




# Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalised patients

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**ABSTRACT** *Pseudomonas aeruginosa* is a challenging bacterium to treat due to its intrinsic resistance to the antibiotics used most frequently in patients with community-acquired pneumonia (CAP). Data about the global burden and risk factors associated with *P. aeruginosa*-CAP are limited. We assessed the multinational burden and specific risk factors associated with *P. aeruginosa*-CAP.

We enrolled 3193 patients in 54 countries with confirmed diagnosis of CAP who underwent microbiological testing at admission. Prevalence was calculated according to the identification of *P. aeruginosa*. Logistic regression analysis was used to identify risk factors for antibiotic-susceptible and antibiotic-resistant *P. aeruginosa*-CAP.

The prevalence of *P. aeruginosa* and antibiotic-resistant *P. aeruginosa*-CAP was 4.2% and 2.0%, respectively. The rate of *P. aeruginosa* CAP in patients with prior infection/colonisation due to *P. aeruginosa* and at least one of the three independently associated chronic lung diseases (*i.e.* tracheostomy, bronchiectasis and/or very severe chronic obstructive pulmonary disease) was 67%. In contrast, the rate of *P. aeruginosa*-CAP was 2% in patients without prior *P. aeruginosa* infection/colonisation and none of the selected chronic lung diseases.

The multinational prevalence of *P. aeruginosa*-CAP is low. The risk factors identified in this study may guide healthcare professionals in deciding empirical antibiotic coverage for CAP patients.

## Introduction

Community acquired pneumonia (CAP) is a leading infectious cause of morbidity and mortality worldwide [1, 2]. 5–6 billion people are diagnosed with CAP and >3.5 million people die annually secondary to CAP [1, 3]. Several viruses and bacteria cause CAP [4], but *Streptococcus pneumoniae* remains the most frequently identified bacterial pathogen in adults [5]. During the past few decades, the aetiology of CAP has been changing: antibiotic-resistant bacteria that were thought to be important only in hospital settings are now becoming more prevalent in community settings [6–8]. The evolution of this new pathogen ecology is threatening our capacity to treat patients with CAP [9–11].

*Pseudomonas aeruginosa*, a Gram-negative bacterium, intrinsically resistant to several groups of antibiotics, such as  $\beta$ -lactams [12], has been reported frequently in CAP patients with specific healthcare associated risk factors, such as residence in a nursing home and hospitalisation during the past 90 days (*i.e.* healthcare-associated pneumonia (HCAP)) [13–15]. Moreover, severe illnesses and poor clinical outcomes have been linked to *P. aeruginosa* infection in patients with CAP [15–17]. During recent years, circulating strains of *P. aeruginosa* have tended to have higher resistance patterns to antipseudomonal antibiotics, leading to infections that are challenging to treat [6].

The prevalence of CAP due to *P. aeruginosa* varies significantly between different patient groups and specific risk factors for *P. aeruginosa*-CAP are controversial [18, 19]. Currently available data about the prevalence of *P. aeruginosa*-CAP and its resistance patterns are limited to single-centre studies [15, 20] and studies with several methodological limitations [15, 21–23]. In a meta-analysis, CHALMERS *et al.* [24] reported data from 22 studies a prevalence ranging from 0% to 23% in different CAP populations and a pool prevalence of 8.6% for *P. aeruginosa* in patients with multidrug-resistant (MDR) risk factors and 4% in patients without risk factors. All were single-centre/-region and the majority were rated as having poor methodological status [24]. As a result, the true prevalence of *P. aeruginosa*-CAP globally is unknown. Currently, the risk factors associated with *P. aeruginosa* infection recognised by Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for HCAP differ from those published in the CAP guidelines [13, 25]. Furthermore, the global prevalence of MDR *P. aeruginosa* in CAP patients is unknown. Therefore, to close the gap regarding the global prevalence and the risk factors associated with *P. aeruginosa*, we designed a multinational, multicentre, worldwide study to determine the point prevalence of *P. aeruginosa*, its antibiotic resistance patterns and the associated risk factors in hospitalised patients with CAP.

## Materials and methods

### Study design

This is a multicentre, point-prevalence study of hospitalised patients with CAP in 222 hospitals in 54 countries. The coordinating institution for this project was the University of Texas Health San Antonio (UT Health) (San Antonio, TX, USA). The UT Health institutional review board approved the project to collect data and serve as a coordinating institution for the study (#HSC20150184E). Study sites had to comply with local and national research regulations to participate in the study. Electronic invitations to participate were sent to members of various medical professional societies representing physicians specialising in infectious diseases, pulmonary, critical care and internal medicine. Additionally, first authors of previously published studies of MDR pathogens in CAP were sent individual invitations. This project received no funding. Subjects were enrolled on four randomly selected days in March, April, May and June 2015. Each site investigator selected the study days to participate in compliance with the IRB stipulations, and avoid potential patient de-identification [26]. Due to the observational nature of the study, patient consent was not required.

### Study subjects

#### Inclusion criteria

Patients aged  $\geq 18$  years hospitalised with CAP were eligible for the study. CAP had to be diagnosed per the current IDSA/ATS guidelines [13]: presence of new pulmonary infiltrates on thoracic imaging (chest radiograph, computed chest tomography or lung ultrasound) during the initial 48 h of hospitalisation and one or more of the following conditions: 1) novel or increased cough with or without sputum production and/or purulent respiratory secretions; 2) fever (oral or rectal temperature  $\geq 37.8^\circ\text{C}$ ) or hypothermia (oral or rectal temperature  $< 36^\circ\text{C}$ ); 3) signs of systemic inflammation (abnormal white blood cell count (leukocytosis  $> 10\,000\text{ cells}\cdot\text{cm}^{-3}$ , bandemia  $> 10\%$ , leukopenia  $< 4000\text{ cells}\cdot\text{cm}^{-3}$ ), procalcitonin levels above the local upper limit of normal or increased C-reactive protein) [26].

