International prevalence and risk factors evaluation for Drug-Resistant Streptococcus pneumoniae pneumonia

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HIGHLIGHTS

- *Streptococcus pneumoniae* was the most frequently identified pathogen in a cohort of patients with community acquired pneumonia (CAP) (268/3,193 [8.3%]).
- The global prevalence of drug resistant *S. pneumoniae* CAP (DRSP-CAP) was 1.3%.
- Macrolide resistance was the most frequently identified in subjects with DRSP-CAP (0.6%) followed by penicillin resistance (0.5%).
- The risk factors associated with specific antibiotic resistance were: asthma (for penicillin and macrolide), liver disease (for tetracycline resistance) and non-cystic fibrosis bronchiectasis (for penicillin resistance).

TITLE: International prevalence and risk factors evaluation for Drug-Resistant *Streptococcus pneumoniae* pneumonia

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KEY WORDS: Pneumonia, pneumococcal infection, global burden of disease, microbial drug resistant (3-5 words, cannot be in title)

RUNNING HEAD: Drug resistant pneumococcal pneumonia

SUMMARY

Objective: *Streptococcus pneumoniae* is the most frequent bacterial pathogen isolated in subjects with Community-acquired pneumonia (CAP) worldwide. Limited data are available regarding the current global burden and risk factors associated with drug-resistant *Streptococcus pneumoniae* (DRSP) in CAP subjects. We assessed the multinational prevalence and risk factors for DRSP-CAP in a multinational point-prevalence study.

Design: The prevalence of DRSP-CAP was assessed by identification of DRSP in blood or respiratory samples among adults hospitalized with CAP in 54 countries. Prevalence and risk factors were compared among subjects that had microbiological testing and antibiotic susceptibility data. Multivariate logistic regressions were used to identify risk factors independently associated with DRSP-CAP.

Results: 3,193 subjects were included in the study. The global prevalence of DRSP-CAP was 1.3% and continental prevalence rates were 7.0% in Africa, 1.2% in Asia, and 1.0% in South America, Europe, and North America, respectively. Macrolide resistance was

most frequently identified in subjects with DRSP-CAP (0.6%) followed by penicillin resistance (0.5%). Subjects in Africa were more likely to have DRSP-CAP (OR: 7.6; 95%CI: 3.34-15.35, p<0.001) when compared to centres representing other continents. .

Conclusions: This multinational point-prevalence study found a low global prevalence of DRSP-CAP that may impact guideline development and antimicrobial policies.

INTRODUCTION

Community acquired pneumonia (CAP) is responsible for more than 3 million annual fatalities worldwide.[1, 2] The economic burden of CAP is at a steady cost in excess of 17 billion dollars annually for the United States alone.[1, 3] Antibiotic resistance associated with CAP is a growing problem for the medical community, and it is estimated that more than 20,000 people die annually in the United States secondary to infections due to resistant bacteria.[4, 5] *Streptococcus pneumoniae*, the most frequently isolated bacterium during CAP, has increasing resistance to the most commonly prescribed antibiotics, including penicillin, macrolides, and fluoroquinolones, and is referred to as drug-resistant *Streptococcus pneumoniae* (DRSP).[6-9] Antibiotic resistance is an emergent threat in healthcare systems worldwide and can limit antibiotic efficacy against common pathogens responsible for CAP.[10, 11]

Geographic variations in the prevalence of DRSP have been recognized in different cohorts in antibiotic surveillance studies.[12-14] A higher prevalence of antibiotic resistant strains of *S. pneumoniae* has been demonstrated in some European countries, such as Spain.[15] Surveillance studies have reported DRSP in up to 35% of *S. pneumoniae* isolated from different sources (i.e., sputum, blood, cerebrospinal fluid, ear secretions, etc.).[16, 17] Risk factors for DRSP infection include older age, recent antibiotic usage, chronic obstructive pulmonary disease (COPD), and nursing home residency; but limited data are available regarding clinically relevant risk factors from larger cohort studies.[6, 9, 10, 18] Additionally, the actual prevalence of DRSP-CAP worldwide is unknown, and there is a need to evaluate the global prevalence of DRSP. In this regard, point-prevalence studies are useful to determine the global burden of infectious diseases in a specific time point.[19]

Our aim was to determine the prevalence of DRSP-CAP and identify specific DRSP risk factors at global, continental, and multinational levels.

STUDY POPULATION AND METHODS

Study Design

We enrolled adult subjects hospitalized with confirmed CAP in 222 hospitals around the world using a point-prevalence study.[20] Subjects were recruited on four days randomly selected by each local investigator during the months between March and June 2015. The University of Texas Health at San Antonio (UT Health San Antonio) functioned as the coordinating centre (IRB# HSC20150184E) and waived the need for informed consent due to the nature of the study. All other associated centres were required

to follow local, regional, or national ethics regulations. Research investigators included respiratory, infectious diseases, emergency, critical care, and internal medicine professionals who consented to voluntarily participate after individual email invitations. The project and investigators did not receive any funding and support was provided by the investigators' institutions.

Study Subjects

Adult subjects over the age of 18 hospitalized for CAP were screened for participation in this study. Subjects had to have at least one of the following signs, symptoms, or laboratory parameters: 1) new or worsening cough with or without sputum production; 2) fever with either a rectal or oral temperature above 37.8°C or hypothermia with a rectal or oral temperature below 36°C; 3) documentation of systemic inflammation with evidence of increased white blood cell count (leucocytosis >10,000/cm^3), leukopenia (<4,000/cm^3), or bandemia greater than 10%, increased C-reactive protein, or procalcitonin with values greater than the local upper limit of normal.[21] Additionally, subjects were required to have new lung infiltrates on chest imaging by lung ultrasound, chest radiograph, or chest computerized tomography during the first 48 hours of their hospital admission.

