Respiratory Research

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Early bacterial co-infections and ventilator-associated lower respiratory tract infections among intubated patients during the first and second COVID-19 waves: a European comparative cohort study

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Abstract

Background The management of severe SARS-CoV-2 pneumonia, alongside logistical constraints, evolved between the first and subsequent COVID-19 waves. This study aimed to compare the prevalence of early bacterial pulmonary co-infections and the incidence of ventilator-associated lower respiratory tract infections (VA-LRTI) across the first and second waves of the pandemic, and to characterize their microbiology.

Methods Latter part of a multicenter retrospective European cohort analysis conducted in 35 ICUs. Adult patients admitted for SARS-CoV-2 pneumonia and requiring invasive mechanical ventilation ≥ 48 h were consecutively included from both waves (February-May 2020 for period 1, October 2020-April 2021 for period 2). Co-infections were defined by bacterial isolation in respiratory secretions or blood cultures, or a positive pneumococcal urinary antigen test, within 48 h after intubation. VA-LRTI, including ventilator-associated tracheobronchitis (VAT) and ventilator-associated pneumonia (VAP), were diagnosed using clinical, radiological and quantitative microbiological criteria. The 28-day cumulative incidence of first VA-LRTI episodes was estimated using the Kalbfleisch and Prentice method, with co-infection prevalence and VA-LRTI incidence compared using multivariable logistic regression and Fine-and-Gray models, respectively.

Results The study included 1,154 patients (558 in period 1 and 596 in period 2). Co-infection prevalence significantly rose from 9.7% in period 1 to 14.9% in period 2 (adjusted odds ratio (95% confidence interval) 1.52 (1.04–2.22),

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$p = 0.03$). Gram-positive cocci dropped from 59 to 48% of co-infections between periods 1 and 2. The overall incidence of VA-LRTI was similar across periods (50.4% and 53.9%, adjusted sub distribution hazard ratio (sHR) 1.14 (0.96–1.35), $p = 0.11$), with a significant increase in VAP incidence in period 2 (36% to 44.8%, adjusted sHR 1.37 (1.12–1.66), $p = 0.001$), predominantly occurring within the initial 14 days after intubation, and a concurrent significant decrease in VAT incidence (14.3% to 9.1%, adjusted sHR 0.61 (0.42–0.88), $p = 0.007$). Gram-negative bacilli, led by *Pseudomonas aeruginosa*, Enterobacter spp., and Klebsiella spp., were responsible for 89% and 84% of VA-LRTI in periods 1 and 2, respectively.

Conclusions Between the first and second COVID-19 waves, the prevalence of early bacterial pulmonary co-infections significantly increased among intubated patients. Although the overall incidence of VA-LRTI remained stable, there was a significant shift from VAT to VAP episodes.

Keywords SARS-CoV-2, COVID-19, Co-infection, Ventilator-associated pneumonia, Ventilator-associated tracheobronchitis, Intensive care

Background

During the first wave of COVID-19, numerous studies investigated the occurrence of bacterial co-infections and ventilator-associated lower respiratory tract infections (VA-LRTI), including ventilator-associated tracheobronchitis (VAT), and ventilator-associated pneumonia (VAP) in critically ill patients. These studies reported a low prevalence of early bacterial pulmonary infections, although antibiotic use was very common [1]. Interestingly, this prevalence was much lower than that observed in patients with influenza pneumonia [2]. Although both are viral respiratory infections, influenza and COVID-19 differ significantly. Influenza triggers distinct immune-response pathways that cause earlier and more severe impairment of phagocytic bacterial clearance [3], and greater bronchial epithelium damage [4], which may explain the higher susceptibility to bacterial co-infection.

In contrast, the cumulative incidence of VA-LRTI in COVID-19 patients was strikingly high, with VAP rates ranging from 19 to 46% [5, 6]. These rates far exceeded those observed in other groups, such as patients with influenza pneumonia, community-acquired pneumonia, or other conditions [7, 8]. This elevated risk can be attributed to multiple factors. Patients with SARS-CoV-2 pneumonia often required prolonged mechanical ventilation, and had a higher incidence of acute respiratory distress syndrome (ARDS), both of which are well-known risk factors for VAP [9]. The unprecedented surge of critically ill patients during the pandemic, combined with the deployment of less experienced staff, might have compromised adherence to VAP prevention measures [10]. However, even in less overwhelmed settings, COVID-19 patients exhibited much higher VAP incidence compared to non-COVID-19 patients during the same period [11]. This suggests that SARS-CoV-2 infection itself plays a significant role in increasing VAP risk, likely due to its unique pathophysiological features. These include severe endothelial pulmonary injuries associated with microthrombi [12], delayed and prolonged dysregulation of innate immunity [3], and gut and lung dysbiosis [13]. These factors may disrupt local immunity, facilitate bacterial colonization, and increase susceptibility to secondary lung infections. Additionally, the widespread use of immunosuppressive treatments, mainly corticosteroids, following the results of the RECOVERY trial [14], may have further influenced VAP risk. While the impact of corticosteroids on VAP incidence remains debated [15, 16], several studies have reported an independent association between corticosteroid exposure and VAP [6, 17–20].

