup> Hospital Complex of Pontevedra, Spain

<sup>fc</sup> Medicina Interna, Hospital Universitario Central de Asturias, Spain

<sup>fd</sup> Department of Respiratory Medicine, Hospital de Sabadell, Institut Universitari Parc Taulí-UAB, Sabadell, Spain

<sup>fe</sup> Department of Respiratory Medicine, Hospital Costa del Sol, Marbella, Málaga, Spain

<sup>ff</sup> Emergency Department, Hospital Universitario Clínico San Carlos, Madrid, Spain

<sup>fg</sup> Hospital General Universitario de Alicante, Alicante, Spain

<sup>fh</sup> Hospital Mollet, Barcelona, Spain

<sup>fi</sup> University Hospital Puerta de Hierro Majadahonda, Madrid

- <sup>fj</sup> Pneumology Service, University and Polytechnic Hospital La Fe, Valencia, Spain
- <sup>fk</sup> Hospital Universitario Central de Asturias, Area de Gestión Clínica de Pulmon. Servicio de Neumología, Oviedo, Spain
- <sup>fl</sup> Microbiology Department and Pneumology Department, Hospital Universitari Germans Trias i Pujol, Institut d'Investigació Germans Trias i Pujol, Badalona, Spain
- <sup>fm</sup> Critical Care Department, Hospital Vall d'Hebron, Barcelona, Spain
- <sup>fn</sup> Servicio de Neumología, Consorci Hospital General Universitari de Valencia, Valencia, Spain
- <sup>fo</sup> Servei de Pneumologia, Hospital de la Santa Creu i Sant Pau, IIB-Sant Pau, Barcelona, Spain
- <sup>fp</sup> Hospital Universitario de Gran Canaria Dr Negrín, Las Palmas de Gran Canaria, Spain
- <sup>fq</sup> Pulmology Department, Hospital of Galdakao-Usansolo, Spain
- <sup>fr</sup> Hospital Universitari Son Espases, Palma de Mallorca, Spain
- <sup>fs</sup> Intensive Care Medicine, Hospital de Mataró, Spain
- <sup>ft</sup> Division of Pulmonology, Department of Internal Medicine, Charlotte Maxeke Johannesburg Academic Hospital, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
- <sup>fu</sup> Inje Univ. Seoul Paik Hospital, South Korea
- <sup>fv</sup> Pulmonology and Infectious Diseases Service/University hospital of Sylvanus Olympio, Lomé, Togo
- <sup>fw</sup> Department of Pneumology, Hospital of Internal Forces Security (I.F.S), Marsa, Tunis, Tunisia
- <sup>fx</sup> Izmir Dr. Suat Seren Training and Research Hospital for Thoracic Medicine and Surgery, Izmir, Turkiye
- <sup>fy</sup> Pulmonary Medicine, Istanbul Bilim University, Istanbul, Turkiye
- <sup>fz</sup> Suat Seren Chest Disease and Surgery Training and Research Hospital, İzmir, Turkiye
- <sup>g0</sup> Vinnitsa National Pirogov Memorial Medical University, Vinnitsa regional antituberculosis hospital, Vinnitsa, Ukraine
- <sup>g1</sup> Dubai Hospital, United Arab Emirates
- <sup>g2</sup> Victoria Hospital, Kirkcaldy, NHS Fife, UK
- <sup>g3</sup> Rhiannon Ions, Julie Skeemer and Gerrit Woltmann, University Hospitals of Leicester NHS Trust and University of Leicester, Leicester, UK
- <sup>g4</sup> Royal Respiratory Research Team, Royal Liverpool University Hospital, Liverpool, UK
- <sup>g5</sup> Royal Infirmary and University of Edinburgh, UK
- <sup>g6</sup> The Royal London Hospital, Barts Health Trust, London, UK
- <sup>g7</sup> Hairmyres Hospital, Eaglesham Road, East Kilbride, G75 8RG, UK
- <sup>g8</sup> Department of Respiratory Medicine, St James's Hospital, Leeds, LS9 7TF, UK
- <sup>g9</sup> Southport and Ormskirk Hospitals NHS Trust, UK
- <sup>ga</sup> Imperial College Healthcare NHS Trust, London, UK
- <sup>gb</sup> University of Oklahoma Health Sciences Center, USA
- <sup>gc</sup> Texas A&M Health Science Center, Division of Pulmonary, Critical Care and Sleep Medicine Baylor Scott & White Health, USA
- <sup>gd</sup> Fargo VA Health Care System, Fargo, North Dakota, USA
- <sup>ge</sup> Clement J. Zablocki VA Medical Center, 5000 W. National Ave Milwaukee, WI 53295, USA
- <sup>gf</sup> Division of Hospital Medicine, Cook County Hospital, Chicago, USA
- <sup>gg</sup> 7th Resp. Med. Dept and Asthma Center, Athens Chest Hospital, USA
- <sup>gh</sup> Department of Medicine, Duke University Medical Center and School of Medicine, Duke Clinical Research Institute, USA
- <sup>gi</sup> Department of Pulmonary Diseases, Critical Care & Environmental Medicine, Tulane University Health Sciences Center, New Orleans, LA, USA
- <sup>gj</sup> Division of Pulmonary and Critical Care Medicine, Northwestern Memorial Hospital, Chicago, IL 60611, USA
- <sup>gk</sup> John Peter Smith Hospital, Fort Worth, TX 76104, USA
- <sup>gl</sup> Interstitial Lung Disease Program and Pulmonary Rehabilitation, SUNY Stony Brook Winthrop University Hospital, Mineola, NY 115501, USA
- <sup>gm</sup> Department of Medicine, Division of General Internal Medicine, Hospital Medicine Group, University of Colorado, USA
- <sup>gn</sup> Henry Ford Hospital, Detroit, IL, USA
- <sup>go</sup> Pulmonary/Critical Care Medicine VA Caribbean Healthcare System, USA
- <sup>gp</sup> Tulane University, New Orleans, USA
- <sup>gq</sup> Divisions of Hospital Medicine & Pulmonary/Critical Care Medicine, South Texas Veterans Health Care System, University of Texas Health Science Center San Antonio, San Antonio, TX, USA
- <sup>gr</sup> Kaweah Delta Health Care District, Department of Emergency Medicine, Visalia, CA, USA
- <sup>gs</sup> Northwestern University Feinberg School of Medicine, Chicago, IL, USA
- <sup>gt</sup> Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia
- <sup>gu</sup> CIBER de Enfermedades Respiratorias, CIBERES, Bunyola, Spain
- <sup>gv</sup> Universitat Autònoma de Barcelona, CIBER Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Spain
- <sup>gw</sup> Division of Infectious Diseases, University of New Mexico School of Medicine, Raymond G. Murphy VA Medical Center, 1501 San Pedro SE Albuquerque, NM 87108, USA

---

## ARTICLE INFO

### Keywords:

Community acquired pneumonia  
 Oseltamivir  
 Viral pneumonia  
 Influenza  
 Viral swab  
 Testing

## ABSTRACT

**Background:** Who should be tested for viruses in patients with community acquired pneumonia (CAP), prevalence and risk factors for viral CAP are still debated. We evaluated the frequency of viral testing, virus prevalence, risk factors and treatment coverage with oseltamivir in patients admitted for CAP.

**Methods:** Secondary analysis of GLIMP, an international, multicenter, point-prevalence study of hospitalized adults with CAP. Testing frequency, prevalence of viral CAP and treatment with oseltamivir were assessed among patients who underwent a viral swab. Univariate and multivariate analysis was used to evaluate risk factors.

**Results:** 553 (14.9%) patients with CAP underwent nasal swab. Viral CAP was diagnosed in 157 (28.4%) patients. *Influenza virus* was isolated in 80.9% of cases. Testing frequency and viral CAP prevalence were inhomogeneous across the participating centers. Obesity (OR 1.59, 95%CI: 1.01–2.48;  $p = 0.043$ ) and need for invasive mechanical ventilation (OR 1.62, 95%CI: 1.02–2.56;  $p = 0.040$ ) were independently associated with viral CAP. Prevalence of empirical treatment with oseltamivir was 5.1%.

**Conclusion:** In an international scenario, testing frequency for viruses in CAP is very low. The most common cause of viral CAP is *Influenza virus*. Obesity and need for invasive ventilation represent independent risk factors for viral CAP. Adherence to recommendations for treatment with oseltamivir is poor.

---

## 1. Introduction

Community acquired pneumonia (CAP) is the most frequent infectious disease of the lower respiratory tract and represents a major clinical burden worldwide, with World Health Organization estimates reporting > 450 million cases annually [1]. Furthermore, it represents a substantial cost for healthcare systems (e.g., > 10 billion dollars in 2011 in the United States [2]).

CAP can be caused by different micro-organisms, but recently viruses have been identified as an important etiological pathogen in CAP patients [2]. Incidence of viral CAP is high, with a major impact on mortality worldwide [3], especially in developing countries [1]. Moreover, from 21% [2] to 28% [4] of hospitalized patients with viral CAP require admission to the intensive care unit (ICU).

The prevalence of viruses as a cause of CAP might be underestimated in clinical practice because new molecular tests to identify viral pathogens are not widely available in clinical practice [2]. Clinical presentation of bacterial and viral pneumonia may overlap [5] and no consensus exists on when and who should be tested and treated for viral CAP [6]. Different reports have shown that its prevalence widely varies from 8.6% to 56.2% [4–7], differing in terms of study design, diagnostic techniques, and study populations. Notably, previous experiences were mainly monocentric or limited to a few countries, and do not represent data outside Europe and North America [4–7]. Importantly, viral CAP-related risk factors differ from study to study [8–11]. Finally, current available data shows that *Influenza virus* is the most prevalent cause of viral CAP, for which oseltamivir is suggested as standard of care [6].

An evaluation of the global prevalence and risk factors associated with viral CAP is necessary to help in the decision-making process.

The primary aim of the present study was to investigate the frequency of testing for viruses and the prevalence of viral CAP at international level. The secondary aim was to describe the population of patients with viral CAP and to evaluate oseltamivir use in a pragmatic point prevalence study.

## 2. Methods

The present study is a secondary analysis of the database collected for the GLIMP study, an international, multicenter, point-prevalence study of hospitalized adult patients with a diagnosis of CAP [12]. Detailed methodology of the GLIMP study was published elsewhere [12]. The study was conducted in accordance with the amended Declaration of Helsinki and was approved by the Institutional Review Board (IRB# HSC20150184E) of The University of Texas Health Science Center at San Antonio, TX, USA, and all participating centers were required to comply with local, regional, or national research regulations to participate in the study.

### 2.1. Inclusion and exclusion criteria

All adults (> 18 years old) hospitalized with CAP were screened for study inclusion. The study sample included only patients who underwent a viral nasopharyngeal or oropharyngeal swab during the first 24 h. Patients hospitalized with a diagnosis of hospital-acquired and/or ventilator-associated pneumonia were excluded from the study [13].