Inclusion Criteria: We included subjects with a diagnosis of CAP in whom bacterial testing were performed within 24 hours of hospitalization.

Exclusion Criteria: Hospitalized subjects diagnosed with hospital-acquired pneumonia (HAP) or ventilator associated pneumonia (VAP).[22]

Microbiological Analysis

Attending physicians in charge of each patient decided the diagnostic work up, including collection of respiratory and blood cultures. Microbiological testing was performed following local standard operating procedures for sputum, pleural fluid, tracheobronchial aspirates, bronchoalveolar lavage (BAL) fluid, blood and urine antigens during the initial 24 hours of hospital admission. The local medical facility's laboratory processed cultures of respiratory and blood samples, as well as drug sensitivity testing using standard protocols. Pneumococcal urinary antigen testing and all susceptibility testing were processed using local regulations and validated methods, per Clinical Laboratory Standards Institute (CLSI) protocols.[23, 24] The CLSI non-meningeal breakpoints to determine antimicrobial resistance were used.[23, 24]

Data Collection

Data collection was performed using REDCap™ (Research Electronic Data Capture), an electronic data-capturing tool, hosted on the UT Health San Antonio's server. REDCap is a secure, web-based product designed to facilitate data capture in research studies.[25] Enrolling medical centres were given seven days to complete data entry and verify microbiological results.

S. pneumoniae-CAP was defined by the isolation of pathogen from sputum, BAL, blood or positive urinary antigen. For subjects in whom the pneumococcal urinary antigen was positive, only those with concomitant *S. pneumoniae* isolated in a culture were included in the antibiotic susceptibility analysis. Drug-resistant *S. pneumoniae* (DRSP)-CAP was defined when a *S. pneumoniae* was documented to be resistant to at least one of the following antibiotics: penicillin, macrolide, levofloxacin, ceftriaxone or tetracycline.[9] Multidrug resistant (MDR) *S. pneumoniae* was defined as a bacterium that was resistant to at least three antibiotics and pan-drug resistant (XDR) *S. pneumoniae* was defined by resistance to all five antibiotics evaluated.

Statistical Analysis

Prevalence was calculated by determining the total number of subjects with *S. pneumoniae* or DRSP among all the subjects that had bacteriological testing. Continuous variables are presented as mean and standard deviation or median and interquartile ranges when appropriate. Chi-squared tests were used to compare categorical variables and results are presented as total counts and percentages. To assess the risk factors for *S. pneumoniae* and its antibiotic resistance (i.e., *S. pneumoniae* resistant to penicillin, levofloxacin, tetracycline or macrolide), logistic regression analyses were done to calculate the odds ratios (OR) with a 95% confidence interval (CI) and risk factors independently associated with *S. pneumoniae*-CAP or DRSP-CAP. A p-value of less than 0.05 defined statistical significance. Variables with less than 10 subjects were removed due to the low likelihood of statistically significant data. Prevalence maps were made using StatPlanet software by StatSilk. All statistical analyses were performed with IBM SPSS, Statistics for Mac, version 22.0, Armonk, NY: IBM Corp.

RESULTS

A total of 3,193 subjects were enrolled from 54 countries. All subjects had pneumonia confirmed by laboratory findings, radiographic imaging, and microbiological testing that were performed within the first 24 hours of hospitalization (Figure 1). Microbiological testing was obtained from blood (2,211/3,193 [69%]), sputum (1,630/3,193 [51%]), pneumococcal urinary antigen (1,106/3,193 [35%]) and bronchoalveolar lavage (311/3,193 [10%]). An etiological pathogen was identified in 1,173/3,193 (37%) of subjects (Figure 1). Subjects were predominantly male (2,143/3,193 [57.9%]), with median age [IQR] of 68 [54-80] years. Table 1 summarizes the demographics, comorbidities, chronic treatment, severity of disease, and other potential risk factors for DRSP-CAP of study subjects.

Streptococcus pneumoniae prevalence

S. pneumoniae was the most frequently identified pathogen in the total study cohort (8.3% [268/3,193]. The majority (81%) of *S. pneumoniae* isolates were obtained from respiratory samples (sputum 195/268, BAL 12/268, tracheal aspirate 7/268 and pleural effusion 2/268), and blood (19% [52/268]). Pneumococcal urinary antigen was positive in 51% (136/268) of subjects. The prevalence rates of *S. pneumoniae* CAP were 10.5% (203/1,941) in Europe, 9.4% (12/128) in Africa, 7.9% (16/203) in South America, 4.3% (21/484) in North America, 4.0% (16/405) in Asia, and 0% (0/32) in Oceania (Figure 2). The country with the highest *S. pneumoniae* prevalence rate was Spain compared to all other participating centres in other countries (19% [111/585] vs. 6% [157/2,608]; OR: 3.65;

95%CI: 2.8-4.75, p-value<0.001). Bulgaria, Moldova, Brazil, Australia, and Montenegro had the lowest prevalence rates with no *S. pneumoniae* identified by microbiological testing (Table 2). Among continents, Europe had the highest *S. pneumoniae* prevalence rate compared to the rest of the participating centres on other continents (10.5% [203/1,941] vs. 5.2% [65/1,252]; OR: 2.13; 95%CI: 1.59-2.84, p-value<0.001) (Table 2).