#### Exclusion criteria

Patients were excluded from participating in the study if they had hospital-acquired pneumonia (HAP) or ventilator associated pneumonia (VAP) [25]. In addition, patients without microbiological testing from

either blood, lower respiratory tract cultures or sputum collected within 24 h of hospital admission were excluded.

#### **Data collection**

Data was collected and managed using REDCap™ (Research Electronic Data Capture), an electronic data capture tool hosted on the UT Health San Antonio server. REDCap™ is a protected web-based application designed to collect research data [27]. Confirmation of microbiological results and all electronic data entry had to be completed within 7 days of study enrolment.

#### **Microbiological analysis**

Diagnostic testing, such as blood cultures and respiratory collection, and clinical care decisions were decided by attending physicians, not per study protocol [26]. Local microbiological testing protocols were used to process blood and sputum samples collected within the first 24 h of hospitalisation. If available, data on pleural fluid, tracheobronchial aspirate and bronchoalveolar lavage fluid were collected. Local testing executed by each hospital included respiratory and blood cultures, urinary antigen and drug susceptibility testing. Local quality control protocols for minimum inhibitory concentration breakpoints and Clinical and Laboratory Standards Institute (CLSI) or the European Committee on Antimicrobial Susceptibility Testing (EUCAST) standards were followed according to local regulations and protocols [28, 29].

#### **Study definitions**

Patients that required invasive respiratory and/or vasopressor support (IRVS) during the initial 24 h of hospitalisation were categorised as IRVS<sup>+</sup> [30]. *P. aeruginosa*-CAP was defined as any patient with a confirmed diagnosis of CAP in whom *P. aeruginosa* was isolated in any respiratory fluid, including pleural effusion, sputum and/or bronchoalveolar lavage and/or in the blood. Drug-resistant *P. aeruginosa* was defined when the isolated pathogen was resistant to at least one antibiotic and MDR *P. aeruginosa* was defined by resistance to at least three of the evaluated antibiotics. Antibiotic resistance to the following antipseudomonal antibiotics were evaluated: piperacillin/tazobactam, cefepime, ceftazidime, amikacin, gentamicin, tobramycin, levofloxacin, ciprofloxacin, imipenem, meropenem, doripenem, colistin and polymyxin B.

Prior *P. aeruginosa* infection/colonisation was defined as confirmed infection/colonisation within the past year before the hospitalisation, documented by the patient or available patient records. Chronic obstructive pulmonary disease (COPD) was defined according to forced expiratory volume in 1 s (FEV<sub>1</sub>)/forced vital capacity ratio <0.7 and a compatible clinical history (including smoking history if relevant). Very severe COPD was defined as patients with COPD with evidence of very severe obstruction, determined by FEV<sub>1</sub> <30% prior to hospital admission (a complete study dictionary can be found in the online supplementary material). Site investigators were given these definitions in the study protocol manual and study dictionary prior to starting data collection [26].

#### **Statistical analysis**

The prevalence of *P. aeruginosa* as microbiological aetiology of CAP (*i.e.* *P. aeruginosa*-CAP) was calculated based on the counts of *P. aeruginosa* isolates divided by the study cohort (*i.e.* CAP patients with completed microbiological test) and is expressed as a percentage. Chi-squared tests were used to compare categorical variables, which were expressed as n (%). Continuous variables are presented as median (interquartile range (IQR)) and the nonparametric Mann–Whitney U-test was used to compare them. To assess the relationship between CAP due to *P. aeruginosa* and 67 demographic, clinical, epidemiological and treatment variables, a stepwise logistic regression model was executed. A p-value<0.05 was defined as statistically significant. Tableau Desktop, Professional for Mac (Seattle, WA, USA), was used to generate prevalence maps. All statistical analyses were performed with IBM SPSS, Statistics for Mac (version 22.0; IBM, Armonk, NY, USA).

## **Results**

A total of 3193 patients were recruited during four study days from 222 hospitals in 54 countries (n=1877 (58.8%) male, median (IQR) age 68 (54–80) years). Demographics, risk factors, comorbidities, severity of illness and chronic treatments are reported in table 1. Among the six continents, most patients were recruited from Europe (n=1941, 60.8%), followed by North America (n=484, 15.2%), Asia (n=405, 12.7%), South America (n=203, 6.4%), Africa (n=128, 4.0%) and Oceania (n=32, 1.0%). Microbiological cultures were obtained from blood (n=2211, 69.2%), sputum (n=1630, 51.0%) and bronchoalveolar lavage (n=311, 9.7%). At least one pathogen was identified in 1173 patients (36.7%) (online supplementary figure E1). Table 2 and online supplementary table E1 display the prevalence of *P. aeruginosa*-CAP and antibiotic-resistant *P. aeruginosa*-CAP per continent and country.

TABLE 1 Characteristics of patients with *Pseudomonas aeruginosa* community-acquired pneumonia (CAP) versus non-*P. aeruginosa*-CAP.

