# Trends in the proportion of resistant bacteria involved in ventilator-associated pneumonia as the first hospital-acquired infection in intensive care units between 2003 and 2016 in Lyon, France

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Brief report

# Trends in the proportion of resistant bacteria involved in ventilator-associated pneumonia as the first hospital-acquired infection in intensive care units between 2003 and 2016 in Lyon, France

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*Key Words:*

Multidrug resistant bacteria
Intensive care unit

The aim of this study was to describe the proportion of multidrug-resistant microorganisms (MDROs) involved in ventilator-associated pneumonia (VAP) as the first hospital-acquired infection in 536 adults with restricted risk factors for MDRO-related infection. We found a significant decrease in the percentage of MDROs involved in VAP between 2003 and 2016 and this percentage increased when VAP occurred after day 10.



## BACKGROUND

Pneumonia is the major cause of hospital-acquired infections (HAI) in the intensive care unit (ICU). In French ICUs, 8% of patients developed a hospital-acquired pneumonia in 2016 and 88.7% among them were ventilator-associated pneumonias (VAP, ie pneumonia occurring ≥48 h after intubation).[1,2] The most frequently isolated bacteria were *Enterobacteriaceae* (41.4%), *Pseudomonas aeruginosa* (20%), and *Staphylococcus aureus* (13.3%) for pneumonias acquired in French ICUs in 2016.[1]

About eleven percent of patients carried multidrug-resistant microorganisms (MDROs) during systematic screening in 2016 in French adult ICUs.[1] MDROs are frequently isolated in patients with VAP, however their incidence varies in ICUs and populations studied.[3] The proportion of meticillin-resistant *Staphylococcus aureus* (MRSA) was 13.2% among *S. aureus* and that of extended spectrum β-Lactamase-producing *Enterobacteriaceae* (ESBL-E) was 14.8% among *Enterobacteriaceae* in pneumonias acquired in French ICUs in 2016[1].

This study was conducted to describe changes in the proportion of incident VAP cases due to MDROs between 2003 and 2016 in Lyon ICUs hospitalized patients. We selected patients with restricted risk factors for MDRO infection in the community. Therefore, to minimize the risk of exposure to factors associated with such infections, the patient population was restricted to those admitted directly from home to ICU without any antibiotics prescription reported at the admission.

## METHODS

This prospective study included adults (≥18 y old) from the Lyon section of the French national HAI Surveillance Network of ICUs ("Réseau REA-Raisin") between 2003 and 2016[1]. Patients were included if the first HAI was a pneumonia based on validated criteria[4], pneumonia onset occurred after ≥48 h in the ICU, admitted in

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ICU directly from their homes (no hospital stay before ICU admission), without antibiotics on admission (from 48 h before admission until 48 h after), intubated since the first day in the ICU, the microorganism(s) involved in the VAP was identified.

Antimicrobial resistance (AMR) was determined according to French Antibiogram Committee criteria. We considered a microorganism with "intermediary" resistance as resistant. The global MDRO group studied contained: MRSA, third-generation cephalosporin-resistant *Enterobacteriaceae* (3GCR-E), ceftazidim-resistant *Pseudomonas aeruginosa* (CRPA), and glycopeptide-resistant *Enterococcus faecalis* (GREF).

The values are expressed as median (interquartile range) or mean (±standard deviation) and counts (percentage). Trends over time were assessed with Cuzik's non-parametric test (nptrend) for categorical variables. Comparison of proportions was based on the chi-square test. All tests were two-sided. A *P*-value <.05 was considered as significant. Statistical analyses were performed with Stata v11.2 (StataCorp, College Station, TX).

## RESULTS AND DISCUSSION

A total of 536 patients met inclusion criteria and 145 (27.1%) had VAP with two germs identified (n = 681 identified germs). Two cultures were negative, and 15 cultures were positive for an unidentified germ. Median age was 56 years (42-69), 374 patients (69.8%) were men, 51 (9.5%) were immunosuppressed (polynuclear neutrophils <0.5 G/L or immunosuppressed according to the APACHE II score criteria), 212 (39.6%) had trauma on admission. The crude in-hospital mortality rate was 20.7% (111/536). The mean SAPS-II was 51 (±18). The median ICU stay was 23 days (d) (14-36). The median duration of intubation was 17d (9-27.5).

The 5 most common agents encountered in the study were: *S. aureus* (n = 184/681, 27.0%), *Haemophilus* spp. (n = 79, 11.6%), *P. aeruginosa* (n = 73, 10.7%), *Escherichia coli* (n = 62, 9.1%), *Streptococcus pneumoniae* (n = 38, 5.6%). *Enterobacteriaceae* represented 30.8% of the total (n = 210).