After the first wave, corticosteroid therapy became the standard of care for severe to critical COVID-19 [21]. Changes in clinical practices, including intubation timing and early empirical antibiotic use, and shifts in the pressure on healthcare systems, also occurred as the pandemic evolved. However, few studies have assessed the longitudinal epidemiology of co-infections and VA-LRTI throughout the pandemic.

We conducted this study to compare the prevalence of early bacterial pulmonary co-infections and the incidence of VA-LRTI between patients from the first and second waves of COVID-19, and to characterize their etiology.

Methods

Study design and population

This study constitutes the second phase of the CoVAPid multicenter retrospective observational cohort study, primarily aimed at assessing the impact of SARS-CoV-2 infection on the epidemiology of early bacterial co-infection [2] and VA-LRTI [7] in intubated critically ill patients. Thirty-five centers across Europe (27 in France, 3 in Spain, 3 in Greece, 1 in Portugal and 1 in Ireland) out of the 36 participating in the first phase, enrolled patients for this subsequent phase.

All adult patients admitted to the ICU for SARS-CoV-2 pneumonia, confirmed by positive polymerase chain

reaction (PCR) testing of a nasopharyngeal or respiratory secretions samples, requiring invasive mechanical ventilation for more than 48 h were eligible. Patients were excluded if another viral respiratory infection was simultaneously diagnosed at ICU admission.

The participating centers retrospectively collected data from consecutive patients admitted to their ICU, during both the first (period 1, part of CoVAPid-1 cohort) and second (period 2) COVID-19 waves. In period 1, patients were included starting at the onset of the pandemic in each center. In period 2, patients were included from October 1, 2020. Each center was invited to include the same number of patients in both periods.

The CoVAPid study protocol obtained approval from the Ethics Committee and Institutional Review Boards (Comité de Protection des Personnes Ouest VI; registration number RIPH:20.04.09.60039). Data collection received authorization from the data protection authority of the French national committee for data privacy (Commission Nationale de l'Informatique et des Libertés; registration number 2214454 v 0). Given the minimal-risk nature of the research, using data collected for routine clinical practice, the need for informed consent was waived. In compliance with French regulations, patients or their proxies received individual written information about the study and were given the possibility to refuse the reuse of their personal data – a requirement not applicable in countries other than France. The study was registered on ClinicalTrials.gov (NCT 05256511).

Definitions

Early bacterial pulmonary co-infection was defined by the isolation of one or more bacterial pathogens, within 48 h after intubation, either in a respiratory tract or blood sample (in this case, only bacterial species consistent with a pulmonary origin were considered), or through a positive *Streptococcus pneumoniae* urinary antigen test.

The diagnosis of VA-LRTI required meeting at least two of the following criteria: a body temperature > 38.5 °C or < 36.5 °C, a leucocyte count > 12,000 cells per µL or < 4,000 cells per µL, and the presence of purulent tracheal secretions [22]. VAP was defined by the presence of new or progressive infiltrates on chest X-ray. VAT was defined with the above-mentioned criteria with no radiographic signs of new pneumonia. Chest X-rays were reviewed by at least two physicians. All episodes of infection needed microbiological confirmation, with at least 10^5 colony-forming units (CFU) per mL in the endotracheal aspirate or 10^4 CFU per mL in bronchoalveolar lavage. Only first episodes of VAT and VAP, occurring more than 48 h after the initiation of invasive mechanical ventilation, were considered. VAP was defined as occurring subsequently to VAT if diagnosed within 96 h and caused by the same microorganism. All VA-LRTI episodes were prospectively identified.

Microbiological identification and susceptibility tests were performed using standard culture-dependent methods. Multidrug resistant (MDR) isolates were defined as non-susceptibility to at least one agent in three or more antimicrobial categories. Initial antibiotic treatment was deemed as appropriate when at least one antibiotic, matching the in vitro susceptibility of the causal pathogen, was administered to treat the infection.

Outcomes

The primary outcomes were the prevalence of early bacterial pulmonary co-infections and the incidence of VA-LRTI, including VAT and VAP, among patients admitted to the ICU with SARS-CoV-2 pneumonia during the first, compared to the second pandemic wave. The secondary endpoints included the etiologies of co-infections and VA-LRTI.

Statistical analysis

Quantitative variables were presented as means (standard deviation) or medians (interquartile range) according to the normality of distribution, while categorical variables were expressed as numbers (percentage). Normality of distributions were assessed using histogram and Shapiro–Wilk test. Patient characteristics at ICU admission and during ICU stay were described for each period, overall and according to the presence or absence of co-infection or VA-LRTI, without formal statistical comparisons. Imbalance in patient characteristics between the two periods were assessed by calculating standardized differences; absolute values > 20% were interpreted as meaningful differences [23, 24].

The prevalence of co-infections was compared between the two study periods using logistic regression analysis before and after adjustment for pre-specified confounders (age, gender, simplified acute physiology score II (SAPS II), chronic obstructive pulmonary disease (COPD), chronic respiratory failure, immunosuppression, Charlson comorbidity index, recent hospitalization, recent antibiotics, antibiotics on ICU admission, and ARDS on ICU admission). Unadjusted and adjusted odds ratios (and their 95% confidence intervals (CIs)) of presence of bacterial co-infection for period 2 *vs* period 1 were derived from logistic regression models as effect sizes. In addition, a sensitivity analysis excluding patients intubated more than 48 h after hospital admission was performed, to focus on community-acquired bacterial co-infections.

