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

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Abbreviation list: CAD, coronary artery disease; CAP, community-acquired pneumonia; CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESBL, extended-spectrum beta-lactamases; FEV_1, 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

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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:

a) 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.
b) 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.
c) 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 Crop), 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).

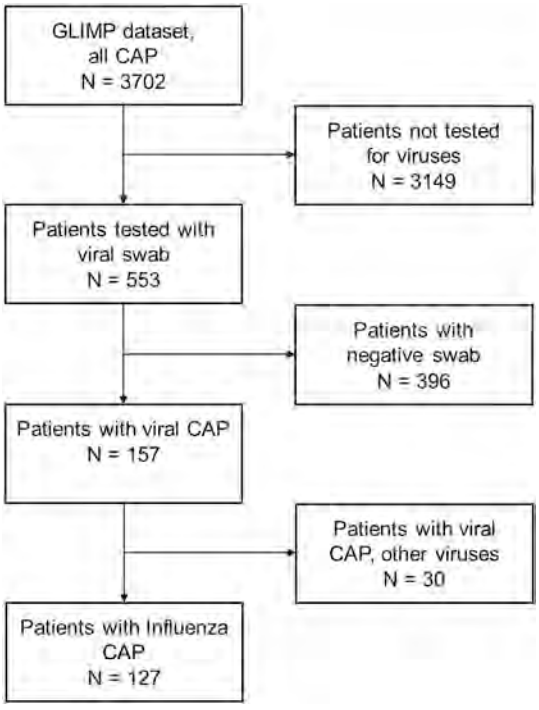

Fig. 1. Flow chart describing the study samples.

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
North America			
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
South America			
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
Africa			
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
Asia			
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
Europe			
Viral swabs performed, n/N (%)	361/2344 (15.4)	192/1358 (14.1)	0.299
Positive viral swabs, n/N (%)	108[a]/361 (29.9)	49/192 (25.5)	0.275
Influenza virus, n (%)	92 (85.2)	35 (71.4)	0.093
Adenovirus, n (%)	1[a] (0.9)	2 (4.1)	0.401
Coronavirus, n (%)	2 (1.9)	4 (8.2)	0.109
RSV, n (%)	6[a] (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
Oceania			
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

[a] 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

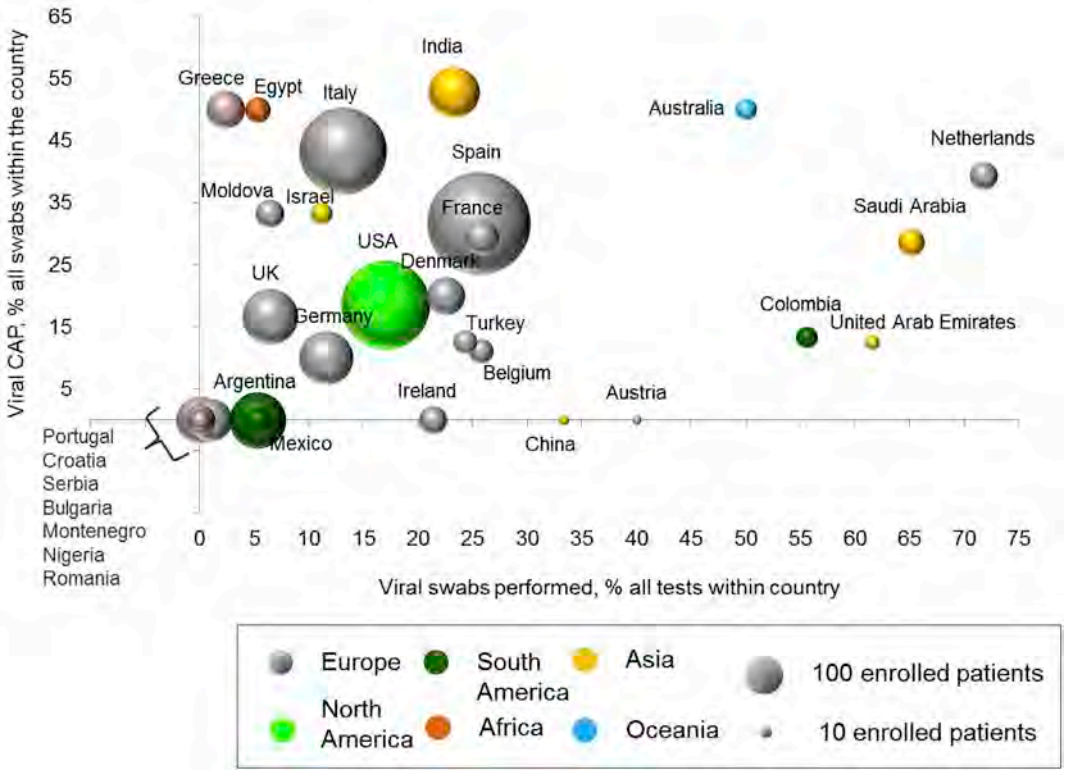

Fig. 2. Frequency of testing for viruses as a percentage of all tests performed in each country and prevalence of viral CAP as a percentage of all the viral swabs performed in each country. The size of each sphere indicates the number of patients with CAP enrolled in the GLIMP sample. Only countries 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

