Prevalence and risk factors for *Enterobacteriaceae* in patients hospitalized with community-acquired pneumonia

David VILLAFUERTE,[1,2] Stefano ALIBERTI,[3,4] Nilam J. SONI,[1,2] Paola FAVERIO,[5] Pedro J. MARCOS,[6] Richard G. WUNDERINK,[7] Alejandro RODRIGUEZ,[8] Oriol SIBILA,[9] Francisco SANZ,[10] Ignacio MARTIN-LOECHES,[11] Francesco MENZELLA,[12] Luis F. REYES,[13] Mateja JANKOVIC,[14] Marc SPIELMANNS,[15] Marcos I. RESTREPO[1,2] AND GLIMP Investigators*

[1]*Division of Pulmonary Diseases and Critical Care Medicine, University of Texas Health – San Antonio, San Antonio, TX, USA;* [2]*Division of Pulmonary Diseases and Critical Care Medicine, South Texas Veterans Health Care System, San Antonio, TX, USA;* [3]*Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Respiratory Unit and Cystic Fibrosis Adult Center, Milan, Italy;* [4]*Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy;* [5]*Cardio-Thoracic-Vascular Department, University of Milan Bicocca, Respiratory Unit, San Gerardo Hospital, ASST di Monza, Monza, Italy;* [6]*Servicio de Neumología, Instituto de Investigación Biomédica de A Coruña (INIBIC), Complejo Hospitalario Universitario de A Coruña (CHUAC) Sergas Universidade da Coruña (UDC), A Coruña, Spain;* [7]*Division of Pulmonary and Critical Care Medicine, Department of Medicine, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA;* [8]*Hospital Universitari Joan XXIII, Critical Care Medicine, Rovira and Virgili University and CIBERes (Biomedical Research Network of Respiratory Disease), Tarragona, Spain;* [9]*Servei de Pneumologia, Departamento de Medicina, Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain;* [10]*Pulmonology Department, Consorci Hospital General Universitari de Valencia, Valencia, Spain;* [11]*St. James's Hospital, Trinity Centre for Health Sciences, CIBERES, Dublin, Ireland;* [12]*Department of Cardiac-Thoracic-Vascular and Intensive Care Medicine, Pneumology Unit, IRCCS – Arcispedale Santa Maria Nuova, Reggio Emilia, Italy;* [13]*Department of Microbiology, Universidad de la Sabana, Bogota, Colombia;* [14]*School of Medicine, Clinic for Respiratory Diseases, University Hospital Center Zagreb, University of Zagreb, Zagreb, Croatia;* [15]*Internal Medicine Department, Pulmonary Rehabilitation and Department of Health, School of Medicine, University Witten-Herdecke, St. Remigius-Hospital, Leverkusen, Germany*

ABSTRACT

Background and objective: **Enterobacteriaceae (EB) spp. family is known to include potentially multidrug-resistant (MDR) microorganisms, and remains as an important cause of community-acquired pneumonia (CAP) associated with high mortality. The aim of this study was to determine the prevalence and specific risk factors associated with EB and MDR-EB in a cohort of hospitalized adults with CAP.**

Methods: **We performed a multinational, point-prevalence study of adult patients hospitalized with CAP. MDR-EB was defined when ≥3 antimicrobial classes were identified as non-susceptible. Risk factors assessment was also performed for patients with EB and MDR-EB infection.**

Results: **Of the 3193 patients enrolled with CAP, 197 (6%) had a positive culture with EB. Fifty-one percent (n = 100) of EB were resistant to at least one antibiotic and 19% (n = 38) had MDR-EB. The most commonly EB identified were *Klebsiella pneumoniae* (n = 111, 56%) and *Escherichia coli* (n = 56, 28%). The risk factors that were independently associated with EB CAP were male gender, severe CAP, underweight (body mass index (BMI) < 18.5) and prior extended-spectrum beta-lactamase (ESBL) infection. Additionally, prior ESBL infection, being underweight, cardiovascular diseases and hospitalization in the last 12 months were independently associated with MDR-EB CAP.**

Conclusion: **This study of adults hospitalized with CAP found a prevalence of EB of 6% and MDR-EB of 1.2%, respectively. The presence of specific risk factors, such as prior ESBL infection and being underweight, should raise the clinical suspicion for EB and MDR-EB in patients hospitalized with CAP.**

SUMMARY AT A GLANCE

Hospitalized adults with community-acquired pneumonia (CAP) have low prevalence of *Enterobacteriaceae* (EB, 6%) and multidrug-resistant (MDR)-EB (1.2%), respectively. Specific risk factors, such as prior extended-spectrum beta-lactamase infection and being underweight, should raise the clinical suspicion for EB and MDR-EB in patients hospitalized with CAP.

Key words: community-acquired pneumonia, *Enterobacteriaceae*, multidrug-resistance, prevalence, risk factors.

INTRODUCTION

Community-acquired pneumonia (CAP) is a leading infectious cause of death worldwide, and is a costly

Correspondence: Marcos I. Restrepo, Division of Pulmonary Diseases and Critical Care Medicine, South Texas Veterans Health Care System, ALMD – 7400 Merton Minter Boulevard, San Antonio, TX 78229, USA. Email: restrepom@uthscsa.edu

*A complete list of collaborators is provided in Appendix S1 in Supplementary Information

illness due to its mortality and long-term morbidity.[1–3] Current Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines recommend the use of a respiratory fluoroquinolone as monotherapy or a β-lactam antibiotic (usually third-generation cephalosporin) plus a macrolide as initial therapy for outpatient and non-intensive care unit (ICU) inpatient treatment of CAP.[4,5] However, after these guidelines were published 10 years ago, an alarming increase in antimicrobial resistance to these first-line antibiotics has emerged in the common bacterial pathogens known to cause CAP.[6,7]

