Ventilator-Associated Pneumonia (VAP), Microbiological Profile and Antibiotic Resistance Pattern: A Systematic Review

Ventilatörle İlişkili Pnömoni (VAP), Mikrobiyolojik Profil ve Antibiyotik Direnç Örüntüsü: Sistematik Bir Derleme

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ABSTRACT

Background: Ventilator-associated pneumonia is one of the most common causes of mortality in intensive care unit patients especially in countries with limited resources. Moreover, the emergence of multi-drug resistance pathogens is an alarming situation for the world healthcare community.This systemic review was designed to find the incidence, microbiological profile, common comorbidities and compare the resistance pattern of the most frequently isolated pathogens in lower-middle-income countries (LMICs), upper-middle-income countries (UMICs), and high-income countries (HICs).
Methods: This systematic review was conducted according to the PRISMA guidelines. The extensive literature search with selected MeSH terms was done by using various databases, till August 30, 2021. The information extracted from each study includes baseline characteristics, incidence, microbiological profile, and resistance pattern.
Results: In the final analysis we included 29 studies. The overall incidence ranged between 20-49%. The microbiological profile suggested that Gram-negative bacteria was the most frequent including *Acinetobacter* spp., followed by *Pseudomonas* spp., and, *Klebsiella* spp. While 8 studies also reported the Candida spp., and 3 studies reported the Aspergillus. The resistance pattern showed the multi-drug resistance (MDR) of all isolated bacteria with the highest prevalence in LMICs followed by UMICs and HICs.
Conclusion: We conclude organisms involved in VAP were highly resistant to commonly used antibiotics. Thus, there is an urgent need for better therapeutic strategies to combat these MDR bugs.
Study Registration: PROSPERO registration number CRD42021264242

Keywords: Ventilator-associated pneumonia; MDR; Nosocomial infection; ICU

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ÖZET

Amaç: Ventilatörle ilişkili pnömoni, özellikle sınırlı kaynaklara sahip ülkelerde yoğun bakım ünitesi hastalarında en sık görülen ölüm nedenlerinden biridir. Ayrıca, çok ilaca dirençli patojenlerin ortaya çıkması dünya sağlık camiası için endişe verici bir durumdur. Bu sistemik derleme, alt-orta gelirli ülkeler (LMICs), üst-orta gelirli ülkeler (UMICs) ve yüksek gelirli ülkelerde (HICs) en sık izole edilen patojenlerin insidansını, mikrobiyolojik profilini, ortak komorbiditelerini bulmak ve direnç paternini karşılaştırmak için tasarlanmıştır.
Yöntem: Bu sistematik derleme PRISMA kılavuzuna göre yürütülmüştür. Seçilen MeSH terimleri ile kapsamlı literatür taraması, 30 Ağustos 2021 tarihine kadar çeşitli veri tabanları kullanılarak yapılmıştır. Her çalışmadan elde edilen bilgiler arasında temel özellikler, insidans, mikrobiyolojik profil ve direnç paterni yer almaktadır.
Bulgular: Son analize 29 çalışma dahil edilmiştir. Genel insidans %20-49 arasında değişmektedir. Mikrobiyolojik profil, Acinetobacter spp. dahil olmak üzere Gram-negatif bakterilerin en sık görüldüğünü, bunu Pseudomonas spp. ve Klebsiella spp. izlediğini ortaya koyarken, 8 çalışma Candida spp. ve 3 çalışma da Aspergillus bildirmiştir. Direnç paterni, izole edilen tüm bakterilerin çoklu ilaç direncini (MDR) göstermiş olup, en yüksek prevalans LMIC'lerde, ardından UMIC'lerde ve HIC'lerde görülmüştür.
Sonuç: VAP'a dahil olan organizmaların yaygın olarak kullanılan antibiyotiklere karşı oldukça dirençli olduğu sonucuna vardık. Bu nedenle, bu MDR böceklerle mücadele etmek için daha iyi terapötik stratejilere acil ihtiyaç vardır.