Drug-resistant *Streptococcus pneumoniae* (DRSP)

DRSP-CAP was diagnosed in 41 subjects (1.3% [41/3,193]) at the global level, with the highest prevalence rate found in Africa compared to other participating continents (7.0% [9/128] vs. 1.0% [32/3,065]; OR: 7.6; 95%CI: 3.34-15.35, p-value<0.001) (Table 2).

The most frequent pneumococcus antibiotic resistance was to macrolides ([0.6%] 19/3,193) and tetracycline ([0.6%] 19/3,193), followed by penicillin ([0.5%] 17/3,193). Africa was the only continent to have a statistically significant higher prevalence rate of penicillin, macrolide, and tetracycline resistance compared to the rest of participating centres on other continents (Table 3). MDR *S. pneumoniae* was detected in 6 subjects (0.2%) and XDR *S. pneumoniae* was identified in only 1 subject (0.03%). Among subjects with MDR *S. pneumoniae*, 4 were resistant to penicillin, macrolides and tetracycline; and the other 2 subjects were resistant to penicillin, macrolides and levofloxacin. Among subjects with *S. pneumoniae* isolated (n=268), MDR and XDR *S. pneumoniae* prevalence rates were 2.2% and 0.4%, respectively, however, specific antibiotic susceptibility rates were higher due to the low denominator (Table 3).

Risk factors

The risk factors associated with specific antibiotic resistance were: asthma (for penicillin and macrolide), liver disease (for tetracycline resistance) and non-cystic fibrosis bronchiectasis (for penicillin resistance) (Table 4). Influenza virus infection was most common among patients with *S. pneumoniae* CAP (p=0.02), but less common among DRSP-CAP (p=0.04). Influenza vaccination rate was higher among *S. pneumoniae* CAP (p=0.04), but not different among DRSP-CAP patients (p=0.93). Pneumococcal vaccination rate was lower than expected (15%) in this cohort of patients with CAP. No differences were observed for PPSP23 and PCV13 among the different groups, with the exception of a higher proportion of patients (n=5 [12%]) who received PCV13 prior to hospitalization in the DRSP group when compared to the non-DRSP cohort (n=9 [4%]), respectively (p=0.03). Previous pneumococcal vaccination was not associated with lower *S. pneumoniae* CAP or DRSP-CAP in the multivariate analysis. In addition pneumococcal vaccination status did not affect the prevalence of *S. pneumoniae* CAP in the different high risk groups according to the Centers for the Disease Control and Prevention recommendations.

DISCUSSION

This multicentre, international, point-prevalence study showed that *S. pneumoniae* is the most common pathogen isolated in subjects with CAP. The global prevalence rates of DRSP, MDR, and XDR *S. pneumoniae* infections in subjects with CAP are 1.3%, 0.2%, and 0.03%, respectively. We identified that DRSP-CAP, penicillin-resistant, macrolide-resistant, and tetracycline-resistant prevalence rates are variable among participating centres, revealing important differences between continents and countries within the

same continent. Asthma, liver disease, and non-cystic fibrosis bronchiectasis are independent risk factors associated with CAP caused by *S. pneumoniae* resistant to penicillin and macrolide, respectively.

The emergence of DRSP-CAP has become a prevalent problem for medical communities worldwide.[9, 26-28] Previous reports demonstrated 18% to 35% of subjects with CAP due to *S. pneumoniae* had DRSP-CAP. Cilloniz *et al*[15] recently reported *S. pneumoniae* resistant to macrolide in 22% (139 of 643 isolated *S. pneumoniae*) in a cohort of 5,878 subjects with CAP, admitted to a single centre in Barcelona, Spain over a 13-year period. Our study identified 41 subjects with DRSP-CAP with a global prevalence rate of 1.3% (41/3,193). The denominator used to calculate the prevalence rate most likely explains the lower prevalence rate in our study. We used the total number of subjects in whom a microbiological diagnosis was attempted (i.e., microbiologically eligible cohort) rather than the total number of subjects with *S. pneumoniae* isolated (i.e., susceptibility specific cohort). Microbiology testing practices are variable and may impact the rate of S. pneumoniae and DRSP as suggested by our group before.[29] Surveillance studies in antimicrobial resistance usually determine the prevalence of certain pathogens such as DRSP by using information provided in cumulative antibiograms for *S. pneumoniae* without considering the clinical context.[16, 17, 30] These studies include bacterial pathogens isolated from different expected normally sterile or non-sterile sites and subjects with a wide range of pathologies (e.g. sinusitis, meningitis, bacteraemia without focus and pneumonia with bacteraemia) to determine the most common antibiotic resistance patterns[16]. In clinical practice, knowing specific antibiotic susceptibilities is important for selection and de-escalation of antibiotics 48-72 hours after hospital admission.[21, 31] In contrast, susceptibility reports are not as useful for empiric selection of antibiotics at the time of admission when the etiological pathogen is not known.[32] Therefore, in our study we attempted to determine the prevalence and risk

factors of DRSP-CAP in the microbiologically eligible cohort as this better represents the prevalence at the time when physicians need to select antibiotic coverage.