Streptococcus pneumoniae remains as the most common bacterial pathogen identified in patients with CAP.[8,9] However, several pathogens thought to be confined to hospital settings have been isolated more frequently in patients with CAP.[9,10] Of these pathogens, Gram-negative rods (GNR), such as *Pseudomonas aeruginosa*, *Acinetobacter* spp. and the *Enterobacteriaceae* (EB) spp. family, have become important causes of lower respiratory tract infections.[11,12] More importantly, these Gram-negative bacteria are often drug-resistant microorganisms associated with high mortality and have been linked to infections in chronically ill, healthcare-exposed and immunocompromised patients.[12,13]

Few studies have assessed the prevalence of the EB spp. family (*Klebsiella pneumoniae*, *Escherichia coli*, *Enterobacter* spp., *Proteus* spp. and *Serratia* spp.) in CAP patients.[14] Thus, limited data are available regarding the risk factors associated with enteric GNR, especially resistant EB spp. pathogens. The aim of the present study was to determine the prevalence and specific risk factors associated with EB and multidrug-resistant (MDR) EB infection in CAP patients using a large international cohort of adults hospitalized with CAP.

METHODS

Study design and setting

This was a multinational (54 countries), multicentre (222 participating hospitals), point-prevalence study of adult patients (>18 years of age) hospitalized with CAP. The University of Texas Health San Antonio was the coordinating centre and received approval by the Institutional Review Board (IRB# HSC20150184E) to administer the study. All centres that participated in the study complied with the local, regional and/or national research regulations. An international research oversight committee was established in October 2014 to oversee all aspects of developing and executing the study protocol (S.A., L.F.R., P.F. and M.I.R.).[15]

Electronic invitations were sent to members of different professional societies worldwide from internal and emergency medicine, infectious diseases, critical care and pulmonary medicine. Invitations were also sent to multiple authors of publications of MDR pathogens in CAP. Site investigators voluntarily agreed to participate and no funding was provided. Study participants were diagnosed and treated as per local standards of care, including microbiological assessment and treatment decisions, without any feedback from the study oversight committee or predetermined protocols. We enrolled participants on 4 days randomly selected by each site investigator during the months of March, April, May and June 2015 to assure patient de-identification.[15]

Inclusion criteria

We included hospitalized adult patients ≥18 years of age with diagnosis of CAP defined by IDSA/ATS CAP guidelines.[4] Briefly, CAP was confirmed by the presence of pulmonary infiltrates <48 h of admission by chest imaging (chest radiography, lung ultrasound or computed tomography) and the presence of ≥1 of the following signs and symptoms: (i) a new or augmentation of the cough reflex with or without sputum production and/or purulent respiratory secretions; (ii) fever (documented by rectal or oral temperature ≥ 37.8°C) or hypothermia (<36°C by rectal or oral temperature); (iii) evidence of systemic inflammation, such as leucocytosis (>10 000/cm^3), leucopenia (<4000/cm^3), bandaemia (>10%), increased C-reactive protein or procalcitonin levels.

Exclusion criteria

We excluded patients with nosocomial pneumonia, such as hospital-acquired and/or ventilator-associated pneumonia, as defined by current clinical guidelines.[16] Patients for whom site investigators did not report blood, sputum or lower respiratory tract cultures obtained within 24 h of hospital admission were also excluded due to our inability to identify the aetiological pathogen.[15]

Data collection

We used the validated data capture tool (REDCap, Research Electronic Data Capture, Vanderbilt University, Nashville, TN) hosted at UT Health San Antonio server to collect and manage study data.[17] After study enrolment, we allowed participating sites 7 days to complete electronic data entry and confirm microbiological results. All data were anonymized before being transmitted to the coordinating centre.

Microbiological analysis

Microbiological testing and processing were conducted according to local standard protocols for sputum, urine and blood during the first 24 h of hospitalization. Additionally, data on pleural fluid, tracheobronchial aspirate and bronchoalveolar lavage fluid were collected if they were available. Each laboratory complied with local quality control protocols or those of the Clinical and Laboratory Standards Institute.[18,19]

Gram-negative bacilli pathogens belonging to the family of EB spp. included *K. pneumoniae*, *E. coli*, *Enterobacter* spp., *Proteus* spp. and *Serratia* spp. Antibiotic resistance was assessed by testing resistance against major classes of antimicrobial agents (e.g. beta-lactams, carbapenems, aminoglycosides, fluoroquinolones, cephalosporins, etc.) according to current clinical practice guidelines.[18,20]

Study definitions

MDR-EB spp. was defined as resistance to ≥3 antimicrobial classes known to be active against these pathogens,[20] when obtained from blood or respiratory sources, such as: sputum, bronchoalveolar lavage or pleural fluid.

Chronic lung diseases were defined as the group of conditions that include asthma, bronchiectasis, chronic obstructive pulmonary disease (COPD), chronic aspiration, tracheostomy present at the time of admission and long-term oxygen therapy.

Severe CAP was defined as patients with a CAP diagnoses who required admission to the ICU, and/or invasive or non-invasive mechanical ventilation, or required vasopressors/inotropes in the first 24 h of hospital admission. All study definitions were provided to local investigators prior to the starting data collection.

Statistical analysis

The EB and MDR-EB prevalence were calculated using EB and MDR-EB isolates as the numerator, and total number of enrolled patients as the denominator, respectively (Fig. 1). Using the chi-square test, we compared categorical variables, expressed as counts (percentages), between the study groups. We performed regressions analyses to compare prevalence among the participating sites, representing different continents and countries. We assessed in a logistic regression analysis the relationship between the two dependent variables (EB and MDR-EB CAP) with the variables that showed a *P*-value <0.05 in the bivariate analysis. Odds ratios (OR) with 95% CI were used to present regression analysis results. Statistical significance of the results was defined as *P*-value <0.05. Statistical analyses were performed with IBM SPSS (Statistics for Mac, version 22.0; IBM Corp., Armonk, NY, USA).

RESULTS

A total of 3702 patients were enrolled in the study and 509 of them were excluded due to the lack of microbiological information. Of the 3702 patients, 3193 with signs and symptoms consistent with CAP in whom at least one microbiological culture was obtained within the first 24 h of hospital admission were enrolled in the study. In 1173 patients, at least one pathogen was identified in the culture samples, and they were considered the culture-positive cohort (Fig. 1).

