

# Influenza and Bacterial Coinfection in Adults With Community-Acquired Pneumonia Admitted to Conventional Wards: Risk Factors, Clinical Features, and Outcomes

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**Background.** Relevance of viral and bacterial coinfection (VBC) in non-intensive care unit (ICU) hospitalized adults with community-acquired pneumonia (CAP) is poorly characterized. We aim to determine risk factors, features, and outcomes of VBC-CAP in this setting.

**Methods.** This is a prospective cohort of adults admitted to conventional wards with CAP. Patients were divided into VBC-CAP, viral CAP (V-CAP), and bacterial CAP (B-CAP) groups. Independent risk and prognostic factors for VBC-CAP were identified.

**Results.** We documented 1123 episodes: 57 (5.1%) VBC-CAP, 98 (8.7%) V-CAP, and 968 (86.1%) B-CAP. Patients with VBC-CAP were younger than those with B-CAP (54 vs 71 years;  $P < .001$ ). Chronic respiratory disease was more frequent in patients with VBC-CAP than in those with V-CAP (26.3% vs 14.3%;  $P = .001$ ). Among those with influenza ( $n = 153$ ), the VBC-CAP group received empirical oseltamivir less often (56.1% vs 73.5%;  $P < .001$ ). Patients with VBC-CAP also had more respiratory distress (21.1% VBC-CAP; 19.4% V-CAP, and 9.8% B-CAP;  $P < .001$ ) and required ICU admission more often (31.6% VBC-CAP, 31.6% V-CAP, and 12.8% B-CAP;  $P < .001$ ). The 30-day case-fatality rate was 3.5% in the VBC-CAP group, 3.1% in the V-CAP group, and 6.3% in the B-CAP group ( $P = .232$ ). Furthermore, VBC-CAP was associated with severity criteria (odds ratio [OR], 5.219;  $P < .001$ ) and lack of empirical oseltamivir therapy in influenza cases (OR, 0.401;  $P < .043$ ).

**Conclusions.** Viral and bacterial coinfection-CAP involved younger patients with comorbidities and with poor influenza vaccination rate. Patients with VBC-CAP presented more respiratory complications and more often required ICU admission. Nevertheless, 30-day mortality rate was low and related either to severity criteria or to delayed initiation of oseltamivir therapy.

**Keywords.** clinical features; coinfection; community-acquired pneumonia; influenza virus; prognostic factors.

Community-acquired pneumonia (CAP) continues to be one of the main causes of morbidity and mortality worldwide [1]. It accounts for over 4.5 million outpatient and emergency room visits annually in the United States [2], leading to 24.8 admissions per 10 000 adults per year, with higher rates in elderly patients [3]. A review of 98 studies assessing the burden of CAP among adults in Europe found that its incidence varied

by country, age, and gender [4]. In Spain, a population-based cohort study of 11 241 patients aged  $\geq 65$  years reported an incidence of 14 cases per 1000 person-years [5].

The prognosis of patients with CAP also varies greatly. It is notable that the in-hospital 30-day mortality ranges from 4% to 18%, rising to 50% in patients admitted to the intensive care unit (ICU) [6]. Several factors other than age are associated with mortality, including comorbidities, frailty, cardiovascular complications [7], inflammatory response [8], and etiology [9]. *Streptococcus pneumoniae* also continues to be the most frequently identified bacteria in patients with CAP, although the overall incidence of pneumococcal pneumonia appears to be decreasing in some institutions [10], and interestingly, respiratory viruses are increasingly being identified [11]. No pathogens are identified by traditional microbiological analysis in up to 62% of cases [12]. With the advent of multiple molecular detection tests, the detection of viral and bacterial coinfection (VBC) in CAP has increased. In a prospective study of 49 adults admitted to ICUs with CAP, 39% of those in whom viral

Received 20 November 2019; editorial decision 20 February 2020; accepted 25 February 2020.

Presented in part: 23rd Congress of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC), 23 May 2019, Madrid, Spain.

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DOI: 10.1093/ofid/ofaa066

polymerase chain reaction (PCR) techniques were applied had VBC [13]. However, the role of VBC is controversial because the presence of bacteria in the airway can lead to viral replication and vice versa [14]. In addition, up to 38% of healthy people who tested positive for influenza viruses in nasal epithelium do not develop disease [15].