### 2.2. Data collection

Study participants were enrolled on a single day in the months of March, April, May, and June 2015. The following variables were collected: age, height, weight, gender, job, smoking history, pharmacological therapy, vaccination status, drug and alcohol abuse, oncological, cardiovascular, respiratory, hepatic, and renal comorbidities, previous healthcare exposure – i.e. emergency room admission, intravenous and oral antibiotics, hospitalization, lower respiratory tract infections in the previous 3, 6, and 12 months - severity of disease in first 24 h of hospital

admission, prior infection or colonisation with multi-drug resistant pathogens. For a detailed list of characteristics and risk factors evaluated please see the [Appendix A](#). Patients' care workup might include any of the following specimens: blood samples, acute-phase serum specimens, urine samples, nasopharyngeal swabs, sputum in case of productive cough, pleural fluid, endotracheal aspirates, and bronchoalveolar lavage samples. Only microbiological tests performed in the first 24 h from admittance to the hospital were considered for the analysis. All antimicrobial, antiviral, and antifungal treatments administered within 24 h from the admission were recorded. Data were collected and managed using an ad hoc report form and a dedicated data capture tool [12].

### 2.3. Microbiological analysis

Patients' clinical management and collection of microbiological samples depended on the attending physician, and not per study protocol. All microbiological examinations were performed according to local standard protocols.

Upper airway specimens were obtained with nasopharyngeal or oropharyngeal swabs for the detection of the following viruses: *Adenovirus*, *Coronavirus*, *human Metapneumovirus* (HMPV), *human Rhinovirus*, *Influenza virus*, and *Respiratory Syncytial virus* (RSV). Tests for virus detection were carried out with polymerase chain reaction, nucleic acid amplification tests (reverse transcriptase polymerase chain reaction, RT-PCR), or rapid influenza diagnostic tests (RIDTs) according to local standard protocols [14]. Classification of viral types and subtypes was not performed. Based on the specificity and sensitivity of the nasopharyngeal and oropharyngeal swabs [14], no other specimens were considered valid for virus detection.

Microbiological testing for bacteria and fungi were performed according to standard local protocols on any of the following: blood, upper and lower tract respiratory cultures (e.g., sputum, pleural fluid, endotracheal aspirate, and bronchoalveolar lavage), sputum gram stain, urinary antigens for *Streptococcus pneumoniae* and *Legionella pneumophila* and serology for *Mycoplasma pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae*.

### 2.4. Study definitions and groups

The detailed definition of CAP is reported in the [Appendix A](#). A viral CAP was defined as a pneumonia case in which at least one virus was microbiologically detected in a respiratory sample. A mixed infection was defined as a CAP in which a virus was detected together with either bacteria or fungi. A coinfection, when present, was considered as a viral CAP [15–18].

The study groups included in the analysis were the following:

- The “tested for virus” group included patients who underwent at least one nasopharyngeal or oropharyngeal swab and were compared with patients not tested for viruses.
- The “swab positive” group included patients of the “tested for virus” group where a virus was microbiologically detected. It was compared with patients tested for viruses and with a negative swab.
- The “*Influenza* CAP” group included patients of the “swab positive” group where *Influenza virus* was isolated; they were compared with patients who performed a viral swab and were negative for *Influenza virus*.

### 2.5. Statistical analysis

The frequency of viral nasopharyngeal swab tests was calculated considering all the CAP patients included in the GLIMP dataset. The prevalence of viral CAP was calculated using viral isolates detected with viral nasopharyngeal swabs performed during the first 24 h of hospital admission. Categorical variables, expressed as counts

(percentages), were compared between groups using the Chi-squared or Fisher test, when appropriate. Regressions analyses were performed to compare prevalence and determine odds ratios (OR) with 95% confidence interval (CI). Logistic regression analyses were performed to assess the relationship between viral pneumonia, influenza virus pneumonia and demographics, therapeutic, epidemiological, and clinical variables. The Chi-squared test was performed to compare the prevalence between countries and continents. Statistical significance was defined as  $p$ -value  $< 0.05$ . All statistical analyses were performed with IBM SPSS, Statistics for Windows, version 21.0 (Armonk, NY: IBM Corp), and STATA 13 (College Station, TX: StataCorp LP).

### 3. Results

From 3702 CAP patients enrolled in the GLIMP study, 553 (14.9%) were tested for viruses (median age: 66 years; 57.3% males), (Table A1 in the data Appendix A and Fig. 1). A total of 157 patients out of 553 (28.4%) had at least one isolated virus (“swab positive” group). *Influenza virus* was isolated in 127/157 (80.9% of viral CAP) and formed the “*Influenza CAP*” group (Fig. 1).

#### 3.1. Frequency of viral testing

The frequency of nasal swab testing was significantly higher in Asia (18.8%) and significantly lower in Africa (1.3%) (Table 1 and Fig. 2). Spain, India, USA, and Italy were the countries with the highest viral swab testing frequency once weighted for the number of patients enrolled (Figs. 2 and 3). Netherlands, and Saudi Arabia had the highest testing frequency, whereas no viral swabs were performed in Portugal, Croatia, Serbia, Montenegro, Bulgaria, Nigeria, and Romania (Fig. 2 and Table A2 in the Appendix A). Compared with those not tested for viruses, tested patients were significantly younger and more obese, and had more often a positive smoking history. The tested group had more respiratory comorbidities, such as asthma and obstructive sleep apnea, were more frequently transplanted and vaccinated with PPSV23, had more frequently severe CAP at admission (Table 2).

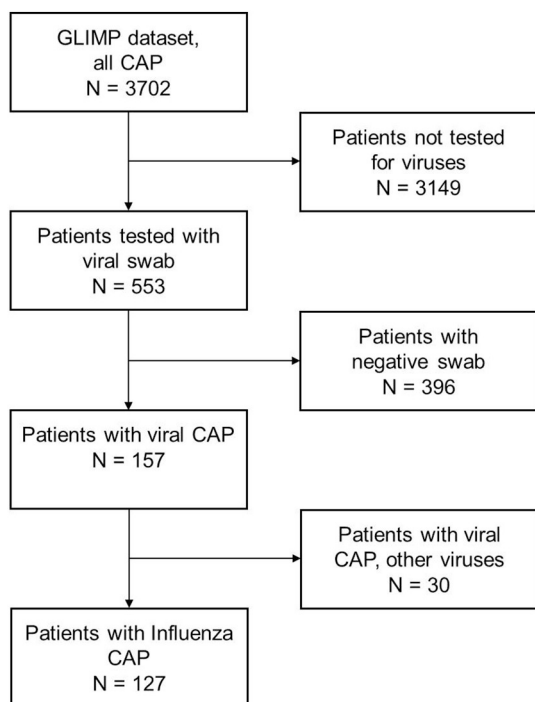


Fig. 1. Flow chart describing the study samples.

Table 1

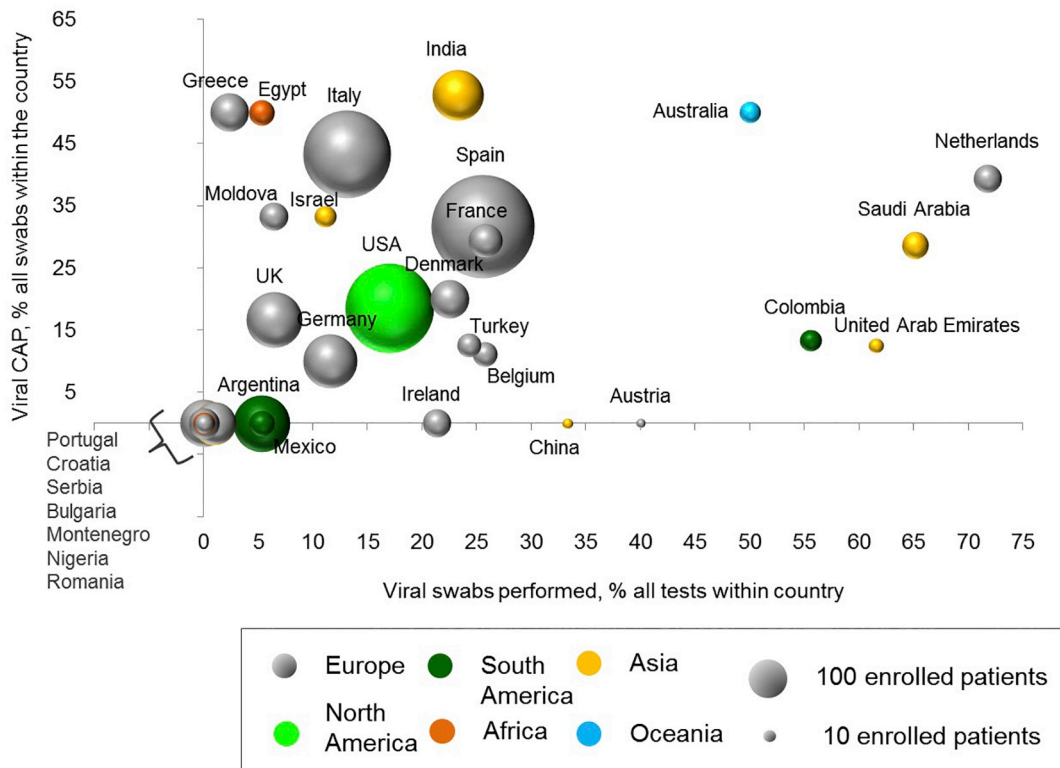
Frequency of viral testing, prevalence of viral community acquired pneumonia and isolated viruses by continent.