Anahtar Sözcükler: Ventilatörle ilişkili pnömoni; ÇİD; Nozokomiyal enfeksiyon; YBÜ

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INTRODUCTION

Ventilator-associated pneumonia (VAP) is defined as pulmonary parenchyma infections in patients exposed to mechanical ventilation for at least two days (1). The diagnosis of VAP needs a high clinical suspicion, radiographic examination, and microbiological analysis of clinical specimens. It is usually confirmed on the basis of fever, high white blood cell count, new or progressive infiltrate, and purulent respiratory secretions (2). Pugin et al. in the early 1990s, introduce a clinical pulmonary infection scoring (CPIS) system which uses both laboratory and clinical criteria for VAP diagnosis. The CPIS score greater than 6 with other laboratory parameters confirmed the diagnosis of ventilator-associated pneumonia (3). It is one of the most common life-threatening nosocomial infections that occurs in approximately one-third of mechanically ventilated intensive-care unit (ICU) patients (4). The results of literature published to date reported the variable incidence of ventilator-associated pneumonia between 10 to 65%. This difference is mainly attributed to the patient population and the use of different diagnostic criteria in several reported studies (5). Ventilator-associated pneumonia affects approximately 8-28% of patients in ICUs especially in patients with prolonging duration on the mechanical ventilator. It is responsible for increasing the burden on the healthcare system and morbidity. Many studies suggested that in 50% of, cases the poor outcome is associated with inappropriate prescribed antimicrobial drugs (6). Various risk factors play a key role in the pathogenesis of VAP including advanced age, male gender, prolonged ventilation, prior antibiotic therapy, level of consciousness, comorbidities, and invasive operations (7). The pathogenesis of ventilator-associated pneumonia involves the bacterial strains that colonize the oropharyngeal tract that reach the respiratory tract mainly through the aspiration of accumulated secretions formed by microorganisms in the endotracheal tubes (8, 9). Several evidence reports suggested that Gram-negative bacteria including the *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp., and *Enterobacteriaceae,* are the predominant microorganisms in VAP. Moreover, multi-drug resistance (MDR) among these isolated Gram-negative pathogens is a huge challenge for the healthcare system (10, 11). The production of enzyme carbapenemase by the bacteria leads to the emergence of resistance in these pathogens to the broad spectrum carbapenems. The pan-drug resistance (PDR) strains also emerges due to antibiotic resistance against many classes of antibiotics including beta-lactam drugs and carbapenems (12). While the lack of novel treatment options specifically the beta-lactamase inhibitor and new class of antibiotics and rapid identification techniques and phenotypic methods further complicates these critically ill-patients suffering from VAP (13).

Rationale

The incidence of ventilator-associated pneumonia is increasing day by day in intensive care units. And the use of broad-spectrum antibiotics causing the emergence of high resistant strains, thus limiting the current treatment option available (12). Thus, it is required to analyze all the available literature that can provide more conclusive results including the current therapeutic option.

Objectives

The present study aims to determine the incidence, microbiological profile, and resistance pattern of microorganisms associated with VAP.

METHODS

The present study was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 guidelines. This systematic review is registered with the International Prospective Register of Systematic Reviews (PROSPERO) (PROSPERO registration number CRD42021264242) (supplementary file 1).

Search strategy

The extensive literature search was performed by using the Cochrane Library, Embase, Web of Science, PubMed, Google Scholar, and MEDLINE (from January 1, 2000, up to August 30, 2021). The following keywords and MeSH terms were used in the literature search: 'Ventilator-associated Pneumonia', 'intensive-care unit', 'microbiology', 'nosocomial infections' 'antibiotic resistance', 'causative organisms of VAP', 'comorbidities associated with VAP' and 'worldwide'. The manual search was done to avoid the exclusion of any potential relevant study and duplicates were removed in the final selected literature.

Inclusion and exclusion criteria

The article was selected when the following conditions met (1) observational, retrospective, prospective studies published in the English language (2) The full-length original studies investigating at least total cases, prevalence, incidence rate, or incidence rate of VAP given as episodes per 1000 ventilators days (3) The microbiological profiling was performed and expressed in numbers or percentage (4) The resistance pattern was performed according to the standard Clinical and Laboratory Standards Institute (CLSI) guidelines. The following exclusion criteria were used in this review: (1) Articles not written in the English language or full-text is unavailable (2) The systematic reviews, meta-analysis, case reports, research protocols, case series, editorials, opinions, commentaries, and book chapters (3) Inadequate information was provided for the selected parameters.

Data extraction

The predesigned data extraction table was used to include the following details: author names, year of publication, country, economic category (according to the World Bank Country classification), study design, sample size, sample type, baseline characteristics, comorbidities, incidence, microbiological profile, and antibiotic resistance pattern. The two researchers (SA, and KA) independently reviewed the articles according to prespecified eligibility criteria. Any disparities among the two authors were resolved by discussion for final decision.