	CAP	<i>P. aeruginosa</i> -CAP	Non- <i>P. aeruginosa</i> -CAP	p-value
<b>Subjects</b>	3193	133	3060	
<b>Demographic characteristics</b>				
Age years	68 [54–80]	64.36 [52.5–78.5]	65.01 [54–80]	0.748
Male	1877 (58.8)	79 (59.4)	1798 (58.8)	0.883
Underweight n/N (%)	150/2055 (7.3)	9/89 (10.1)	141/1966 (7.2)	0.297
Obese	510 (16)	17 (12.8)	493 (16.1)	0.305
<b>Respiratory past medical history</b>				
Active lung cancer	92 (2.9)	5 (3.8)	87 (2.8)	0.536
Asthma	234 (7.3)	8 (6)	226 (7.4)	0.553
Bronchiectasis	168 (5.3)	31 (23.3)	137 (4.5)	<0.001
Chronic aspiration	218 (6.8)	15 (11.3)	203 (6.6)	0.038
COPD	834 (26.1)	57 (42.9)	777 (25.4)	<0.001
Very severe COPD (FEV <sub>1</sub> ≤30%)	90 (2.8)	16 (12.0)	74 (2.4)	<0.001
Current/former smoker	1114 (34.9)	46 (34.6)	1068 (34.9)	0.940
Interstitial lung disease	91 (2.8)	6 (4.5)	85 (2.8)	0.240
Obstructive sleep apnoea	123 (3.9)	6 (4.5)	117 (3.8)	0.687
Oxygen therapy at home	208 (6.5)	26 (19.5)	182 (5.9)	<0.001
Lung transplantation	7 (0.2)	1 (0.8)	6 (0.2)	0.180
Tracheostomy	50 (1.6)	15 (11.3)	35 (1.1)	<0.001
<b>Cardiovascular past medical history</b>				
Arrhythmia	455 (14.2)	20 (15)	435 (14.2)	0.791
Coronary artery disease	526 (16.5)	33 (24.8)	493 (16.1)	0.008
Heart failure	418 (13.1)	25 (18.8)	393 (12.8)	0.046
Hypertension	1444 (45.2)	62 (46.6)	1382 (45.2)	0.742
Stroke	250 (7.8)	13 (5.2)	237 (7.7)	0.394
<b>Chronic medication</b>				
Inhaled corticosteroids	544 (17)	48 (36.1)	496 (16.2)	<0.001
Proton pump inhibitor	907 (28.4)	58 (6.4)	849 (27.7)	<0.001
Statins	670 (21)	37 (27.8)	633 (20.7)	0.048
Steroids	268 (8.4)	21 (15.8)	268 (8.4)	0.002
<b>Chronic interventions</b>				
Enteric tube feeding	48 (1.5)	8 (6)	40 (1.3)	<0.001
Haemodialysis	51 (1.6)	4 (3)	47 (1.5)	0.185
Indwelling catheter	67 (2.1)	11 (8.3)	56 (1.8)	<0.001
<b>Immunosuppressive conditions</b>				
Active solid tumour	245 (7.7)	11 (4.5)	234 (7.6)	0.791
AIDS	57 (1.8)	1 (0.8)	56 (1.8)	0.358
Aplastic anaemia	13 (0.4)	0 (0)	13 (0.4)	0.451
Asplenia	12 (0.4)	0 (0)	12 (0.4)	0.469
Biological drug use	35 (1.1)	3 (2.3)	32 (1)	0.190
Chemotherapy in the past 3 months	134 (4.2)	4 (3)	130 (4.2)	0.485
Haematological malignancy	150 (4.70)	3 (2.3)	147 (4.8)	0.174
HIV infection	107 (3.4)	3 (2.3)	104 (3.4)	0.473
Immunocompromised patients	623 (19.5)	28 (21.1)	595 (19.4)	0.647
Neutropenia	44 (1.4)	1 (0.8)	43 (1.4)	0.527
Other immunosuppressive condition	125 (3.9)	11 (8.3)	114 (3.7)	0.008
<b>Other chronic medical conditions</b>				
Chronic renal failure	349 (10.9)	15 (11.3)	334 (10.9)	0.895
Dementia	333 (10.4)	14 (10.5)	319 (10.4)	0.970
Diabetes mellitus	681 (21.3)	28 (4.1)	653 (21.3)	0.937
Liver disease	129 (4)	4 (3)	125 (4.1)	0.537
Malnutrition	289 (9.1)	20 (15)	269 (8.8)	0.014
Mental illness	220 (0.726)	10 (7.5)	210 (6.9)	0.770
Prosthetic material	100 (3.1)	2 (1.5)	98 (3.2)	0.271
Recurrent skin infections	55 (1.7)	4 (3.0)	51 (1.7)	0.245
<b>Other, nonmedical conditions</b>				
Bedridden	353 (11.1)	28 (21.1)	325 (92.1)	<0.001
Contact sport	5 (0.2)	0 (0)	5 (0.2)	0.641
Healthcare worker	44 (1.4)	4 (3)	40 (1.3)	0.100
Homeless	31 (1)	0 (0)	31 (1)	0.243