Continent	Within the country	Other continents	p-Value
<b>North America</b>			
Viral swabs/all tests, n/N (%)	83/529 (15.6)	470/3173 (14.8)	0.600
Positive viral swabs, n/N (%)	15/83 (18.1)	142/470 (30.2)	0.024
Influenza virus, n (%)	8 (53.3)	119 (83.8)	0.002
Adenovirus, n (%)	0 (0.0)	3 (2.1)	1.000
Coronavirus, n (%)	1 (6.7)	5 (3.5)	0.127
RSV, n (%)	1 (6.7)	8 (5.6)	0.256
Metapneumovirus, n (%)	1 (6.7)	3 (2.1)	0.107
Rhinovirus/Enterovirus, n (%)	4 (26.7)	4 (2.8)	< 0.001
<b>South America</b>			
Viral swabs performed, n/N (%)	25/218 (11.5)	528/3484 (15.2)	0.138
Positive viral swabs, n/N (%)	2/25 (8.0)	155/528 (29.4)	0.021
Influenza virus, n (%)	1 (50.0)	126 (81.3)	0.025
Adenovirus, n (%)	0 (0.0)	3 (1.9)	1.000
Coronavirus, n (%)	0 (0.0)	6 (3.9)	1.000
RSV, n (%)	1 (50.0)	8 (5.2)	0.084
Metapneumovirus, n (%)	0 (0.0)	4 (2.6)	1.000
Rhinovirus/Enterovirus, n (%)	0 (0.0)	8 (5.2)	1.000
<b>Africa</b>			
Viral swabs performed, n/N (%)	2/156 (1.3)	551/3546 (15.5)	< 0.001
Positive viral swabs, n/N (%)	1/2 (50.0)	156/551 (28.3)	0.497
Influenza virus, n (%)	1 (100.0)	126 (80.8)	0.390
Adenovirus, n (%)	0 (0.0)	3 (1.9)	1.000
Coronavirus, n (%)	0 (0.0)	6 (3.8)	1.000
RSV, n (%)	0 (0.0)	9 (5.8)	1.000
Metapneumovirus, n (%)	0 (0.0)	4 (2.6)	1.000
Rhinovirus/Enterovirus, n (%)	0 (0.0)	8 (5.1)	1.000
<b>Asia</b>			
Viral swabs performed, n/N (%)	78/415 (18.8)	475/3287 (14.5)	0.019
Positive viral swabs, n/N (%)	29/78 (37.2)	128/475 (26.9)	0.063
Influenza virus, n (%)	23 (79.3)	104 (81.3)	0.151
Adenovirus, n (%)	2 (6.9)	1 (0.8)	0.004
Coronavirus, n (%)	3 (10.3)	3 (2.3)	< 0.001
RSV, n (%)	1 (3.4)	8 (6.3)	0.242
Metapneumovirus, n (%)	0 (0.0)	4 (3.1)	1.000
Rhinovirus/Enterovirus, n (%)	0 (0.0)	8 (6.3)	1.000
<b>Europe</b>			
Viral swabs performed, n/N (%)	361/2344 (15.4)	192/1358 (14.1)	0.299
Positive viral swabs, n/N (%)	108 <sup>a</sup> /361 (29.9)	49/192 (25.5)	0.275
Influenza virus, n (%)	92 (85.2)	35 (71.4)	0.093
Adenovirus, n (%)	1 <sup>a</sup> (0.9)	2 (4.1)	0.401
Coronavirus, n (%)	2 (1.9)	4 (8.2)	0.109
RSV, n (%)	6 <sup>a</sup> (5.6)	3 (6.1)	< 0.001
Metapneumovirus, n (%)	3 (2.8)	1 (2.0)	0.008
Rhinovirus/Enterovirus, n (%)	4 (3.7)	4 (8.2)	0.008
<b>Oceania</b>			
Viral swabs performed, n/N (%)	4/40 (10.0)	549/3662 (15.0)	0.378
Positive viral swabs, n/N (%)	2/4 (50.0)	155/549 (28.2)	0.320
Influenza virus, n (%)	2 (100.0)	125 (80.6)	0.210
Adenovirus, n (%)	0 (0.0)	3 (1.9)	1.000
Coronavirus, n (%)	0 (0.0)	6 (3.9)	1.000
RSV, n (%)	0 (0.0)	9 (5.8)	1.000
Metapneumovirus, n (%)	0 (0.0)	4 (2.6)	1.000
Rhinovirus/Enterovirus, n (%)	0 (0.0)	8 (5.2)	1.000

<sup>a</sup> In Europe 110 viruses were isolated in total. In 2 cases, 2 viruses were isolated at the same time (*Influenza virus* + *Adenovirus* and *Influenza virus* + *RSV*). In the latter cases, only the first reported virus was considered as the cause of CAP, i.e. *Influenza virus* in both cases.

#### 3.2. Viral CAP prevalence and characteristics

In the swab positive group, 159 viruses were isolated, and the most prevalent were *Influenza virus* (80.9%), *RSV* (5.7%), and *Rhinovirus/Enterovirus* (5%) (Table 1). Two patients had two viruses isolated at the same time, and, therefore, the total number of patients with viral CAP was 157. Nineteen patients had a bacterial coinfection. The most



**Fig. 2.** Frequency of testing for viruses as a percentage of all tests performed in each country and prevalence of viral CAP as a percentage of all the viral swabs performed in each country. The size of each sphere indicates the number of patients with CAP enrolled in the GLIMP sample. Only countries with > 20 patients enrolled are shown, excepted for United Arab Emirates, China and Austria that had a high frequency of testing despite the lower number of patients enrolled.

frequent bacteria isolated in patients with Influenza CAP were *Staphylococcus aureus* strains (21% of all coinfections) (Table A3 in the Appendix A).

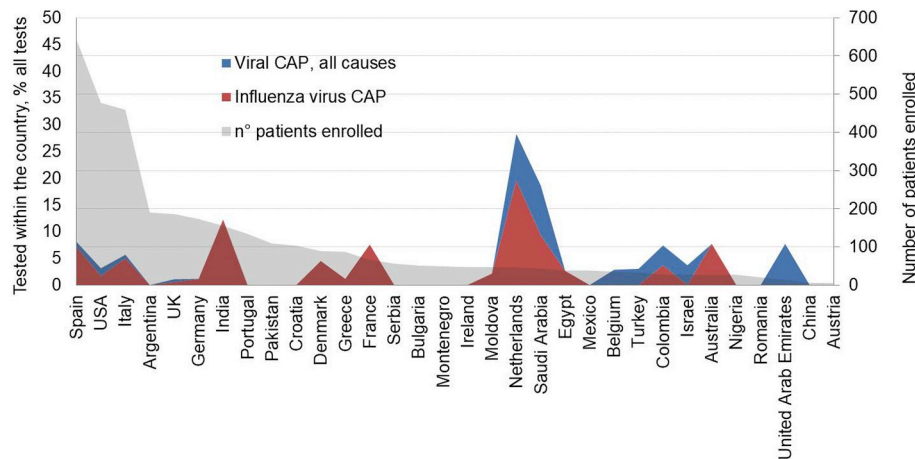
The overall prevalence of viral CAP was 28.4% of those tested. North and South America had a significantly lower prevalence compared with the other participating centers representing the continents, whereas Asian countries had the highest prevalence. Compared with other participating countries, North America had significantly lower prevalence of *Influenza virus* and the highest prevalence of *Rhinovirus/Enterovirus* (Table 1). Compared with all the other countries, India and Italy had significantly higher prevalence of viral CAP, whereas USA and Argentina had a significantly lower frequency (Table A2 in the Appendix A).

Patients with viral CAP significantly differed from the rest of the sample in terms of obesity, respiratory comorbidities, vaccination

status, and CAP severity (Table 2). Independent risk factors for viral CAP were represented by obesity (OR 1.59, 95% CI: 1.01–2.48;  $p$ -value = 0.043) and need for invasive mechanical ventilation on hospital admission (OR 1.62, 95% CI: 1.02–2.56;  $p$ -value = 0.040), (Table A4 in the Appendix A).

Focusing the analysis only on patients with influenza, the only significant risk factor associated with *Influenza* CAP was obesity. The Influenza group significantly differed from the rest of the population also in terms of inhaled corticosteroid use, vaccination status, and hospitalization during the prior year to the admission (Table 2). No independent risk factors for the occurrence of *Influenza* CAP were found.

A total of 188 (5.1%) patients with CAP were empirically treated with oseltamivir, 158 (28.6%) among all tested with nasal viral swabs, and 93 (59.2%) among those with a viral CAP (Fig. 4). Among patients



**Fig. 3.** Prevalence of influenza virus CAP (red area) in relation to all cause viral CAP (blue area). The ratio between swabs positive for influenza compared to all positive swabs by each country is reported in the left sided vertical axis. Absolute patients enrolled in the study (grey area) are reported in the right sided vertical axis. Only countries that have performed at least one viral swab are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2

Characteristics and risk factors for being tested for viruses, have a viral CAP and have an *Influenza virus* CAP.