Quality score assessment and analysis

The Newcastle–Ottawa Scale (NOS) was used to evaluate the quality of each included article. The NOS ranged between 0 (minimum) to 9 (maximum) stars. The Statistical Package for Social Sciences (SPSS) version 22 was used for the data analysis. The microbiological profile of highly resistant bacteria was expressed as frequency or percentage.

RESULTS

Literature screening and study selection

A total of 412 articles were identified after a thorough literature search, of which 37 duplicates were removed. After screening abstracts, a total of 338 articles were excluded because they did not follow the eligibility requirements. Then the full text was obtained for the remaining 37 articles of which eight studies were rejected as they did not investigate the parameters of interest. Thus, a total of twenty-nine studies were further included in the final review (11, 14–42). The detailed screening method is explained in Figure 1.

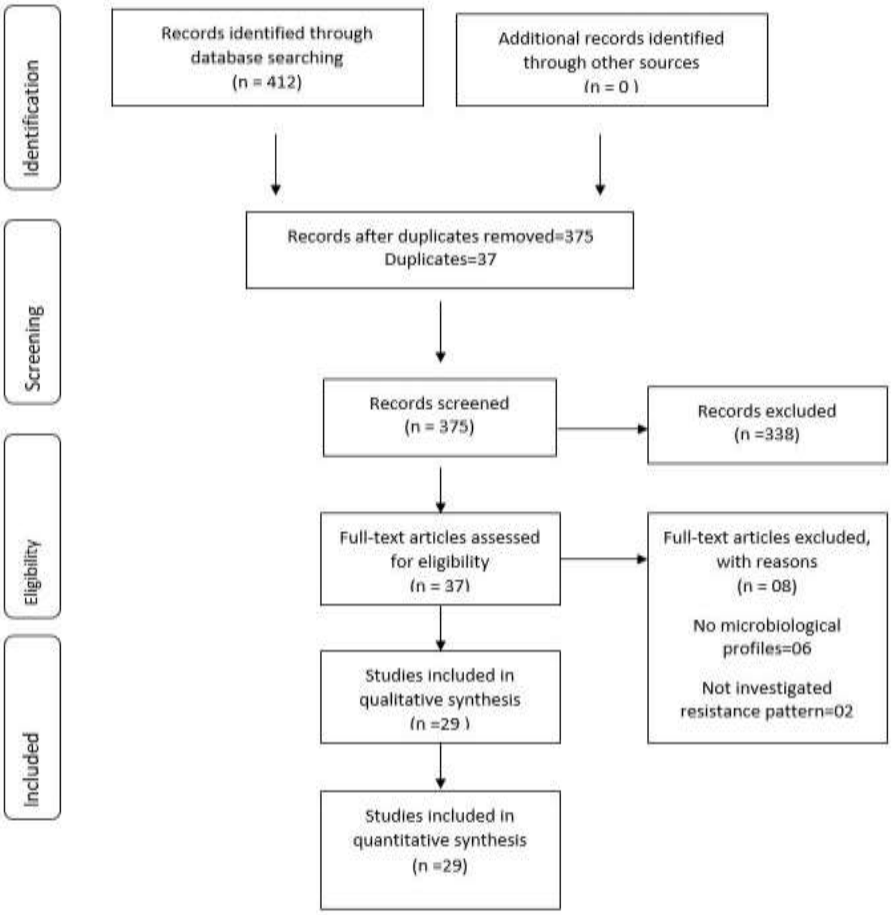

Figure 1: PRISMA diagram of study selection according to inclusion criteria

Characteristics of final included studies

After a comprehensive literature search, 29 studies (retrospective, prospective) conducted in intensive care units of hospitals were qualitatively analyzed. Among these twenty-nine studies, 3 studies were from high-income countries (HICs), 10 studies were from upper-middle-income countries (UMICs), while 16 studies were from lower-middle-income countries (LMICs). The baseline data suggested that patients above 40 years of age are more susceptible to the disease with a high frequency of male patients. The most common comorbidity in these studies were chronic obstructive pulmonary diseases (COPD), cardiovascular diseases (CVDs), diabetes mellitus, hypertension, and neurological disorders. Moreover, the initial microbiological processing indicates the most of the pathogen’s profiles were monomicrobial as compared to the polymicrobial. The quality score evaluation of the final selected studies ranged between7 to 8. The final NOS scores are given in Table 1.