Continued

TABLE 1 Continued

	CAP	<i>P. aeruginosa</i> -CAP	Non- <i>P. aeruginosa</i> -CAP	p-value
Injection of illicit drugs	37 (1.2)	1 (0.8)	36 (1.2)	0.654
Living in crowded conditions	671 (21)	24 (18)	647 (21.1)	0.391
Nursing home resident	258 (8.1)	18 (13.5)	240 (7.8)	0.018
Worker in livestock meat industry	29 (0.9)	0 (0)	29 (0.9)	0.259
<b>Previous infection/colonisation</b>				
Prior MRSA infection/colonisation	81 (2.5)	10 (7.5)	71 (2.3)	<0.001
Prior ESBL-producing bacterial infection	54 (1.7)	5 (3.8)	49 (1.6)	0.059
Prior <i>Pseudomonas aeruginosa</i> infection/colonisation	96 (3)	44 (33.1)	52 (1.7)	<0.001
<b>Prior healthcare exposure (during the past 12 months)</b>				
Antibiotic infusion at home	140 (4.4)	12 (9)	128 (4.2)	0.008
Emergency room admission	972 (30.4)	63 (47.4)	909 (29.7)	<0.001
Hospitalisations	1026 (32.1)	70 (52.6)	956 (31.2)	<0.001
Intravenous antibiotics	812 (25.4)	64 (48.1)	748 (24.4)	<0.001
LRTI	928 (29.1)	66 (49.6)	862 (28.5)	<0.001
Oral antibiotics	1219 (38.2)	77 (57.9)	1142 (37.3)	<0.001
<b>Pneumonia severity</b>				
Invasive respiratory or vasopressor support	404 (12.7)	34 (25.6)	370 (12.1)	<0.001
ICU admission	599 (18.8)	43 (32.3)	556 (18.2)	<0.001
Noninvasive mechanical ventilation	334 (10.5)	15 (11.3)	319 (10.4)	0.753

Data are presented as n, median (interquartile range) or n (%), unless otherwise stated. COPD: chronic obstructive pulmonary disease; FEV<sub>1</sub>: forced expiratory volume in 1 s; MRSA: methicillin-resistant *Staphylococcus aureus*; ESBL: extended-spectrum  $\beta$ -lactamases; LRTI: lower respiratory tract infection; ICU: intensive care unit.

#### Prevalence of *P. aeruginosa*-CAP

*P. aeruginosa*-CAP was identified in 133 (4.2%) patients, representing 11.3% (133 out of 1173) of all patients who had a positive culture for bacterial pathogens. The continental prevalence of *P. aeruginosa*-CAP was 3.8% in Europe, 4.3% in North America, 5.2% in Asia, 4.9% in South America, 5.5% in Africa and 3.1% in Oceania (figure 1). The prevalence of *P. aeruginosa*-CAP in each country, and a comparison between continents and countries is shown in table 2 and online supplementary table E1. No statistically significant difference was found in the prevalence of *P. aeruginosa*-CAP among different continents. Croatia was the only country with statistically significant higher prevalence of *P. aeruginosa*-CAP (online supplementary table E1).

#### Prevalence of antibiotic-resistant *P. aeruginosa*-CAP

Antibiotic-resistant *P. aeruginosa*-CAP was identified in 64 (2.0%) patients, representing 5.4% (64 out of 1173) of all patients who had a positive culture. The continental prevalence of antibiotic-resistant *P. aeruginosa*-CAP was 1.6% in Europe, 2.5% in North America, 2.2% in Asia, 3.0% in South America, and 3.9% in Africa (figure 1). There were no patients with antibiotic-resistant *P. aeruginosa*-CAP identified in Oceania. No statistically significant difference was found in the prevalence of antibiotic-resistant *P. aeruginosa*-CAP among different continents (table 2).

#### Prevalence of MDR *P. aeruginosa*-CAP

MDR *P. aeruginosa* was identified in 33 (1.0%) patients, representing 2.8% (33 out of 1173) of all patients who had a positive culture. The continental prevalence of MDR *P. aeruginosa*-CAP was 0.9% in Europe, 1.2% in North America, 0.5% in Asia, 2% in South America and 2.3% in Africa. There were no patients with MDR *P. aeruginosa* identified in Oceania. No statistically significant difference was found in the prevalence of MDR *P. aeruginosa*-CAP among different continents. No patients were infected with pan-drug resistant *P. aeruginosa* (i.e. resistant to three or more groups of antibiotics and colistin) [31].

#### Risk factors

Patient demographics and risk factors were compared among *P. aeruginosa*-CAP and non-*P. aeruginosa* CAP (table 1). The risk factors independently associated with *P. aeruginosa*-CAP in the multivariate analysis were prior *Pseudomonas* infection/colonisation (OR 16.10, 95% CI 9.48–27.35), prior tracheostomy (OR 6.50, 95% CI 2.61–16.19), bronchiectasis (OR 2.88, 95% CI 1.65–5.05), IRVS (OR 2.33, 95% CI 1.44–3.78) and very severe COPD (OR 2.76, 95% CI 1.25–6.06) (table 3, online supplementary figure E2). Moreover, the risk factors associated with antibiotic-resistant *P. aeruginosa*-CAP were prior *Pseudomonas* infection/colonisation (OR 17.29, 95% CI 9.95–33.42), tracheostomy (OR 5.55, 95% CI 1.73–

TABLE 2 Prevalence of antibiotic-resistant *Pseudomonas aeruginosa*-community-acquired pneumonia (CAP) and antibiotic-resistant *P. aeruginosa*-CAP in participating centres representing different continents

