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Ventilator associated pneumonia in intensive care unit patients: a systematic review

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Abstract

Ventilator-associated pneumonia (VAP) is the most common ICU acquired pneumonia among patients who are invasively intubated for mechanical ventilation. Patients with VAP suffer an increased mortality risk, financial burden, and length of stay in the hospital. The authors aimed to review the literature to describe the incidence, mortality, and microbiological evidence of VAP. We selected 13 peer-reviewed articles published from 1 January 2010 to 15 September 2022 from electronic databases for studies among adult or pediatric patients diagnosed with VAP expressed per thousand days admitted in the ICU. The VAP rates ranged from 7 to 43 per thousand days, varying among different countries of the world. A significant rate of mortality was observed in 13 studies ranging from 6.3 to 66.9%. Gram-negative organisms like Acinetobacter spp., Pseudomonas aeruginosa Gram-positive organisms like Staphylococcus aureus were frequently found. Our findings suggest an alarming situation of VAP among patients admitted to the intensive care units with increasing incidence and mortality. The review also found that VAP is more common in males and that there is a significant variation in the incidence and mortality rates of VAP among different countries. The findings of this review can inform the development of infection control and prevention strategies to reduce the burden of VAP. Thus, there is a crucial need for control and preventive measures like interventional studies and educational programs on staff training, hand-hygiene, and the appropriate use of ventilator bundle approach to curb this preventable threat that is increasing at an alarming rate.

Keywords: Adult, artificial, intensive care units, incidence pneumonia, ventilator-associated, respiration

Introduction

Ventilator-associated pneumonia (VAP) or intubation-associated pneumonia is a pneumonia that arises more than 48–72 h after endotracheal intubation and is not incubating at the time of admission[1]. Infiltrates that are either new or progressive in nature, systemic infection (fever, altered white blood cell counts), changes in the characteristics of sputum, and the detection of a causative agent are seen in patients with VAP[2]. VAP is the most common ICU acquired pneumonia among patients who are invasively intubated for mechanical ventilation[3]. Patients having VAP have an attributable mortality of 13.5%. It leads to an increase in the length of stay at the hospital as well as an increase in financial burden.

HIGHLIGHTS

- Ventilator-associated pneumonia (VAP) is the most common ICU acquired pneumonia among patients who are invasively intubated for mechanical ventilation.
- The VAP rates ranged from 7 to 43 per thousand days, varying among different countries of the world.
- Our findings suggest an alarming situation of VAP among patients admitted to the ICUs with increasing incidence and mortality.
- The review also found that VAP is more common in males and that there is a significant variation in the incidence and mortality rates of VAP among different countries.

While delayed antimicrobial medication delivery has been linked to higher mortality, early detection of VAP is essential. The hazards of overusing antibiotics, such as resistance to antibiotics and superinfections, should be weighed against the necessity of administering antibiotics quickly, especially in the ICU. VAP is tricky to diagnose, making finding the proper balance difficult. The perceived incidence and consequences of VAP vary greatly based on the definition used, and up to two-thirds of people diagnosed for VAP do not always genuinely have VAP because there is no realistic reference standard for the condition. There is an urgent need for improved approaches to diagnose VAP and guide the use of empirical antibiotics[4].

For determining the presence of VAP and starting empiric antibiotics, clinicians often depend on diagnostic, radiological, and laboratory signs. Symptoms include fever, sputum production, hypoxemia, a chest radiography infiltrate that has developed

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or is new, a raised white blood cell count, and abnormal cultures from ETA or bronchoscopic sample procedures (bronchoalveolar lavage and protected specimen brush). Several of these have been incorporated into clinical models, with the clinical lung infection score (CPIS) being the most well-liked. Yet, despite the fact that these symptoms and tests are often used, nothing is known about how accurate they are at diagnosing VAP[5].

The main objective of our review is to estimate the incidence, mortality, and etiological agents associated with VAP. This reliable and upgraded information would help in assessing the significance of the situation and providing evidence for patients, clinicians, and policy makers for planning infection control and other prevention strategies to control this preventable disease and lower the mortality associated with it for future.

Methods

We organized this systematic review in accordance with the Cochrane Manual for Diagnostic Accuracy Level, PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)[4] recommendations for Diagnostics Accuracy Level, and other reviews of Diagnostics Give Accurate information guidelines. Via PROSPERO, we validated the study procedures (CRD42019124907).