The role of VBC in CAP has been analyzed in some reports, but many of these have had important limitations. Some have focused on patients admitted to the ICU [13, 16, 17], and others have involved only pediatric patients [18], both of which can lead to significant bias when determining the impact of VBC on the overall population of patients with CAP. In other research, severely immunocompromised patients have been included, which risks significant host-dependent bias in potential severity [19]. Moreover, the etiology of CAP may be different in immunocompromised hosts, with the results of a large multicenter study by Di Pasquale et al [20] reporting that these patients more often had a viral etiology.

Given the limitations of existing research, the relevance of VBC in immunocompetent adults hospitalized to non-ICU setting with CAP remains poorly characterized. Therefore, in the present study, we aim to determine risk factors, clinical features, and outcomes of VBC-CAP in adults without severe immunocompromise who are admitted to conventional wards.

## METHODS

### Study Design, Setting, and Participants

The study consisted of a prospective cohort that was not originally designed to perform this analysis of patients admitted to 2 tertiary hospitals in Barcelona, Spain: Hospital Universitari de Bellvitge and SCIAS-Hospital de Barcelona. Hospital Universitari de Bellvitge is a referral public center for Southern Hospitalet and El Prat de Llobregat. SCIAS-Hospital de Barcelona is a private center, which does not cover a specific geographical area. Furthermore, the 2 centers are located in different parts of Barcelona. The study was approved by the Ethics Committee of the coordinating center as Spanish legislation requires, and the procedures followed were in accordance with the ethical standards of the Helsinki Declaration. Due to the retrospective analysis of the prospectively observational collected data, written informed consent was waived by the local Ethics Committee.

We included all immunocompetent adults (age >18 years old) initially admitted to conventional medical wards with a radiologically and microbiologically confirmed diagnosis of CAP between January 2009 and December 2016. Immunocompromised patients such as those with human immunodeficiency virus infection, active malignancy, or receiving any immunosuppressant drug were excluded from the study. Approximately half of the patients were included during the winter season. Patients admitted to the hospital with the diagnosis of pneumonia were

identified from a hospital admissions' list by the research team during the first 48 hours from admission. For analysis, we divided patients with CAP into 3 groups according to their etiology: VBC-CAP, viral CAP (V-CAP), and bacterial CAP (B-CAP).

### Clinical Assessment

There was no standardization of the microbiological studies, hospital admission criteria, or treatment decisions, which were instead at the discretion of attending physicians, thereby replicating real-world practice. Patients were seen during their hospital stays by 1 or more of the investigators, and their data were recorded with the aid of a standardized computer-based protocol. To stratify patients with pneumonia according by prognosis, the pneumonia severity index, Simplified Acute Physiology Score, and CURB-65 score were determined.

### Definitions

Pneumonia was defined as the presence of a new infiltrate on a chest radiograph plus fever (temperature  $\geq 38^{\circ}\text{C}$ ) and/or respiratory symptoms including dyspnea, chest pain, and productive cough. Pneumonia due to coinfection (VBC-CAP) was diagnosed in patients presenting a positive viral PCR test and evidence of bacterial infection by blood culture, Gram stain and sputum culture, pleural effusion culture, or urinary antigen for *S pneumoniae* and *Legionella pneumophila*. Primary viral pneumonia (V-CAP) was diagnosed in patients presenting pneumonia with negative respiratory and blood cultures for bacteria and with negative urinary antigen tests and positive viral PCR from a nasopharyngeal swab. Bacterial pneumonia (B-CAP) was diagnosed in patients with  $\geq 1$  positive culture (blood, Gram stain and sputum, pleural aspirate, or urinary antigen). The absence of PCR viral diagnostic test was not an exclusion criterion to the B-CAP group. An etiologic diagnosis was considered definitive in the following situations: positive viral PCR from a nasopharyngeal swab, isolation of a respiratory pathogen in a usually sterile specimen, isolation of *L pneumophila* in sputum, detection of *L pneumophila* serogroup 1 or pneumococcal antigen in the urine, a 4-fold increase in the antibody titer, or seroconversion for atypical pathogens. Presumptive aspiration pneumonia was diagnosed on a clinical and radiological basis in patients with risk factors (eg, compromised consciousness, altered gag reflex, dysphagia, severe periodontal diseases, putrid sputum and radiographic evidence of involvement of a dependent pulmonary segment, or necrotizing pneumonia). Cases that did not meet any of the criteria in this section were considered pneumonias of unknown etiology and were excluded. Septic shock was diagnosed when the systolic blood pressure was  $< 90$  mmHg and the patient required vasopressor therapy.