The 28-day cumulative incidence of first episodes of VA-LRTI (VA-LRTI, VAT, VAP) was estimated using the Kalbfleisch and Prentice method [25], considering

extubation within 28 days (dead or alive) as a competing event. For VAT and VAP incidence, occurrence of VAP and VAT was respectively treated as a competing event, in addition to extubation. The cumulative incidence of first episodes of VA-LRTI was compared between the two study periods using Gray's test, accounting for competing events. Comparisons were further adjusted for the aforementioned pre-specified confounders by using multivariable Fine-and-Gray models. Sub distribution hazard ratios (95% CIs) were calculated using univariable and multivariable Fine-and-Gray models as effect sizes. The proportional sub distribution hazard assumption was assessed by using Schoenfeld residuals plots and by introduction of a time*period interaction term. Since we found a non-proportional hazard for VA-LRTI and VAP events, the effect of period was also modelled by using time-dependent coefficients, with a specification of time-varying effects guided by visual inspection of Scaled Schoenfeld residuals plots.

To address missing data in covariates, multivariable logistic and Fine-and-Gray regression models were performed after handling missing data using multiple imputation procedure [26]. Statistical analyses were performed using SAS software, release 9.4 (SAS Institute, Cary, NC), with significance testing at a two-tailed α level of 0.05. Additional details on methods are available in additional file 1.

Results

A total of 1,154 patients were included in the 35 participating centers, with 558 admitted during period 1 (between February 18th and May 28th, 2020) and 596 during period 2 (between October 1st, 2020 and April 20th, 2021) (Fig. 1).

Patient characteristics at ICU admission

The Charlson comorbidity index, the percentage of chronic respiratory failure and the presence of acute respiratory failure upon ICU admission were higher in period 2 compared to period 1. Patients had a longer hospital length of stay before ICU admission and intubation in period 2 compared to period 1. Intubation occurred within the first 48 h of hospital admission for 42% of patients in period 2 *vs* 68% in period 1. The percentage of antibiotics administered upon ICU admission was lower in period 2 compared to period 1 (Table 1, and Tables S2 and S3 in additional file 1).

Patient characteristics during ICU stay

Antiviral treatment was less frequent in period 2 compared to period 1. The use of corticosteroids, mainly dexamethasone, was more frequent in period 2. Exposure durations to both corticosteroids and antibiotic treatment before VA-LRTI were longer in period 2 compared to period 1, while the dose of corticosteroids was lower

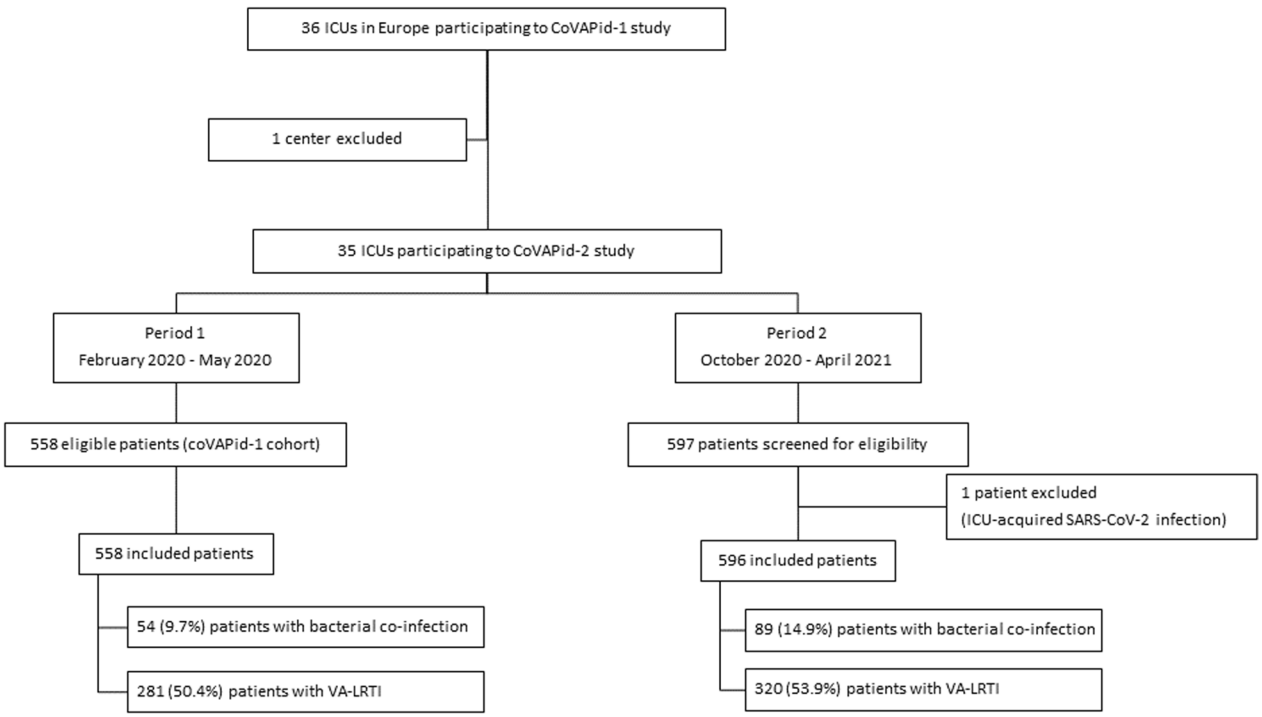

Fig. 1 Patient flowchart. *SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; VA-LRTI, ventilator-associated respiratory tract infection*