EB prevalence and geographical distribution

EB were identified in 197 (6%) of 3193 patients enrolled in the study (Fig. 2A,Table S1 in Supplementary Information). Among the 197 patients with EB pneumonia, 190 were monomicrobial EB and 7 were polymicrobial (combinations of two EB) (Fig. 2C). Of the EB identified, the most frequently isolated pathogens were *K. pneumoniae* (*n* = 111, 56%), *E. coli* (*n* = 56, 28%), *Enterobacter* spp. (*n* = 25, 13%), *Proteus* spp. (*n* = 8, 4%) and *Serratia* spp. (*n* = 4, 2%) (Fig. 3A). The prevalence of EB among the six continents was highest in Africa (*n* = 23, 18%) (Table 1). The countries that showed the highest prevalence of EB above 10% were: Colombia, Nigeria, Moldova, Croatia, Egypt and Germany compared to other participating countries (Table S1 in Supplementary Information).

Antibiotic resistance patterns

From the 197 EB identified, 97 (49%) were sensitive to the antibiotics tested, 62 (31%) were resistant to one or two antimicrobials and 38 (19%) were classified as MDR-EB (Fig. 3B). EB showed resistance to fluoroquinolones (*n* = 61, 31%), piperacillin-tazobactam (*n* = 60, 30%), cephalosporins (*n* = 56, 28%), aminoglycosides (*n* = 27, 14%) and carbapenems (*n* = 16, 8%) (Fig. 3E).

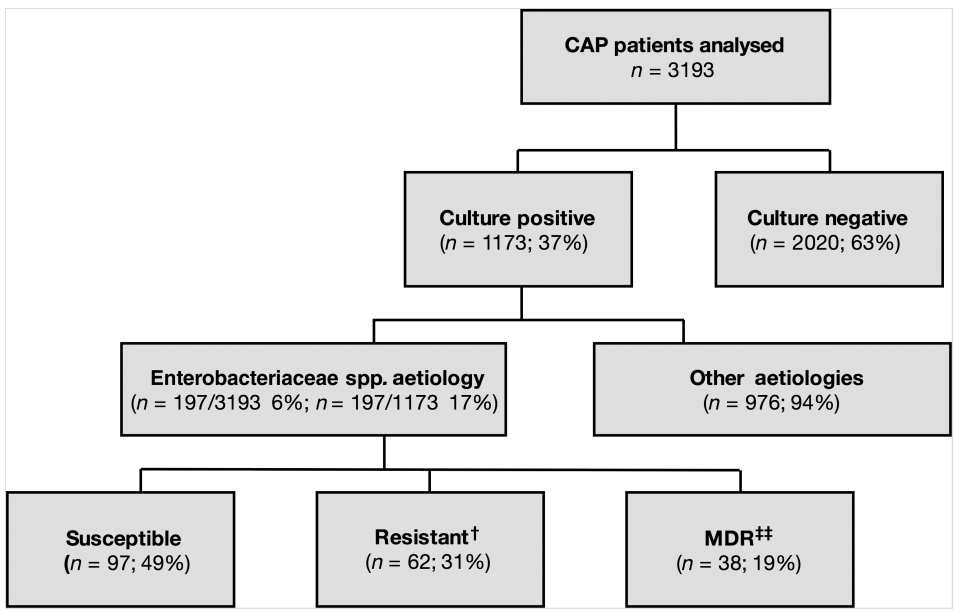

Figure 1 Study flow diagram. †EB that showed resistance to at least one or two of the tested antibiotics. ‡EB resistant to three or more of the tested antibiotics. CAP, community-acquired pneumonia; EB, *Enterobacteriaceae*; MDR, multidrug resistant.

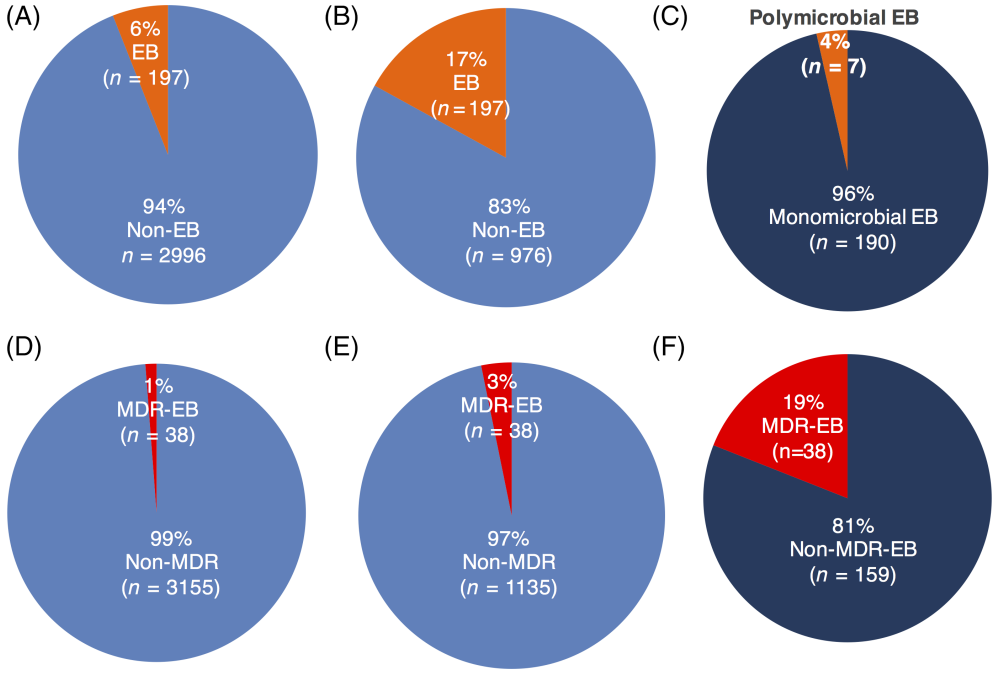

Figure 2 (A) Prevalence of EB among patients with CAP (microbiologically tested cohort). (B) Prevalence of EB in culture-positive CAP. (C) Percentage of monomicrobial and polymicrobial EB CAP. (D) Prevalence of MDR-EB among the microbiologically tested cohort. (E) Prevalence of MDR-EB in culture-positive CAP. (F) Prevalence of resistant and MDR-EB. CAP, community-acquired pneumonia; EB, *Enterobacteriaceae*; MDR, multidrug resistant.