Vaccination status was assessed from interviews with the patients or their relatives and from review of hospital and personal

health records. A person was considered vaccinated against the *S pneumoniae* and influenza at admission if they had been given a 23-valent polysaccharide pneumococcal vaccine within 5 years or had received a seasonal influenza vaccine in the prior year, respectively. Comorbidities were recorded and assessed by the Charlson comorbidity index.

Time to clinical stability was established from admission with CAP to patients reaching the following objective criteria: oral intake capacity, absence of exacerbation of underlying diseases, and stable vital signs (body temperature  $\leq 37.8^{\circ}\text{C}$ , respiratory rate  $\leq 24$  breaths/minute, and systolic blood pressure  $\geq 90$  mmHg without vasoactive support). Complications were defined as any untoward events that occurred during hospitalization. Prehospital antibiotic treatment was defined as the oral intake of antimicrobials prescribed  $>24$  hours for the acute episode. Empirical treatment was defined as the first treatment received with no microbiological information. Broad-spectrum treatment includes carbapenem, piperacillin-tazobactam, and any type of antipseudomonal treatment. The in-hospital 30-day case-fatality rate was defined as death from any cause within 30 days of hospital admission.

#### Microbiological Studies

Microbiological diagnostic techniques were performed following the local guidelines in all patients, and viral PCR was requested based on clinical suspicion. In the case of viral PCR, information in adults with CAP was only available in patients in whom the result was positive.

Viral infection was established by 2 specific multiplex real-time PCR devices used for typing and subtyping influenza virus, as detailed in the real-time RT-PCR Protocol for Detection and Characterization of Influenza A supplied by the Centers for Disease Control and Prevention (Atlanta, GA) [21]. Human respiratory syncytial respiratory virus and human metapneumovirus (hMPV) were also detected using 2 specific multiplex real-time PCR devices [22].

The investigation of bacterial pathogens in blood, sputum, and other samples was performed by standard microbiologic procedures within the first 48 hours after admission. We detected *S pneumoniae* antigen in urine by rapid immunochromatographic assay (NOW Assay; Binax Inc., Portland, ME) or enzyme-like immunosorbent assay (ELISA-Bartels, Wicklow, Ireland) and *L pneumophila* serogroup 1 antigen by an immunochromatographic method (NOW Legionella Urinary Antigen; Binax Inc.). Standard serologic methods were used to determine antibodies against atypical bacteria.

#### Statistical Analysis

Descriptive statistical analysis was performed for all study variables, with proportions calculated as percentages of patients with available data. We compared patients among the VBC-CAP, V-CAP, and B-CAP groups. The Kolmogorov-Smirnoff

test was used to check for normality. Significant differences were then tested using the  $\chi^2$  test between qualitative variables and the Student's *t* distribution or Mann-Whitney *U* test between quantitative variables. To determine the factors potentially associated with developing VBC-CAP, compared with V-CAP and B-CAP, we performed a multivariate analysis by multinomial logistic regression for variables with statistical significance in the univariate analysis. Severity variables (ie, ICU admission, mechanical ventilation, shock, and vasoactive drug use) were grouped together based on multicollinearity (the correlation coefficient was  $>0.6$ ).

## RESULTS

#### Patient Characteristics and Clinical Features

We assessed a total of 1916 patients during the study period, and after excluding those without a documented microbiological diagnosis, 1123 were finally evaluated. This cohort comprised 57 cases of VBC-CAP (5.07%), 98 cases of V-CAP (8.72%), and 968 cases of B-CAP (86.16%). Of note, coinfection accounted for only 36.77% of cases among patients with pneumonia and viral involvement. The demographic and clinical characteristics of the 3 groups are shown in Tables 1 and 2. The median age of patients with VBC-CAP was similar to that of the V-CAP group, but it was significantly lower than that of the B-CAP group ( $P < .001$ ). However, comorbidities, particularly chronic respiratory diseases, were more frequent in the VBC-CAP group than in the V-CAP group ( $P = .001$ ). Furthermore, the rate of seasonal influenza vaccination was significantly lower in the VBC-CAP group compared with the B-CAP group ( $P < .001$ ).