Variables	All CAP N = 3702								
	Other tests N = 3149	Viral swabs N = 553	P-value	All viral swabs N = 553					
				Swab positive N = 157	Swab negative N = 396	p-value	Influenza positive N = 127	Influenza negative N = 427	p-value
Age, median (IQR) years	69.0 (54-80)	66.0 (51-77)	< 0.001	62.0 (47-75)	67.0 (52-78)	0.083	63.0 (48-77)	67.0 (52-78)	0.160
Male, n (%)	1,826 (58.0)	317 (57.3)	0.771	97 (61.8)	220 (55.6)	0.180	79 (62.2)	238 (55.9)	0.205
Underweight, n (%)	141/1987 (7.1)	25/342 (7.3)	0.887	3/103 (2.9)	22/239 (9.2)	0.040	3/92 (3.3)	22/250 (8.8)	0.081
Obesity, n (%)	459 (14.6)	118 (21.3)	< 0.001	44 (28.0)	74 (18.7)	0.016	36 (28.3)	82 (19.2)	0.028
Active lung cancer, n (%)	99 (3.1)	10 (1.8)	0.087	5 (3.2)	5 (1.3)	0.156	4 (3.1)	6 (1.4)	0.196
Asthma, n (%)	210 (6.7)	51 (9.2)	0.030	12 (7.6)	39 (9.8)	0.419	10 (7.9)	41 (9.6)	0.550
Bronchiectasis, n (%)	150 (4.8)	28 (5.1)	0.761	3 (1.9)	25 (6.3)	0.032	3 (2.4)	25 (5.9)	0.114
Chronic aspiration, n (%)	230 (7.3)	43 (7.8)	0.039	6 (3.8)	21 (5.3)	0.466	4 (3.1)	23 (5.4)	0.302
COPD, n (%)	795 (25.2)	27 (4.9)	0.900	40 (25.5)	101 (25.5)	0.995	32 (25.2)	109 (25.6)	0.929
FEV1 ≤ 30%, n (%)	84 (2.7)	141 (25.5)	0.763	5 (3.2)	11 (2.8)	0.782	5 (3.9)	11 (2.6)	0.424
Current/former smoker, n (%)	1,011 (32.1)	234 (42.3)	< 0.001	72 (45.9)	162 (40.9)	0.288	58 (45.7)	176 (41.3)	0.383
Interstitial lung disease, n (%)	75 (2.4)	20 (3.6)	0.090	0 (0.0)	20 (5.1)	0.002	0 (0.0)	20 (4.7)	0.013
Obstructive sleep apnoea, n (%)	96 (3.0)	34(6.1)	< 0.001	8 (5.1)	26 (6.6)	0.516	7 (5.5)	27 (6.3)	0.734
Long term oxygen therapy (LTOT), n (%)	186 (5.9)	38 (6.9)	0.380	5 (3.2)	33 (8.3)	0.039	4 (3.1)	34 (8.0)	0.059
Lung transplantation, n (%)	2 (0.1)	5 (0.9)	< 0.001	0 (0.0)	5 (1.3)	0.328	0 (0.0)	5 (1.2)	0.220
Tracheostomy, n (%)	44 (1.4)	9 (1.6)	0.674	0 (0.0)	9 (2.3)	0.067	0 (0.0)	9 (2.1)	0.099
Arrhythmia, n (%)	454 (14.4)	73 (13.2)	0.450	18 (11.5)	55 (13.9)	0.448	12 (9.4)	61 (14.3)	0.155
Coronary artery disease, n (%)	520 (16.5)	66 (11.9)	0.127	17 (10.8)	60 (15.2)	0.185	11 (8.7)	66 (15.5)	0.051
Heart failure, n (%)	423 (13.4)	62 (11.2)	0.153	11 (7.0)	51 (12.9)	0.048	9 (7.1)	53 (12.4)	0.093
Hypertension, n (%)	1,417 (45.0)	238 (43.0)	0.392	64 (40.8)	174 (43.9)	0.497	49 (38.6)	189 (44.4)	0.248
Stroke, n (%)	267 (8.5)	39 (7.1)	0.261	8 (5.1)	31 (7.8)	0.258	5 (3.9)	34 (8.0)	0.118
Inhaled corticosteroids use, n (%)	492 (15.6)	98 (17.7)	0.214	18 (11.5)	80 (20.2)	0.015	12 (9.4)	86 (20.2)	0.005
Proton Pump Inhibitor use, n (%)	851 (27.0)	177 (32.0)	0.016	48 (30.6)	129 (32.6)	0.649	35 (27.6)	142 (33.3)	0.221
Statins use, n (%)	612 (19.4)	143 (25.9)	0.001	40 (25.5)	103 (26.0)	0.897	28 (22.0)	115 (27.0)	0.264
Steroids use, n (%)	239 (7.6)	55 (9.9)	0.059	17 (10.8)	38 (9.6)	0.662	10 (7.9)	45 (10.6)	0.374
Enteric tube feeding, n (%)	41 (1.3)	11 (2.0)	0.205	0 (0.0)	11 (2.8)	0.039	0 (0.0)	11 (2.6)	0.067
Haemodialysis, n (%)	43 (1.4)	9 (1.6)	0.629	3 (1.9)	6 (1.5)	0.718	2 (1.6)	7 (1.6)	0.957
Indwelling catheter, n (%)	72 (2.3)	7 (1.3)	0.126	1 (0.6)	6 (1.5)	0.679	0 (0.0)	7 (1.6)	0.146
Active solid tumour, n (%)	250 (7.9)	37 (6.7)	0.311	15 (9.6)	22 (5.6)	0.090	11 (8.7)	26 (6.1)	0.311
AIDS, n (%)	56 (1.8)	9 (1.6)	0.803	1 (0.6)	8 (2.0)	0.457	1 (0.8)	8 (1.9)	0.394
Aplastic anaemia, n (%)	13 (0.4)	1 (0.2)	0.412	1 (0.6)	0 (0.0)	0.284	1 (0.8)	0 (0.0)	0.067
Asplenia, n (%)	9 (0.3)	3 (0.5)	0.327	2 (1.3)	1 (0.3)	0.196	1 (0.8)	2 (0.5)	0.669
Biological drug use, n (%)	28 (0.9)	9 (1.6)	0.107	3 (1.9)	6 (1.5)	0.718	2 (1.6)	7 (1.6)	0.957
Chemotherapy in the last 3months, n (%)	115 (3.7)	30 (5.4)	0.047	13 (8.3)	17 (4.3)	0.062	9 (7.1)	21 (4.9)	0.346
Haematological malignancy, n (%)	118 (3.7)	44 (8.0)	< 0.001	13 (8.3)	31 (7.8)	0.859	9 (7.1)	35 (8.2)	0.680
HIV infection, n (%)	105 (3.3)	18 (3.3)	0.923	3 (1.9)	15 (3.8)	0.425	3 (2.4)	15 (3.5)	0.518
Immunocompromised patients, n (%)	546 (17.3)	119 (21.5)	0.018	35 (22.3)	84 (21.2)	0.780	24 (18.9)	95 (23.3)	0.413
Neutropenia, n (%)	38 (1.2)	10 (1.8)	0.249	2 (1.3)	8 (2.0)	0.732	2 (1.6)	8 (1.9)	0.822
Other immunosuppressive condition, n (%)	108 (3.4)	34 (6.1)	0.002	4 (2.5)	30 (7.6)	0.030	2 (1.6)	32 (7.5)	0.015
Chronic renal failure, n (%)	343 (10.9)	57 (10.3)	0.683	16 (10.2)	41 (10.4)	0.955	13 (10.2)	44 (10.3)	0.976
Dementia, n (%)	369 (11.7)	39 (7.1)	0.001	8 (5.1)	31 (7.8)	0.258	8 (6.3)	31 (7.3)	0.706
Diabetes mellitus, n (%)	658 (20.9)	124 (22.4)	0.417	35 (22.3)	89 (22.5)	0.963	27 (21.3)	97 (22.8)	0.720
Liver disease, n (%)	115 (3.7)	25 (4.5)	0.323	5 (3.2)	20 (5.1)	0.496	5 (3.9)	20 (4.7)	0.718
Cirrhosis, n (%)	57 (1.8)	13 (2.4)	0.389	5 (3.2)	8 (2.0)	0.533	5 (3.9)	8 (1.9)	0.179
Malnutrition, n (%)	270 (8.6)	53 (9.6)	0.438	5 (3.2)	48 (12.1)	0.001	5 (3.9)	48 (11.3)	0.014
Alcoholism	242 (7.7)	52 (9.4)	0.168	14 (8.9)	38 (9.6)	0.805	12 (9.4)	40 (9.4)	0.984
Mental illness, n (%)	222 (7.0)	32 (5.8)	0.278	13 (8.3)	19 (4.8)	0.114	11 (8.7)	21 (4.9)	0.114
Prosthetic material, n (%)	98 (3.1)	18 (3.3)	0.859	3 (1.9)	15 (3.8)	0.425	3 (2.4)	15 (3.5)	0.518
Recurrent skin infections, n (%)	49 (1.6)	9 (1.6)	0.901	0 (0.0)	9 (2.3)	0.067	0 (0.0)	9 (2.1)	0.099
Bedridden, n (%)	376 (11.9)	39 (7.1)	0.001	9 (5.7)	30 (7.6)	0.445	7 (5.5)	32 (7.5)	0.440
Contact sport, n (%)	6 (0.2)	0 (0.0)	0.304	0 (0.0)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Healthcare worker, n (%)	38 (1.2)	9 (1.6)	0.415	2 (1.3)	7 (1.8)	1.000	0 (0.0)	9 (2.1)	0.099
Homeless, n (%)	31 (1.0)	4 (0.7)	0.558	0 (0.0)	4 (1.0)	0.582	0 (0.0)	4 (0.9)	0.273
Injection of illicit drugs, n (%)	30 (1.0)	12 (2.2)	0.013	2 (1.3)	10 (2.5)	0.524	1 (0.8)	11 (2.6)	0.223
Living in crowded conditions, n (%)	628 (19.9)	93 (16.8)	0.087	23 (14.6)	70 (17.7)	0.391	20 (15.7)	73 (17.1)	0.714
Nursing home resident, n (%)	261 (8.3)	41 (7.4)	0.488	7 (4.5)	34 (8.6)	0.095	6 (4.7)	35 (8.2)	0.187
Worker in livestock meat industry, n (%)	29 (0.9)	2 (0.4)	0.183	0 (0.0)	2 (0.5)	1.000	0 (0.0)	2 (0.5)	0.439
Prior mycobacterial diseases, n (%)	85 (2.7)	11 (2.0)	0.333	2 (1.3)	9 (2.3)	0.448	2 (1.6)	9 (2.1)	0.703
Prior MRSA infection/colonisation, n (%)	69 (2.2)	17 (3.1)	0.204	3 (1.9)	14 (3.5)	0.419	2 (1.6)	15 (3.5)	0.265
Prior ESBL-producing bacterial infection, n (%)	46 (1.5)	9 (1.6)	0.765	2 (1.3)	7 (1.8)	1.000	1 (0.8)	8 (1.9)	0.394
Prior Pseudomonas spp. infection, n (%)	94 (3.0)	7 (1.3)	0.022	0 (0.0)	7 (1.8)	0.200	0 (0.0)	7(1.6)	0.146
Antibiotic infusion at home in the last 12 months, n (%)	141 (4.5)	13 (2.4)	0.471	3 (1.9)	18 (4.5)	0.216	2 (1.6)	19 (4.5)	0.135

(continued on next page)

Table 2 (continued)

Variables	All CAP N = 3702								
	Other tests N = 3149	Viral swabs N = 553	P-value	All viral swabs N = 553					
				Swab positive N = 157	Swab negative N = 396	p-value	Influenza positive N = 127	Influenza negative N = 427	p-value
Emergency room admission in the last 12 months, n (%)	993 (29.6)	91 (16.5)	0.721	41 (26.1)	127 (32.1)	0.170	34 (26.8)	134 (31.5)	0.314
Hospitalisation in the last 12 months, n (%)	992 (31.5)	108 (19.5)	0.786	36 (22.9)	135 (34.1)	0.010	28 (22.0)	143 (33.6)	0.014
IV antibiotics in the last 12 months, n (%)	771 (24.5)	90 (16.3)	0.899	30 (19.1)	104 (26.3)	0.077	25 (19.7)	109 (25.6)	0.173
LRTI in the last 12 months, n (%)	891 (28.3)	103 (18.6)	0.572	35 (22.3)	115 (29.0)	0.108	33 (26.0)	117 (27.5)	0.742
Oral antibiotics in the last 12 months, n (%)	1,207 (38.3)	115 (20.8)	0.029	55 (35.0)	130 (32.8)	0.620	45 (35.4)	140 (32.9)	0.590
Influenza vaccine	868 (27.6)	153 (27.7)	0.960	30 (19.1)	123 (31.1)	0.005	23 (18.1)	130 (30.5)	0.006
PCV13	115 (3.7)	12 (2.2)	0.077	2 (1.3)	10 (2.5)	0.524	1 (0.8)	11 (2.6)	0.223
PPSV23	331 (10.5)	76 (13.7)	0.025	12 (7.6)	64 (16.2)	0.009	9 (7.1)	67 (15.7)	0.013
Severe CAP, n (%)	811 (25.8)	219 (39.6)	< 0.001	73 (46.5)	146 (36.9)	0.037	57 (44.9)	162 (38.0)	0.166
Invasive mechanical ventilation	243 (7.7)	111 (20.1)	< 0.001	43 (27.4)	68 (17.2)	0.007	33 (26.0)	78 (18.3)	0.058
Non-invasive mechanical ventilation	272 (8.6)	77 (13.9)	< 0.001	28 (17.8)	49 (12.4)	0.094	20 (15.7)	57 (13.4)	0.499

CAD = Coronary artery disease; CAP = Community-acquired pneumonia; COPD = chronic obstructive pulmonary disease; ESBL = extended-spectrum beta-lactamases; FEV1 = Forced expiratory volume in one second; HIV = Human Immunodeficiency virus; LRTI = lower respiratory tract infection; LTOT = long term oxygen therapy; MRSA = methicillin resistant *Staphylococcus aureus*; PCV13 = pneumococcal conjugate vaccine; PPSV23 = pneumococcal polysaccharide vaccine.

with a severe CAP at presentation (N = 1030, 27.8%), 105 (10.2%) patients were started on oseltamivir, while 83 (3.1%) patients without a severe CAP received empirical oseltamivir (p-value < 0.001). Differences in frequency of oseltamivir treatment among continents and countries are reported in Table A5.

#### 4. Discussion

This secondary analysis of an international, multicenter, point-prevalence study showed that patients with CAP had a low rate of viral testing, low prevalence of viral pathogens, and a geographical heterogeneity regarding the viral assessment. Immunocompromised state, prior respiratory comorbidities, and clinical severity of CAP were the variables more frequently associated with viral testing. Obesity and need for invasive mechanical ventilation were the only risk factors independently associated with the diagnosis of viral CAP. Furthermore, only one third of CAP patients with suspected viral infection who underwent viral testing were empirically treated with oseltamivir for influenza coverage.