	CAP patients					
	Continent		Rest of the world		OR (95% CI)	p-value
<b>Subjects n</b>	3193					
<b><i>P. aeruginosa</i>-CAP</b>						
Global	4.2	133/3193				
Africa	5.5	7/128	4.1	126/3065	1.34 (0.61–2.95)	0.57
Asia	5.2	21/405	4.0	112/2788	1.30 (0.81–2.10)	0.27
Europe	3.8	73/1941	4.8	60/1252	0.77 (0.54–1.10)	0.15
North America	4.3	21/484	4.1	112/2709	1.0 (0.65–1.69)	0.83
Oceania	3.1	1/32	4.2	132/3161	0.74 (0.10–5.46)	0.76
South America	4.9	10/203	4.1	123/2990	1.20 (0.62–2.33)	0.57
<b>Antibiotic-resistant <i>P. aeruginosa</i>-CAP</b>						
Global	2	64/3193				
Africa	3.9	5/128	1.9	59/3065	2.071 (0.817–5.252)	0.125
Asia	2.2	9/405	2	55/2788	1.129 (0.554–2.303)	0.738
Europe	1.6	32/1941	2.6	32/1252	0.639 (0.389–1.049)	0.076
North America	2.5	12/484	1.9	52/2709	0.770 (0.408–1.453)	0.420
Oceania	0	0/32	2	64/3161	.	0.416
South America	3	6/203	1.9	58/2990	1.540 (0.656–3.612)	0.321
<b>Multidrug-resistant <i>P. aeruginosa</i>-CAP (<math>\geq 3</math> antibiotic groups)</b>						
Global	1.0	33/3193				
Africa	2.3	3/128	1	30/3065	2.428 (0.731–8.063)	0.135
Asia	0.5	2/405	1.1	31/2788	0.441 (0.105–1.851)	0.250
Europe	0.9	18/1941	1.2	15/1252	0.772 (0.388–1.537)	0.460
North America	1.2	6/484	1	27/2709	1.247 (0.512–3.036)	0.626
Oceania	0	0/32	1	33/3161		0.561
South America	2	4/203	1	29/2990	2.052 (0.714–5.895)	0.173
<b>Carbapenem-resistant <i>P. aeruginosa</i>-CAP</b>						
Global	1.1	34/3193				
Africa	1.6	2/128	1.0	32/3065	1.504 (0.357–6.348)	0.576
Asia	0.7	3/405	1.1	31/2788	0.664 (0.202–2.181)	0.496
Europe	0.9	18/1941	1.3	16/1252	0.723 (0.367–1.423)	0.346
North America	1.7	8/484	1.0	26/2709	1.734 (0.781–3.854)	0.171
Oceania	0	0/32	1.1	34/3161		0.555
South America	1.5	3/203	1.0	31/2990	1.432 (0.434–4.724)	0.554
<b>Colistin-resistant <i>P. aeruginosa</i>-CAP</b>						
Global	0.4	12/3193				
Africa	0	0/128	0.4	12/3065		0.478
Asia	0.7	3/405	0.3	9/2788	2.304 (0.621–8.547)	0.199
Europe	0.4	7/1941	0.4	5/1252	0.903 (0.286–2.850)	0.861
North America	0	0/484	0.4	12/2709		0.142
Oceania	3.1	1/32	0.3	11/3161	9.238 (1.157–73.754)	0.011
South America	0.5	1/203	0.4	11/2990	1.341 (0.172–10.436)	0.779

Data are presented as % or n/N, unless otherwise stated.

17.80) and IRVS (OR 3.12, 95% CI 1.63–5.97). The risk factors found to be only statistically significant in the bivariate analysis were COPD, coronary artery disease, inhaled corticosteroid use, indwelling catheter and lower respiratory tract infection/emergency room visits/hospitalisations/antibiotic treatments during the past 12 months (online supplementary table E3). Table 3 shows all the risk factors that had a statistically significant association with the different antibiotic resistance patterns (multivariate analyses are presented in online supplementary table E2).

Figure 2 emphasises the importance of the prevalence of *P. aeruginosa*-CAP, either one of the two main clusters of risk factors were tested among all the patients hospitalised with CAP or after stratifications based on the requirement of IRVS. Among all the patients with CAP, only 11% had risk factors (previous infection/colonisation by *Pseudomonas* and had chronic lung diseases (*i.e.* tracheostomy, bronchiectasis and/or very severe COPD). The lack of these two sets of risk factors (*i.e.* previous infection/colonisation by *Pseudomonas* and tracheostomy, bronchiectasis and/or very severe COPD based on FEV<sub>1</sub>) confirms that