Search methods

Four authors independently conducted an extensive literature search of the four electronic databases, namely PubMed, Google Scholar, and PLOS ONE to identify all the peer-reviewed research articles published within the time frame of 1 January 2010 to 15 September 2022. The complete search strategy in detail for PubMed and PLOS ONE is given in the supporting file for the search strategy. All the databases were searched using relevant MeSH Terms in PubMed, as well as PLOS ONE and Google Scholar. The terms 'Ventilator-associated Pneumonia', 'Healthcare-Associated Pneumonia', were searched under MeSH terms. All the references to the studies qualified for the review were also thoroughly searched for additional relevant articles.

Selection criteria

Inclusion criteria

Randomized controlled trials and cohort studies that were published in English including information on at least the prevalence, incidence, or incidence rate of VAP among adults expressed as episodes per 1000 ventilator days were considered eligible for inclusion.

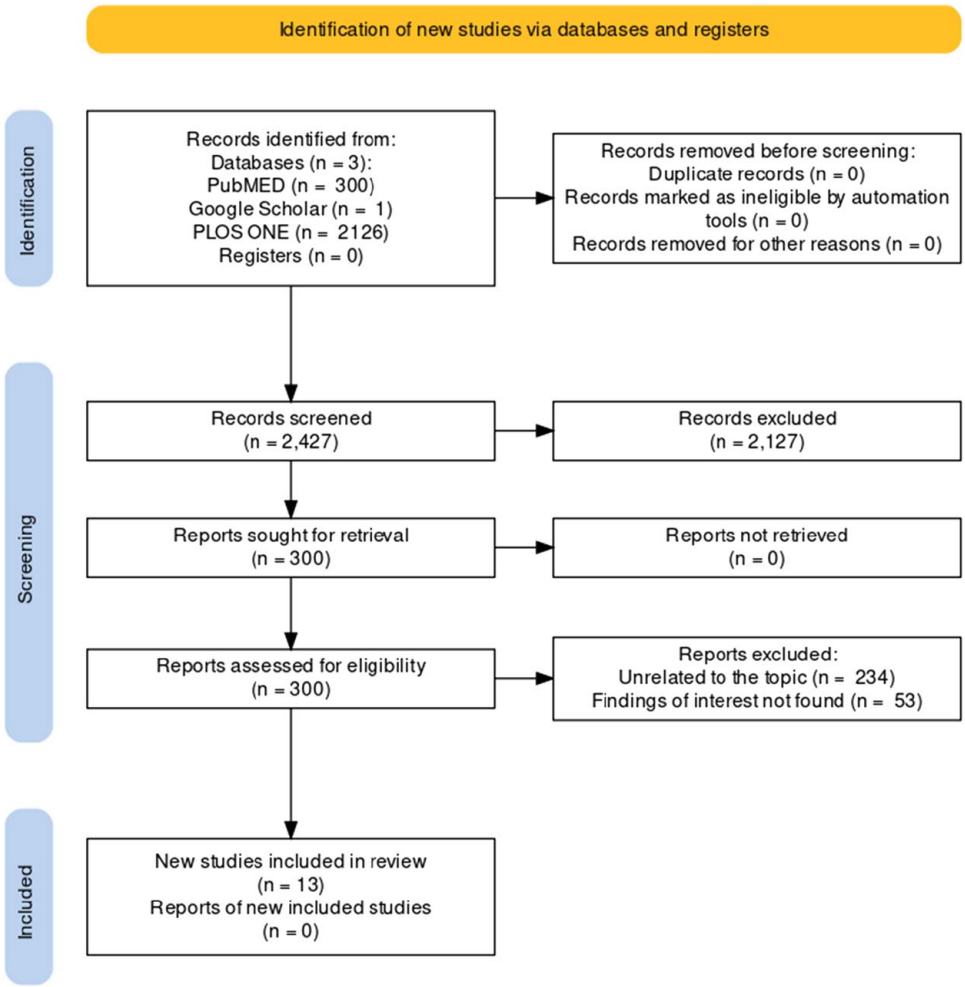

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart.