MDR-EB prevalence and geographical distribution

Among the isolated EB, 19% (n = 38) were confirmed to be MDR-EB with a prevalence rate of 1.2% (Fig. 2D). In addition, the continent with the highest prevalence of MDR-EB was Africa (n = 8, 6.3%) (Table 1). The countries with the highest prevalence of MDR-EB above 5% were: Nigeria (7.7%), Colombia (7.4%) and Moldova (6.5%) (Table S1 in Supplementary Information).

Risk factors for EB

In the univariate analysis, several variables were associated with EB CAP (Tables 1,S2 in Supplementary Information). In the multivariate logistic regression analysis, we found that the risk factors that were independently associated with EB CAP were prior extended-spectrum beta-lactamase (ESBL) infection (OR: 4.04, 95% CI: 2.04–8.01, $P < 0.01$), being underweight (OR: 2.25, 95% CI: 1.31–3.86, $P < 0.01$), severe CAP (OR: 2.41, 95% CI: 1.79–3.25, $P < 0.01$) and male gender (OR: 1.48, 95% CI: 1.08–2.02, $P = 0.01$) (Table 2). In culture-positive CAP patients, risk factors independently associated were prior ESBL infection (OR: 3.71, 95% CI: 1.65–8.35, $P < 0.01$), being underweight (OR: 2.02, 95% CI: 1.13–3.63, $P = 0.02$) and severe CAP (OR: 1.78, 95% CI: 1.30–2.45, $P < 0.01$) (Table 2).

Risk factors for MDR-EB

Prior ESBL infection (OR: 8.50, 95% CI: 3.12–23.16, $P < 0.01$), being underweight (OR: 2.76, 95% CI: 1.07–7.12, $P = 0.04$), cardiovascular diseases (OR: 0.44, 95% CI: 0.22–0.90, $P = 0.02$) and hospitalization in the last 12 months (OR: 2.67, 95% CI: 1.18–6.03, $P = 0.02$) were the risk factors independently associated with MDR-EB CAP (Table 2). The risk factors independently associated with MDR-EB enrolled in the culture-positive cohort were prior ESBL infection (OR: 5.60, 95% CI: 1.86–16.80, $P < 0.01$), cardiovascular diseases (OR: 0.43, 95% CI: 0.21–0.91, $P = 0.03$) and hospitalization in the last 12 months (OR: 2.36, 95% CI: 1.17–4.78, $P = 0.02$) (Table 2).

DISCUSSION

This multinational study showed that patients with CAP have a 6% prevalence of EB as an aetiological pathogen. The prevalence among the six continents enrolled varied, ranging from 4% to 18% for EB CAP and 0.6% to 6.3% for MDR-EB CAP, with the highest prevalence rates found in Africa. Prior ESBL infection and being underweight were independently associated with both EB and MDR-EB in patients with CAP.

The overall prevalence rates of EB and MDR-EB CAP identified in this study were higher (6% and 1%, respectively) compared to the 1–3% prevalence rate of EB CAP (excluding *P. aeruginosa* and *Acinetobacter* spp.) reported in three observational studies from Spain[21–23] and in one from Germany.[24] Moreover, in patients with culture-positive results, the denominator drives a higher prevalence of EB and MDR-EB in CAP patients, resulting in 17% and 3%, in contrast to ~2–6% (only for EB CAP) reported in the previously mentioned