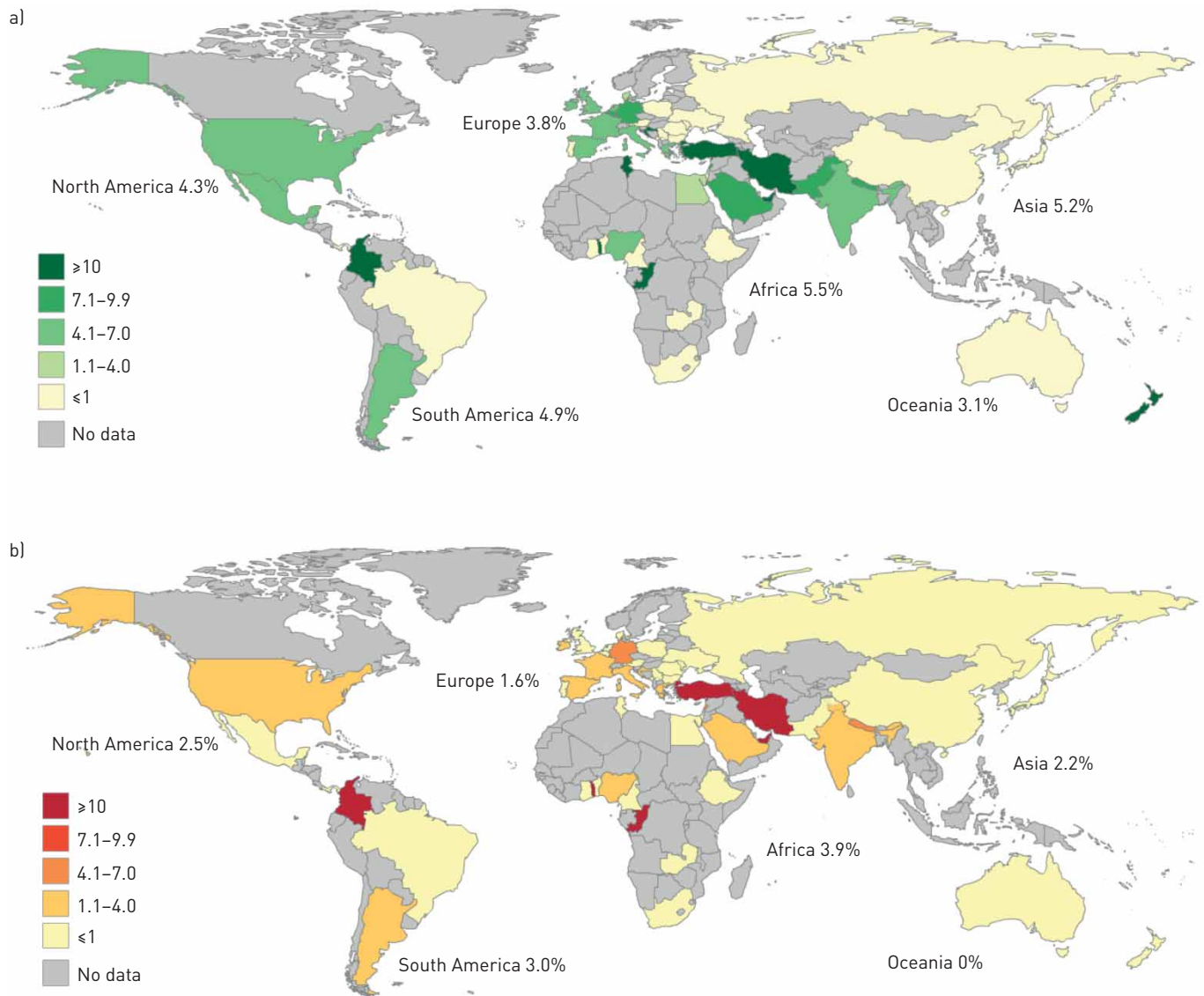


FIGURE 1 Prevalence of a) *Pseudomonas aeruginosa*-community-acquired pneumonia [CAP] and b) antibiotic-resistant *P. aeruginosa*-CAP by continent.

only 2–6% of patients might still be affected, independent of the need for IRVS. The sensitivity, specificity, positive/negative predictive values and positive/negative likelihood ratios of these risk factors are presented in online supplementary table E3.

### Discussion

This multinational point-prevalence study found a low prevalence of *P. aeruginosa* among hospitalised patients with CAP. Only 4.2%, 2.0% and 1.0% of hospitalised patients had CAP due to *P. aeruginosa*, antibiotic-resistant *P. aeruginosa* or multidrug-resistant (MDR) *P. aeruginosa*, respectively. No patients were identified with pan-drug resistant *P. aeruginosa*. There was no statistically significant difference in prevalence rates between different continents. Croatia was the only country with statistically significant higher *P. aeruginosa*-CAP prevalence. Prior *Pseudomonas* infection/colonisation, tracheostomy, bronchiectasis, IRVS and very severe COPD were independently associated with *P. aeruginosa*-CAP. Moreover, patients admitted with CAP with a past medical history of *Pseudomonas* infection/colonisation or chronic lung diseases (*i.e.* tracheostomy, bronchiectasis and/or very severe COPD) had a higher risk of being infected with antibiotic-resistant *P. aeruginosa*.

Deciding empirical treatment for CAP patients has become challenging due to the emerging prevalence of drug-resistant bacteria, such as *P. aeruginosa* [6]. In a large retrospective study of culture-positive patients

TABLE 3 Multivariate analysis of risk factors for *Pseudomonas aeruginosa*-community-acquired pneumonia (CAP), antibiotic-resistant *P. aeruginosa*-CAP, multidrug-resistant (MDR) *P. aeruginosa*-CAP and specific antibiotic resistance patterns