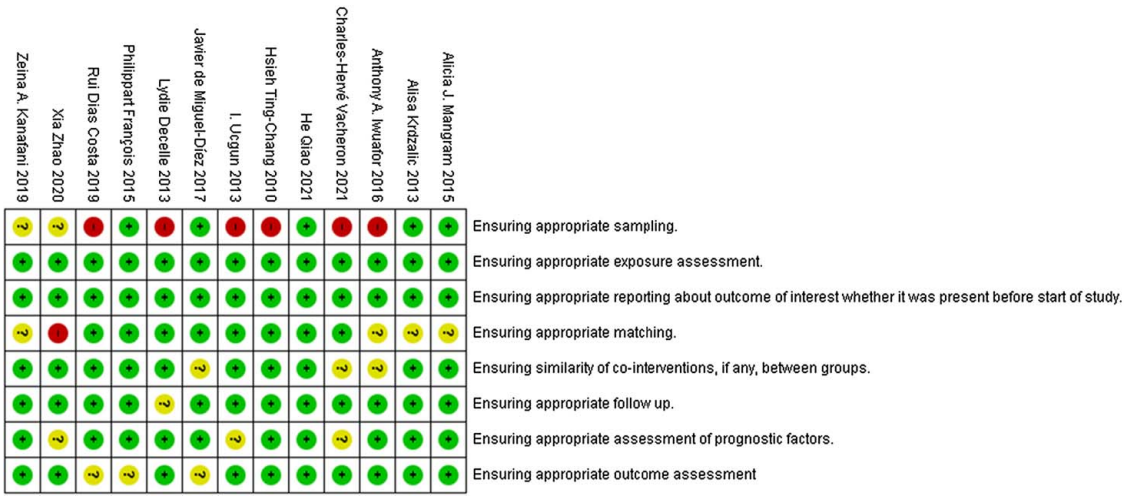

Figure 2. Risk of bias summary.

The search method has been briefly described in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA)[4] flowchart in Figure 1.

Exclusion criteria

Review articles, research protocols, case series/case reports, symposium/conference proceedings, commentaries/editorials/letters, views/opinions and articles that were not in English language as well as those whose full-text was not available were excluded from our review.

Data collection and analysis

According to prespecified inclusion and exclusion criteria, four independent authors screened the articles remaining after duplicates removal. Full-text articles were retrieved, and studies were shortlisted to be included in the review, which met the eligibility criteria. The disparities and confusions among the two authors were resolved by the consultation of a third author involved in the supervision of the study. The data was extracted using the data abstraction spreadsheet in Microsoft Excel version 2013 (Microsoft Corp) under the following variables: Name of the author, country where the study was done, year of the publication, study design, sample size, inclusion criteria, exclusion criteria, primary outcome, secondary outcome, and duration of study. The work has been reported in line with AMSTAR (Assessing the methodological quality of systematic reviews) Guidelines. Descriptive statistical analysis was done using IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 23.0.: IBM Corp. Risk of bias analysis was done using Review Manager (RevMan) [Computer program]. Version 5.4, The Cochrane Collaboration, 2020.

Risk of bias analysis

The Cochrane risk of bias tool for nonrandomized studies was used to assess the risk of bias for studies included in this review[5]. The analysis is graphically represented in Figure 2 and Figure 3.

Main results

The results of our systematic review are as follows:

Study selection

A total of 2427 articles were obtained after a thorough search through the databases. After the first scanning, a total of 300

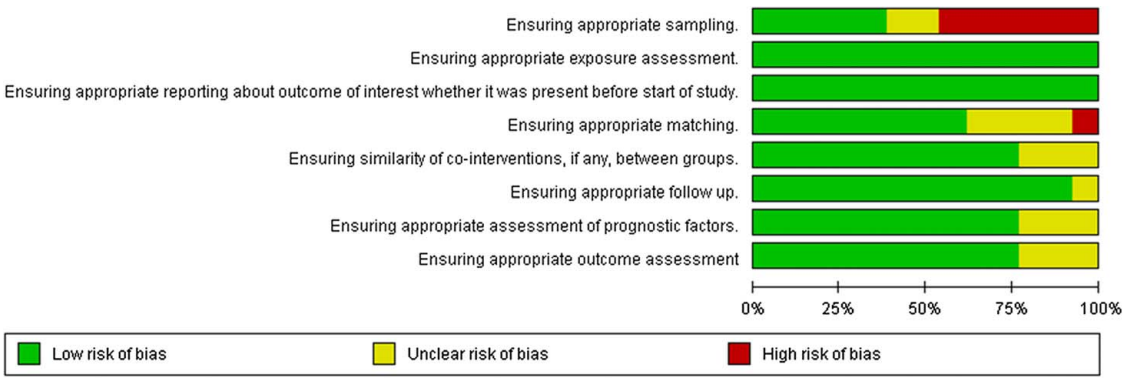

Figure 3. Risk of bias analysis.