Viral CAP is a relevant cause of morbidity and mortality worldwide

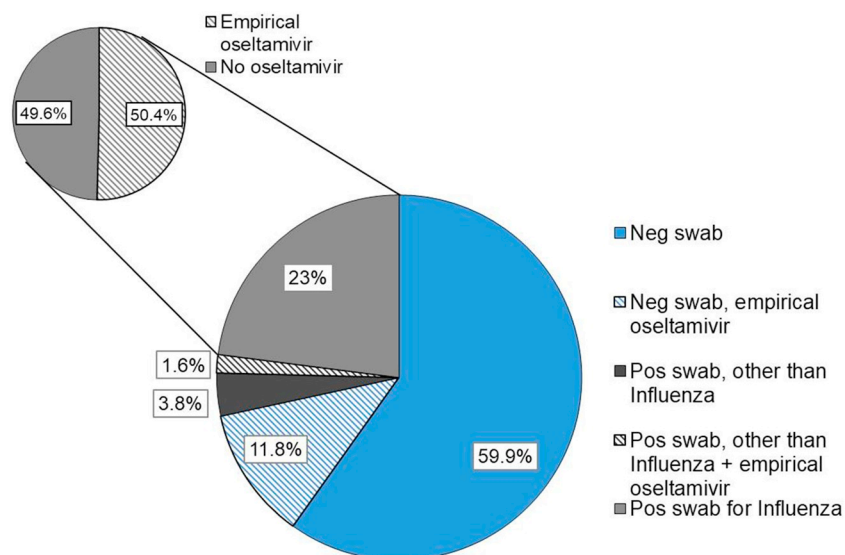


Fig. 4. Prevalence of empiric treatment with oseltamivir among patients tested with a viral swab. Blue areas represent negative swabs, while grey areas represent swabs positive for either *Influenza virus* (light grey) or all other viruses (dark grey). For every area, the striped part indicates the percentage of patients empirically covered with oseltamivir. Pos = positive; neg = negative. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

highest viral swab testing frequency once weighted for the number of patients enrolled. We can speculate that this finding is most likely related to the epidemiology of Influenza and to differences in local standard procedures.

Several factors are inconsistently considered by clinicians to make decisions regarding when to test for viral pathogens. Literature shows that patients are more likely to be tested based on severity of presentation [26], advanced age [10], presence of specific symptoms or findings on imaging studies [9], and presence of inflammatory markers [27,28]. However, patient's signs and symptoms, are not specific for viral infections, overlapping with bacterial CAP [9,29]. Our observations may be supported by previous experience during the influenza H1N1 pandemic, showing a higher prevalence and more severe presentation in younger and obese patients compared with non-severely obese patients [30,31]. This evidence may have influenced current clinical practice raising clinical suspicion on patients with these characteristics. Furthermore, previous large studies adopted restrictive selection criteria, excluding immunocompromised patients [2], transplant recipients, or patients with previous tuberculosis [9] so may lack application to real life clinical circumstances. In the current study, we found that patients were more likely to undergo testing for viruses if they had more severe CAP, had prior respiratory comorbidities, were obese, or were immunocompromised due to malignancy, transplant history, or previous chemotherapy. Our group recently studied the etiology of CAP in immunocompromised patients and found that the prevalence of *Influenza virus* was similar in immunocompromised and immunocompetent patients [32]. Based on this epidemiological background, immunocompromised patients with CAP should be tested for other viruses, avoiding the underestimation of the risk of other pathogens.

We found that obesity and need for invasive mechanical ventilation were the only two risk factors associated with increased incidence of viral CAP; however, obesity was the only independent risk factor associated with influenza CAP. This is consistent with findings of animal models which suggested a role of leptin dysregulation in more severe disease [33,34], while a higher incidence and severity of viral CAP was found in obese patients [30,31,35,36]; on the other hand, several studies showed that severity of CAP and need for ICU admittance with invasive ventilation were not associated with etiology [10,17,21,37–39]. Thus, we conclude that obesity is the only independent risk factor predisposing patients to influenza infection, although the association of obesity and viral CAP, and then, with influenza CAP, could be over-represented by the large proportion of patients with Influenza virus diagnosed in this cohort.

The ATS/IDSA guidelines strongly recommend early treatment with oseltamivir in patients with influenza [6]. A systematic review carried out in 2014 reported inconclusive data on the efficacy of influenza therapy [40], but several prospective and retrospective studies showed that treatment with oseltamivir reduced median time to symptoms' recovery and incidence of complications associated with influenza [41,42], as well as improved outcomes in patients requiring admittance to ICU [43]. Furthermore, a recent systematic review showed that early administration of neuraminidase inhibitors, such as oseltamivir, reduced mortality and pneumonia, as well as secondary transmission [44]. The present study showed that only 5.1% of patients admitted with CAP were empirically treated within 24 h and only half of patients with confirmed influenza infection were started on therapy with oseltamivir or another neuraminidase inhibitor. Moreover, severity of CAP at admittance appeared to represent a reason to start empirical coverage with oseltamivir.

Oseltamivir, which should be administered in the first 48–72 h from symptoms occurrence, seems to be the most preferred treatment for influenza despite its costs [45]. An increase in influenza vaccination coverage could reduce the burden of the disease and the prescription-related costs.

Viral CAP was recently demonstrated to be a major cause of

pneumonia in critically ill patients requiring mechanical ventilation [46], and our data confirm the need for systematic viral testing in all patient admitted with CAP. Vast global heterogeneity in treatment and low treatment rates can be explained by the lack of specific treatment protocols at many institutions and poor adherence to recommendations.

The present study has several limitations. Firstly, based on the study design across multiple institutions, investigators did have different policies for viral testing. If centers were selectively using kits only for influenza, our findings could be biased underestimating the role played by other viruses. Moreover, only upper airway specimens were tested for viruses, decreasing the diagnostic yield. Many countries had no patients tested for viruses, and in the majority of the cases this was associated with the missing prescription of oseltamivir. This disparity could be influenced by several factors, including: 1) lack of or inadequate standard operating procedures and local guidelines for viral testing, 2) poor healthcare resources, or 3) delay of referral to the hospital from symptoms initiation, making the oseltamivir administration ineffective. The study period may also have influenced the prevalence of viral testing, especially for influenza in the northern hemisphere. Furthermore, the present study did not evaluate outcomes of patients treated with oseltamivir in comparison with those who did not receive therapy. Finally, viral identification was assessed by local protocol and not per study guidelines. In fact, compared with other participating centers, North America had the highest prevalence of Rhinovirus/Enterovirus pneumonia. This is line with data from the EPIC study [2], although it may be explained by different PCR sensitivity which increased the diagnostic yield for those specific pathogens [47]. We acknowledge that the pragmatic approach of the study represents an important limitation: microbiological sampling and patients' management depend on local standard procedures and not by a study protocol. However, the results of the present study show the everyday clinical practice in different real-life settings, thus, integrating data from randomized clinical trials and describing weaknesses and strengths of the current management of CAP patients.

In conclusion, on an international scale the frequency of testing for viral infections in patients admitted for CAP is very low and there is significant variability between countries. Globally, the most common cause of viral CAP is *Influenza virus*, with high geographical heterogeneity, and obese patients were more likely to undergo testing. It will be important to develop specific guidelines and protocols on testing patients for viruses to avoid leaving this decision to the clinician's preference. Finally, empiric treatment with oseltamivir was low and only half of patients with confirmed influenza infection received treatment with oseltamivir. Further evaluation on viral testing other than influenza virus is needed, based on the poor usefulness in the clinical management.

#### Author contributions

DR, GS, SA and MIR participated in study design, analysis of data and writing of the manuscript; DR, GS, SA and MIR had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MJ, PAM, PJM, MIA, MDP, AG, ST, FB, PS, and LFR critically reviewed and approved the final manuscript.

#### Financial disclosure

DR, GS, MJ, PAM, PJM, MIA, MFDP, AG, ST, PS, SA, LFR, MIR declare no conflict of interest in regard to this article. FB reports grants and personal fees from AstraZeneca, Bayer, Chiesi, Grifols, GSK, Guidotti-Malesci, Menarini, Novartis, Pfizer, Teva, Zambon outside the submitted work.

## Conflict of interest statement

DR, GS, MJ, PAM, PJM, MIA, MFDP, AG, ST, PS, SA, LFR, MIR declare no conflict of interest in regard to this article. FB reports grants and personal fees from AstraZeneca, Bayer, Chiesi, Grifols, GSK, Guidotti-Malesci, Menarini, Novartis, Pfizer, Teva, Zambon.

## Funding

This project was not funded and relied solely on voluntary site and

investigator participation.

## Prior abstract publication

The results of the present study were partially presented the 23rd of May 2017 during the American Thoracic Society 2017 International Conference in form of an abstract and thematic poster presentation (please see: *Am J Respir Crit Care Med* 2017; 195:A6.059).

## Appendix A

### A.1. Risk factors and patients' characteristics

For every patient, the following characteristics and risk factors were included in the report form:

- a) Anthropometric variables: age, gender, height and weight (from which the variables obesity and underweight were calculated).
- b) Respiratory tract comorbidities included the presence of: active lung cancer, asthma, bronchiectasis, chronic aspiration, chronic obstructive pulmonary disease (COPD), forced expiratory volume in one second (FEV<sub>1</sub>) ≤ 30% predicted value according to gender, age and ethnicity, smoke history (current/former smoker), interstitial lung disease, obstructive sleep apnea, long term oxygen therapy, lung transplantation, tracheostomy.
- c) Cardiovascular comorbidities included the presence of: arrhythmia, coronary artery disease, heart failure, arterial hypertension, stroke.
- d) Pharmacological therapy included the chronic treatment with: inhaled corticosteroids, proton pump inhibitors, statins use, steroids use,
- e) Presence of prosthetic materials: enteric tube feeding, haemodialysis, indwelling catheter
- f) Presence of immunodepressive conditions within 6 months of hospital admission: active solid tumour, acquired immune deficiency syndrome, aplastic anaemia, asplenia, biological drug use, chemotherapy in the last 3 months, hematological malignancy, HIV infection, neutropenia,
- g) Presence of other comorbidities and risk factors: chronic renal failure, dementia, diabetes mellitus, liver disease, cirrhosis, malnutrition, alcoholism, mental illness, prosthetic material, recurrent skin infections, bedridden, contact sport, healthcare worker, homeless, injection of illicit drugs, living in crowded conditions, nursing home resident, worker in livestock meat industry, prior mycobacterial diseases,
- h) Known infection or colonisation within 12 months of hospital admission with any of the following: methicillin resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa* or extended spectrum beta-lactamase producing gram-negative bacilli (ESBL).
- i) Previous healthcare exposure including: Antibiotic infusion at home in the last 3, 6 and 12 months, emergency room admission in the last 3, 6 and 12 months, hospitalization in the last 3, 6 and 12 months, intravenous antibiotics in the last 3, 6 and 12 months, lower respiratory tract infections (LRTI) in the last 3, 6 and 12 months, oral antibiotics in the last 3, 6 and 12 months,
- j) Vaccine status: influenza vaccine in the current or past influenza season, pneumococcal conjugate vaccine (PCV), pneumococcal polysaccharide vaccine (PPSV23),
- k) Need for the following within 24 h after hospital admission: invasive and/or non-invasive mechanical ventilation, intensive care unit (ICU) or high dependency unit/semi-intensive care unit admittance, vasopressors, inotropes.