	Subjects	Prior <i>P. aeruginosa</i>	IRVS	Tracheostomy	Bronchiectasis	COPD	Very severe COPD
<i>P. aeruginosa</i> -CAP	133	16.10 (9.48–27.35)	2.33 (1.44–3.78)	6.50 (2.61–16.19)	2.88 (1.65–5.05)		2.76 (1.25–6.06)
Antibiotic-resistant <i>P. aeruginosa</i> -CAP	64	17.29 (9.95–33.42)	3.12 (1.63–5.97)	5.55 (1.73–17.80)			
Anti-pseudomonal cephalosporins	38	17.79 (7.32–43.22)				2.58 (1.07–6.19)	
Piperacillin/tazobactam	30	9.72 (3.88–24.36)	4.14 (1.75–9.81)		3.33 (1.21–9.19)		
Carbapenems	34	10.62 (4.26–26.45)	2.70 (1.14–6.34)	10.77 (3.09–37.52)			
Aminoglycosides	31	17.32 (7.21–41.61)	3.02 (1.24–7.31)				
Quinolones	50	17.35 (8.28–36.38)	2.84 (1.39–5.78)	4.35 (1.21–15.60)			
MDR <i>P. aeruginosa</i> -CAP	33	12.34 (5.05–30.14)	3.42 (1.47–7.97)			2.69 (1.10–6.55)	

Data are presented as n or OR (95% CI), unless otherwise stated. IRVS: invasive respiratory or vasopressor support; COPD: chronic obstructive pulmonary disease.

in the United States, KOLLEF *et al.* [15] reported a 19% prevalence of *P. aeruginosa* in hospitalised patients with CAP. In a prospective cohort study in Europe, CHALMERS *et al.* [32] reported a 0.7% prevalence of *P. aeruginosa* among all patients enrolled with CAP and 2.2% among those with positive cultures. JAIN *et al.* [5] found *P. aeruginosa* in 0.4% of patients with CAP in a prospective cohort study in the United States and 1% among the patients with culture-positive pneumonia. We found the multinational point prevalence of *P. aeruginosa* as the causative pathogen of CAP was 4.2%, which corresponds to 11.3% of patients with positive-culture pneumonia. Variations in the prevalence rates reported by different studies may be explained by differences in study design, especially the denominator used to calculate the prevalence rates [26]. However, these newly reported prevalence rates of *P. aeruginosa*-CAP are lower than prior reports [13–15], suggesting that only a small subgroup of patients may require empiric antipseudomonal antibiotic coverage.

The IDSA/ATS CAP guidelines recommend an antipseudomonal  $\beta$ -lactam antibiotic plus a fluoroquinolone or aminoglycoside in patients with risk factors for *P. aeruginosa*-CAP [13]. Dual antibiotic coverage has been recommended for HCAP, HAP or VAP where MDR *Pseudomonas* is thought to be an important problem [25]. Our results challenge this approach, by showing that the worldwide

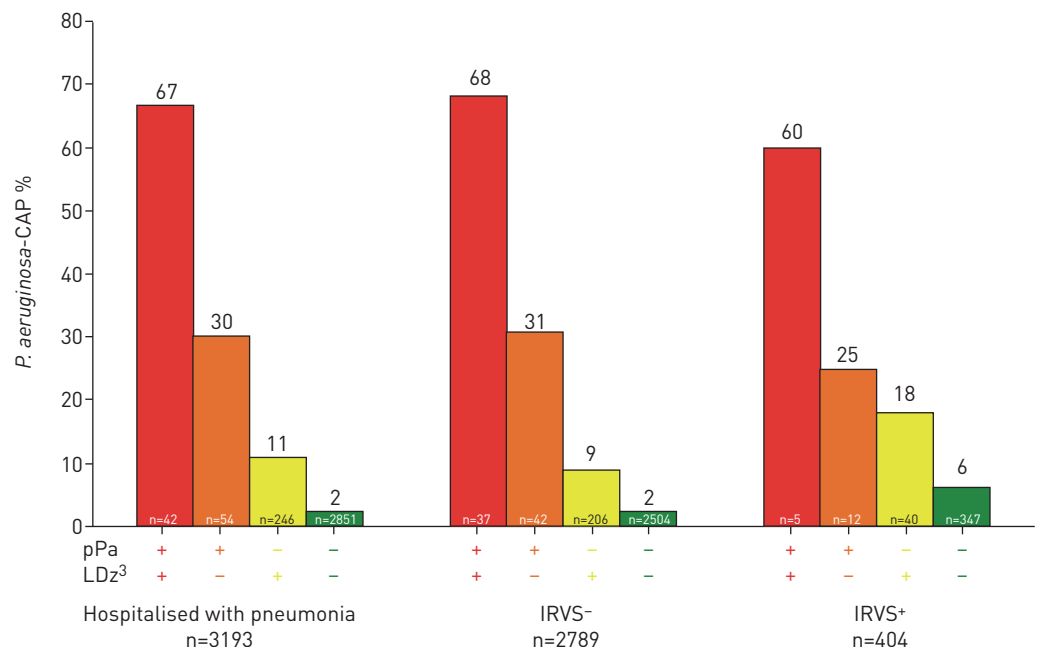


FIGURE 2 Prevalence of *Pseudomonas aeruginosa*-community-acquired pneumonia (CAP) according to the relevant risk factors, including prior *P. aeruginosa* (pPa) infection/colonisation, grouped variables of severe lung diseases (LDz<sup>3</sup>: tracheostomy, bronchiectasis and very severe chronic obstructive pulmonary disease [i.e. forced expiratory volume in 1 s <30%]) and stratified according to the need of invasive respiratory and/or vasopressor support (IRVS).



prevalence of MDR *P. aeruginosa* in patients with CAP is very low (1% or 3% among culture-positive pneumonia patients). Our results are consistent with the evidence from Spain by CILLÓNIZ *et al.* [33] who reported a prevalence of multidrug-resistant *P. aeruginosa* of 1.1% in a prospective cohort study of culture-positive CAP patients. Therefore, the recommended use of double antipseudomonal empirical coverage overestimates the actual rate of MDR *P. aeruginosa* compared to that found in infections acquired in hospital settings, where the resistance rates seems to be higher than in patients coming from the community. However, it is suggested that patients critically ill with septic shock due to pneumonia should receive empiric double antipseudomonal coverage [25].