Geographical differences in the prevalence of *S. pneumoniae* and its antimicrobial resistance patterns have been described previously.[8, 13, 15, 33] Prior studies present data that were gathered at different times and from different parts of the world, but our results represent a multinational study that evaluated several countries at the same point in time.[20] Thus, comparing continental and country prevalence rates of *S. pneumoniae* and DRSP in a large multicentre study provides data that is generalizable. In our study, DRSP-CAP prevalence rates varied from 0% to 7.0% among different continents, as well as among different countries within each continent. The prevalence rates observed suggest that Africa has the highest prevalence of DRSP-CAP considering all the antibiotic classes evaluated. The high prevalence rate of DRSP-CAP in Africa is consistent with the findings reported by other investigators. For instance, Borg *et al.*[34] reported penicillin resistance in 26%, and macrolide resistance in 46% of subjects with invasive pneumococcal disease (IPD) among seven African countries, although they included isolations from blood, sputum, and cerebrospinal fluid.[34] The authors stated that the lack of strong antibiotic stewardship programs and over-the-counter availability of antibiotics in several African countries might account for the high rates of antibiotic resistance in Africa.[35] Therefore, geographical variations represent a challenge to define clinical practice guidelines for the management of patients with CAP, particularly those due to pneumococcus.

We found that asthma, liver disease, and non-cystic fibrosis bronchiectasis were independently associated with resistance to specific antibiotics (i.e. penicillin, macrolides, and tetracycline). More importantly, risk factors previously reported in the literature, such as recent antimicrobial therapy, prior hospitalization within the last year, older age,[9, 15] and nursing home residency were found to

be significant only in the univariate analysis but not in the multivariate analysis. Our data on global DRSP-CAP risk factors may assist clinicians in identifying subjects that are at higher risk of being infected with DRSP.

Influenza viral infection and vaccination are important determinants for patients with pneumococcal CAP and DRSP-CAP. However, influenza viral coinfection and influenza vaccination were not independent risk factors for pneumococcal- and DRSP-CAP in our study, respectively. This should not undervalue the importance of influenza vaccination among patients at risk in the community as coinfection of influenza virus and pneumococcus may affect the risk of complications, admission to the hospital and poor outcomes. In addition to influenza vaccination, efforts to improve vaccination rates among patients at risk for pneumococcal infection around the globe are critical to impact the acquisition of invasive pneumococcal disease. In addition, it is possible that PCV13 may have an impact on antimicrobial resistance pneumococcal strains.

We recognize that our study has limitations. Similar to other point-prevalence studies, differences in hospitals, health care systems, and local/regional regulations and clinical practices in management of CAP is a limitation of our study. In addition, our point-prevalence study was not designed to address the impact of herd immunity among communities at risk and also did not include information regarding the timing the vaccine administration. An important strength is that we enrolled diverse groups of subjects from 222 hospitals in 54 countries worldwide, although we were not able to recruit many investigators from Asia and Africa resulting in a modest evaluation of DRSP-CAP prevalence rates on these continents. Even though differences in prevalence rates across continents and countries may be explained by seasonal variations, we enrolled subjects through June to ensure inclusion of subjects during the southern hemisphere's winter season to minimize the effects of seasonal variations.

CONCLUSION

The multinational prevalence rate of drug-resistant *Streptococcus pneumoniae* as the causative agent of CAP in this point-prevalence study is lower than previously reported. Differences in DRSP-CAP prevalence rates exist among continents and countries. Therefore, local treatment guidelines and hospital protocols should be based on local prevalence rates. Lastly, global risk factors independently associated with DRSP-CAP may assist medical professionals to appropriately select antibiotic coverage against DRSP. Multinational studies are needed to evaluate the ever-changing patterns of drug resistance among pathogens and understand the fluctuations globally over time.

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TABLES

Table 1. Characteristics of subjects with *Streptococcus pneumoniae* community-acquired pneumonia (CAP) vs. Non-*S. pneumoniae* CAP; subjects with Drug Resistant *S. pneumoniae* (DRSP)-CAP vs. Non-resistant *S. pneumoniae* CAP subjects.

	CAP n=3,193	***S. pneumoniae* CAP n=268**	**Non - *S. pneumoniae* CAP n=2,925**	**p value**	**DRSP-CAP n=41**	**Non-resistant *S. pneumoniae* CAP n=227**	**P value**
Demographic characteristics							
Age, median (IQR) years	68 (54, 80)	70 (54, 81)	68 (54, 80)	0.50	62 (48, 74)	70 (56, 81)	**0.008**
Male, n (%)	1,877 (58.8)	159 (59.3)	1,718 (58.7)	0.91	29 (70.7)	130 (57.3)	0.10
Underweight, n (%)	150 (4.7)	15 (5.6)	135 (4.6)	0.48	3 (7.3)	12 (5.3)	0.60
Obesity, n (%)	510 (16.0)	38 (14.2)	472 (16.1)	0.39	4 (9.8)	34 (15.0)	0.38
Alcoholism	267 (8.4)	25 (9.3)	242 (8.3)	0.56	8 (19.5)	17 (7.5)	**0.01**
Respiratory past medical history							
Asthma, n (%)	234 (7.3)	29 (10.8)	205 (7.0)	**0.02**	6 (14.6)	23 (10.1)	0.39
Bronchiectasis, n (%)	168 (5.3)	28 (10.4)	140 (4.8)	**<0.01**	6 (14.6)	22 (9.7)	0.34
Chronic aspiration, n (%)	218 (6.8)	13 (4.8)	205 (7.0)	0.18	1 (2.4)	12 (5.3)	0.44
Cirrhosis	64 (2.0)	10 (3.7)	54 (1.8)	**0.04**	2 (4.9)	8 (3.5)	0.67
COPD, n (%)	834 (26.1)	68 (25.4)	766 (26.2)	0.74	9 (22.0)	59 (26.0)	0.59
Current/former smoker, n (%)	1,114 (34.9)	104 (38.8)	1,010 (34.5)	0.17	14 (34.1)	90 (39.5)	0.52
Oxygen therapy at home, n (%)	208 (6.5)	13 (4.8)	195 (6.7)	0.24	3 (7.3)	10 (4.4)	0.42
Cardiovascular past medical history							
Arrhythmia, n (%)	455 (14.2)	34 (12.7)	421 (14.4)	0.43	3 (7.3)	31 (13.7)	0.26
Coronary artery disease, n (%)	526 (16.5)	38 (14.2)	488 (16.7)	0.28	2 (4.9)	36 (15.9)	0.06