Symptom onset was shorter in the VBC-CAP group than in the V-CAP group ( $P = .017$ ), and patients were more likely to present with purulent sputum ( $P = .008$ ) and cough ( $P < .001$ ), whereas myalgia was more frequent in the VBC-CAP group than in the B-CAP group ( $P < .001$ ). It is interesting to note that the VBC-CAP group received prehospital antibiotics less often than the V-CAP and B-CAP groups ( $P < .001$ ). Although all severity scores were significantly higher in the B-CAP group, bilateral pulmonary involvement and septic shock at presentation were significantly more common in the VBC-CAP group.

#### Microbiological Results

Table 3 summarizes the viral and bacterial etiologies. Blood culture was performed in 86.16% of patients, sputum culture was performed in 65.29%, *S pneumoniae* urine antigen test was performed in 89.19%, *Legionella* spp urine antigen test was performed in 58.82%, and serology for atypical pathogens was performed in 43.78%. There were no significant differences in the number of diagnostic tests performed in the 2 centers or among study groups, except for atypical pathogens serology: 68.42% was performed in the VBC-CAP group, 68.36% was performed in the V-CAP group, and 38.73% was performed in B-CAP

**Table 1. Baseline Characteristics**

Characteristics	VBC-CAP (n = 57)	V-CAP (n = 98)	B-CAP (n = 968)	PValue
Age (years, media, IQR)	54 (42.50–69.50)	55 (42.75–70)	71 (56–80)	<.001
Male sex	39 (68.42% <sup>a</sup> )	56 (54.36%)	633 (65.4%)	.224
Charlson index (IQR)	2 (0–3)	2 (1–3)	3 (1–4)	.062
Comorbidities	32 (56.1%)	54 (55.1%)	760 (78.5%)	<.001
Chronic respiratory disease	15 (26.3%)	14 (14.3%)	309 (31.9%)	.001
Diabetes mellitus	9 (15.8%)	20 (20.4%)	220 (22.7%)	.428
Chronic cardiac failure	8 (14%)	21 (21.4%)	237 (24.5%)	.168
Malignancy	3 (5.3%)	5 (5.1%)	111 (11.5%)	.061
Chronic kidney disease <sup>b</sup>	6 (10.5%)	10 (10.2%)	135 (13.9%)	.470
Chronic liver disease <sup>c</sup>	6 (10.5%)	6 (6.1%)	95 (9.8%)	.478
Cerebrovascular disease	2 (3.5%)	6 (6.1%)	102 (10.5%)	.098
Dementia	2 (3.5%)	5 (5.1%)	92 (9.5%)	.119
Corticosteroids	3 (5.4%)	10 (11%)	58 (6.3%)	.210
Immunosuppressors	8 (14.3%)	12 (13.2%)	114 (12.3%)	.894
Chemotherapy	1 (1.8%)	1 (1.1%)	12 (1.3%)	.937
HIV	2 (3.6%)	3 (3.3%)	47 (5.1%)	.675
Prehospital antibiotics	2 (3.5%)	29 (29.6%)	164 (17%)	<.001
Influenza vaccine (season)	16 (30%)	23 (26.7%)	483 (53.3%)	<.001
Pneumococcal vaccine (≤5 years)	10 (19.2%)	12 (14.10%)	187 (21.7%)	.251

Abbreviations: B-CAP, bacterial community-acquired pneumonia; HIV, human immunodeficiency virus; IQR, interquartile range; V-CAP, viral CAP; VBC-CAP, viral and bacterial coinfection CAP.

<sup>a</sup>Proportions were calculated as percentages of patients with available data.

<sup>b</sup>Includes patients with mild and moderate and severe chronic renal disease according to Charlson comorbidity index.