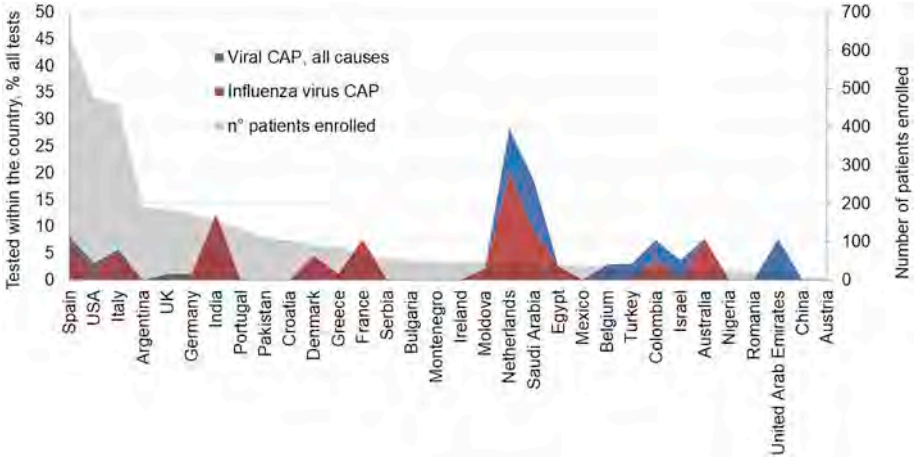

Fig. 3. Prevalence of influenza virus CAP (red area) in relation to all cause viral CAP (blue area). The ratio between swabs positive for influenza compared to all positive swabs by each country is reported in the left sided vertical axis. Absolute patients enrolled in the study (grey area) are reported 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.

	All CAP N = 3702								
Variables	**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 12months, 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 and its prevalence is likely underestimated due to low rates of and inconsistent testing for viruses in general practice [19]. Presently, there are no specific guidelines available for when to test for viruses in hospitalized patients with CAP [6]. However, early diagnosis and treatment of viral CAP caused by *Influenza virus* is known to have notable clinical implications [20]. In this regard, several studies showed that prevalence of viral CAP varies from 15% to 35% [2,7,9,10,21–23]; however, these studies limit data analyses to only tested patients or all the patients enrolled were systematically tested for viral infection [2,7,9,10,21–23]. In the present study, which was an attempt to assess real-life scenarios, < 15% of patients were tested for viruses with a prevalence of viral CAP of 28.4% among those tested, consistent with the recent results of a systematic review [7]. In line with previous reports [7,24,25], our results showed that *Influenza* virus was the most prevalent pathogen isolated, accounting for 80.9% of positive swabs, and this was consistent with the majority of the participating countries. Nevertheless, a remarkable difference in testing frequency occurred between the Northern and the Southern hemisphere. In fact, although the study period included the influenza season in both boreal and austral areas, Spain, India, USA, and Italy were the countries with the

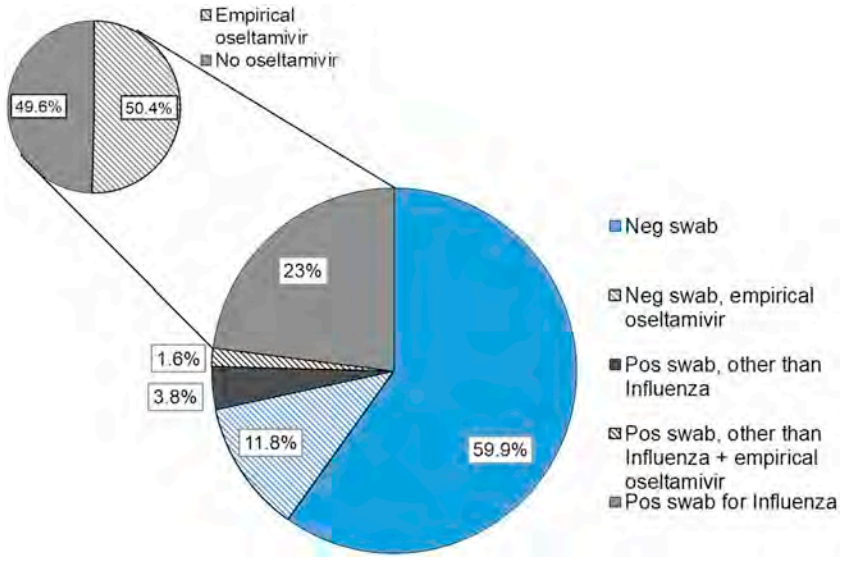

Fig. 4. Prevalence of empiric treatment with oseltamivir among patients tested with a viral swab. Blue areas represent negative swabs, while grey areas represent swabs positive for either *Influenza virus* (light grey) or all other viruses (dark grey). For every area, the striped part indicates the percentage 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.