Table 1 Patient characteristics at ICU admission

	Period 1 n = 558	Period 2 n = 596	Standardized difference[(1)], %
Age, years	63.0 (12.0)	65.0 (11.5)	17.3
Men	398/558 (71.3)	436/596 (73.2)	4.1
Body mass index[*], kg/m^2	30.1 (6.5)	30.4 (6.6)	3.8
Severity scores			
SAPS II[†]	44.1 (16.5)	42.3 (16.0)	− 11.2
SOFA score[‡]	6.3 (3.6)	5.9 (3.5)	− 11.4
Comorbidities scores			
McCabe classification Non fatal	469/533 (88.0)	509/595 (85.5)	6.2
Fatal < 5 years	58/533 (10.9)	77/595 (12.9)	
Fatal < 1 year	6/533 (1.1)	9/595 (1.5)	
Charlson Comorbidity Index[§]	3 (1 to 4)	3 (2 to 5)	30.9
Chronic diseases			
Diabetes mellitus	165/555 (29.7)	198/596 (33.2)	7.5
Chronic kidney disease	33/549 (6.0)	42/596 (7.0)	4.2
Heart disease	103/550 (18.7)	127/596 (21.3)	6.5
Chronic heart failure	21/548 (3.8)	15/596 (2.5)	− 7.5
COPD	37/550 (6.7)	57/596 (9.6)	10.4
Chronic respiratory failure	19/548 (3.5)	57/596 (9.6)	24.9
Cirrhosis	8/549 (1.5)	4/596 (0.7)	− 7.7
Immunosuppression	50/549 (9.1)	88/596 (14.8)	17.5
Active smoking	28/550 (5.1)	42/596 (7.0)	8.2
Alcohol abuse	33/548 (6.0)	25/596 (4.2)	− 8.3
Recent hospitalization (< 3 months)	41/556 (7.4)	50/595 (8.4)	3.8
Recent antibiotics (< 3 months)	71/557 (12.7)	99/594 (16.7)	11.1
Location before ICU admission			25.5
Home	269/558 (48.2)	258/596 (43.3)	
Hospital ward	207/558 (37.1)	285/596 (47.8)	
Another ICU	82/558 (14.7)	53/596 (8.9)	
Time from hospital to ICU admission, days	1 (0 to 2)	1 (0 to 3)	16.9
≤ 48 h	425/537 (79.1)	416/596 (69.8)	− 21.6
Time from hospital admission to intubation, days	1 (0 to 3)	3 (1 to 6)	60.5
≤ 48 h	360/526 (68.4)	253/596 (42.4)	− 54.2
Antibiotic treatment on ICU admission	494/558 (88.5)	440/596 (73.8)	− 38.3
Causes for ICU admission			
Shock	101/547 (18.5)	85/596 (14.3)	− 11.4
Acute respiratory failure	512/557 (91.9)	590/596 (99.0)	34.5
ARDS	383/553 (69.3)	451/596 (75.7)	14.4
Neurological failure	25/539 (4.6)	19/596 (3.2)	− 7.5
Cardiac arrest	3/538 (0.6)	8/596 (1.3)	8.1
Acute kidney injury	95/539 (17.6)	81/596 (13.6)	− 11.1
At co-infection diagnosis (≤ 48 h after intubation)			
At least 1 respiratory sample taken	410/548 (74.8)	421/542 (77.7)	9.8
Antibiotics at the time of sample	350/410 (85.4)	315/420 (75.0)	− 26.3
Highest level of procalcitonin, µg/L	0.5 (0.2 to 1.6)	0.5 (0.2 to 1.5)	− 14.9

in period 2. Prone position was more common in period 2. 28-day mortality as well as mechanical ventilation duration and ICU length of stay in survivors were

Table 2 Patient characteristics during ICU stay

	Period 1 n = 558	Period 2 n = 596	Standardized difference[(1)], %
Antiviral treatment	316/556 (56.8)	108 / 596 (18.1)	– 87.3
Corticosteroids	200/533 (37.5)	559 / 596 (93.8)	147.1
Hydrocortisone	58/528 (11.0)	80 / 596 (13.4)	7.5
Dexamethasone	48/528 (9.1)	457 / 596 (76.7)	186.9
Methylprednisolone	90/528 (17.0)	120 / 596 (20.1)	8.0
Highest daily dose, mg[*]	100 (50 to 133)	40 (40 to 100)	– 78.7
Exposure duration (before VA-LRTI), days[†]	6 (4 to 9)	9 (7 to 11)	82.8
Antibiotic treatment	500/525 (95.2)	582 / 596 (97.7)	13.1
Exposure duration (before VA-LRTI), days[‡]	7 (5 to 9)	8 (6 to 11)	28.5
Total duration, days[§]	13 (7 to 19)	14 (8 to 21)	14.1
Prone positioning	374/557 (67.1)	461 / 595 (77.5)	28.5
ECMO	61/557 (11.0)	75 / 596 (12.6)	5.1
28-day outcomes			
Mechanical ventilation duration, days[‖]			
Survivors	15 (9 to 24)	17 (9 to 28)	12.2
Non-survivors	13 (7 to 19)	14 (9 to 19)	11.7
ICU length of stay, days[¶]			
Survivors	21 (14 to 28)	25 (13 to 28)	13.9
Non-survivors	12 (7 to 17)	16 (11 to 21)	49.3
28-day mortality	162/558 (29.0)	181/596 (30.4)	2.9