Table 1. Characteristics of final included studies

Author (s)	Year	Journal	Country	Economy	Sample size	Sample type	Study Design	Monomicrobial vs Polymicrobial/ Total bacterial number	Gender wise distribution	Age	Comorbidity	NOS score
Ahmed et al.	2014	Journal of Rawalpindi Medical College	Pakistan	LMIC	48	NBL	Descriptive	MM=32 (66.67%) PM=16 (33.33%)	Males=60.42% Females=39.58%	0-30=13(27.08%) 31-60=22 (45.83%) 61-90= 13(27.08%) 90>=0%	N	07
Bahrami et al.	2014	British Microbiology Research Journal	Iran	LMIC	101	Tracheal Aspirate	Prospective	Total bacteria=126	Males=61 (60.39%) Female=40 (39.61%)	Old age	N	08
Patil et al.	2017	Journal of Natural Science, Biology and Medicine	India	LMIC	74	Endotracheal aspirate	Prospective observational	Total bacteria=126 MM=33 (44.59%) PM=41 (55.40%)	Males=53 (71.62%) Females= 21 (28.37%)	Males mean age=57±17 years Females mean age=49±14 years	Y COPD (12.16%) CAD (10.81%) LV systolic dysfunction (12.16%) Multi-organ dysfunction (14.86%)	08
Oliveira et al.	2016	The Brazilian Journal of Infectious Diseases	Brazil	UMIC	132	Tracheal	Retrospective	Total bacteria=136	Males=74% Females=26%	49±19 years	Y HD (1%) LD (1%) SAH (10%) DM (3%) Smoking (10%) Alcoholism (10%)	08
Lakhal et al.	2021	Infectious Disease Reports	Tunisia	LMIC	60	Blinded protected specimen	Retrospective	MM=77% PM=23%	Males=29 Females=31	38±16 years	No underlying comorbidity (48%) Other includes COPD (8.5%) Hypertension (6.5%) DM (3%) PD (33%)	08
Chaudhury et al.	2016	Indian Journal of Medical Research	India	LMIC	847	Endotracheal aspirate specimen	Retrospective cross-sectional descriptive	NT	NT	NT	NT	08
Chittawtanarat et al.	2014	Infection and Drug Resistance	Thailand	UMIC	150	Endotracheal aspirate specimen	Retrospective	NT	Males=70.7% Females=29.3%	52.6±20.7	Cardiovascular=10.7% Diabetics=8.7% Hypertension=6%	07
Rocha et al.	2008	The Brazilian Journal of Infectious Diseases	Brazil	UMIC	84	Endotracheal aspirate specimen	Case-control	MM=75% PM=25%	Males=64.2% Females=35.8%	47.8±17.4	Diabetes=14.2% COPD=1.1%	08
Medell et al.	2013	MEDICC Review	Cuban	UMIC	77	Tracheal aspirates	Retrospective cross-sectional descriptive	NT	Males=55.8% Females= 44.2%	42.9% in >65 year age group	NT	07
Erdem et al.	2008	Japanese Journal of Infectious Diseases	Turkey	UMIC	226	Deep tracheal aspirate	Observational	MM=78% PM=22%	Males=61% Females=39%	55.73	NT	07
Nusrat et al.	2020	Hospital Practice	Bangladesh	LMIC	105	Endotracheal aspirate	Cross-sectional	MM=92.2% PM=7.8%	Males=68.6% Females=31.4%	47.8±21.7	NT	08
Gupta et al.	2017	Journal of Global Antimicrobial Resistance	India	LMIC	87	Tracheal aspirates	Prospective	MM=66 PM=11	Males=50 Females=37	NT	NT	08
Wang et al.	2018	Infection and Drug Resistance	China	UMIC	76	Protective specimen brush	Retrospective observational	NT	Males=60.5% Females=39.5%	59.3±18.0 years	COPD=27.6% Severe pneumonia=14.5% Sepsis with ARDS=11.8% Cerebrovascular=10.5% Acute pancreatitis=9.2% Trauma=7.9% Asthma=6.6% Tumor=6.6% Drug poisoning=5.3%	08
Patro et al.	2018	Indian Journal of Pathology & Microbiology	India	LMIC	100	Endotracheal aspirate	Observational cross-sectional	MM=65.71% PM=34.29%	NT	41-60 years	COPD=14.29% Renal failure 22.86% Accidents=25.71%	07
Tran et al.	2017	BMC Infectious Diseases	Vietnam	LMIC	220	Bronchoalveolar lavage	Observational	MM=92.66% PM=7.34%	Males=50% Females=50%	71±16.7 years	Respiratory failure=60% Hypertension=37% Diabetes=26% Chronic kidney disease=16% Heart failure=16% Sepsis shock=11%	08