We observed a reduction in the proportions of *S. aureus*-related VAP (*P* = .007) and MDRO-related VAP (*P* = .017), and an increase in the proportions of *P. aeruginosa* (*P* = .050) and *Enterobacteriaceae*-related VAP (*P* = .009) throughout the period 2003-2016 (Fig 1). The decrease in the proportion of MDROs over the years in this population might be related to an improvement in the use of antibiotics and an improvement of preventive measures for controlling the risks of infection by MDROs.

We observed a reduction in the proportions of *S. aureus*-related VAP (*P* = .029), and an increase in the proportions of *P. aeruginosa* (*P* < .001), *Enterobacteriaceae* (*P* = .040) and MDRO-related VAP (*P* = .033) throughout the number of days between hospitalization and the onset of VAP (Fig 2).

In VAP that occurred on day 2 (D2) after ICU admission (ie D2 after the start of intubation), a substantial percentage of MDRO-related VAP was observed (23.9%, 17/71 germs) (Fig 2). VAP that occurs on D2 following hospitalization could be related to a microorganism already present in a patient's oropharynx flora prior to admission or to a rapid acquisition of nosocomial bacteria including MDROs. In the studied patients, the median interval were 5 d over the 2003-2016 period, whereas it was 8 d in all patients in French adult ICUs in 2016.[1] In this study, the patients were intubated on the first day of hospitalization and not covered by antibiotic on admission, suggesting these two factors could accelerate the occurrence of VAP related to microorganisms from a patient's oropharynx flora. The likelihood of colonization with MDROs from the community would therefore appear to be reasonable in early-onset VAP (with onset up to 4 d following intubation).[5,6]

According to some authors, bacteria isolated in late-onset VAP (starting at least 5 d after intubation) are more frequently MDROs and could be related to patient colonization or microbial ecology of ICU and antibiotic selection pressure.[5–8] In the present study, we noted a significant increase in the proportion of the MDROs when the onset of VAP was after D10 (29.2%, 38/130 bacteria) than between D2 and D9 (19.8%, 109/551 bacteria) (*P* = .019) (Fig 2).

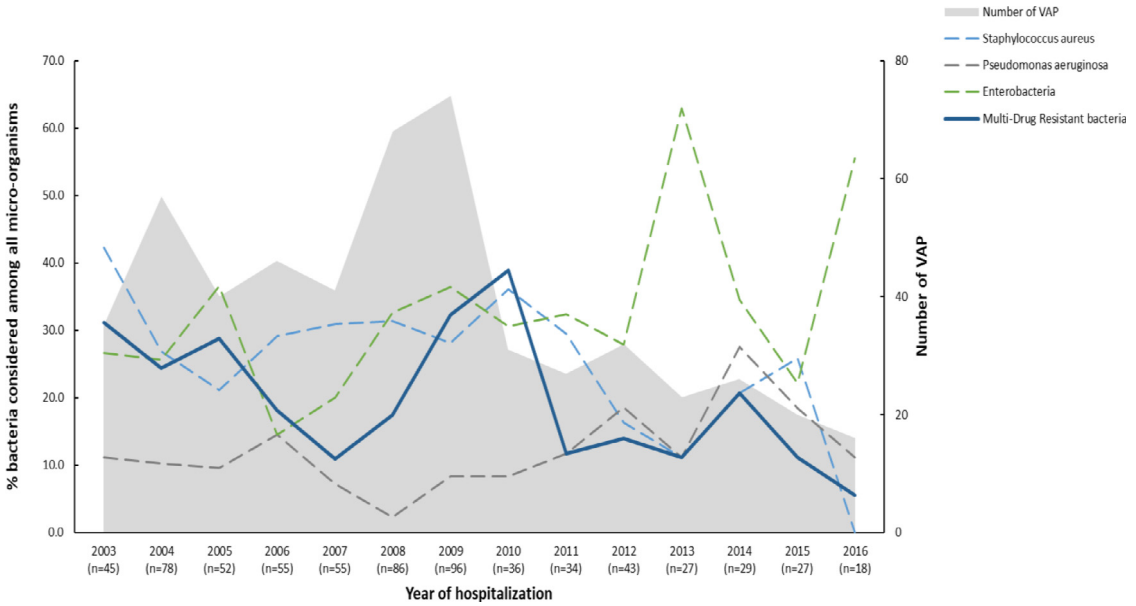


**Fig. 1.** Evolution of *Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacteriaceae*, Multi-Drug Resistant bacteria proportions and of the number of VAP by year between 2003 and 2016.