Heart failure, n (%)	418 (13.1)	30 (11.2)	388 (13.3)	0.32	5 (12.2)	25 (11.9)	0.82
Hypertension, n (%)	1,444 (45.2)	134 (50.0)	1,310 (44.8)	0.09	23 (56.1)	112 (49.3)	0.41
Stroke, n (%)	250 (7.8)	16 (6.1)	234 (8.0)	0.23	3 (7.3)	13 (5.7)	0.69
Chronic medications							
Inhaled corticosteroids use, n (%)	544 (17.0)	55 (20.5)	489 (16.7)	0.12	9 (22)	46 (20.3)	0.80
Proton Pump Inhibitor use, n (%)	907 (28.4)	76 (28.4)	831 (28.4)	0.95	9 (22)	67 (29.5)	0.33
Statins use, n (%)	670 (21.0)	64 (23.9)	606 (20.7)	0.24	10 (24.4)	54 (23.8)	0.92
Steroids use, n (%)	268 (8.4)	18 (6.7)	250 (8.5)	0.29	3 (7.3)	15 (6.6)	0.86
Immunosuppressive conditions							
Active solid tumor, n (%)	245 (7.7)	18 (6.7)	227 (7.8)	0.53	1 (2.4)	17 (7.5)	0.24
Hematological malignancy, n (%)	150 (4.7)	14 (5.2)	136 (4.6)	0.68	0 (0)	14 (6.1)	0.10
HIV infection, n (%)	107 (3.4)	12 (4.5)	95 (3.2)	0.29	3 (7.3)	9 (4.0)	0.34
Immunocompromised subjects, n (%)	623 (19.5)	55 (20.5)	568 (19.4)	0.69	4 (9.8)	51 (22.5)	0.06
Other chronic medical conditions							
Chronic renal failure, n (%)	349 (10.9)	25 (9.3)	324 (11.1)	0.37	3 (7.3)	22 (9.7)	0.64
Dementia, n (%)	333 (10.4)	25 (9.3)	308 (10.5)	0.52	3 (7.3)	22 (9.7)	0.64
Diabetes mellitus, n (%)	681 (21.3)	55 (20.5)	626 (21.4)	0.71	11 (26.8)	44 (19.4)	0.27
Liver disease, n (%)	129 (4.0)	19 (7.1)	110 (3.8)	**0.01**	6 (14.6)	13 (5.7)	**0.04**
Malnutrition, n (%)	289 (9.1)	27 (10.1)	262 (9.0)	0.56	5 (12.2)	22 (9.7)	0.62
Mental illness, n (%)	220 (6.9)	12 (4.5)	208 (7.1)	0.10	2 (4.9)	10 (4.4)	0.89
Prosthetic material, n (%)	100 (3.1)	13 (4.9)	87 (3.0)	0.09	1 (2.4)	12 (5.3)	0.44
Other non-medical conditions							
Bedridden, n (%)	353 (11.1)	14 (5.2)	339 (11.6)	**0.001**	4 (9.8)	10 (4.4)	0.15
Living in crowded conditions, n (%)	671 (21)	57 (21.3)	614 (21.0)	0.94	10 (24.4)	47 (20.7)	0.59
Nursing home resident, n (%)	258 (8.1)	23 (8.6)	235 (8.0)	0.77	6 (14.6)	17 (7.5)	0.13
Prior healthcare exposure							

Antibiotic infusion at home during the last 12 months, n (%)	140 (4.4)	13 (4.9)	127 (4.3)	0.71	5 (12.2)	8 (3.5)	**0.02**
Emergency room admission in the last 12 months, n (%)	972 (30.4)	85 (31.7)	887 (30.3)	0.67	15 (36.6)	70 (30.8)	0.46
Hospitalization during the last 12 months, n (%)	1,026 (32.1)	68 (25.4)	958 (32.8)	**0.01**	13 (31.7)	55 (24.2)	0.30
IV antibiotics during the last 12 months, n (%)	812 (25.4)	66 (24.6)	746 (25.5)	0.72	16 (39)	50 (21.9)	**0.02**
LRTI in the last 12months, n (%)	928 (29.1)	82 (30.6)	846 (28.9)	0.59	15 (36.6)	67 (29.5)	0.36
Oral antibiotics during the last 12 months, n (%)	1,219 (38.2)	101 (37.7)	1,118 (38.2)	0.82	19 (46.3)	82 (36.1)	0.21
Interventions within the first 24 hours of hospital admission							
ICU/PCU admission, n (%)	845 (26.5)	65 (24.3)	780 (26.75)	0.39	10 (24.4)	55 (24.2)	0.98
Mechanical ventilation (invasive and non-invasive), n (%)	632 (19.8)	52 (19.4)	580 (19.8)	0.86	6 (14.6)	46 (20.3)	0.40
Vasopressors, n (%)	233 (7.3)	21 (7.8)	212 (7.2)	0.72	2 (4.9)	19 (8.4)	0.44
Concurrent pathogen							
Influenza virus infection	154 (4.8)	21 (7.8)	133 (4.5)	**0.02**	0 (0)	21 (9.3)	**0.04**
Pneumococcal Vaccination							
Pneumococcal conjugate vaccine (PCV13 or PPSV23**)**	481 (15.1)	47 (17.5)	434 (14.8)	0.23	12 (29.3)	35 (15.4)	**0.03**
• PPSV23	365 (11.4)	33 (12.3)	332 (11.4)	0.69	7 (17.1)	26 (11.5)	0.31
• PCV13	116 (3.6)	14 (5.2)	102 (3.5)	0.15	5 (12.2)	9 (4.0)	**0.03**
Influenza vaccination	897 (28.1)	90 (33.6)	807 (27.6)	**0.04**	14 (34.1)	76 (33.5)	0.93