<sup>c</sup>Includes patients with mild, moderate, and severe chronic liver diseases according to Charlson comorbidity index.

patients. As shown, *S pneumoniae* was the most frequently documented bacteria in the VBC-CAP (80.70%) and B-CAP (63.22%) group. Influenza A H1N1 was the most frequently documented virus in the VBC-CAP (66.66%) and V-CAP (85.70%) groups. Coinfection due to *S pneumoniae* and influenza A H1N1 was present in 54.38% of cases in the VBC-CAP group. Most patients in this group presented with an influenza A virus (82.2%), none had coinfection with gram-negative bacilli and *Staphylococcus aureus* isolation in this group was scarce (7.01%).

#### Antibiotic Treatment and Clinical Outcomes

Data regarding antibiotic treatment and clinical outcomes in the different study groups are summarized in Table 4. It is notable that the VBC-CAP group received empirical treatment with oseltamivir less frequently than the V-CAP group ( $P < .001$ ), with most patients receiving empirical combination therapy. This typically comprised a beta-lactam plus a fluoroquinolone, especially in VBC-CAP group ( $P = .001$ ). Fluoroquinolone monotherapy was used significantly more often in the V-CAP group ( $P < .001$ ). Intensive care unit admission ( $P < .001$ ) and mechanical ventilation ( $P < .001$ ) were required significantly more often for patients with VBC-CAP-C and V-CAP. Overall, the 30-day case-fatality rate was similar in all groups, with a trend toward a higher frequency in the B-CAP group ( $P = .232$ ).

#### Factors Associated With Coinfection

Table 5 shows that factors that were associated with coinfection. Lack of prehospital antibiotic administration, purulent sputum,

and lack of empirical oseltamivir therapy were independent risk factors for VBC-CAP when compared with the V-CAP and B-CAP groups. Compared with the B-CAP group, severity criteria were more likely to be present in the VBC-CAP group (OR, 5.219;  $P < .001$ ) and showed a trend to being more likely in the V-CAP group (OR, 2.715;  $P = .060$ ).

#### DISCUSSION

To date, few studies have assessed the clinical features and outcomes of VBC-CAP in immunocompetent adults admitted to conventional medical wards [23, 24]. Most studies addressing VBC have analyzed different clinical presentations of respiratory viral infection together and have included patients without pneumonia [25, 26]. In addition, the majority have been performed in ICU settings [16, 17, 27]. Although VBC was first described at the beginning of the 20th century during an influenza pandemic [28], it was only during the pandemic of 2009 that VBC was highlighted as a complication of V-CAP. The recent introduction of comprehensive molecular tests for diagnosing adults with CAP could help to demonstrate VBC-CAP as a separate diagnostic category [29].

In our large cohort of patients with CAP, we found an overall low percentage with VBC-CAP. Nevertheless, when analyzing the sum of patients with viral infection, the rate of coinfection varied significantly from 5.07% to 36%, and it was higher than reported in previous studies of patients with influenza pneumonia [30]. Patients with VBC-CAP were significantly younger