### A.2. Study definitions

#### A.2.1. CAP

Community-acquired pneumonia (CAP) was defined by evidence of new pulmonary infiltrates on thoracic imaging (chest radiograph, computed tomography scan, or ultrasound) during the first 48 h in hospital and at least one of the following criteria: new or increased cough with or without sputum production or with purulent respiratory secretions; fever (documented rectal or oral temperature ≥ 37.8 °C) or hypothermia (documented rectal or oral temperature < 36 °C); and evidence of systemic inflammation, such as abnormal white blood cell count (leukocytosis [ > 10,000 cells per mL], leucopenia [ < 4000 cells per mL], or bandaemia [ > 10%]) and increased C-reactive protein or procalcitonin concentrations above the local upper limit of normal.

#### A.2.2. Severe CAP

Severe CAP was defined by patients requiring any of the following: ICU admission, invasive or non-invasive mechanical ventilation, vasopressors/inotropes during the first 24 h of hospital admission.

#### A.2.3. Severe COPD

Severe COPD was defined having either a FEV<sub>1</sub> < 30% predicted value or being on long term oxygen therapy.

#### A.2.4. Vaccination

Influenza vaccination was considered valid if done during the prior and/or current influenza season. Previous pneumococcal vaccination included conjugate - i.e. PCV7, PCV10 or PCV13 - or PPSV23.

#### A.2.5. Immunodepression

Immunodepression was defined as the presence during at least six months prior to hospital admission of any of the following: hematological malignancy, asplenia, aplastic anaemia, neutropenia, chronic biological drugs use, chronic steroid treatment, HIV/AIDS and chemotherapy.

### A.2.6. Other immunosuppressive conditions

Any immunosuppressive state including congenital/genetic immunosuppression and immunosuppressive therapy due to hematological/solid organ transplantation other than lung (excluding hematological malignancies, asplenia, aplastic anaemia, neutropenia, chronic biological drugs, chronic steroid treatment, HIV/AIDS and chemotherapy) during.

At least six months before hospital admission.

Table A1

Anthropometric and clinical characteristics of patients that were tested with viral swabs.

Variables	Patients tested for viral Swab N = 553
<b>Demographic characteristics</b>	
Age, median (IQR) years	(47–77)
Male, n (%)	317 (57.3)
Underweight, n (%)	25/342 (7.3)
Obesity, n (%)	118 (21.3)
<b>Respiratory past medical history</b>	
Active lung cancer, n (%)	10 (1.8)
Asthma, n (%)	51 (9.2)
Bronchiectasis, n (%)	28 (5.1)
Severe COPD, either FEV1 < 30% or LTOT, n (%)	43 (7.8)
COPD, n (%)	141 (25.5)
FEV1 ≤ 30%, n (%)	16(2.9)
Chronic aspiration, n (%)	27 (4.9)
Current/former smoker, n (%)	234 (42.3)
Interstitial lung disease, n (%)	20 (3.6)
Obstructive sleep apnea, n (%)	34(6.1)
Oxygen therapy at home (LTOT), n (%)	38 (6.9)
Lung transplantation, n (%)	5 (0.9)
Tracheostomy, n (%)	9 (1.6)
<b>Cardiovascular past medical history</b>	
Arrhythmia, n (%)	73 (13.2)
Coronary artery disease, n (%)	66 (11.9)
Acute myocardial infarction, n (%)	39 (7.1)
Coronary artery disease with AMI, n (%)	77 (13.9)
Heart failure, n (%)	62 (11.2)
Hypertension, n (%)	238 (43.0)
Stroke, n (%)	39 (7.1)
<b>Chronic medications</b>	
Inhaled corticosteroids use, n (%)	98 (17.7)
Proton Pump Inhibitor use, n (%)	177 (32.0)
Statins use, n (%)	143 (25.9)
Steroids use, n (%)	55 (9.9)
<b>Chronic interventions</b>	
Enteric tube feeding, n (%)	11 (2.0)
Haemodialysis, n (%)	9 (1.6)
Indwelling catheter, n (%)	7 (1.3)
<b>Immunosuppressive conditions</b>	
Active solid tumour, n (%)	37 (6.7)
AIDS, n (%)	9 (1.6)
Aplastic anaemia, n (%)	1 (0.2)
Asplenia, n (%)	3 (0.5)
Biological drug use, n (%)	9 (1.6)
Chemotherapy in the last 3 months, n (%)	30 (5.4)
Hematological malignancy, n (%)	44 (8.0)
HIV infection, n (%)	18 (3.3)
Immunocompromised patients, n (%)	119 (21.5)
Neutropenia, n (%)	10 (1.8)
Other immunosuppressive condition, n (%)	34 (6.1)
<b>Other chronic medical conditions</b>	
Chronic renal failure, n (%)	57 (10.3)
Dementia, n (%)	39 (7.1)
Diabetes mellitus, n (%)	124 (22.4)
Liver disease, n (%)	25 (4.5)
Cirrhosis, n (%)	13 (2.4)
Malnutrition, n (%)	53 (9.6)
Alcoholism	52 (9.4)
Mental illness, n (%)	32 (5.8)
Prosthetic material, n (%)	18 (3.3)
Recurrent skin infections, n (%)	9 (1.6)
<b>Other non-medical conditions</b>	
Bedridden, n (%)	39 (7.1)
Contact sport, n (%)	0 (0.0)
Healthcare worker, n (%)	9 (1.6)

(continued on next page)

Table A1 (continued)

Variables	Patients tested for viral Swab N = 553
Homeless, n (%)	4 (0.7)
Injection of illicit drugs, n (%)	12 (2.2)
Living in crowded conditions, n (%)	93 (16.8)
Nursing home resident, n (%)	41 (7.4)
Worker in livestock meat industry, n (%)	2 (0.4)
<b>Previous infections/colonisation</b>	
Prior mycobacterial diseases, n (%)	11 (2.0)
Prior MRSA infection/colonisation, n (%)	17 (3.1)
Prior ESBL-producing bacterial infection, n (%)	9 (1.6)
Prior Pseudomonas spp. infection, n (%)	7 (1.3)
<b>Prior healthcare exposure</b>	
Antibiotic infusion at home in the last 12 months, n (%)	13 (2.4)
Emergency room admission in the last 12 months, n (%)	91 (16.5)
Hospitalization in the last 12 months, n (%)	108 (19.5)
IV antibiotics in the last 12 months, n (%)	90 (16.3)
LRTI in the last 12 months, n (%)	103 (18.6)
Oral antibiotics in the last 12 months, n (%)	115 (20.8)
Influenza vaccine	153 (27.7)
PSV13	12 (2.2)
PPV23	76 (13.7)
<b>Current pneumonia episode</b>	
Severe CAP, n (%)	219 (39.6)
Inotropes	11 (2.0)
Vasopressor	88 (15.9)
Invasive mechanical ventilation	111 (20.1)
Non-invasive mechanical ventilation	77 (13.9)
Either ICU or HDU, n (%)	195 (35.3)
ICU admission, n (%)	163 (29.5)
HDU admission, n (%)	36 (6.5)

CAP = community-acquired pneumonia; MRSA = methicillin resistant *Staphylococcus aureus*; COPD = chronic obstructive pulmonary disease; FEV1 = forced expiratory volume in one second; CAD = coronary artery disease; ESBL = extended-spectrum beta-lactamases; LRTI = lower respiratory tract infection.

Table A2

Frequency of viral swab testing and prevalence of viral CAP (positive viral swabs) by country. Countries are listed according to the number of patients enrolled.

Country	Viral swab testing (1)		Viral CAP (2)		p-Value (1)	p-Value (2)
	Within the country, n/N (%)	Other participating countries, n/N (%)	Within the country, n/N (%)	Other participating countries, n/N (%)		
Spain	164/643 (25.5)	389/3059 (12.7)	52/164 (31.7)	105/389 (27.0)	<b>0.000</b>	0.261
USA	81/477 (17.0)	472/3225 (14.6)	15/81 (18.5)	142/472 (30.1)	0.180	<b>0.033</b>
Italy	60/459 (13.1)	493/3243 (15.2)	26/60 (43.3)	131/493 (26.6)	0.231	<b>0.007</b>
Argentina	10/190 (5.3)	543/3512 (15.5)	0/10 (0.0)	157/543 (28.9)	<b>0.000</b>	<b>0.044</b>
UK	12/186 (6.5)	541/3516 (15.4)	2/12 (16.7)	155/541 (28.7)	<b>0.001</b>	0.362
Germany	20/173 (11.6)	533/3529 (15.1)	2/20 (10.0)	155/533 (29.1)	0.202	0.063
India	36/155 (23.2)	517/3547 (14.6)	19/36 (52.8)	138/517 (26.7)	<b>0.003</b>	<b>0.001</b>
Portugal	0/134 (0.0)	553/3568 (15.5)	0/0 (0.0)	157/553 (28.4)	<b>0.000</b>	1.000
Pakistan	1/109 (0.9)	552/3593 (15.4)	0/1 (0.0)	157/552 (28.4)	<b>0.000</b>	0.529
Croatia	1/103 (1.0)	552/3599 (15.3)	0/1 (0.0)	157/552 (28.4)	<b>0.000</b>	0.529
Denmark	20/89 (22.5)	533/3613 (14.8)	4/20 (20.0)	153/533 (28.7)	<b>0.044</b>	0.397
Greece	2/87 (2.3)	551/3615 (15.2)	1/2 (50.0)	156/551 (28.3)	<b>0.001</b>	0.497
France	17/66 (25.8)	536/3636 (14.7)	5/17 (29.4)	152/536 (28.4)	<b>0.013</b>	0.924
Serbia	0/56 (0.0)	553/3646 (15.2)	0/0 (0.0)	157/553 (28.4)	<b>0.002</b>	1.000
Bulgaria	0/51 (0.0)	553/3651 (15.1)	0/0 (0.0)	157/553 (28.4)	<b>0.003</b>	1.000
Montenegro	0/49 (0.0)	553/3653 (15.1)	0/0 (0.0)	157/553 (28.4)	<b>0.003</b>	1.000
Ireland	10/47 (21.3)	543/3655 (14.9)	0/10 (0.0)	157/543 (28.9)	0.220	<b>0.044</b>
Moldova	3/47 (6.4)	550/3655 (15.0)	1/3 (33.3)	156/550 (28.4)	0.098	0.849
Netherlands	33/46 (71.7)	520/3656 (14.2)	13/33 (39.4)	144/520 (27.7)	<b>0.000</b>	0.148
Saudi Arabia	28/43 (65.1)	525/3659 (14.3)	8/28 (28.6)	149/525 (28.4)	<b>0.000</b>	0.983
Egypt	2/38 (5.3)	551/3664 (15.0)	1/2 (50.0)	156/551 (28.3)	0.093	0.497
Mexico	2/38 (5.3)	551/3664 (15.0)	0/2 (0.0)	157/551 (28.5)	0.093	0.372
Belgium	9/35 (25.7)	544/3667 (14.8)	1/9 (11.1)	156/544 (28.7)	0.072	0.246
Turkey	8/33 (24.2)	545/3669 (14.9)	1/8 (12.5)	156/545 (28.6)	0.132	0.315
Colombia	15/27 (55.6)	538/3675 (14.6)	2/15 (13.3)	155/538 (28.8)	<b>0.000</b>	0.190
Israel	3/27 (11.1)	550/3675 (15.0)	1/3 (33.3)	156/550 (28.4)	0.576	0.849
Nigeria	0/27 (0.0)	553/3675 (15.0)	0/0 (0.0)	157/553 (28.4)	<b>0.029</b>	1.000
Australia	4/26 (15.4)	549/3676 (14.9)	2/4 (50.0)	155/549 (28.2)	0.949	0.336
Romania	0/20 (0.0)	553/3682 (15.0)	0/0 (0.0)	157/553 (28.4)	0.060	1.000
Lebanon	0/19 (0.0)	553/3683 (15.0)	0/0 (0.0)	157/553 (28.4)	0.067	1.000