Values are as n/N (%) or median (interquartile range). [(1)] Standardized differences absolute values > 20% are interpreted as meaningful differences. [*] 3 missing values (period 1, n = 3; period 2, n = 0); [†] 8 missing values (period 1, n = 6; period 2, n = 2); [‡] 6 missing values (period 1, n = 6; period 2, n = 0); [§] 14 missing values (period 1, n = 12; period 2, n = 2); [‖] reported for 425 survivors and 133 deceased patients in period 1, and 503 survivors and 91 deceased patients in period 2; [¶] reported for 398 survivors and 160 deceased patients in period 1, and 419 survivors and 177 deceased patients in period 2

Data were collected until day 28 from ICU admission or ICU discharge, whichever occurs first. Antiviral treatment included Remdesivir, Lopinavir-Ritonavir, Lopinavir-Ritonavir + interferon, or Hydroxychloroquine. In patients with VA-LRTI, duration of exposure to antibiotic treatment and corticosteroids was only taken into account before VA-LRTI. Corticosteroid regimens are reported as prednisone equivalent

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit

comparable between the two periods (Table 2, and Table S4 in additional file 1).

Early bacterial pulmonary co-infection

The prevalence of co-infections was significantly higher in period 2 compared to period 1 (14.9% *vs* 9.7%, unadjusted odds ratio (OR) 1.64 (95% confidence interval (CI) 1.14–2.35), adjusted OR 1.52 (95%CI 1.04–2.22), $p = 0.03$) (Table 3). At least one respiratory sample could be collected within 48 h after intubation in 78% of patients in period 2 *vs* 75% in period 1. Antibiotic treatment rate was lower at the time of sampling in period 2 (75% of cases) compared to period 1 (85% of cases) (Table 1). To note, among patients with a hospital stay of less than 48 h, the prevalence of co-infections was similar between the two periods (11.9% in period 2 *vs* 8.1% in period 1, adjusted OR 1.40 (95%CI 0.79–2.48), $p = 0.244$).

Bacteria were primarily isolated from endotracheal aspirate (Table S5 in additional file 1). The procalcitonin levels within 48 h of intubation were higher in patients with co-infection compared to those without (Table S2 in additional file 1). The proportion of Gram-positive cocci, *Staphylococcus aureus* and *Streptococcus pneumoniae*, as etiologies of co-infections, decreased from period 1 to period 2, in favor of *Pseudomonas aeruginosa*, and Enterobacter spp. (Fig. 2). No positive urinary antigen tests for *Legionella* were reported in the cohort. The rate of multidrug-resistant (MDR) bacteria increased from 5.6% of co-infected patients in period 1 to 11.2% in period 2 (Table S6 in additional file 1). Empirical antibiotic treatment was less frequently appropriate in period 2 (54%) compared to period 1 (70%).

Ventilator-associated lower respiratory tract infection

The 28-day cumulative incidence of first episodes of VA-LRTI was similar between the two periods (53.9% in period 2 *vs* 50.4% in period 1, adjusted sub distribution hazard ratio (sHR) 1.14 (95%CI 0.96–1.35), $p = 0.11$) (Table 3, Fig. 3). However, a significant difference in VA-LRTI incidence was observed for the first two weeks

Table 3 Study outcomes

Prevalence of early bacterial pulmonary co-infections					
	Period 1 n = 558	**Period 2 n = 596**	**Unadjusted OR (95% CI)**	**Adjusted OR[*] (95% CI)**	***p*-value[*]**
Overall population	54 (9.7)	89 (14.9)	1.64 (1.14 to 2.35)	1.52 (1.04 to 2.22)	0.030
< 48 h hospital stay[†]	*29 (8.1)*	*30 (11.9)*	*1.54 (0.89 to 2.63)*	*1.40 (0.79 to 2.48)*	*0.244*
Incidence of first episodes of ventilator-associated lower respiratory tract infections					
	Period 1	**Period 2**	**Unadjusted sHR (95% CI)**	**Adjusted sHR[*] (95% CI)**	***p*-value[*]**
VA-LRTI	281 (50.4)	320 (53.9)	1.15 (0.98 to 1.35)	1.14 (0.96 to 1.35)	0.110
< 14 days[‡]			*1.25 (1.05 to 1.50)*	*1.21 (1.01 to 1.45)*	*0.038*
≥ 14 days			*0.80 (0.55 to 1.16)*	*0.85 (0.57 to 1.28)*	*0.440*
VAP	201 (36.0)	266 (44.8)	1.36 (1.13 to 1.63)	1.37 (1.12 to 1.66)	0.001
< 14 days[‡]			*1.47 (1.20 to 1.81)*	*1.43 (1.16 to 1.76)*	*< 0.001*
≥ 14 days			*0.99 (0.65 to 1.49)*	*1.09 (0.69 to 1.71)*	*0.720*
VAT	80 (14.3)	54 (9.1)	0.63 (0.44 to 0.88)	0.61 (0.42 to 0.88)	0.007