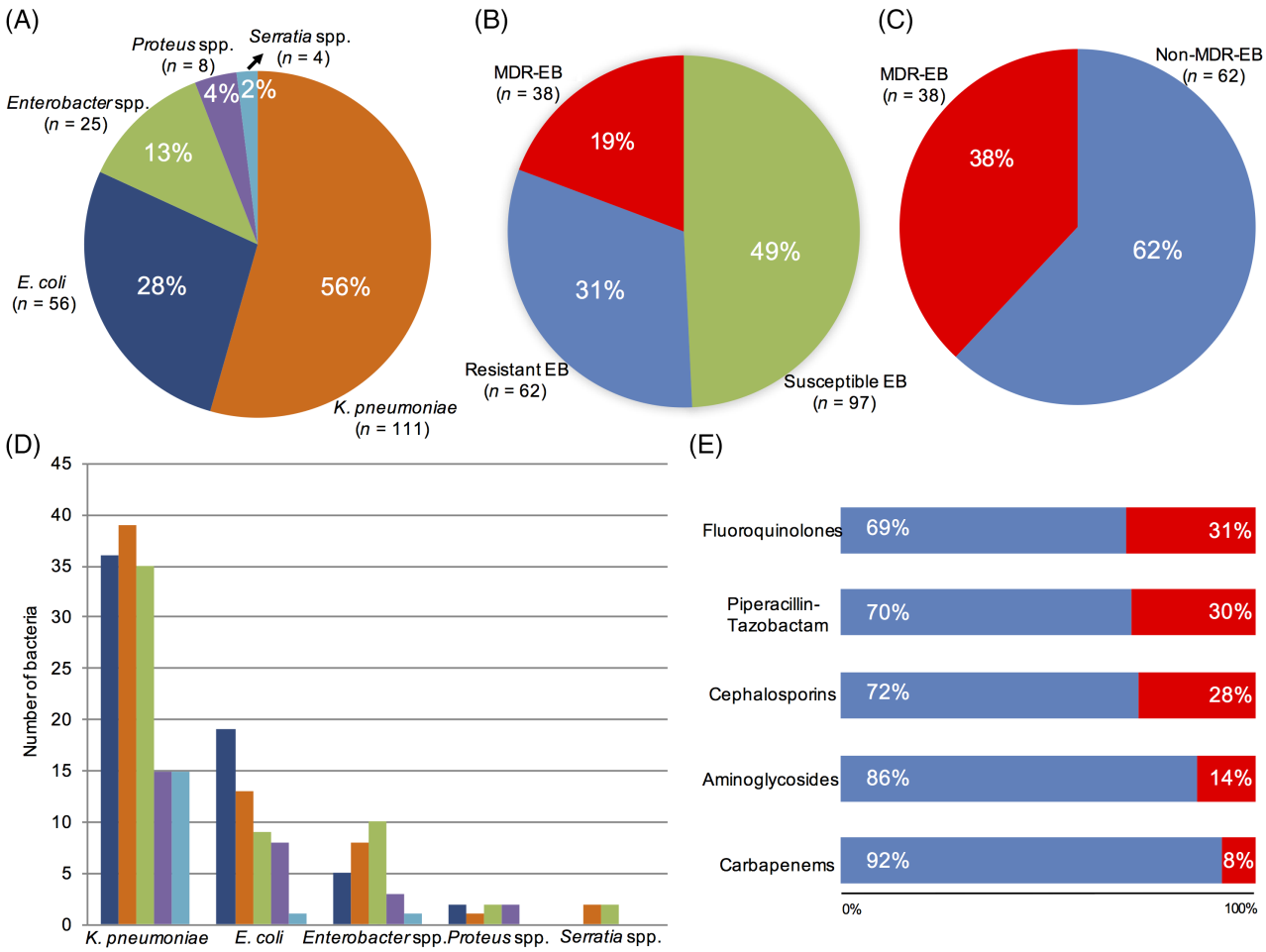

Figure 3 (A) Types of EB among total EB isolated (n = 197). (B) Antibiotic susceptibility among isolated EB. (C) Percentage of resistance and multidrug resistance among EB that showed to be resistant to at least one antibiotic (n = 100). (D) Number of bacteria by type that showed resistance to each one of the five antibiotics tested (■, fluoroquinolones; ■, piperacillin-tazobactam; ■, cephalosporins; ■, aminoglycosides; ■, carbapenems). (E) Antibiotic resistance profile among isolated EB (■, susceptible; ■, resistant). EB, *Enterobacteriaceae*; MDR, multidrug resistant.

studies.[21–24] It is important to mention that participation for this study was voluntary and it could have certainly accounted for some countries and continents contributing to a higher number of patients enrolled. We hypothesized that regional variability between patients' characteristics, healthcare systems in developed and developing countries, risk factors and antibiotic resistance patterns might have played a role in the differences observed. Therefore, these data suggest that identifying the common pathogens that cause CAP is necessary to appreciate the frequency of these pathogens at any given time, which can guide antimicrobial treatment strategies.

The EB pathogens isolated in our study are consistent with previous reports that found *K. pneumoniae* and *E. coli* to be the most commonly isolated EB in CAP.[21,24,25] *Enterobacter* spp., *Proteus* spp. and *Serratia* spp. were less commonly identified in patients hospitalized with CAP among the 54 participating countries in our study. Current guideline-recommended empiric antibiotic therapy that include a third-generation cephalosporin and a macrolide or monotherapy with a respiratory fluoroquinolone[4] for patients with CAP would not cover 30% of isolated EB due to in vitro resistance at presentation. More than half of the EB isolated pathogens showed resistance to ≥1 of the tested antibiotics and one-third of the EB demonstrated to be MDR. These numbers should raise awareness of the emerging antimicrobial resistance to bacterial pathogens, particularly in CAP patients.

A major finding of the present study is that prior ESBL infection and being underweight were both independent risk factors for EB and MDR-EB CAP. Few studies have evaluated the risk factors associated with EB CAP, and these studies often included *P. aeruginosa* and *Acinetobacter* spp. as EB.[21,22,24,26] Underweight has been associated with the development of CAP, but not specifically with EB or MDR-EB. A detailed systematic review that evaluated the risk factors associated with CAP found that poor nutritional status in different studies is related to hypoalbuminaemia, hypoproteinaemia, malnourishment, malnutrition or a low nutritional score, and was a strong predictor of CAP.[27] However, in contrast, Cillóniz *et al.* presented a comprehensive

Table 1 Characteristics of all patients with CAP (n = 3193) due to EB and MDR-EB in comparison to the rest of the population (including continents) with CAP