Several researchers have hypothesised that studies assessing the prevalence of pathogens responsible for CAP are difficult to generalise, because these studies are conducted in different environments (*i.e.* single hospital, regional, country or continent) with specific differences in healthcare delivery, including antibiotic availability and policies for antimicrobial use [19, 21, 23, 34]. In our study, we found that the prevalence of *P. aeruginosa*-CAP was not significantly different between participating centres representing different continents. In contrast, Croatia was the only country that had statistically significant higher *P. aeruginosa*-CAP prevalence. The novelty of this study is that it enrolled patients in a large number of centres representing more than 50 countries from all over the world to identify the prevalence of *P. aeruginosa* in CAP patients.

In general, many hospitalised patients receive initial empirical antipseudomonal coverage while waiting 48–72 h for specific pathogen identification and antibiotic susceptibilities [1, 3]. This practice has increased the use of broad-spectrum antibiotic agents and promoted antibiotic overuse with the risk of inducing antimicrobial resistance [11, 26]. Additionally, the delay between initial diagnosis and availability of antibiotic susceptibilities could negatively affect outcomes in patients with CAP due to inappropriate antibiotic coverage [13]. Therefore, initiation of empiric antipseudomonal coverage should be based on the likelihood that a pathogen circulates in the affected community and the presence of specific risk factors for *P. aeruginosa*-CAP [6, 13, 25]. In this regard, the risk factors listed in the IDSA/ATS pneumonia guidelines for *P. aeruginosa*-CAP are intensive care unit admission, structural lung diseases such as bronchiectasis or COPD with multiple exacerbations [13]. Several risk factors have been reported for *P. aeruginosa*-CAP during the past few decades [6], but these previously reported risk factors (*e.g.* heart failure, tube feeding [35], *etc.*) were statistically significant in the bivariate analysis of our study, but not in the multivariable analysis. In contrast, we found that prior *Pseudomonas* infection/colonisation, prior tracheostomy, bronchiectasis, IRVS and very severe COPD ( $FEV_1 \leq 30\%$ ) were independently associated with *P. aeruginosa*-CAP. These findings support the recommendation to consider these risk factors for empirical antipseudomonal antibiotics in patients with severe pulmonary diseases, but not in all patients with structural lung diseases. More importantly, patients with previous *P. aeruginosa* infection/colonisation are at highest risk for *P. aeruginosa*-CAP and could benefit from empiric antipseudomonal antibiotic coverage, regardless of disease severity. Using these specific risk factors differs from the approach recommended by the IDSA/ATS guidelines and may help prevent overuse of antipseudomonal antibiotics in patients with CAP. More importantly, antimicrobial stewardship programmes that attempt to minimise the use of antipseudomonal coverage among patients without specific *Pseudomonas* risk factors may help prevent adverse events and overuse of unnecessary antimicrobial therapies.

This point prevalence study has some limitations. First, we were not able to determine clinical outcomes due to the study design. However, to determine prevalence rates and identify risk factors, point prevalence studies are ideal because they generate large sample sizes and gather generalisable data. Second, microbiological samples were not collected for centralised antibiotic susceptibility testing due to the experimental design and feasibility. Nevertheless, laboratories at study sites were encouraged to follow the CLSI or EUCAST guidelines to determine antibiotic resistance [28, 29]. Third, microbiological diagnosis of patients with CAP could be confounded by other pathogens colonising the respiratory tract; however, in our study we only reported pathogens with representative growth according to current clinical guidelines for CAP. Fourth, infections other than pneumonia are possible, but less likely to present in patients with clinical signs and symptoms and radiological confirmation of CAP. Fifth, quality assessments were not performed because all data gathered were de-identifiable; however, all local investigators were instructed on how to enrol patients and how to use the data collection platform as described in the study protocol, data dictionary and the instructional video. Sixth, cystic fibrosis (CF) is a frequent cause of chronic *P. aeruginosa* colonisation; although the majority of patients with CF might be included in the bronchiectasis group, CF was not directly recorded in our study. Finally, the empirical selection of antibiotics and diagnostic approach was performed according to the healthcare provider and not according to prespecified criteria.

In conclusion, this multinational, point prevalence study found that the burden of *P. aeruginosa*, antibiotic-resistant *P. aeruginosa* and multidrug-resistant *P. aeruginosa* as the aetiologic pathogen of CAP

is low (<5%). We identified five risk factors associated with *P. aeruginosa*-CAP: prior *Pseudomonas* infection/colonisation, tracheostomy, bronchiectasis, IRVS and very severe COPD. These risk factors could serve to guide empirical antipseudomonal antibiotic treatment. Absence of these specific risk factors suggests that the empirical antibiotic treatment recommended for CAP patients will cover the most likely prevalent bacterial pathogens. Empirical antipseudomonal coverage should be reserved for a small subgroup of well-defined patients with a past medical history of *Pseudomonas* infection/colonisation and severe lung diseases (*i.e.* prior tracheostomy, bronchiectasis and/or very severe COPD), regardless of disease severity. Importantly, not all patients with chronic pulmonary diseases would require empiric antipseudomonal coverage for CAP.

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