Table 1

Table of studies included in this systematic review.

Serial number	References	Title	Country	Sample size	Study design
1	Javier de Miguel-Díez [6]	Decreasing incidence and mortality among hospitalized patients suffering a ventilator-associated pneumonia - Analysis of the Spanish national hospital discharge database from 2010 to 2014.	Spain	9336	Retrospective cohort study
2	Lydie Decelle [7]	Ventilation-associated pneumonia after intubation in the prehospital or the emergency unit.	Belgium	75	Retrospective descriptive (case–control) study
3	Ting-Chang Hsieh [8]	Frequency of Ventilator-associated Pneumonia With 3-day Versus 7-day Ventilator Circuit Changes.	Taiwan	397	Retrospective cohort study
4	Xia Zhao [9]	Epidemiological and clinical characteristics of healthcare-associated infection in elderly patients in a large Chinese tertiary hospital: a 3-year surveillance study.	China	134637	Prospective cohort study
5	Charles-Hervé Vacheron [10]	Increased Incidence of Ventilator-Acquired Pneumonia in Coronavirus Disease 2019 Patients: A Multicentric Cohort Study.	France	3758	Prospective cohort study
6	Zeina A. Kanafani [11]	Ten-year surveillance study of ventilator-associated pneumonia at a tertiary care center in Lebanon.	Lebanon	162	Retrospective cohort study
7	Rui Dias Costa [12]	Hospital-Acquired Pneumonia in a Multipurpose Intensive Care Unit: One-Year Prospective Study.	Portugal	60	Prospective cohort study
8	Alicia J. Mangram [13]	Trauma-associated pneumonia: time to redefine ventilator-associated pneumonia in trauma patients.	United States	1044	Retrospective cohort study
9	I. Ucgun [14]	Effects of isolation rooms on the prevalence of hospital-acquired pneumonia in a respiratory ICU.	Turkey	532	Prospective cohort study
10	Alisa Krdzalic [15]	Influence of Remifentanil/Propofol Anesthesia on Ventilator-associated Pneumonia Occurence After Major Cardiac Surgery.	Bosnia and Herzegovina	82	Retrospective-prospective study
11	François Philippart [16]	Decreased Risk of Ventilator-Associated Pneumonia in Sepsis Due to Intra-Abdominal Infection.	France	2623	Retrospective cohort study
12	Anthony A. Iwuafor [17]	Incidence, Clinical Outcome and Risk Factors of Intensive Care Unit Infections in the Lagos University Teaching Hospital (LUTH), Lagos, Nigeria.	Nigeria	71	Prospective cohort study
13	Qiao He [18]	The epidemiology and clinical outcomes of ventilator-associated events among 20 769 mechanically ventilated patients at intensive care units: an observational study.	China	22343	Analytical randomized study

Table 2

Descriptive statistics of variables.

Descriptive statistics of variables							
	Males (%)	Females (%)	Sample size of the study (*n*)	Overall age distribution in years (mean)	Length of stay in the intensive care unit in days (mean)	Incidence of ventilator-associated pneumonia (%)	Intensive care unit mortality (%)
Mean	64.88	35.12	13470.77	53.55	8.62	20.05	22.24
Median	66.35	33.65	532.00	57.50	8.50	17.29	20.30
Percentiles							
25	54.71	28.40	78.50	50.70		8.65	16.22
50	66.35	33.65	532.00	57.50		17.29	20.30
75	71.60	45.29	6547.00	62.05		25.21	29.23

articles remained for further processing. After the title and abstract screening, 234 of those papers were omitted because they did not follow the inclusion requirements. The full-text was obtained for the remaining 66 articles. Of the 66 full-text posts, 53 were rejected because the findings of interest were not found. Finally, 13 articles were included in the review.