For co-infections, values are as n/N (%). For VA-LRTI, values are number of first events (28-day cumulative incidence expressed as %, considering extubations (dead or alive) as competing events). For VAT episodes, VAP is considered as a competing event (in addition to extubations). For VAP episodes, VAT is considered as a competing event (in addition to extubations). sHR are calculated using Fine-and-Gray models

CI, confidence interval; OR, odds ratio; sHR, sub distribution hazard ratio; VA-LRTI, ventilator-associated respiratory tract infection; VAT, ventilator-associated tracheobronchitis; VAP, ventilator-associated pneumonia

[*] Adjusted for predefined confounders (age, gender, simplified acute physiology score II, chronic obstructive pulmonary disease, chronic respiratory failure, immunosuppression, Charlson comorbidity index, recent hospitalization, recent antibiotics, antibiotics on ICU admission, and acute respiratory distress syndrome on ICU admission), and calculated after handling missing values on covariates by multiple imputation

[†] Sensitivity analysis performed among patients intubated in the first 48 h after hospital admission (360 in period 1, 253 in period 2)

[‡] Modeled using time-dependent coefficient to account the non-proportional hazard of sub-distribution

after intubation, with an adjusted sHR of 1.21 (95%CI 1.01–1.45), $p=0.038$. The 28-day cumulative incidence of VAP was significantly higher in period 2 compared to period 1 (44.8% *vs* 36%, adjusted sHR 1.37 (95%CI 1.12–1.66), $p=0.001$), predominantly occurring in the first two weeks after intubation. Regarding VAT, the incidence was concurrently lower in period 2 compared to period 1, with a 28-day cumulative rate of 9.1% *vs* 14.3% (adjusted sHR 0.61 (95%CI 0.42–0.88), $p=0.007$).

In both periods, the sequential organ failure assessment (SOFA) score and modified clinical pulmonary infection score (CPIS) were higher, while the PaO_2/FiO_2 ratio was lower in patients with VAP, compared to those with VAT (Table S7 in additional file 1). VA-LRTI episodes were predominantly documented through endotracheal aspirates, although a higher rate of bronchoalveolar lavage was observed in patients with VAP. The proportion of antibiotic treatment was higher in patients with VAP, compared to those with VAT. Transition from VAT to VAP occurred in 24.1% of patients diagnosed with VAT in period 2, *vs* 12.5% in period 1.

Gram-negative bacilli accounted for 84.4% of cases in period 2 and 89.3% in period 1, with a comparable distribution among species (Fig. 2, Table S8 in additional file 1). *Pseudomonas aeruginosa*, Enterobacter spp. and Klebsiella spp. were the primary causative agents of VA-LRTI episodes. The rate of MDR bacteria was comparable between the two periods (22.2% in period 2 and 23.5% in period 1). Empirical treatment was appropriate in 49% and 72% of VAT episodes, and in 72 and 68% of VAP episodes, in periods 1 and 2, respectively (Table S7 in additional file 1).

Discussion

We observed, between the first and second pandemic waves, a significant increase in the prevalence of bacterial co-infections diagnosed within 48 h of intubation, yet remaining below 15%, with a decrease in the involvement of Gram-positive cocci. The cumulative incidence of VA-LRTI was similar between the two waves, affecting more than half of the patients, but a significant increase in VAP incidence, predominantly occurring within the initial 14 days following intubation, and a concurrent significant decrease in VAT incidence was noted during the second wave. Gram-negative bacilli, mainly *Pseudomonas aeruginosa*, Enterobacter spp., and Klebsiella spp., were responsible for the vast majority of VA-LRTI episodes in both waves.

To the best of our knowledge, our study is the first multicenter study comparing the prevalence of bacterial co-infections and the incidence of VA-LRTI across the first and second waves of the COVID-19 pandemic in a large

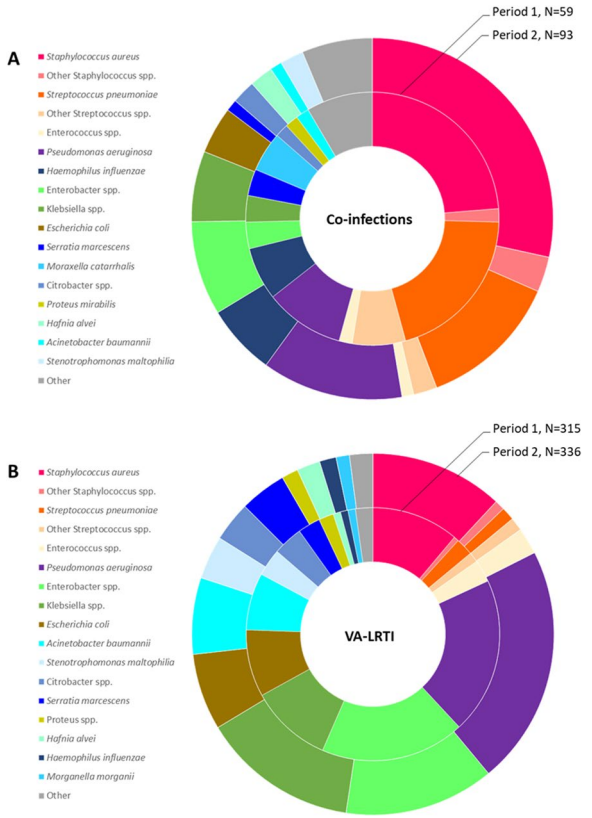

Fig. 2 Etiological diagnosis of early bacterial pulmonary co-infections (**A**) and ventilator-associated lower respiratory tract infections (**B**), according to the period. *The data are presented as a percentage of the total number of bacteria involved during episodes of co-infection or VA-LRTI. The inner circle corresponds to period 1, and the outer circle to period 2. VA-LRTI, ventilator-associated respiratory tract infection*