Table 1. continued

Japoni et al.	2011	The Journal of Infection in Developing Countries	Iran	LMIC	58	Sputum, Endotracheal tube tips	Observational cross-sectional	MM=96.6% PM=3.4%	Males=42 Females=16	39	Neurological disorder=44.8% Post-operative care=20.7% Head/Chest trauma=19% Respiratory disorders= 8.6% Other syndromes=6.9%	07
Namiduru et al.	2004	The Journal of International Medical Research	Turkey	UMIC	140	Deep tracheal aspirate	Retrospective	MM=78 PM=62	NT	NT	NT	07
Balkhy et al.	2014	Annals of Thoracic Medicine	Saudi Arabia	HIC	297	Endotracheal aspirate & Bronchoalveolar lavage	Retrospective	NT	Males=71.2% Females=28.8%	47.3±21.7	Hypertension=28.8% Diabetes=28.8% Liver diseases=9.6% Cardiovascular diseases=23.3% Respiratory diseases=26.7% Renal diseases=14.4% Immunocompromising condition=10.3%	08
Joseph et al.[a,b]	2009 2010	The Journal of Infection in Developing Countries	India	LMIC	200	Endotracheal aspirate	Prospective observational cohort	NT	Males=66.7% Females=33.3%	41.4 ± 14.7	Neurological disorders=70.5% Other includes poisoning, CVDs=29.5%	07
Tehrani et al.	2019	Tanaffos	Tehran	LMIC	29	Endotracheal aspirate & Bronchoalveolar lavage	Cross-sectional	NT	Males=53.3% Females=46.7%	72.9	NT	07
Xie et al.	2011	Journal of Hospital Infection	China	UMIC	868	Tracheal aspirate, Sputum & Bronchoalveolar lavage	Multicenter prospective cohort	NT	Males=60.1% Females=39.9%	46.65	COPD=36.6% Coma=30.8% Immunosuppressant= 27.9% Serious diseases= 32.5% Infection in other sites=41.9%	08
Golia et al.	2013	Journal of Clinical and Diagnostic Research	India	LMIC	52	Endotracheal aspirate	Retrospective	MM=45 PM=07	Males=39 Females=18	40-60 years age group	NT	07
Farag et al.	2020	The Journal of Infection in Developing Countries	Egypt	LMIC	50	Endotracheal aspirate	Observational	MM=94% PM=06%	Males=70% Females=30%	55	NT	07
Resende et al.	2013	BMC Infectious Diseases	Brazil	UMIC	33	Tracheal	Descriptive prospective cohort	MM=68.8% PM=31.2%	Males=24 Females=09	59	Comorbidities=51.5%	07
Injac et al.	2017	Vojnosanitetski pregled	Serbia	UMIC	122	Endotracheal aspirate	Retrospective	MM=84.4% PM=15.6%	Males=78 Females=44	56.8 ± 14.6	Hypertension=50.8% CVDs =41.8% COPD=28.7%	07
Kapaganty et al.	2018	Indian Journal of Microbiology Research	India	LMIC	56	Endotracheal aspirates	Prospective	MM=67.9% PM=32.1%	Males=39.24% Females=45.45%	52.13 ± 15.92	NT	07
Mishra et al.	2020	Journal of Family Medicine and Primary Care	Nepal	LMIC	25	Endotracheal aspirates	Prospective	MM=73.9% PM=26.1%	NT	NT	NT	07
Turkovic et al.	2015	Acta Clinica Croatica	Croatia	HIC	113	Endotracheal aspirates	Retrospective	MM=58.1% PM=41.9%	Males=63.7% Females=36.3%	68	Diabetes mellitus=16.8% COPD=14.2% HD=24.8% Hypertension=46% Malignant disease=13.3% Kidney failure=7.1%	07
Ali et al.	2016	BioMed Research International	Qatar	HIC	106	Deep tracheal aspirate or Bronchoalveolar lavage	Retrospective	MM=50% PM=50%	Males=80.2% Females=19.8%	46.6 ± 18.6	Diabetes mellitus=28.3% Hypertension=34% CVDs=14.2% Respiratory diseases=9.4% Renal diseases=6.6% Neurological disorders=6.6% Hepatic diseases=7.5% Malignancy=4.7%	08

