



The current epidemiological landscape of ventilator-associated pneumonia in the intensive care unit: a multicenter prospective observational study in China – study critique, ventilator-associated pneumonia incidence rates, and pathogen distribution

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Among the nosocomial infections, ventilator-associated pneumonia (VAP) has an attributable mortality rate of approximately 10% (1). VAP incidence rates and its trends through time are essential metrics for the monitoring of the effectiveness of preventive strategies. In a study recently published in *Clinical Infectious Diseases*, Xie *et al.*, have made a notable effort in reporting VAP epidemiological data from the China Critical Care Infection Surveillance (CRISIS) study (2).

Asia-Pacific countries (Australia, Singapore, and South Korea) have the second highest prevalence of VAP, 16%; followed by Latin America countries (Chile, Colombia, and Mexico), 13.8% (3). Data on VAP epidemiology in the China, however, is limited. Xie *et al.* calculated an incidence of VAP based on a representative sample of China intensive care units (ICU).

In addition to variations in the frequency of VAP from country to country, the causative organisms involved in VAP have a varying distribution worldwide (4); *Acinetobacter baumannii* was the most common bacteria found in this study. In contrast, *Pseudomonas aeruginosa* and *Staphylococcus aureus* are predominant in the United States (5,6). We will review the internal and external validity of this study, and compare the bacterial distribution findings with other epidemiological studies or databases identified through

a PubMed search for VAP incidence and VAP pathogen-related distributions in other parts of the world.

The CRISIS VAP incidence was 4.5 episodes per 1,000 ventilator-days, similar to the rate reported by the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) in 2006 (Medical ICUs-3.1 and Surgical ICUs-5.2 episodes per 1,000 ventilator-days), and lower than the International Nosocomial Infection Control Consortium (INICC) that reported data from fifty countries, finding an average rate of 13.9 episodes per 1,000 ventilator-days (7).

Other noteworthy findings from the CRISIS study were that the VAP prevention bundle was implemented only in 48.8% of patients. There was a high prevalence of multidrug-resistant organism (MDRO). The 28-day mortality among patients who developed VAP was 45%. Factors associated with VAP-related mortality were advanced age and increased severity of critical illness. There was no difference in mortality between early and late-onset VAP.

A comprehensive review of the literature and meta-analysis from Ding *et al.*, evaluated studies published from 2010 to 2015 and estimated the incidence of VAP in China. It showed an incidence density of 24.14 episodes per 1,000 ventilator-days. This meta-analysis used a large sample size, but the heterogeneity of VAP incidence rates by factors

such as differences in VAP diagnostic criteria between analyzed studies was among the limitations that probably affected results of this meta-analysis (8). On the other hand, the CRISIS VAP methodology had specific and consistent definitions and used updated VAP diagnostic criteria. The investigators addressed all known risk factors for VAP in their demographic variables.

In 2019, another meta-analysis estimated the VAP incidence in twenty-two Asian countries including China, stratified by national income-level, and demonstrated a lower VAP incidence in high-income countries when compared with lower income countries (9 vs. 18.5 per 1,000 ventilator-days respectively) (9).

There are several limitations in the data reported by Xie *et al.* The patients were probably not representative of China overall; the researchers may have incurred sample selection bias because eleven out of the 14 hospitals were university hospitals, which likely have very different patient populations and processes of care than more rural, non-teaching Chinese hospitals.

Type of ICU is a crucial missing demographical variable. The ICUs participating in the study were general ICUs, also known as mixed medical-surgical. There are variations in VAP rates among ICU type of location. For example, trauma and burn ICUs appear to have higher VAP incidence rates according to reports of CDC/NHSN (10-12).

In the United States, *S. aureus* is involved in approximately 20% of all VAPs (~50% are methicillin resistant) and *P. aeruginosa* causes approximately 25% (13); in contrast with Asian countries and China where bacteria frequencies are different, and *A. baumannii* has the highest prevalence. Many organisms that cause VAP have high rates of multi-drug resistance. In the CRISIS study, MDROs were not associated with a significantly higher mortality, nor were there differences in survival between early and late-onset VAP. These findings differ from other countries or continents like Europe, where the presence of MDROs and late-onset VAP are strongly associated with elevated mortality (14,15). Furthermore, there is substantial scientific evidence and biological plausibility to conclude that mortality worsens with extensively- and pan-drug resistance, in particular with the presence of *A. baumannii* (16). In this study, only 17.6% of patients infected with *A. baumannii* received appropriate early antibiotics, demonstrating a significant opportunity for improvement in providing effective initial empiric antibiotic treatment in Chinese patients with VAP. The variables that impacted mortality in this study were advanced age, chronic heart failure, elevated SOFA, and Apache II scores.

These findings were also in parallel to other VAP and sepsis observational studies (17,18).

The implementation of VAP bundles has been associated with a substantial decrease in reported VAP incidence rates in the United States based on the CDC/NHSN data (19). However, a discrepancy in VAP rates among the CDC/NHSN versus the United States Medicare Patient Safety Monitoring System have raised the question of potential reporting bias affecting the VAP rates reported by the CDC/NHSN (20). Nonetheless, we consider that it is essential to mention the relatively low adherence to VAP prevention strategies seen in this observational study. This important finding suggests an opportunity to improve the utilization of VAP preventive interventions in China and provides a baseline rate for comparison.

Overall, we believe that the CRISIS is a promising initiative that can provide the underpinnings for future VAP quality improvement efforts in China. This study provides an important status report of VAP in China. As such, these data will serve as a guide for empiric antibiotic treatment for VAP and as a baseline measurement to assess the effect of future preventative and therapeutic interventions to improve VAP rates and outcomes in China. Future epidemiologic studies might benefit from the inclusion of more non-teaching (presumably smaller and more rural) hospitals and more detailed characterization of the type of ICU.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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