	Non-EB CAP n = 2996	EB CAP n = 197	P-value	Non-MDR-EB CAP n = 3155	MDR-EB CAP n = 38	P-value
Demographic characteristics						
Age, median (IQR) years	68 (54–80)	66 (54–78)	0.68	68 (54–80)	66 (47–76)	0.17
Male gender, n (%)	1744 (58.2)	133 (67.5)	0.01	1855 (58.8)	22 (57.9)	0.91
Underweight, n (%)	132 (4.4)	18 (9.1)	<0.01	144 (7.1)	6 (20.7)	0.04
Alcoholism	250 (8.3)	17 (8.6)	0.89	266 (8.4)	1 (2.6)	0.20
Current/former smoker, n (%)	1043 (34.8)	71 (36)	0.73	1099 (34.8)	15 (39.5)	0.55
Bedridden, n (%)	322 (10.7)	31 (15.7)	0.03	345 (10.9)	8 (21.1)	0.04
Nursing home resident, n (%)	238 (7.9)	20 (10.2)	0.27	252 (8.0)	6 (15.8)	0.08
Chronic medical co-morbidities						
Chronic lung diseases						
Active lung cancer, n (%)	86 (2.9)	6 (3.0)	0.89	91 (2.9)	1 (2.6)	0.92
Asthma, n (%)	225 (7.5)	9 (4.6)	0.13	234 (7.4)	0 (0.0)	0.81
Bronchiectasis, n (%)	153 (5.1)	15 (7.6)	0.13	161 (5.1)	7 (18.4)	<0.01
Chronic aspiration, n (%)	191 (6.4)	27 (13.7)	<0.01	210 (6.7)	8 (21.1)	<0.01
COPD, n (%)	775 (25.9)	59 (29.9)	0.21	823 (26.1)	11 (28.9)	0.69
$FEV_1 \leq 30\%$, n (%)	82 (2.7)	8 (4.1)	0.28	88 (2.8)	2 (5.3)	0.36
Oxygen therapy at home, n (%)	187 (6.2)	21 (10.7)	0.02	202 (6.4)	6 (15.8)	0.02
Tracheostomy, n (%)	38 (1.3)	12 (6.1)	<0.01	47 (1.5)	3 (7.9)	<0.01
Cardiovascular diseases						
Coronary artery disease, n (%)	487 (16.3)	39 (19.8)	0.19	524 (16.6)	2 (5.3)	0.06
Heart failure, n (%)	383 (12.8)	35 (17.8)	0.04	412 (13.1)	6 (15.8)	0.62
Hypertension, n (%)	1370(45.7)	74 (37.6)	0.03	1435 (45.5)	9 (23.7)	<0.01
Other co-morbid conditions						
Diabetes mellitus, n (%)	637 (21.3)	44 (22.3)	0.72	674 (21.4)	7 (18.4)	0.66
Enteral tube feeding, n (%)	39 (1.3)	9 (4.6)	<0.01	44 (1.4)	4 (10.5)	<0.01
Liver disease, n (%)	121 (4)	8 (4.1)	0.99	125 (4)	4 (10.5)	0.04
Cirrhosis, n (%)	59 (2)	5 (2.5)	0.58	62 (2)	2 (5.3)	0.15
Chronic renal failure, n (%)	329 (11)	20 (10.2)	0.72	344 (10.9)	5 (13.2)	0.66
Stroke, n (%)	231 (7.7)	19 (9.6)	0.33	245 (7.8)	5 (13.2)	0.22
Active solid tumour, n (%)	227 (7.6)	18 (9.1)	0.43	243 (7.7)	2 (5.3)	0.57
Immunocompromised patients, n (%)	550 (18.4)	37 (18.8)	0.88	578 (18.3)	9 (23.7)	0.40
Previous infections/colonization						
Prior ESBL-producing bacterial infection, n (%)	41 (1.4)	13 (6.6)	<0.01	48 (1.5)	6 (15.8)	<0.01
Prior healthcare exposure						
Hospitalization during the last 12 months, n (%)	950 (31.7)	76 (38.6)	0.04	1004 (31.8)	22 (57.9)	<0.01
IV antibiotics during the last 12 months, n (%)	747 (24.9)	65 (33.0)	0.01	796 (25.2)	16 (42.1)	0.02
Severity of illness						
Severe CAP, n (%)	866 (28.9)	99 (50.3)	<0.01	950 (30.1)	15 (39.5)	0.21
Continents						
Europe (n = 1.941)	1837 (94.6)	104 (5.4)	0.02	1923 (99.1)	18 (0.9)	0.1
North America (n = 484)	463 (95.7)	21 (4.3)	0.08	481 (99.4)	3 (0.6)	0.26
Asia (n = 405)	376 (92.8)	29 (7.2)	0.38	400 (98.8)	5 (1.2)	0.81
South America (n = 203)	186 (91.6)	17 (8.4)	0.18	200 (98.5)	3 (1.5)	0.73
Africa (n = 128)	105 (82.0)	23 (18)	<0.01	120 (93.8)	8 (6.3)	<0.01
Oceania (n = 32)	29 (90.6)	3 (9.4)	0.45	31 (96.9)	1 (3.1)	0.32

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; EB, *Enterobacteriaceae* spp.; ESBL, extended-spectrum beta-lactamase; FEV_1, forced expiratory volume in 1 s; IQR, interquartile range; IV, intravenous; MDR, multidrug resistant.

Table 2 Multivariate regression analysis among CAP and culture-positive CAP patients demonstrating the risk factors independently associated with ED and MDR-EB CAP

	CAP				Culture-positive CAP			
	EB (n = 197/3193)		MDR-EB (n = 38/3193)		EB (n = 197/1173)		MDR-EB (n = 38/1173)	
Risk factors	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Sex (male)	1.48 (1.08–2.02)	0.01			1.37 (0.99–1.92)	0.06		
Underweight	2.25 (1.31–3.86)	<0.01	2.76 (1.07–7.12)	0.04	2.02 (1.13–3.63)	0.02	2.29 (0.85–6.12)	0.10
Chronic lung diseases[†]	1.20 (0.88–1.63)	0.24	1.36 (0.68–2.73)	0.38	1.19 (0.86–1.64)	0.30	1.27 (0.62–2.58)	0.51
Enteral tube feeding	1.78 (0.78–4.08)	0.17	3.50 (1.02–12.02)	0.05	1.76 (0.68–4.58)	0.25	3.17 (0.86–11.76)	0.08
Bedridden status	1.11 (0.72–1.72)	0.62	1.32 (0.56–3.10)	0.53	1.19 (0.74–1.90)	0.48		
Prior ESBL infection	4.04 (2.04–8.01)	<0.01	8.50 (3.12–23.16)	<0.01	3.71 (1.65–8.35)	<0.01	5.60 (1.86–16.80)	<0.01
Hospitalization during the last 12 months	1.13 (0.77–1.68)	0.53	2.67 (1.18–6.03)	0.02			2.36 (1.17–4.78)	0.02
IV antibiotics during the last 12 months	1.07 (0.71–1.62)	0.76	0.75 (0.32–1.77)	0.52				
Severe CAP	2.41 (1.79–3.25)	<0.01			1.78 (1.30–2.45)	<0.01		
Chronic liver disease			2.67 (1.01–7.11)	0.05				
Cardiovascular diseases[‡]	0.84 (0.62–1.13)	0.25	0.44 (0.22–0.90)	0.02	1.00 (0.73–1.39)	0.98	0.43 (0.21–0.91)	0.03
Chronic renal failure							1.75 (0.62–4.91)	0.29

[†]Chronic lung diseases include asthma, bronchiectasis, COPD, chronic aspiration, tracheostomy present at the time of admission and long-term oxygen therapy.