Altogether, 13 studies conducted in various hospital settings among different adult patients and pediatric patients presented in the ICU were reviewed qualitatively. Studies included The US Centers for Disease Control and Prevention and CPIS as diagnostic criteria for VAP expressed per thousand ventilator days. Countries where studies were conducted includes the United States, Spain, Belgium, Taiwan, China, France, Lebanon, Portugal, Turkey, Bosnia and Herzegovina, and Nigeria. A description of the individual studies is provided in the Table 1 (available from the supplementary file Table 1). Detailed descriptive statistics are tabulated in Table 2.The statistical results showed the males ratio (71.60) is higher than female (45.29) and the highest incidence rate of ventilator-associated pneumonia (%), that is, 25.21% and the highest ICU mortality (%) rate, that is, 29.23%.

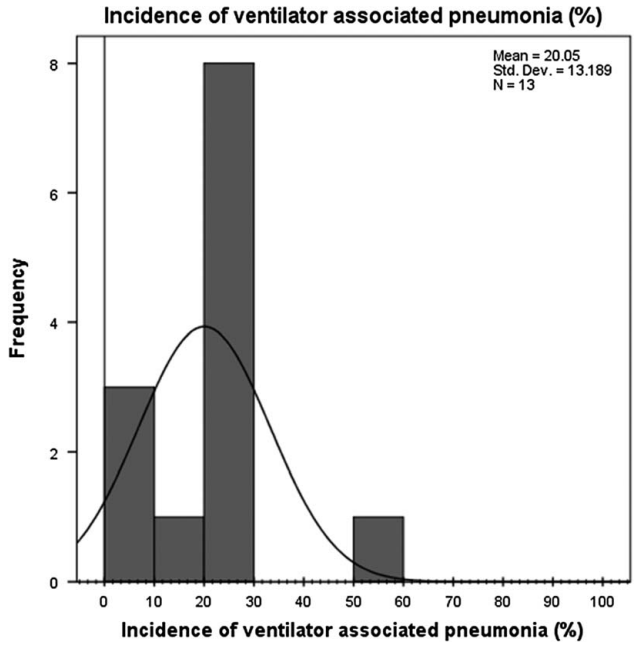

Figure 4. Incidence of ventilator-associated pneumonia graph. (Frequency is the frequency with which an incidence value [in percentage] was reported in our studies).

Ventilator-associated pneumonia incidence rate

The VAP incidence rate ranged from 7 to 43 per thousand ventilator days (95% CI 20.05 + 13.189) as shown in Figure 4 showing a great difference between countries. The pooled mean of sex from our studies resulted with males consisting of 64.88% (95% CI 64.88 + 10.78) and females 35.12% (95% CI 35.12 + 10.78) as shown in the sex distribution graph in Figure 5. The highest VAP prevalence rate was reported from a database study of Spain. The lowest was from Portugal. The VAP rate reported from various studies are reported in the table of VAP prevalence rates.

Mortality

Ten of the 13 articles included in the review reported the mortality rate in hospitalized patients. The mortality rate ranged from 6.3 to 66.9%. The highest mortality rate was reported from a study of Turkey[19]. No mortality rates were reported from studies of Lebanon, Bosnia, and Herzegovina, and one study of China[6–8]. The detailed description of the mortality rate reported from studies of different countries is graphically presented in Figure 6 and tabulated in Table 3.

Microbiology of VAP

Ten studies included data on microbiology, causing VAP, as shown in the table of microbiology of VAP. Acinetobacter baumannii caused the majority of VAP episodes followed by Pseudomonas aeruginosa.

Comparison among the microbiology of VAP of 13 a studies table of the microbiology of VAP showed Acinetobacter sp., followed by Pseudomonas aeruginosa as common gram-negative organisms causing VAP while Staphylococcus aureus as common gram-positive organisms. Studies also isolated resistant forms of gram-positive bacteria like MRSA (Methicillin resistant Staphylococcus Aureus). Candida sp. was the most common of the fungal isolates described in the studies by Iwuafor[16], Diez[9], and Zhao[8] as shown in Figure 7.

Different countries across the globe whose studies have been included in this review are the United States, China, Taiwan, Nigeria, France, Portugal, Belgium, Portugal, Bosnia and Herzegovina, Spain, and Turkey.