CAD; Coronary artery disease; CAP; Community-acquired pneumonia, MRSA; Methicillin resistant Staphylococcus aureus, ESBL; Extended spectrum, beta-lactamases, COPD; Chronic obstructive pulmonary disease, HIV; human immunodeficiency virus, FEV_1; Forced expiratory volume in 1 second. Definitions for all the variables are in the supplementary material.

Table 2. Prevalence of *Streptococcus pneumoniae* per countries and continents.

	***Streptococcus pneumoniae* CAP n=268**					
			Rest of the world		**OR (95% CI)**	**p value**
	%	**n**	**%**	**n**		
Continent						
Global	8.3	268/3,193	.	.	.	.
Africa	9.4	12/128	8.4	256/3,065	1.13 (0.61-2.08)	0.68
Asia	4.0	16/405	9.0	252/2,788	0.41 (0.24-0.69)	**0.001**
Europe	10.5	203/1,941	5.2	65/1,252	2.13 (1.59-2.84)	**<0.001**
North merica	4.3	21/484	9.1	247/2,709	0.45 (0.28-0.71)	**<0.001**
Oceania	0	0/32	8.5	268/3,161	.	0.08
South merica	7.9	16/203	8.4	252/2,990	0.93 (0.54-1.57)	0.78
Countries						
Argentina	7.4	13/175	8.4	255/3,018	0.636 (0.48-1.55)	0.63
Bulgaria	0	0/37	8.5	268/3,156	.	0.06
Croatia	5.3	5/94	8.5	263/3,099	0.606 (0.24-1.50)	0.27
Denmark	3.5	3/86	8.5	265/3,107	0.388 (0.12-1.24)	0.09
France	6.3	4/63	8.4	264/3,130	0.736 (0.26-2.04)	0.55
Germany	7.5	10/134	8.4	258/3,059	0.876 (0.45 - 1.69)	0.69
Greece	9.4	8/85	8.4	260/3,108	1.138 (0.54-2.38)	0.73
India	2.0	3/150	8.7	265/3,04	0.214 (0.06-	**0.004**

				3	0.676)	
Ireland	3.1	1/32	8.4	267/3,161	0.350 (0.04-2.57)	0.28
Italy	6.3	24/381	8.7	244/2,812	0.708 (0.45-1.09)	0.11
Moldova	0	0/31	8.5	268/3,162	.	0.09
Montenegro	0	0/1	8.4	268/3,192	.	0.76
Netherlands	16.3	7/43	8.3	261/3,150	2.15 (0.94 - 4.88)	0.06
Pakistan	3.7	4/107	8.6	264/3,086	0.415 (0.15-1.14)	0.07
Portugal	12.9	13/101	8.2	255/3,092	1.644 (0.90-2.98)	0.09
Saudi Arabia	2.4	1/42	8.5	267/3,151	0.263 (0.03-1.92)	0.15
Serbia	2.4	1/41	8.5	267/3,152	0.270 (0.03-1.97)	0.16
Spain	19.0	111/585	6.0	157/2,608	3.65 (2.81-4.75)	**<0.001**
United Kingdom	5.7	8/140	8.5	260/3,053	0.651 (0.31-1.34)	0.24
United States	4.3	19/442	9.1	249/2,751	0.451 (0.28-0.728)	**0.001**

Table 3. Prevalence of Drug Resistant *S. pneumoniae* (DRSP) per continents.