[‡]Cardiovascular diseases included coronary artery disease, hypertension and heart failure.

CAP, community-acquired pneumonia; COPD, chronic obstructive pulmonary disease; EB, *Enterobacteriaceae* spp.; ESBL, extended-spectrum beta-lactamase; IV, intravenous; MDR, multidrug resistant; OR, odds ratio.

review of the topic and did not mention low body mass index or underweight associated with any of the potential MDR pathogens including EB.[28] Despite this, prior investigations showed that CAP due to EB tends to be associated with exposure to the healthcare system, such as previous antibiotic use, current use of corticosteroids, prior hospital admission, probable aspiration, severe CAP and co-morbidities of the cardiovascular, cerebrovascular and pulmonary systems.[21,22,26] Our assessment of individual risk factors identified that the prior evidence of *P. aeruginosa* infection and at least one of the three lung diseases (i.e. tracheostomy present on admission, bronchiectasis and very severe COPD (forced expiratory volume in 1 s <30%)) were independently associated with *P. aeruginosa* CAP.[29] Therefore, our data suggest that there is no significant overlap among the risk factors associated with *P. aeruginosa* CAP and the ones associated with EB CAP. The EB risk factors suggested in our study may assist clinicians to further individualize the selection of antibiotics by limiting the unnecessary coverage for *P. aeruginosa* in certain patients with CAP.

This is one of the first international studies involving more than 50 countries around the world that systematically evaluated the prevalence and risk factors for EB and MDR-EB in CAP patients, and should be considered one of its main strengths. This point-prevalence study carries some limitations inherent to the study design, such as the inability to follow-up patients over time and to track the outcomes beyond the period of observation. In addition, due to the nature of the study, we were not allowed to report identifiable data and, therefore, it was not possible to return to the individual patient medical records to confirm that each variable was entered appropriately. We relied on the honesty and the accountability of each one of the site investigators to follow the ethical rules defined by the individual study centres. Additionally, we attempted to standardize the methodology through the training videos, data abstraction form and data dictionary, as well as microbiological standard testing according to international standards. This study does not attempt to generalize other epidemiological reports or outbreaks in centres not participating in this study and from sources other than CAP. In addition, MDR-EB could represent an important source of hospital-acquired infections not evaluated in our study. Microbiological genetic testing was not performed, as it is not available in resource-limited countries included in this study. Finally, there is a possibility that a small proportion of patients (n = 13, 6.6%) with prior ESBL infection may represent a relapse or recurrence infection with the same microorganism. However, the data obtained in this point-prevalence study did not include the source of prior ESBL infection, the resolution of the prior disease and/or the time from prior infection to current EB CAP event.

In conclusion, the prevalence of EB and MDR-EB as aetiological pathogens of CAP is 6% worldwide. Despite the alarming rise of MDR-EB, most of the guideline-recommended empiric antibiotic regimens would still cover the pathogens most frequently causing CAP. Selection of empiric antibiotic therapy for patients with CAP should consider the prevalence of antibiotic-resistant pathogens in the community and identify certain risk factors that may change the probability of MDR-EB CAP. Future studies should explore how these variables influence the use of empiric antibiotics in different communities around the world.

Acknowledgements: We would like to thank the European Respiratory Society, the World Federation of Societies of Intensive and Critical Care Medicine, the American College of Chest Physicians, the Asociación Latinoamericana de Tórax (ALAT) and the Sociedad Argentina de Infectología (SAI) for supporting this project. N.J.S. is partially funded by the Department of Veterans Affairs, Quality Enhancement Research Initiative (QUERI) Partnered Evaluation Initiative Grant (HX002263-01A1). The content of this manuscript is solely the responsibility of the authors and does not necessarily represent the official views of the Department of Veterans Affairs.

Disclosure statement: This study was previously presented as an abstract and oral presentation at the Annual Chest Congress in 2017.

Author contributions: Conceptualization: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Data curation: M.I.R., D.V., S.A., N.J.S., L.F.R., P.F., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Formal analysis: M.I.R., D.V., S.A., N.J.S., L.F.R., P.F., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Investigation: M.I.R., D.V., S.A., N.J.S., L.F.R., P.F., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S., GLIMP Investigators. Methodology: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Project administration: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Software: M.I.R., S.A., D.V. and L.F.R. Supervision: M.I.R., S.A., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Validation: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Visualization: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Writing—original draft: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S. Writing—review and editing: M.I.R., S.A., D.V., P.F., L.F.R., N.J.S., P.J.M., R.G.W., A.R., O.S., F.S., I.M.-L., F.M., M.J., M.S.

Abbreviations: CAP, community-acquired pneumonia; EB, *Enterobacteriaceae*; ESBL, extended-spectrum beta-lactamase; GNR, Gram-negative rod; ICU, intensive care unit; IDSA/ATS, Infectious Diseases Society of America/)/American Thoracic Society; MDR, multidrug resistant.

REFERENCES

1 Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Ten-year mortality after community-acquired pneumonia. A prospective cohort. *Am. J. Respir. Crit. Care Med.* 2015; **192**: 597–604.