**Table 2. Clinical Characteristics<sup>a</sup>**

Characteristics	VBC-CAP (n = 57)	V-CAP (n = 98)	B-CAP (n = 968)	P Value
Days from onset of symptoms to admission (median, IQR)	4 (3–7)	5 (3–7)	4 (2–7)	.017
<b>Clinical Manifestations</b>				
Axillary temperature $\geq 38^{\circ}\text{C}$	31 (54.4%)	54 (55.1%)	757 (43.0%)	.017
Previous URTI	15 (26.3%)	35 (35.7%)	294 (30.5%)	.766
Chills	21 (36.8%)	29 (29.6%)	368 (38.1%)	.249
Diarrhea/vomiting	7 (12.3%)	25 (25.5%)	202 (20.9%)	.148
Cough	56 (98.2%)	95 (96.9%)	833 (86.1%)	<.001
Purulent sputum	36 (63.20%)	34 (37%)	435 (46.7%)	.008
Chest pain	15 (26.3%)	15 (15.3%)	351 (36.3%)	<.001
Dyspnea	40 (70.20%)	73 (74.5%)	660 (68.2%)	.427
Headache	7 (12.30%)	17 (17.3%)	136 (14.0%)	.612
Myalgia	29 (50.9%)	54 (55.10%)	176 (18.2%)	<.001
Confusion	3 (5.3%)	5 (5.1%)	170 (17.6%)	<.001
Septic shock at presentation	6 (10.5%)	7 (12.1%)	63 (9.1%)	.028
<b>Radiological Findings</b>				
Multilobular involvement	3 (5.3%)	7 (7.1%)	222 (12.6%)	.047
Bilateral pulmonary infiltrates	20 (35.1%)	31 (31.6%)	363 (20.6%)	<.001
Interstitial pattern	5 (8.8%)	32 (32.7%)	31 (1.8%)	<.001
Unilobular pulmonary infiltrates	28 (49%)	28 (28.6%)	1159 (65.8%)	<.001
Pleural effusion	8 (14%)	7 (7.2%)	277 (15.7%)	.073
<b>Laboratory Findings</b>				
Respiratory insufficiency	38 (67.9%)	58 (63.73%)	504 (59.7%)	.163
Leukocytes ( $\times 10^9/\text{L}$ )	9.6 (5.55–14.95)	7.0 (4.7–10.92)	12.8 (9.15–18.10)	<.001
Neutrophils ( $\times 10^9/\text{L}$ )	83.6% (78.75–88.25%)	81.55% (72.55–86.97)	84% (77.4%–88%)	.018
SAPS $\geq 6$	11 (19.3%)	15 (15.3%)	306 (31.6%)	.001
PSI score $\geq 4$	23 (40.4%)	40 (40.8%)	651 (67.3%)	<.001
CURB-65 score $\geq 2$	25 (43.9%)	42 (42.9%)	675 (69.7%)	<.001

Abbreviations: B-CAP, bacterial community-acquired pneumonia; IQR, interquartile range; PSI, pneumonia severity index for adult; SAPS, simplified acute physiology score; URTI, upper respiratory tract infection; V-CAP, viral CAP; VBC-CAP, viral and bacterial coinfection CAP.

<sup>a</sup>Proportions were calculated as percentages of patients with available data.

than those with B-CAP, but they each presented with similar rates of chronic respiratory disease. Of note, patients with VBC-CAP had a low rate of vaccination for seasonal influenza. These findings may reflect the previous report that seasonal influenza vaccine coverage may be lower in patients with chronic underlying conditions than in older patients [31]. However, perhaps of greatest note, we found that patients with VBC-CAP received antibiotics less often before admission than patients with B-CAP. This is remarkable given that clinical manifestations were similar in both groups, including cardinal findings such as purulent sputum and lobar infiltrates. These findings could be related to an overall low index of suspicion of coinfection, particularly out of the flu season.

As reported by other investigators [32], patients with VBC-CAP presented in respiratory failure at admission more often than patients with B-CAP. In this scenario, severity scores might not help to assess the potential risk of poor outcomes because they rely mostly on age and the presence of comorbidities [33]. Patients with VBC-CAP also received empirical oseltamivir therapy less frequently than those with V-CAP, which is highly

relevant given that a delay in antiviral treatment has been associated with poor outcomes in V-CAP [34, 35]. Of note, as recently addressed in the Infectious Diseases Society of America/American Thoracic Society guidelines [36], there have been no clinical trials evaluating the impact of antiviral treatment in patients with VBC-CAP.

As previously reported, we confirmed that coinfection was mainly caused by influenza A virus and *S pneumoniae* [32]. However, we found that the rate of coinfection with *S aureus* was lower. This could be explained by geographical differences in CAP etiology [37] and by the observation that *S aureus* coinfection is mostly observed in ICU settings [38].

As is expected to a cohort initially admitted to conventional medical wards, case-fatality rate was low. Despite the fact that we did not find a significant difference among groups, patients with V-CAP and VBC-CAP presented less mortality than B-CAP patients. This fact probably reflected the older age and high frequency of comorbidities in the B-CAP group, which could have limited ICU admissions. Nevertheless, VBC-CAP did present with more