(continued on next page)

Table A2 (continued)

Country	Viral swab testing (1)		Viral CAP (2)		p-Value (1)	p-Value (2)
	Within the country, n/N (%)	Other participating countries, n/N (%)	Within the country, n/N (%)	Other participating countries, n/N (%)		
Japan	0/17 (0.0)	553/3685 (15.0)	0/0 (0.0)	157/553 (28.4)	0.083	1.000
Nepal	0/17 (0.0)	553/3685 (15.0)	0/0 (0.0)	157/553 (28.4)	0.083	1.000
New Zealand	0/14 (0.0)	553/3688 (15.0)	0/0 (0.0)	157/553 (28.4)	0.116	1.000
Panama	0/14 (0.0)	553/3688 (15.0)	0/0 (0.0)	157/553 (28.4)	0.116	1.000
South Africa	0/13 (0.0)	553/3689 (15.0)	0/0 (0.0)	157/553 (28.4)	0.130	1.000
United Arab Emirates	8/13 (61.5)	545/3689 (14.8)	1/8 (12.5)	156/545 (28.6)	<b>0.000</b>	0.315
Zambia	0/13 (0.0)	553/3689 (15.0)	0/0 (0.0)	157/553 (28.4)	0.130	1.000
Benin	0/12 (0.0)	553/3690 (15.0)	0/0 (0.0)	157/553 (28.4)	0.146	1.000
Ghana	0/12 (0.0)	553/3690 (15.0)	0/0 (0.0)	157/553 (28.4)	0.146	1.000
Ethiopia	0/10 (0.0)	553/3692 (15.0)	0/0 (0.0)	157/553 (28.4)	0.185	1.000
Togo	0/9 (0.0)	553/3693 (15.0)	0/0 (0.0)	157/553 (28.4)	0.208	1.000
Cameroon	0/8 (0.0)	553/3694 (15.0)	0/0 (0.0)	157/553 (28.4)	0.235	1.000
Tunisia	0/7 (0.0)	553/3695 (15.0)	0/0 (0.0)	157/553 (28.4)	0.267	1.000
China	2/6 (33.3)	551/3696 (14.9)	0/2 (0.0)	157/551 (28.5)	0.206	0.372
Russia	0/6 (0.0)	553/3696 (15.0)	0/0 (0.0)	157/553 (28.4)	0.304	1.000
Austria	2/5 (40.0)	551/3697 (14.9)	0/2 (0.0)	157/551 (28.5)	0.116	0.372
Ukraine	0/5 (0.0)	553/3697 (15.0)	0/0 (0.0)	157/553 (28.4)	0.348	1.000
Iran	0/4 (0.0)	553/3698 (15.0)	0/0 (0.0)	157/553 (28.4)	0.402	1.000
Poland	0/4 (0.0)	553/3698 (15.0)	0/0 (0.0)	157/553 (28.4)	0.402	1.000
Gambia	0/4 (0.0)	553/3698 (15.0)	0/0 (0.0)	157/553 (28.4)	0.402	1.000
Bahrain	0/3 (0.0)	553/3699 (14.9)	0/0 (0.0)	157/553 (28.4)	0.468	1.000
Congo	0/3 (0.0)	553/3699 (14.9)	0/0 (0.0)	157/553 (28.4)	0.468	1.000
South Korea	0/2 (0.0)	553/3700 (14.9)	0/0 (0.0)	157/553 (28.4)	0.553	1.000
Brazil	0/1 (0.0)	553/3701 (14.9)	0/0 (0.0)	157/553 (28.4)	0.675	1.000

Statistically significant frequencies compared with other continents/countries are in bold.

Table A3

Bacterial and fungal coinfections in patients with viral CAP.

Pathogen	None	<i>S. aureus</i>	<i>S. pneumoniae</i>	<i>Aspergillus spp.</i>	<i>H. influenzae</i>	<i>E. faecalis</i>	<i>coagulase neg. Staphylococci</i>	<i>Nocardia spp.</i>	<i>Actinomycetes</i>	<i>Mixed anaerobic bacteria</i>	<i>Adenovirus</i>	<i>RSV</i>	Total
<i>Adenovirus</i>	3	/	/	/	/	/	/	/	/	/	/	/	3
<i>Corona virus</i>	6	/	/	/	/	/	/	/	/	/	/	/	6
<i>Influenza virus</i>	110	4	3	2	2	1	1	1	1	/	1	1	127
<i>Metapneumovirus</i>	4	/	/	/	/	/	/	/	/	/	/	/	4
<i>RSV</i>	7	/	1	/	/	/	/	/	/	1	/	/	9
<i>Rhinovirus/Enterovirus</i>	6	1	/	/	1	/	/	/	/	/	/	/	8

RSV = Respiratory Syncytial virus; spp. = species.

Table A4

Independent risk factors for viral CAP in multivariate logistic regression analysis among all the patients who underwent at least one viral swab and had a concomitant virus isolated.

	OR (95% IC)	p-Value
Obesity	1.59 (1.01–2.48)	0.043
LTOT	0.74 (0.26–2.16)	0.582
ICS use	0.68 (0.38–1.24)	0.207
Influenza vaccine	0.79 (0.47–1.33)	0.377
PPSV23	0.59 (0.28–1.21)	0.148
Age (categorized)	0.90 (0.61–1.35)	0.623
Bronchiectasis	0.53 (0.14–1.93)	0.334
ILD	0	0.988
Hospitalization in previous 12 months	0.81 (0.51–1.30)	0.385
Need for invasive mechanical ventilation	1.62 (1.02–2.56)	0.040

LTOT = long term oxygen therapy; ICS = inhaled corticosteroids; PPSV23 = pneumococcal polysaccharide vaccine 23-valent; ILD = interstitial lung disease; OR = odds ratio

Table A5

Frequency of oseltamivir empirical coverage by continent and by country.

Continent	Within the continent n/N (%)	Other continents n/N (%)	p-Value
North America	9/529 (1.7)	179/3173 (5.6)	< <b>0.001</b>
South America	15/218 (6.9)	13/3484 (5.0)	0.212
Africa	0/156 (0.0)	188/3546 (5.3)	<b>0.003</b>
Asia	63/415 (15.2)	125/3287 (3.8)	< <b>0.001</b>
Europe	99/2344 (4.2)	89/1358 (6.6)	<b>0.002</b>
Oceania	2/40 (5.0)	186/3662 (5.1)	0.982

Country	Within the country n/N (%)	Other participating countries n/N (%)	p-Value
Spain	46/643(7.2)	142/3059 (4.6)	<b>0.008</b>
USA	7/477 (1.5)	181/3225 (5.6)	< <b>0.001</b>
Italy	24/459 (5.2)	164/3/3243 (5.1)	0.875
Argentina	10/190 (5.3)	178/3512 (5.1)	0.905
UK	3/186 (1.6)	158/3516 (5.3)	<b>0.027</b>
Germany	0/173 (0.0)	188/3529 (5.3)	<b>0.002</b>
India	41/155 (26.5)	147/3547 (4.1)	< <b>0.001</b>
Portugal	0/134 (0.0)	188/3568 (5.3)	<b>0.006</b>
Pakistan	0/109 (0.0)	188/3593 (5.2)	<b>0.014</b>
Croatia	0/103 (0.0)	188/3599 (5.2)	<b>0.017</b>
Denmark	1/89 (1.1)	187/3613 (5.2)	0.085
Greece	11/87 (12.6)	177/3615 (4.9)	<b>0.001</b>
France	6/66 (9.1)	182/3636 (5.0)	0.134
Serbia	1/56 (1.8)	187/3646 (5.1)	0.258
Bulgaria	2/51 (3.9)	186/3651 (5.1)	0.705
Montenegro	0/49 (0.0)	188/3653 (5.1)	0.103
Ireland	0/47 (0.0)	188/3655 (5.1)	0.111
Moldova	1/47 (2.1)	187/3655 (5.1)	0.354
Netherlands	0/46 (0.0)	188/3656 (5.1)	0.114
Saudi Arabia	14/43 (32.6)	174/3659 (4.8)	< <b>0.001</b>
Egypt	0/38 (0.0)	188/3664 (5.1)	0.152
Mexico	2/38 (5.3)	186/3664 (5.1)	0.958
Belgium	1/35 (2.9)	187/3667 (5.1)	0.548
Turkey	2/33 (6.1)	186/3669 (5.1)	0.796
Colombia	5/27 (18.5)	183/3675 (5.0)	<b>0.001</b>
Israel	0/27 (0.0)	188/3675 (5.1)	0.228
Nigeria	0/27 (0.0)	188/3675 (5.1)	0.228
Australia	2/26 (7.7)	186/3676 (5.1)	0.542
Romania	0/20 (0.0)	188/3682 (5.1)	0.300
Lebanon	0/19 (0.0)	188/3683 (5.1)	0.312
Japan	0/17 (0.0)	188/3685 (5.1)	0.339
Nepal	0/17 (0.0)	188/3685 (5.1)	0.339
New Zealand	0/14 (0.0)	188/3688 (5.1)	0.386
Panama	0/14 (0.0)	188/3688 (5.1)	0.386
South Africa	0/13 (0.0)	188/3689 (5.1)	0.403
United Arab Emirates	8/13 (61.5)	180/3689 (4.9)	< <b>0.001</b>
Zambia	0/13 (0.0)	188/3689 (5.1)	0.403
Benin	0/12 (0.0)	188/3690 (5.1)	0.422
Ghana	0/12 (0.0)	188/3690 (5.1)	0.422
Ethiopia	0/10 (0.0)	188/3692 (5.1)	0.464
Togo	0/9 (0.0)	188/3693 (5.1)	0.487
Cameroon	0/8 (0.0)	188/3694 (5.1)	0.513
Tunisia	0/7 (0.0)	188/3695 (5.1)	0.540
China	0/6 (0.0)	188/3696 (5.1)	0.571
Russia	0/6 (0.0)	188/3696 (5.1)	0.571
Austria	1/5 (20.0)	187/3697 (5.1)	0.128
Ukraine	0/5 (0.0)	188/3697 (5.1)	0.605
Iran	0/4 (0.0)	188/3698 (5.1)	0.643
Poland	0/4 (0.0)	188/3698 (5.1)	0.643
Gambia	0/4 (0.0)	188/3698 (5.1)	0.643
Bahrain	0/3 (0.0)	188/3699 (5.1)	0.689
Congo	0/3 (0.0)	188/3699 (5.1)	0.689
South Korea	0/2 (0.0)	188/3700 (5.1)	0.744
Brazil	0/1 (0.0)	188/3701 (5.1)	0.817

Statistically significant frequencies compared with other continents/countries are in bold.