Discussion

Our review highlights the situation of VAP among the populations of 11 different countries across the globe, from the United

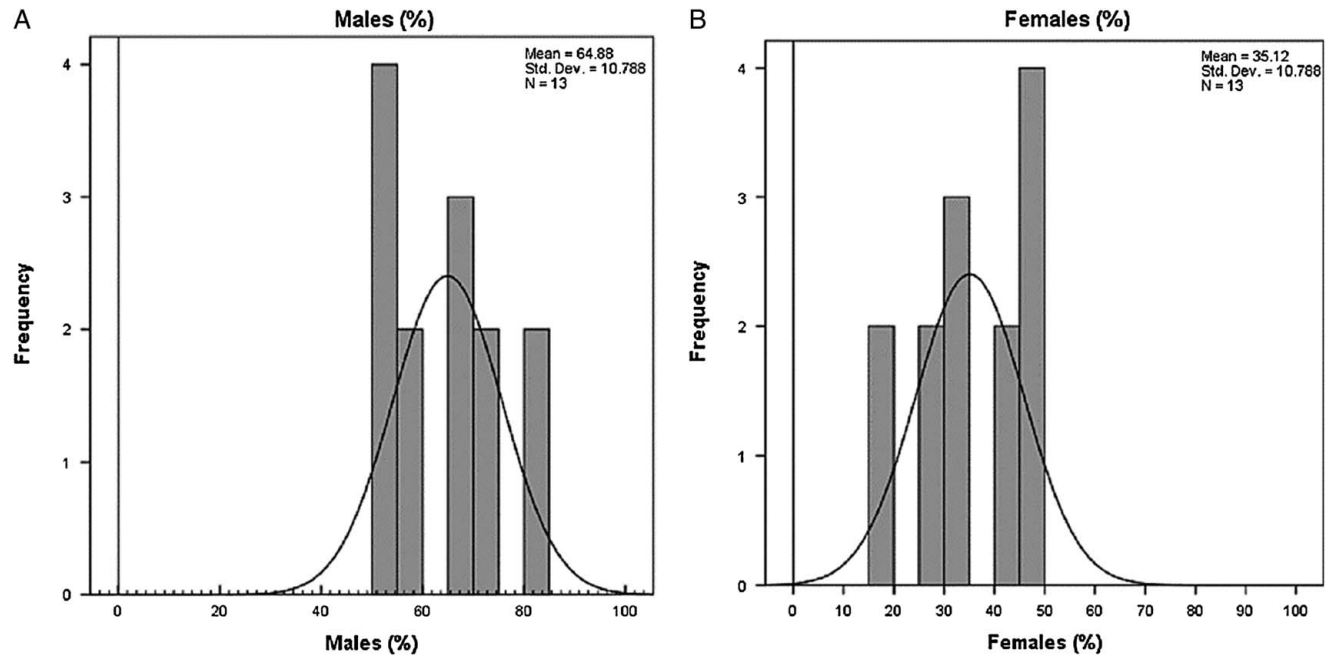

Figure 5. Sex distribution graph;(a) Males; Females (b); frequency is the frequency with which a particular gender [in percentage] was reported in our studies.

States in North America to Taiwan in Asia. We found a wide range of VAP burden with much variability in the VAP rate, ranging from 7 to 43 per thousand ventilator days among these countries, showing most studies with disturbing VAP situations. Mortality rates reported by the majority of the studies included in our review were caused by gram-negative organisms followed by gram-positive bacteria.

The economical differences, which can then lead to a lack of advancement and availability of health facilities in some regions can be a reason for the higher VAP rate in those countries. Differences in the study setting such as pediatric or adult ICU or surgical and medical ICU can also be another probable reason why there is a wide variation in the VAP rate. As there is no unanimous worldwide gold-standard definition for VAP, the criteria can also be a reason why sometimes VAP is over or under reported.

Patients diagnosed with many comorbidities especially neurologic, cardiorespiratory diseases as well as coronavirus disease 2019 are associated with a higher VAP rate[8,10,12].

Finally, staff practices, be it the prehospital emergency team or the medical staff in the hospital and ICU premises, which do not follow infection prevention guidelines could cause a variability in the VAP rate with an increased rate in areas where guidelines are not properly followed by the staff[14].

In a study of 22 Asian countries by Bonnel *et al.*[18] , they concluded that VAP incidence was on the lower side in rich countries where the average income was higher compared to countries where people had a low-income (9 vs. 18.5 per 1000 ventilator days, respectively). Studies across the globe from the Middle East and Japan also varied between 8 and 12.6 per thousand ventilator days[20].