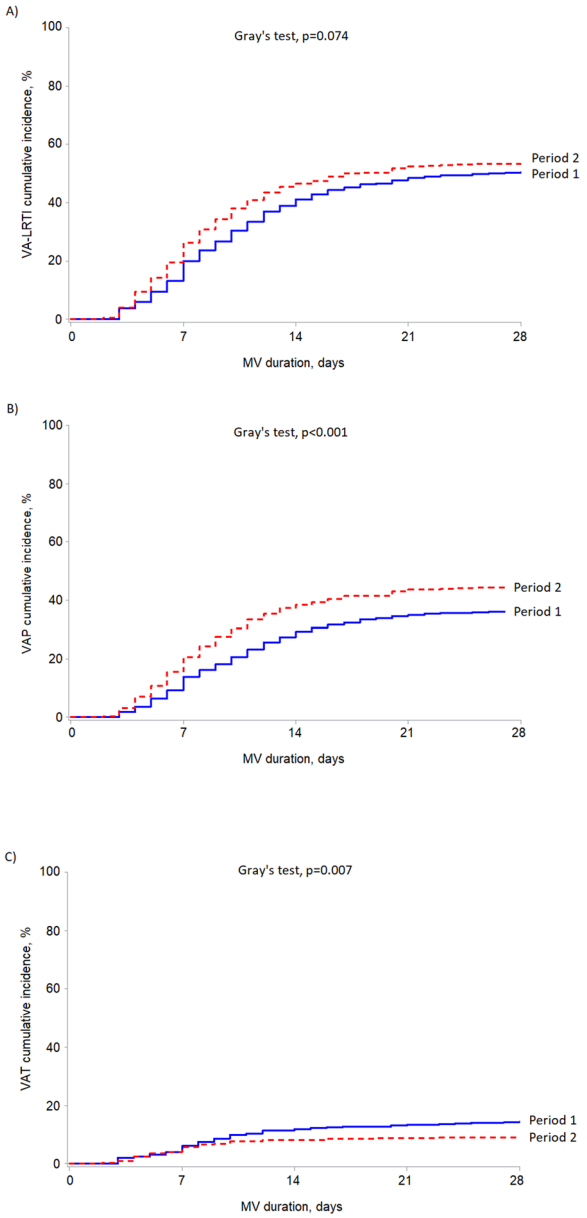

Fig. 3 Cumulative incidence of first episodes of ventilator-associated lower respiratory tract infections (**A**), ventilator-associated pneumonia (**B**), and ventilator-associated tracheobronchitis (**C**), according to the period. *Cumulative incidence are estimated using Kalbfleish and Prentice method, considering extubation (dead or alive) within 28 days as a competing event. For VAT episodes, VAP is considered as a competing event (in addition to extubations). For VAP episodes, VAT is considered as a competing event (in addition to extubations). The cumulative incidence is compared between the periods using Gray's test. The blue solid line corresponds to period 1, the red dashed line corresponds to period 2. MV, mechanical ventilation; VA-LRTI, ventilator-associated respiratory tract infection; VAP, ventilator-associated pneumonia; VAT, ventilator-associated tracheobronchitis*

European cohort of critically ill patients. Previous studies, mainly conducted during the first wave, reported a low prevalence of bacterial co-infections, predominantly caused by Gram-positive cocci. Our results indicate an increase in the prevalence of bacterial co-infections between the first and the second pandemic waves, similarly noted in a single-center Spanish cohort of critically ill patients [27]. This rise could be explained, at least in part, by the decreased rate of antimicrobial administration prior to respiratory specimen collection in the second wave. In addition, the percentage of patients with chronic respiratory disease was higher during the second wave compared to the first one. However, the logistic regression model was adjusted for these factors. Further, the sensitivity analysis restricted to patients intubated within the first 48 h of their hospital stay did not show a significant difference in the prevalence of bacterial co-infections, meaning that the rate of community-acquired co-infections remained similar across both waves. Our study might be underpowered to detect a difference

in this subgroup. However, the later intubation in the course of the ICU stay during the second wave, well-documented in the literature [28, 29], could explain to a large extent the observed increase in the rate of co-infections, including the higher proportion of Gram-negative bacilli and MDR bacteria involved. Limiting early empirical antibiotic therapy is highly relevant to prevent antimicrobial resistance among intubated COVID-19 patients with prolonged ICU stay [30], and still supported by our findings showing less than 15% of bacterial co-infections diagnosed within 48 h following intubation. The risk of co-infection, pragmatically considered in our study at the point of intubation, when a respiratory sample could be readily obtained, must however be balanced against the duration of hospital stay before intubation.