**Table 3. Etiology in 1123 Cases of CAP<sup>a</sup>**

Etiology	VBC-CAP (n = 57)	V-CAP (n = 98)	B-CAP (n = 968)
<i>Streptococcus pneumoniae</i>	46 (80.70%)	–	612 (63.22%)
<i>Haemophilus influenzae</i>	5 (8.77%)	–	73 (7.6%)
<i>Staphylococcus aureus</i>	4 (7.01%)	–	21 (2.2%)
<i>Chlamydophila pneumoniae</i>	1 (1.75%)	–	40 (4.1%)
<i>Moraxella catarrhalis</i>	1 (1.75%)	–	13 (1.3%)
<i>Legionella</i> spp	0	–	48 (5%)
<i>Coxiella burnetii</i>	0	–	1 (0.1%)
<i>Pseudomonas aeruginosa</i>	0	–	36 (3.7%)
Gram-negative bacilli	0	–	17 (1.756%)
Aspiration CAP	1 (1.75%) <sup>b</sup>	–	107 (11.1%) <sup>c</sup>
Influenza A H1N1	38 (66.66%)	84 (85.7%)	–
Influenza A H3N2	9 (15.78%)	13 (13–3%)	–
Influenza B	8 (14.03%)	1 (1%)	–
Respiratory syncytial virus	2 (3.50%)	0	–

Abbreviations: B-CAP, bacterial community-acquired pneumonia; CAP, community-acquired pneumonia; V-CAP, viral CAP; VBC-CAP, viral and bacterial coinfection CAP.

<sup>a</sup>Proportions were calculated as percentages of patients with available data.

<sup>b</sup>Only 1 case was microbiologically confirmed in VBC-CAP group: *Enterobacter cloacae* (n = 1).

<sup>c</sup>Cases microbiologically confirmed in B-CAP group: *Bacteroides* spp (n = 3) *Prevotella bivia* (n = 4), *Porphyromonas asaccharolytica* (n = 2), *Streptococcus anginosus* group (n = 5), *Eggerthella lenta* (n = 4), *Enterobacter cloacae* (n = 3).

severity criteria and respiratory distress than V-CAP. This is consistent with research showing that the host-pathogen interaction in VBC-CAP leads to an exposition of the alveoli membrane, an inability of the respiratory epithelium

to repair itself [39], and a potent cytokine reaction, which combine to induce respiratory distress [40].

This study has some limitations that should be acknowledged. It should be noted that it was a prospective cohort that was not

**Table 4. Empirical Antimicrobial Therapy and Outcomes<sup>a</sup>**

Therapy and outcomes	VBC-CAP (n = 57)	V-CAP (n = 98)	B-CAP (n = 968)	PValue
Time to antimicrobial therapy initiation (hours, IQR)	4 (3–6)	5 (3–7)	4 (3–6)	.885
Empirical Antibiotic Therapy				
Beta-lactam monotherapy	8 (14.03%)	8 (8.16%)	32 (34.97%)	<.001
Beta-lactam + fluoroquinolone	31 (54.38%)	45 (45.91%)	431 (44.52%)	<.001
Fluoroquinolone	8 (14.03%)	30 (30.61%)	56 (5.78%)	<.001
Beta-lactam + macrolide	1 (1.75%)	1 (1.02%)	34 (3.51%)	<.001
Macrolide monotherapy	0	0	1 (0.1%)	.921
Broad-spectrum antibiotics	2 (3.51%)	6 (6.12%)	68 (7.02%)	.534
Others	1 (1.75%)	3 (3.06%)	41 (4.23%)	.281
Empirical oseltamivir therapy	32 (56.12%)	72 (73.56%)	71 (3.63%)	<.001
Antibiotic de-escalation	35 (61.4%)	57 (58.2%)	171 (65.7%)	.283
Complications	17 (29.8%)	30 (30.6%)	267 (27.6%)	.956
Respiratory distress	12 (21.10%)	19 (19.4%)	91 (9.4%)	<.001
Pleural effusion	3 (5.3%)	4 (4.1%)	57 (5.9%)	.755
Nosocomial infection	2 (3.5%)	8 (8.2%)	23 (1.7%)	.005
Acute cardiac event	3 (5.3%)	14 (14.3%)	95 (9.8%)	.177
Confusion	1 (1.8%)	5 (5.1%)	32 (3.3%)	.505
Renal failure	5 (8.8%)	2 (2%)	47 (4.9%)	.165
Acute hepatitis	0	0	11 (1.1%)	.411
Septic shock	5 (8.8%)	5 (5.1%)	44 (4.6%)	.349
ICU admission	18 (31.6%)	31 (31.6%)	171 (12.8%)	<.001
Mechanical ventilation	11 (19.3%)	13 (13.4%)	69 (3.1%)	<.001
Time to clinical stability (days, IQR)	5 (2–11.5)	5 (2–9)	4 (2–7)	.870
Relapse	1 (1.8%)	4 (4.4%)	37 (4%)	.687
30-day case-fatality rate	2 (3.5%)	3 (3.1%)	101 (6.3%)	.232

Abbreviations: B-CAP, bacterial community-acquired pneumonia; ICU, intensive care unit; IQR, interquartile range; V-CAP, viral CAP; VBC-CAP, viral and bacterial coinfection CAP.