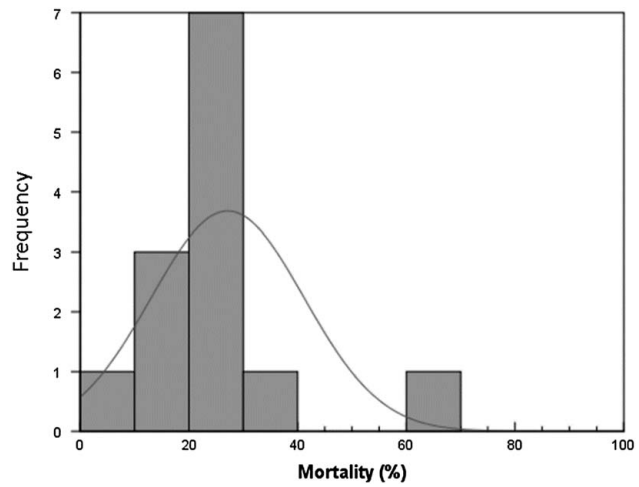

Figure 6. Percent mortality graph; only studies that reported mortality were included in this graph; frequency is the frequency with which a particular mortality value [in percentage] was reported in our studies.

Table 3

Mortality rates reported in each study.

Serial number	References	Mortality rate (%)
1	Javier de Miguel-Díez [9]	34.88
2	Lydie Decelle [10]	17.33
3	Ting-Chang Hsieh [11]	28.85
4	Charles-Hervé Vacheron [12]	28.50
5	Rui Dias Costa [13]	18.30
6	Alicia J. Mangram [14]	6.30
7	I. Ucgun [19]	66.30
8	François Philippart [15]	29.95
9	Anthony A. Iwuafor [16]	27.11
10	Qiao He [17]	15.10

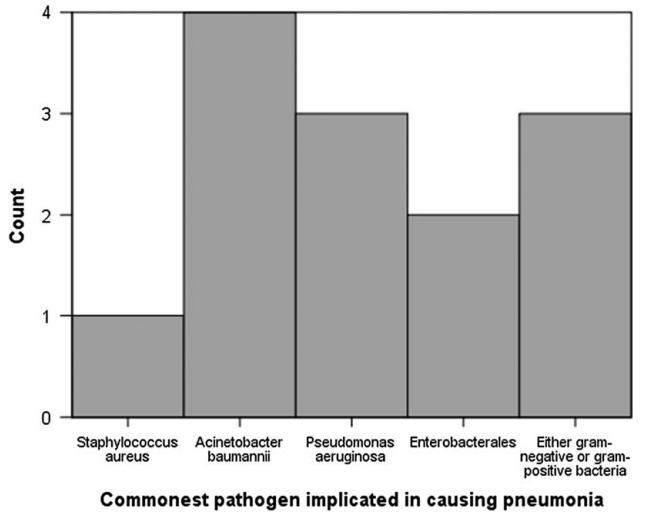

Figure 7. Commonest pathogen implicated in causing pneumonia. (Count represents the number of times an organism was reported as the most common in all studies)

The studies in our review show heterogenous results. Some studies resemble the rates reported as of the above studies, but other studies have a variedly higher incidence of VAP increasing the VAP burden. Some of the risk factors which were reported to increase the risk of VAP were old age, longer time on ventilation, infection with coronavirus disease 2019, and macroaspiration[8,10,12]. In those who had trauma, fractures of the ribs, lung contusions, and a failed attempt at intubation before reaching the hospital were associated with a greater risk of developing VAP[14]. Patients who had cardiac surgery with cardiopulmonary bypass and required a longer respiratory tie were also prone to a greater risk of developing VAP[7].

Interestingly, in one of our studies, it was reported that the mortality associated with hospital-acquired pneumonia was higher if the initial cause of admission was HAP compared to patients who were admitted to the ICU for another reason and later developed HAP— 32 vs 8.6%, respectively[13]. This may be due to the fact that patients in the ICU are under higher vigilant supervision than any other ward in general, and any deterioration that may occur in these patients may be promptly diagnosed and treated by the ICU healthcare staff before the patients deteriorate. This may not be the case for patients who develop pneumonia elsewhere and seek medical attention once symptoms have deteriorated enough for them to be admitted to the ICU.