2 World Healht Organization. The top 10 causes of death. [Accessed 4 Dec 2018.] Available from URL: http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death

3 Wunderink RG, Waterer GW. Clinical practice. Community-acquired pneumonia. *N. Engl. J. Med.* 2014; **370**: 543–51.

4 Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, Dowell SF, File TM Jr, Musher DM, Niederman MS *et al.*; Infectious Diseases Society of America; American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-

acquired pneumonia in adults. *Clin. Infect. Dis*. 2007;**44**(Suppl. 2): S27–72.
5 Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, Restrepo MI. The management of community-acquired pneumonia in the elderly. *Eur. J. Intern. Med.* 2014; **25**: 312–9.
6 Wunderink RG, Yin Y. Antibiotic resistance in community-acquired pneumonia pathogens. *Semin. Respir. Crit. Care Med.* 2016; **37**: 829–38.
7 Sibila O, Restrepo MI, Anzueto A. What is the best antimicrobial treatment for severe community-acquired pneumonia (including the role of steroids and statins and other immunomodulatory agents). *Infect. Dis. Clin. North Am.* 2013; **27**: 133–47.
8 Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, Reed C, Grijalva CG, Anderson EJ, Courtney DM *et al*.; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N. Engl. J. Med*. 2015; **373:** 415–27.
9 Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. *Lancet* 2015; **386**: 1097–108.
10 Chalmers JD, Reyes LF, Aliberti S, Restrepo MI. Empirical coverage of methicillin-resistant *Staphylococcus aureus* in community-acquired pneumonia: those who do not remember the past are doomed to repeat it. *Clin. Infect. Dis.* 2016; **63**: 1145–6.
11 Cillóniz C, Ewig S, Polverino E, Marcos MA, Prina E, Sellares J, Ferrer M, Ortega M, Gabarrús A, Mensa J *et al*. Community-acquired pneumonia in outpatients: aetiology and outcomes. *Eur. Respir. J.* 2012; **40**: 931–8.
12 Sibila O, Laserna E, Maselli DJ, Fernandez JF, Mortensen EM, Anzueto A, Waterer G, Restrepo MI. Risk factors and antibiotic therapy in *P. aeruginosa* community-acquired pneumonia. *Respirology* 2015; **20**: 660–6.
13 Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005; **128**: 3854–62.
14 Torres A, Cillóniz C, Ferrer M, Gabarrús A, Polverino E, Villegas S, Marco F, Mensa J, Menéndez R, Niederman M. Bacteraemia and antibiotic-resistant pathogens in community acquired pneumonia: risk and prognosis. *Eur. Respir. J.* 2015; **45**: 1353–63.
15 Aliberti S, Reyes LF, Faverio P, Sotgiu G, Dore S, Rodriguez AH, Soni NJ, Restrepo MI; GLIMP Investigators. Global initiative for methicillin-resistant *Staphylococcus aureus* pneumonia (GLIMP): an international, observational cohort study. *Lancet Infect. Dis.* 2016; **16**: 1364–76.
16 Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, Napolitano LM, O'Grady NP, Bartlett JG, Carratalà J *et al*. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin. Infect. Dis.* 2016; **63**: e61–111.
17 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J. Biomed. Inform.* 2009; **42**: 377–81.
18 Hsueh PR, Ko WC, Wu JJ, Lu JJ, Wang FD, Wu HY, Wu TL, Teng LJ. Consensus statement on the adherence to Clinical And Laboratory Standards Institute (CLSI) Antimicrobial Susceptibility Testing guidelines (CLSI-2010 and CLSI-2010-update) for Enterobacteriaceae in clinical microbiology laboratories in Taiwan. *J. Microbiol. Immunol. Infect.* 2010; **43**: 452–5.
19 Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Fifth Informational Supplement. Wayne, PA: Clinical and Laboratory Standards Institute, 2015.
20 Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist B *et al*. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin. Microbiol. Infect.* 2012; **18**: 268–81.
21 Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, Torres A. Community-acquired pneumonia due to gram-negative bacteria and *Pseudomonas aeruginosa*: incidence, risk, and prognosis. *Arch. Intern. Med.* 2002; **162**: 1849–58.
22 Falguera M, Carratalà J, Ruiz-Gonzalez A, Garcia-Vidal C, Gazquez I, Dorca J, Gudiol F, Porcel JM. Risk factors and outcome of community-acquired pneumonia due to Gram-negative bacilli. *Respirology* 2009; **14**: 105–11.
23 Prina E, Ranzani OT, Polverino E, Cillóniz C, Ferrer M, Fernandez L, Puig dela Bellacasa J, Menéndez R, Mensa J, Torres A. Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann. Am. Thorac. Soc.* 2015; **12**: 153–60.
24 von Baum H, Welte T, Marre R, Suttorp N, Ewig S; CAPNETZ Study Group. Community-acquired pneumonia through Enterobacteriaceae and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur. Respir. J.* 2010; **35**: 598–605.
25 Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, Goto Y, Fukui Y, Iwaki M, Okumura J *et al*. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am. J. Respir. Crit. Care Med.* 2013; **188**: 985–95.
26 Sibila O, Rodrigo-Troyano A, Shindo Y, Aliberti S, Restrepo MI. Multidrug-resistant pathogens in patients with pneumonia coming from the community. *Curr. Opin. Pulm. Med.* 2016; **22**: 219–26.
27 Almirall J, Serra-Prat M, Bolíbar I, Balasso V. Risk factors for community-acquired pneumonia in adults: a systematic review of observational studies. *Respiration* 2017; **94**: 299–311.
28 Cillóniz C, Dominedò C, Torres A. Multidrug resistant Gram-negative bacteria in community-acquired pneumonia. *Crit. Care* 2019; **23**: 79.
29 Restrepo MI, Babu BL, Reyes LF, Chalmers JD, Soni NJ, Sibila O, Faverio P, Cilloniz C, Rodriguez-Cintron W, Aliberti S; GLIMP. Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *Eur. Respir. J*. 2018; **52:** pii: 1701190.

Supplementary Information

Additional supplementary information can be accessed via the *html* version of this article at the publisher's website.

Appendix S1 GLIMP collaborators.
Table S1 Prevalence of *Enterobacteriaceae* (EB) spp. and multidrug-resistant EB per countries in patients with community-acquired pneumonia.
Table S2 Characteristics of patients with community-acquired pneumonia (CAP) due to EB and MDR-EB in comparison to the rest of the population with culture-positive CAP ($n = 1173$).