## References

- [1] Rudan I, Boschi-Pinto C, Biloglav Z, Mulholland K, Campbell H. Epidemiology and etiology of childhood pneumonia. *Bull World Health Organ* 2008;86(5):408–16.
- [2] Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. CDC EPIC study team. community-acquired pneumonia requiring hospitalization among U.S. Adults *N Engl J Med* 2015;373(5):415–27.
- [3] File TM. Community-acquired pneumonia. *Lancet* 2003;362(9400):1991–2001.
- [4] Jain S, Kamimoto L, Bramley AM, Schmitz AM, Benoit SR, Louie J, et al. 2009 Pandemic influenza A (H1N1) Virus hospitalizations investigation team. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June

2009. *N Engl J Med* 2009;361(20):1935–44.
- [5] Sangil A, Calbo E, Robles A, Benet S, Viladot ME, Pascual V, et al. Aetiology of community-acquired pneumonia among adults in an H1N1 pandemic year: the role of respiratory viruses. *Eur J Clin Microbiol Infect Dis* 2012;31(10):2765–72.
- [6] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious diseases society of America; American thoracic society. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(Suppl. 2). [S27–72].
- [7] Burk M, El-Kersh K, Saad M, Wiemken T, Ramirez J, Cavallazzi R. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. *Eur Respir Rev* 2016;25(140):178–88.
- [8] Cesario TC. Viruses associated with pneumonia in adults. *Clin Infect Dis* 2012;55(1):107–13.
- [9] Kim JE, Kim UJ, Kim HK, Cho SK, An JH, Kang SJ, et al. Predictors of viral pneumonia in patients with community-acquired pneumonia. *PLoS One* 2014;9(12):e114710.
- [10] Johnstone J, Majumdar SR, Fox JD, Marrie TJ. Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation. *Chest* 2008;134(6):1141–8.
- [11] Kim HJ, Choi SM, Lee J, Park YS, Lee CH, Yim JJ, et al. Respiratory virus of severe pneumonia in South Korea: prevalence and clinical implications. *PLoS One* 2018;13(6). e0198902.
- [12] Aliberti S, Reyes LF, Faverio P, Sotgiu G, Dore S, Rodriguez AH, et al. GLIMP investigators. Global initiative for metiicillin-resistant *Staphylococcus aureus* pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect Dis* 2016;16(12):1364–76.
- [13] American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171(4):388–416.
- [14] Fiore AE, Fry A, Shay D, Gubareva L, Bresee JS, Uyeki TM. Centers for Disease Control and Prevention (CDC). Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2011;60(1):1–24.
- [15] Centers for Disease Control and Prevention (CDC). Severe coinfection with seasonal influenza A (H3N2) virus and *Staphylococcus aureus*—Maryland, February–March 2012. *MMWR Morb Mortal Wkly Rep* 2012;61(16):289–91.
- [16] Martin-Loeches IJ, Schultz M, Vincent JL, Alvarez-Lerma F, Bos LD, Solé-Violán J, et al. Increased incidence of co-infection in critically ill patients with influenza. *Intensive Care Med* 2017;43(1):48–58.
- [17] Martín-Loeches I, Sanchez-Corral A, Diaz E, Granada RM, Zaragoza R, Villavicencio C. Community-acquired respiratory coinfection in critically ill patients with pandemic 2009 influenza A(H1N1) virus. *Chest* 2011;139(3):555–62.
- [18] Morris DE, Cleary DW, Clarke SC. Secondary bacterial infections associated with influenza pandemics. *Front Microbiol* 2017;8:1041.
- [19] Nicholson KG, Wood JM, Zambon M. Influenza. *Lancet* 2003;362(9397):1733–45.
- [20] Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials. *Lancet* 2015;385(9979):1729–37.
- [21] Farida H, Gasem MH, Suryanto A, Keuter M, Zulkarnain N, Satoto B, et al. Viruses and Gram-negative bacilli dominate the etiology of community-acquired pneumonia in Indonesia, a cohort study. *Int J Infect Dis* 2015;38:101–7.
- [22] Luchsinger V, Ruiz M, Zunino E, Martínez MA, Machado C, Piedra PA, et al. Community-acquired pneumonia in Chile: the clinical relevance in the detection of viruses and atypical bacteria. *Thorax* 2013;68(11):1000–6.
- [23] Holter JC, Müller F, Bjørang O, Samdal HH, Marthinsen JB, Jenum PA, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. *BMC Infect Dis* 2015;15:64.
- [24] Alimi Y, Lim WS, Lansbury L, Leonardi-Bee J, Nguyen-Van-Tam JS. Systematic review of respiratory viral pathogens identified in adults with community-acquired pneumonia in Europe. *J Clin Virol* 2017;95:26–35.
- [25] Garg S, Jain S, Dawood FS, Jhung M, Pérez A, D’Mello T. Pneumonia among adults hospitalized with laboratory-confirmed seasonal influenza virus infection—United States, 2005–2008. *BMC Infect Dis* 2015;15:369.
- [26] Marcos MA, Esperatti M, Torres A. Viral pneumonia. *Curr Opin Infect Dis* 2009;22(2):143–7.
- [27] Angeles Marcos M, Camps M, Pumarola T, Antonio Martinez J, Martinez E, Mensa J, et al. The role of viruses in the aetiology of community-acquired pneumonia in adults. *Antivir Ther* 2006;11(3):351–9.
- [28] Jennings LC, Anderson TP, Beynon KA, Chua A, Laing RT, Werno AM, et al. Incidence and characteristics of viral community-acquired pneumonia in adults. *Thorax* 2008;63(1):42–8.
- [29] Ruuskanen O, Lahti E, Jennings LC, Murdoch DR. Viral pneumonia. *Lancet* 2011;377(9773):1264–75.
- [30] Fezeu L, Julia C, Henegar A, Bitu J, Hu FB, Grobbee DE, et al. Obesity is associated with higher risk of intensive care unit admission and death in influenza A (H1N1) patients: a systematic review and meta-analysis. *Obes Rev* 2011;12(8):653–9.
- [31] Mertz D, Kim TH, Johnstone J, Lam PP, Science M, Kuster SP, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. *BMJ* 2013;347:f5061.
- [32] Di Pasquale MF, Sotgiu G, Gramegna A, Radovanovic D, Terraneo S, Reyes LF, et al. Prevalence and etiology of community-acquired pneumonia in immunocompromised patients. *Clin Infect Dis* 2018. [In press].
- [33] Zhang AJ, To KK, Li C, Lau CC, Poon VK, Chan CC, et al. Leptin mediates the pathogenesis of severe 2009 pandemic influenza A(H1N1) infection associated with cytokine dysregulation in mice with diet-induced obesity. *J Infect Dis* 2013;207(8):1270–80.
- [34] Radigan KA, Morales-Nebreda L, Soberanes S, Nicholson T, Nigdelioglu R, Cho T, et al. Impaired clearance of influenza A virus in obese, leptin receptor deficient mice is independent of leptin signaling in the lung epithelium and macrophages. *PLoS One* 2014;9(9):e108138.
- [35] Fisher-Hoch SP, Mathews CE, McCormick JB. Obesity, diabetes and pneumonia: the menacing interface of non-communicable and infectious diseases. *Trop Med Int Health* 2013;18(12):1510–9.
- [36] Kok J, Blyth CC, Foo H, Bailey MJ, Pilcher DV, Webb SA, et al. Viral pneumonitis is increased in obese patients during the first wave of pandemic A (H1N1) 2009 virus. *PLoS One* 2013;8(2):e55631.
- [37] Huijskens EG, Koopmans M, Palmén FM, van Erkel AJ, Mulder PG, Rossen JW. The value of signs and symptoms in differentiating between bacterial, viral and mixed aetiology in patients with community-acquired pneumonia. *J Med Microbiol* 2014;63(Pt 3):441–52.
- [38] Choi SH, Hong SB, Ko GB, Lee Y, Park HJ, Park SY, et al. Viral infection in patients with severe pneumonia requiring intensive care unit admission. *Am J Respir Crit Care Med* 2012;186(4):325–32.
- [39] Tessmer A, Welte T, Schmidt-Ott R, Eberle S, Barten G, Suttorp N, et al. CAPNETZ study group. Influenza vaccination is associated with reduced severity of community-acquired pneumonia. *Eur Respir J* 2011;38(1):147–53.
- [40] Jefferson T, Jones MA, Doshi P, Del Mar CB, Hama R, Thompson MJ, et al. Neuraminidase inhibitors for preventing and treating influenza in healthy adults and children. *Cochrane Database Syst Rev* 2014;4:CD008965.
- [41] Shun-Shin M, Thompson M, Heneghan C, Perera R, Harnden A, Mant D. Neuraminidase inhibitors for treatment and prophylaxis of influenza in children: systematic review and meta-analysis of randomised controlled trials. *BMJ* 2009;339:b3172.
- [42] Yu H, Liao Q, Yuan Y, Zhou L, Xiang N, Huai Y, et al. Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China. *BMJ* 2010;341:c4779.
- [43] Heru R, Chroboczek T, Madelaine T, Casalegno JS, Lina B, Cour M, et al. On behalf the “Flu in Lyon ICUs” Study Group. Early oseltamivir therapy improves the outcome in critically ill patients with influenza: a propensity analysis. *Intensive Care Med* 2018;44(2):257–60.
- [44] Boikos C, Caya C, Doll MK, Kraicer-Melamed H, Dolph M, Delisle G, et al. Safety and effectiveness of neuraminidase inhibitors in situations of pandemic and/or novel/variant influenza: a systematic review of the literature, 2009–15. *J Antimicrob Chemother* 2017;72(6):1556–73.
- [45] Rothberg MB, Bellantonio S, Rose DN. Management of influenza in adults older than 65 years of age: cost-effectiveness of rapid testing and antiviral therapy. *Ann Intern Med* 2003;139(5 Pt 1):321–9.
- [46] Shorr AF, Fisher K, Micek ST, Kollef MH. The burden of viruses in pneumonia associated with acute respiratory failure: an underappreciated issue. *Chest* 2018;154(1):84–90.
- [47] Ruuskanen O, Järvinen A. What is the real role of respiratory viruses in severe community-acquired pneumonia? *Clin Infect Dis* 2014;59(1):71–3.