	CAP cohort n=3,193						**Susceptibility specific cohort n=268**					
	Continent		**Rest of the world**		**OR (95% CI)**	**p value**	**Continent/Country**		**Rest of the world**		**OR (95% CI)**	**p value**
	%	**n**	**%**	**n**			**%**	**n**	**%**	**n**		
Drug resistant *Streptococcus pneumonia* (DRSP)												
Global	1.3	41/3,193	.	.	.	.	14.9	41/268	.	.	.	.
Africa	7.0	9/128	1.0	32/3,065	7.16 (3.34-15.35)	**<0.001**	75.0	9/12	12.5	32/256	14 (3.98-49.1)	**<0.001**
Asia	1.2	5/405	1.3	36/2,788	0.92 (0.37-2.44)	0.92	31.2	5/16	14.2	36/252	2.81 (0.92-8.60)	0.06
Europe	1.0	20/1,941	1.7	21/1,252	0.61 (0.32-1.13)	0.11	9.8	20/203	32.3	21/65	0.24 (0.12-0.49)	**<0.001**
North America	1.0	5/484	1.3	36/2,709	0.77 (0.30-1.98)	0.59	23.8	5/21	14.6	36/247	1.89 (0.65-5.49)	0.24
Oceania	0	0/32	1.3	41/3,161	.	0.62	0	0/0	15.2	41/268	.	.
South America	1.0	2/203	1.3	39/2,990	0.75 (0.18-3.14)	0.69	12.5	2/16	15.4	39/252	0.80 (0.17-3.68)	0.77
***S. pneumoniae* Penicillin resistant**												
Global	0.5	17/3,193	.	.	.	.	6.3	17/268	.	.	.	.
Africa	4.7	6/128	0.4	11/3,065	13.6 (4.96-37.5)	**<0.001**	50.0	6/12	4.3	11/256	15.9 (4.34-58.1)	**<0.001**
Asia	0.5	2/405	0.5	15/2,788	0.91 (0.20-4.02)	0.90	12.5	2/16	5.9	15/252	2.42 (0.50-11.7)	0.27
Europe	0.3	6/1,941	0.9	11/1,252	0.35 (0.12-0.94)	**0.03**	3.0	6/203	16.9	11/65	0.16 (0.05-0.48)	**0.001**
North America	0.2	1/484	0.6	16/2,709	0.34 (0.04-2.63)	0.28	4.8	1/21	6.4	16/247	0.77 (0.09-6.16)	0.80
Oceania	0	0/32	0.5	17/3,161	.	0.67	0	0/0	6.3	17/268	.	.
South America	1.0	2/203	0.5	15/2,990	1.97 (0.44-8.68)	0.36	12.5	2/16	5.9	15/252	2.42 (0.50-11.7)	0.27
***S. pneumoniae* Macrolide resistant**												
Global	0.6	20/3,193	.	.	.	.	7.5	20/268	.	.	.	.
Africa	3.9	5/128	0.5	15/3,065	8.26 (2.95-23.1)	**<0.001**	41.6	5/12	5.8	15/256	8.03 (2.17-29.7)	**0.002**
Asia	0.5	2/405	0.6	18/2,788	0.76 (0.17-3.30)	0.71	12.5	2/16	7.1	18/252	1.97 (0.41-9.40)	0.39
Europe	0.6	11/1,941	0.7	9/1,252	0.78 (0.32-1.90)	0.59	5.4	11/203	13.8	9/65	0.40 (0.15-1.06)	0.06
North America	0.4	2/484	0.7	18/2,709	0.62 (0.14-2.68)	0.51	9.5	2/21	7.3	18/247	1.42 (0.30-6.63)	0.65
Oceania	0	0/32	0.6	20/3,161	.	0.65	0	0/0	7.5	20/268	.	.
South America	0	0/203	0.7	20/2,990	.	0.24	0	0/16	7.9	20/252	.	0.69
***S. pneumoniae* Tetracycline resistant**												
Global	0.6	19/3,193	.	.	.	**.**	6.7	19/268	.	.	.	.
Africa	2.3	3/128	0.5	16/3,065	4.57 (1.31-15.9)	**0.009**	16.7	3/12	6.3	16/256	3.00 (0.60-14.8)	0.17
Asia	1.0	4/405	0.5	15/2,788	1.84 (0.60-5.58)	0.27	25	4/16	5.9	15/252	5.66 (1.61-19.8)	**0.007**
Europe	0.6	11/1,941	0.6	8/1,252	0.88 (0.35-2.21)	0.79	5.4	11/203	12.3	8/65	0.47 (0.17-1.28)	0.14
North America	0.2	1/484	0.7	18/2,709	0.31 (0.04-2.32)	0.22	4.8	1/21	7.3	18/247	0.67 (0.08-5.35)	0.71
Oceania	0	.	0.6	19/3,161	.	0.66	0	0/0	7.1	19/268	.	.

South America	0	0/203	0.6	19/2,990	.	0.25	0	0/16	7.5	19/252	.	0.71

Table 4. ***S. pneumoniae and DRSP risk factors by multivariate analyses***

Group n= 3,193	**Asthma**	**Liver Disease**	**Non-cystic fibrosis bronchiectasis**	**Alcoholism**
Streptococcus pneumoniae	.	1.81 (1.08-3.03)	2.27 (1.47-3.49)	.
Drug resistant *S. pneumoniae*	.	.	.	.
Penicillin resistant *S. pneumoniae*	5.85 (1.85-18.43)	.	4.00 (1.02-15.64)	4.48 (1.26-15.82)
Macrolide resistant *S. pneumoniae*	3.36 (1.06-10.61)	.	.	.
Tetracycline resistant *S. pneumoniae*	.	4.57 (1.24-16.81)	.	.

Table 5. ***Prevalence of S. pneusmoniae-CAP among patients at risk for pneumococcal infection stratified according to the Centers for Disease Control and Prevention (CDC)* recommendations for pneumococcal vaccination status.***