<sup>a</sup>Proportions were calculated as percentages of patients with available data.

**Table 5. Risk Factors for Viral and Bacterial Coinfection CAP**

	Risk factors	V-CAP (n = 98)	PValue	B-CAP (n = 968)	PValue
VBC- CAP (n = 57)	Prehospital antibiotics	0.117 (0.024–0.571)	.008	0.160 (0.035–0.733)	.018
	Acute onset	0.241 (0.055–1.054)	.059	0.424 (0.117–1.539)	.192
	Purulent sputum	2.141 (1.02 – 3.241)	.050	2.313 (1.072–4.992)	.033
	Empirical oseltamivir	0.401 (0.401–0.972)	.043	19.489 (9.09–41.742)	<.001
	Severity criteria <sup>a</sup>	2.715 (0.959–7.688)	.060	5.219 (2.130–12.788)	<.001

Abbreviations: B-CAP, bacterial community-acquired pneumonia; CAP, community-acquired pneumonia; V-CAP, viral CAP; VBC-CAP, viral and bacterial coinfection CAP.

<sup>a</sup>Severity criteria (intensive care unit admission, mechanical ventilation, shock, and vasoactive drugs) were grouped into one after the multicollinearity study for a correlation coefficient >0.6.

originally designed to perform this analysis in a single geographical location. In addition, PCR was performed based on clinical suspicion, leading to potential unidentified cases and to failure to implement comprehensive multiple PCR testing, as is usual in clinical practice. Moreover, PCR technique used was limited to respiratory syncytial virus, influenza A and B virus, and hMPV. In addition, *Mycoplasma pneumoniae* PCR was not included in the atypical pathogens testing. Consequently, compared with the coinfection rate provided by some recent studies [32], the number of patients included in the VBC-CAP group was small and some cases could have been misclassified as B-CAP group. Furthermore, this was not a population based study, and despite its multicenter intention, it was limited to 2 centers in the same city in Spain. In addition, although both are tertiary centers, there is an asymmetry in recruitment in favor of the larger center.

## CONCLUSIONS

In conclusion, this study provides a real-world perspective of the relevance of VBC-CAP as a potential separate diagnostic category in adults admitted with CAP to conventional medical wards. Our work also emphasizes the urgent need to improve influenza vaccination coverage in patients with chronic underlying diseases. Randomized clinical trials are now required that use multiple PCR diagnostic tests as standard if we are to identify the true burden of coinfection in CAP. Such data can then be used to determine appropriate empirical and definitive treatment protocols.

## Acknowledgments

We thank CERCA Programme/Generalitat de Catalunya for institutional support. We also thank Plan Nacional de I+D+i 2013–2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0008; RD16/0016/0008), co-financed by European Development Regional Fund “A way to achieve Europe” Operative program Intelligent Growth 2014–2020.

**Author contributions.** G. A. A. contributed to the following: conceived of and designed the study; acquired, analyzed, and interpreted the data; and drafted the manuscript. A. R. analyzed and interpreted the data. C. G. analyzed and interpreted the data and critically revised the manuscript for important intellectual content. Y. M., L. O., and M. C. acquired the data. C. A. and J. N. acquired and validated the microbiological data. J. C. critically revised the manuscript for important intellectual content and agreed to be accountable for all aspects of the work in ensuring that

questions related to the accuracy or integrity of any part of the work was appropriately investigated and resolved. All authors read and approved the final manuscript.

**Financial support.** Study resulting from the 201808-10 project, funded by La Marató de TV3. We thank CERCA Programme/Generalitat de Catalunya for institutional support.

**Potential conflicts of interest.** G. A. A. reports grants from TV3—Fundación La Marató (201808-10), outside the submitted work. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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