Although the overall incidence of VA-LRTI was comparable between the two COVID-19 waves, we observed a higher incidence of VAP, mainly occurring within the first 14 days after starting mechanical ventilation, and a lower incidence of VAT during the second wave compared to the first one. To note, transition from VAT to VAP was also more common during the second wave. Some single-center studies observed a significant increase in either VA-LRTI or VAP incidences from the first to the second COVID-19 waves [31, 32]. Two multicenter cohorts also reported a significant rise in the incidence of VA-LRTI [33] or VAP [34] during the combined second and third waves, as compared to the first one, as well as shorter times to first VA-LRTI [33]. Our study is the first to identify a significant shift from VAT to VAP in the distribution of VA-LRTI after the first COVID-19 wave. Several potential explanations could be provided for the higher incidence of VAP during the second COVID-19 wave. First, patients had more comorbidities during the second wave. Second, corticosteroid use, and longer exposure duration was more common during the second wave compared to the first one. Several observational studies have identified early corticosteroids as a risk factor for VAP in COVID-19 patients [6, 17–20], although this association hasn't been consistently found across all studies [15, 16]. Third, antibiotic treatment upon admission and intubation was less common, potentially contributing to a higher risk of early VAP. Fourth, better awareness of the risk of VA-LRTI in COVID-19 population might have resulted in better identification of these infections. Fifth, VAP prevention measures could have been better applied during the first pandemic wave. However, we did not collect data on compliance with infection control measures in our study. The similar rate of MDR bacteria between the two waves at least suggest consistent hand hygiene practices. Our findings highlight the increased risk of VAP in COVID-19 patients. Additionally, the impact of VAP on mortality has been reported to be higher in this specific population, compared to others [35]. Implementing targeted prevention strategies is therefore crucial.

Strengths of our study are the large number of included patients, multicenter design, the strict definition of co-infections and VA-LRTI, requiring microbiological confirmation in all patients, and appropriate statistical analyses to account for competing events and confounding factors. However, our study has some limitations. First, it was retrospective, with no standardized protocol for microbiological sampling. No multiplex PCR was used for microbiological testing, which would likely have resulted in higher bacterial infection rates. Second, differentiating bacterial airway colonization from early co-infection can be challenging in COVID-19 patients. We considered all positive microbiological specimens collected within 48 h post-intubation as co-infections, as this timing indicated recent clinical worsening and suggested the potential pathogenicity of the identified bacteria. Third, no blind external adjudication was performed to confirm VA-LRTI. However, all VA-LRTI were prospectively identified in all centers. Further, the presence of new infiltrate on chest X-ray was evaluated by at least two physicians. Fourth, we did not collect data on ventilation modalities prior to intubation, procalcitonin kinetics, specific VAP preventive measures, sedation and neuromuscular-agent use, or on compliance with hand-hygiene, and contact isolation measures. Additionally, we did not report COVID-19-associated pulmonary aspergillosis as part of VA-LRTI episodes [36]. Finally, all centers were located in Western Europe, mainly in France, with different distribution of MDR bacteria among participating countries. Therefore, our results could not be generalized to other world regions.

Conclusions

Between the first and second COVID-19 waves, the prevalence of early bacterial pulmonary co-infection significantly increased among intubated patients, but remained below 15%. Although the overall incidence of VA-LRTI remained stable, there was a significant shift towards a higher incidence of VAP, accounting for almost half of the patients, at the expense of VAT.

Abbreviations

ARDS	Acute respiratory distress syndrome
CFU	Colony-forming units
COPD	Chronic obstructive pulmonary disease
COVID-19	Coronavirus disease 19
CPIS	Clinical pulmonary infection score
ECMO	Extracorporeal membrane oxygenation
ICU	Intensive care unit
MDR	Multidrug-resistant
PCR	Polymerase chain reaction
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAPSII	Simplified acute physiology score II
SOFA	Sequential organ failure assessment
VA-LRTI	Ventilator-associated lower respiratory tract infections

VAP Ventilator-associated pneumonia
VAT Ventilator-associated tracheobronchitis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12931-025-03148-2.

Additional file1.

Acknowledgements
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Funding
This study was supported in part by a grant from the French government through the ≪Programme Investissement d'Avenir≫ (I-SITE ULNE) managed by the Agence Nationale de la Recherche (coVAPid project). The funders of the study had no role in the study design, data collection, analysis, or interpretation, writing of the report, or decision to submit for publication.

Availability of data and materials
The individual de-identified datasets that underlie the results reported in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study was approved by the Ethics Committee and Institutional Review Boards (Comité de Protection des Personnes Ouest VI, registration number RIPH:20.04.09.60039), registered with the French national committee for data privacy (Commission Nationale de l'Informatique et des Libertés, registration number 2214454 v 0), and performed in accordance with the French ethical and regulatory standards for minimal-risk research conducted on already available data. Given the minimal-risk nature of the research, using data collected for routine clinical practice, the need for informed consent was waived. In compliance with French regulations, patients or their proxies received individual written information about the study and were given the possibility to refuse the reuse of their personal data – a requirement not applicable in countries other than France.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 25 July 2024 Accepted: 9 February 2025
Published online: 05 March 2025

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