The highest incidence rate in our study among ICU admitted patients was reported from a database of the Spanish National Healthcare Discharge database, while the lowest was found in a Portuguese hospital[11]. Possible reasons for the high rate may be due to a greater number of males, a higher number of comorbidities, and a higher number of readmissions in the patients of the database; all factors associated with a higher risk of VAP. The study in a Portuguese hospital probably had a lower VAP rate because they had a smaller sample size and a shorter duration of study follow-up.

Our study showed the mortality rate ranged from 6.3 to 66.3%. The highest mortality rate was reported from among Turkish patients[19]. This rate is similar to a study among developing countries by Kharel S, *et al.*[21] The mortality rate reported by the Infectious Diseases Society of America and the American Thoracic Society is 13%. In Europe, the 30-day mortality rate is reported to be 29.9%, which is generally lower than what the studies in our review reported[22,23]. This may be because our study has heterogenous population sample sizes with the highest number of patients from China. This may skew the direction from the values reported by American and European societies, which do not include Chinese and Turkish data into their results. The highest mortality rate reported among the Turkish patients[19] was probably due to a lack of a specialized ICU unit and high antibiotic resistance in the cohort.

Data on microbiology shows that the most common organism responsible for the majority of the VAP cases in our studies was gram-negative Acinetobacter baumannii followed closely by Pseudomonas aeruginosa. This data closely resembles a recent analysis done by Kharel S, *et al.*[21], which reported similar results on microbiology in VAP. An analysis done by Fathy, *et al.*[24] in an Egyptian patients also showed common causative organisms, which included Pseudomonas aeruginosa and methicillin resistant Staph. aureus.

To curb and decrease the burden of VAP, heat humidifying systems can be employed[25]. Proper education of ICU and hospital staff as well as strict adherence to hand-hygiene protocols and proper handling of bronchial secretions in patients admitted to ICU can be used, which can be effective even in countries where the income is low. Ventilator bundle approaches such as elevation of the head of the bead to decrease aspiration of gastric secretions, prophylaxis against gastric ulcer disease during the ICU stay, prophylaxis against venous thromboembolism, and oral chlorhexidine contamination can be embraced, which can surely decrease the burden of VAP in patients in the ICU[26].

Strengths and limitations of the study

The major strength of our study lies in its huge total sample size as well as its global nature, including countries from four different continents with data spanning more than a decade. This gives us a unique picture into an often ignored but highly prevalent issue in the ICU. The main limitation in our study was that we did not expound on detailed information about the different subgroups of VAP such as early-onset VAP vs. late-onset VAP and the subcategories of ventilator-associated events individually, such as infection-related ventilator-associated complications, possible ventilator-associated pneumonia, and ventilator-associated complications. The other limitation in our study was that we did not utilize literature in a language other than English. Lastly, we did not utilize articles that were not available as free-access articles, which may have had an effect on our results.

Conclusions

According to this comprehensive review, the traditional clinical signs for diagnosing VAP—fever, purulent discharges, leukocytosis, chest radiograph, cultures from three different sample procedures (protected specimen brush, ETA, and bronchoalveolar lavage), and CPIS—had low specificity. Relying only on the existence of any one of these signs might lead to incorrect diagnoses and probably inappropriate use of antibiotics. These findings underline the difficulty of identifying VAP and the demand for new tools to assist doctors in determining when to initiate and discontinue empiric antibiotics for potential VAP.

Ethical approval and Consent to participate

Not applicable.

Consent for publication

All authors have reviewed the final version of this paper and given full consent for submission and publication of this paper.

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Author contributions

H.M. and M.S.: conceptualization; M.S., W.K.: methodology; H.M., M.S., and S.M.I.: formal analysis; M.S., W.K.: investigation; H.S., M.M.: data curation; M.S., H.M.: writing – original draft preparation; S.S.S. and M.S.: writing – review and editing; M.S. and H.M.: visualization; H.M.: supervision. All authors reviewed the final version and approved it for submission.

Conflicts of interest disclosure

All authors declare that they have no conflict of interest with regards to the content of this paper.

Research registration unique identifying number (UIN)

Not applicable.

Guarantor

Hassan Mumtaz and Muhammad Saqib.

Availability of data and materials

Data used in this study is available upon reasonable request to the corresponding author.

Provenance and peer-review

Not commissioned, externally peer-reviewed.

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