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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_1) ≤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_1 < 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
Demographic characteristics	
Age, median (IQR) years	(47–77)
Male, n (%)	317 (57.3)
Underweight, n (%)	25/342 (7.3)
Obesity, n (%)	118 (21.3)
Respiratory past medical history	
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)
Cardiovascular past medical history	
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)
Chronic medications	
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)
Chronic interventions	
Enteric tube feeding, n (%)	11 (2.0)
Haemodialysis, n (%)	9 (1.6)
Indwelling catheter, n (%)	7 (1.3)
Immunosuppressive conditions	
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)
Other chronic medical conditions	
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)
Other non-medical conditions	
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)
Previous infections/colonisation	
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)
Prior healthcare exposure	
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)
Current pneumonia episode	
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)	**0.000**	0.261
USA	81/477 (17.0)	472/3225 (14.6)	15/81 (18.5)	142/472 (30.1)	0.180	**0.033**
Italy	60/459 (13.1)	493/3243 (15.2)	26/60 (43.3)	131/493 (26.6)	0.231	**0.007**
Argentina	10/190 (5.3)	543/3512 (15.5)	0/10 (0.0)	157/543 (28.9)	**0.000**	**0.044**
UK	12/186 (6.5)	541/3516 (15.4)	2/12 (16.7)	155/541 (28.7)	**0.001**	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)	**0.003**	**0.001**
Portugal	0/134 (0.0)	553/3568 (15.5)	0/0 (0.0)	157/553 (28.4)	**0.000**	1.000
Pakistan	1/109 (0.9)	552/3593 (15.4)	0/1 (0.0)	157/552 (28.4)	**0.000**	0.529
Croatia	1/103 (1.0)	552/3599 (15.3)	0/1 (0.0)	157/552 (28.4)	**0.000**	0.529
Denmark	20/89 (22.5)	533/3613 (14.8)	4/20 (20.0)	153/533 (28.7)	**0.044**	0.397
Greece	2/87 (2.3)	551/3615 (15.2)	1/2 (50.0)	156/551 (28.3)	**0.001**	0.497
France	17/66 (25.8)	536/3636 (14.7)	5/17 (29.4)	152/536 (28.4)	**0.013**	0.924
Serbia	0/56 (0.0)	553/3646 (15.2)	0/0 (0.0)	157/553 (28.4)	**0.002**	1.000
Bulgaria	0/51 (0.0)	553/3651 (15.1)	0/0 (0.0)	157/553 (28.4)	**0.003**	1.000
Montenegro	0/49 (0.0)	553/3653 (15.1)	0/0 (0.0)	157/553 (28.4)	**0.003**	1.000
Ireland	10/47 (21.3)	543/3655 (14.9)	0/10 (0.0)	157/543 (28.9)	0.220	**0.044**
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)	**0.000**	0.148
Saudi Arabia	28/43 (65.1)	525/3659 (14.3)	8/28 (28.6)	149/525 (28.4)	**0.000**	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)	**0.000**	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)	**0.029**	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)	**0.000**	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	*S. aureus*	*S. pneumoniae*	*Aspergillus spp.*	*H. influenzae*	*E. faecalis*	*coagulase neg. Staphilococci*	*Nocardia spp.*	*Actinomices*	*Mixed anaerobic bacteria*	*Adenovirus*	*RSV*	*Total*
Adenovirus	3	/	/	/	/	/	/	/	/	/	/	/	3
Corona virus	6	/	/	/	/	/	/	/	/	/	/	/	6
Influenza virus	110	4	3	2	2	1	1	1	1	/	1	1	127
Metapneumovirus	4	/	/	/	/	/	/	/	/	/	/	/	4
RSV	7	/	1	/	/	/	/	/	/	1	/	/	9
Rhinovirus/Enterovirus	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)	< **0.001**
South America	15/218 (6.9)	13/3484 (5.0)	0.212
Africa	0/156 (0.0)	188/3546 (5.3)	**0.003**
Asia	63/415 (15.2)	125/3287 (3.8)	< **0.001**
Europe	99/2344 (4.2)	89/1358 (6.6)	**0.002**
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)	**0.008**
USA	7/477 (1.5)	181/3225 (5.6)	< **0.001**
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)	**0.027**
Germany	0/173 (0.0)	188/3529 (5.3)	**0.002**
India	41/155 (26.5)	147/3547 (4.1)	< **0.001**
Portugal	0/134 (0.0)	188/3568 (5.3)	**0.006**
Pakistan	0/109 (0.0)	188/3593 (5.2)	**0.014**
Croatia	0/103 (0.0)	188/3599 (5.2)	**0.017**
Denmark	1/89 (1.1)	187/3613 (5.2)	0.085
Greece	11/87 (12.6)	177/3615 (4.9)	**0.001**
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)	< **0.001**
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)	**0.001**
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)	< **0.001**
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.

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