Risk stratification	CAP n=3,193 n(%)	*S. pneumoniae* CAP n=268 n(%)	Non-*S. pneumoniae* CAP - n=2,925 n(%)	p value
All CAP Patients n=3,193				
≥ 65 years of age	1810 (56.7)	157 (58.6)	1653 (56.5)	0.51
Immunocompromised	1018 (31.9)	81 (30.2)	937 (32.0)	0.54
• Immunocompromised with < 65 years of age	419 (30.3)	33 (29.7)	386 (30.3)	0.89
Comorbidities	2118 (66.3)	184 (68.7)	1934 (66.1)	0.40
• < 65 years of age	809 (58.5)	71 (64.0)	738 (58.0)	0.22
• < 65 years of age with no immunocompromised	555 (57.6)	47 (60.3)	508 (57.3)	0.62
Healthy	409 (12.8)	31 (11.6)	378 (12.9)	0.62
Vaccinated – n=481				
≥ 65 years of age	349 (72.6)	33 (70.2)	316 (72.8)	0.70
• Immunocompromised	197 (41.0)	18 (38.3)	179 (41.2)	0.70
• Immunocompromised with < 65 years of age	72 (54.5)	6 (42.9)	66 (55.9)	0.35
Comorbidities	378 (78.6)	38 (80.9)	340 (78.3)	0.69
• < 65 years of age	100 (75.8)	11 (78.6)	89 (75.4)	0.79
• < 65 years of age with no immunocompromised	45 (75.0)	5 (62.5)	40 (26.9)	0.38
Healthy	15 (25.0)	3 (37.5)	12 (23.1)	0.38
Unvaccinated				
≥ 65 years of age	1461 (53.9)	1241 (52.1)	1337 (53.7)	0.49
Immunocompromised	821 (30.3)	63 (28.5)	758 (30.4)	0.55
• Immunocompromised with < 65 years of age	347 (27.7)	27 (27.8)	320 (27.7)	0.98
Comorbidities	1740 (64.2)	146 (66.1)	1594 (64.0)	0.54
• < 65 years of age	709 (56.7)	60 (61.9)	649 (56.2)	0.28
• < 65 years of age with no immunocompromised	510 (56.4)	42 (60.0)	468 (56.1)	0.53
Healthy	394 (34.6)	28 (40.0)	366 (43.9)	0.53

* Centers for disease control and prevention recommendations

(https://www.cdc.gov/vaccines/vpd/pneumo/downloads/pneumo-vaccine-timing.pdf)

FIGURE LEGENDS

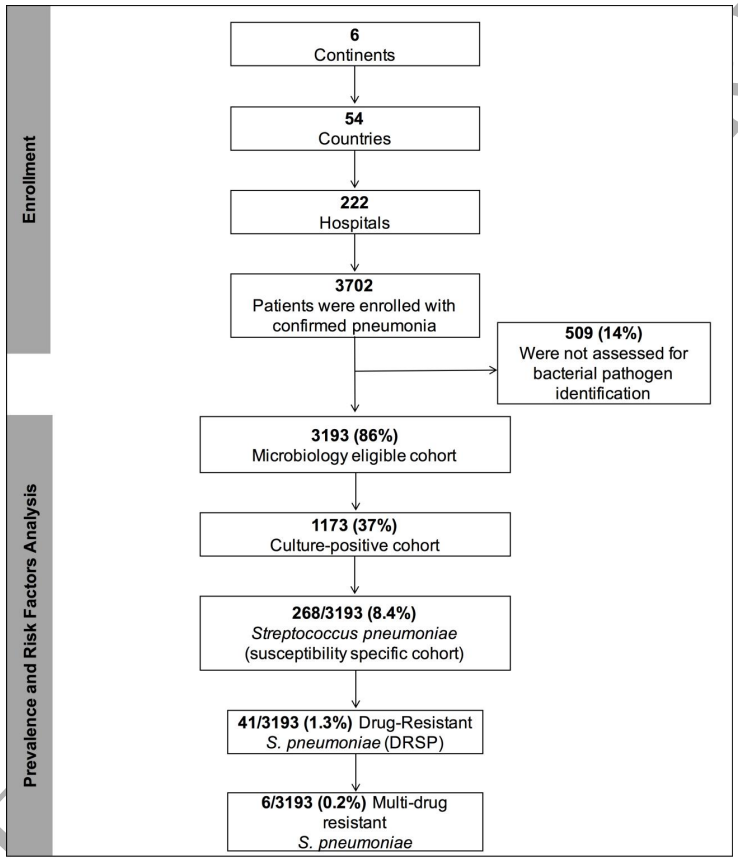

Figure 1. Study flow diagram of hospitalized patients with pneumonia.

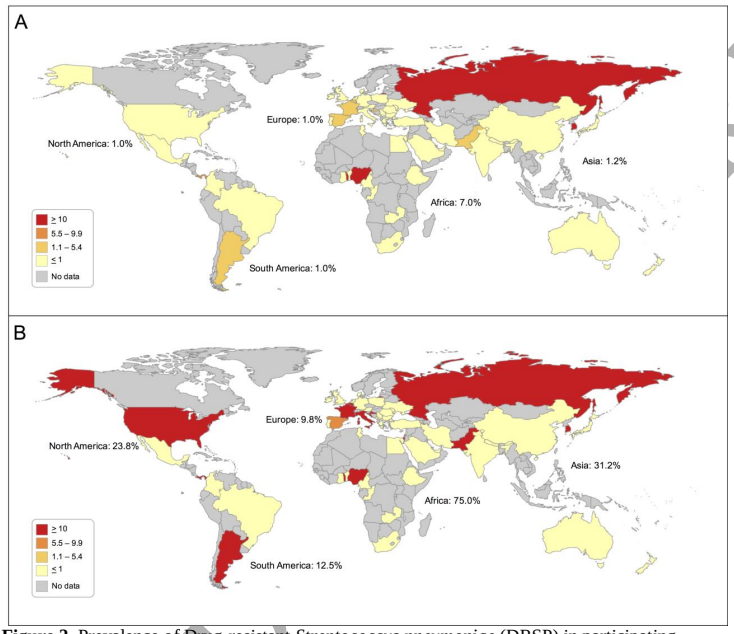

Figure 2. Prevalence of Drug-resistant *Streptococcus pneumoniae* (DRSP) in participating centres representing different countries and continents in a cohort of subjects with CAP (A) and subjects with antibiotic susceptibility reports available after *Streptococcus pneumoniae* isolation (B).