Evolution of the proportions of *S. aureus* regardless the resistance profile (declining trend, *P* = .007), *P. aeruginosa* regardless the resistance profile (increasing trend at the limit of the significance threshold, *P* = .050), Enterobacteriaceae regardless the resistance profile (increasing trend, *P* = .009) are represented by a dotted line. Evolution of Multi-Drug Resistant bacteria (declining trend, *P* = .017) is represented by a full line. Evolution of the number of VAP is represented by a gray area. For each year, the number of identified germs is specified on the x-axis. VAP: Ventilator-associated pneumonia.

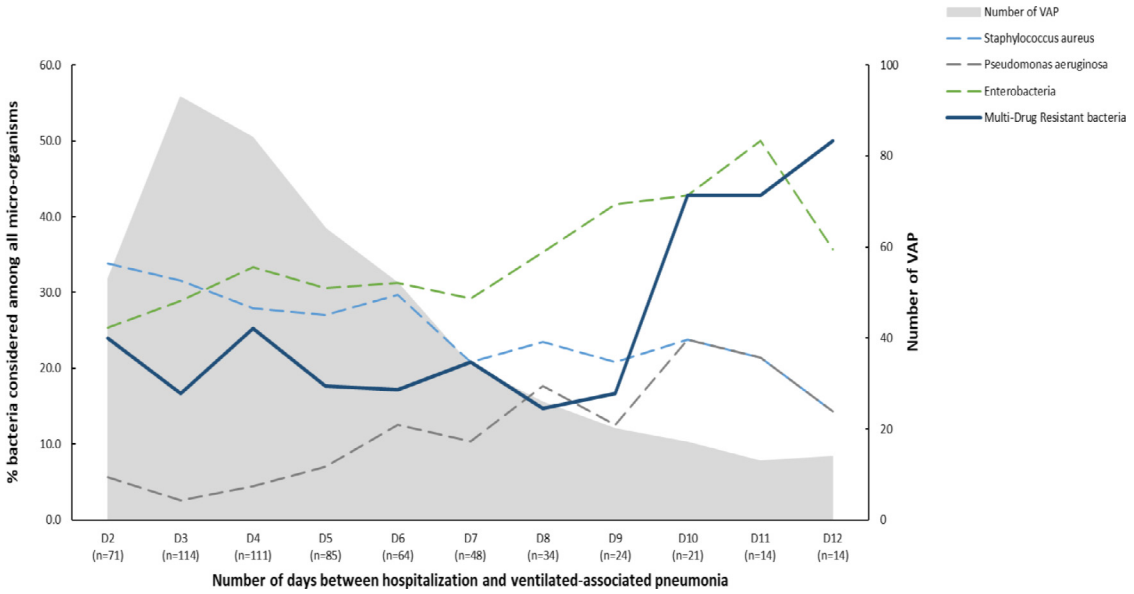


**Fig 2.** Evolution of Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacteriaceae, Multi-Drug Resistant bacteria proportions and of the number of VAP as a function of the interval between hospitalization and the onset of the first ventilator-associated pneumonia.

Evolution of the proportions of *S. aureus* regardless the resistance profile (declining trend, $P = .029$), *P. aeruginosa* regardless the resistance profile (increasing trend, $P < .001$), Enterobacteriaceae regardless the resistance profile (increasing trend, $P = .040$) are represented by a dotted line. Evolution of Multi-Drug Resistant bacteria (increasing trend, $P = .033$) is represented by a full line. Evolution of the number of VAP is represented by a gray area. For each number of days between hospitalization and the onset of the VAP, the number of identified germs is specified on the x-axis. VAP: Ventilator-associated pneumonia.

This study has some limitations. Because of the low number of microorganisms detected: global *Enterobacteriaceae* were studied instead of species, and global MDROs were studied instead of MRSA, 3GCR-E, CRPA and GREF individually. AMR data were limited and the ESBL profile for 3CGR-E was not systematically determined. A survival bias (patients had to survive during the first days after ICU admission) and selection bias to less severe patients could have occurred. The population hospitalized in ICUs and medical practices could have changed over the years.

Nevertheless, multicenter, prospective data and standardized procedures of VAP diagnosis, patient recruitment, and laboratory procedures reinforce the validity of the study.

To conclude, in this specific group of severely ill patients, the proportion of MDROs in VAP decreased between 2003 and 2016 and increased significantly when VAP started after 10 days in ICUs.

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