Abbreviations: NBL: Nasobronchial lavages, MM: Monomicrobial; PP: Polymicrobial; JRMC: Journal of Rawalpindi Medical College, LMIC: lower middle income country, N=No: Y=Yes, UMIC: Upper middle income countries, HIC: High-income countries COPD: Chronic obstructive pulmonary disease, CAD: Coronary artery disease, CVDs: Cardiovascular diseases, HD: Heart disease, LD: Lung disease, SAH, systemic arterial hypertension, DM: Diabetes mellitus, PD: Psychiatric disorders, ARDS: Acute respiratory distress syndrome, NT: Not tested

Incidence and microbiological profile of organisms causing VAP

The incidence of ventilator-associated pneumonia mostly ranges between 20 to 49% with the highest incidence reported from lower-middle-income countries followed by upper-middle-income countries. The microbiological profiles suggested the Gram-negative bacteria were common as compared to the Gram-positive microorganisms.

The further analysis suggested that the *Acinetobacter* spp. was the most commonly isolated organism followed by *Pseudomonas* spp., *Klebsiella* spp. *Escherichia coli*, *Staphylococcus aureus*, *Enterobacter* spp., *Citrobacter* spp., and *Haemophilus influenzae*. In addition, two major fungal pathogens *Candida* spp., and *Aspergillus* spp., were reported in eight and two studies respectively (Table 2).

Table 2. Incidence/total cases and most common isolated organisms

Author (s)	Incidence of VAP/Total cases	Microbiological Profile n (%)												
		Acinetobacter spp.	*Pseudomonas* spp.	*Klebsiella* spp.	*Escherichia coli*	*Enterobacter* spp.	*Citrobacter* spp.	Other *Enterobacteriaceae*	*H. influenza*	*S.aureus*	MRSA	Mixed Growth	*Candida* spp.	*Aspergillus fumigatus*
Ahmed et al.	48	29 (40.28%)	10 (13.89%)	12(16.67%)	5(6.94%)	1 (1.39%)	1 (1.39%)	4 (5.56%)	-----	7 (9.7%)	-----	-----	-----	-----
Bahrami et al.	101	46 (36.50%)	19 (15.07%)	13(10.31%)	09 (7.14%)	1 (0.79%)	-----	1 (0.79%)	-----	31 (25%)	-----	-----	1(0.79%)	-----
Patil et al.	74(27.71%)	24 (19.04%)	27 (21.42%)	29 (23.01%)	19 (15.7%)	-----	-----	-----	-----	22 (17%)	-----	-----	-----	-----
Oliveira et al.	32%	26 (19%)	42 (30.8%)	8 (5.9%)	2(1.5%)	6 (4.4%)	-----	10 (7.4%)	-----	30 (24%)	-----	-----	-----	-----
Lakhal et al.	60	21 (35%)	12 (20%)	10 (17%)	-----	-----	-----	10(17%)	-----	3 (5%)	-----	14, (23%)	-----	-----
Chaudhury et al.	21.3% ,2011 32.9%,2012 29.6%,2013	24.7%, 143 24.5%, 181 24.8%, 127	23.2%, 134 24.1%, 178 22.1%, 113	23.7%, 137 22.2%, 164 19.3%, 99	86, 14.9% 99, 13.4% 59, 11.5%	49, 8.5% 41, 5.6% 87, 16.9%	-----	29, 5% (2011) 74, 10% (2012) 27, 5.3% (2013)	-----	37, 50% 47,40.2% 29,34.9%	-----	-----	18, 2011 22, 2012 23, 2013	-----
Chittawtanarat et al.	6.3±2.8 cases	58 (38.7%)	25 (16.7%)	26 (17.3%)	6 (4%)	7 (4.7%)	1(0.7%)	1(0.7%)	15 (10%)	6 (4%)	-----	-----	-----	-----
Rocha et al.	30.5%	18 (18%)	29 (29%)	-----	-----	-----	2(2%)	19(19%)	-----	28(28%)	-----	-----	-----	-----
Medell et al.	44.25%	56 (72.7%)	49 (63.7%)	16 (20.8%)	12 (15.6%)	9 (11.7%)	3 (3.9%)	18 (23.4%)	-----	-----	11(14.3%)	-----	-----	-----
Erdem et al.	22.6%	121 (37%)	77 (23.5%)	4 (1.2%)	7 (2.2%)	27(8.3%)	-----	-----	-----	-----	91 (28%)	-----	-----	-----
Nusrat et al.	90%	41 (43.2%)	17 (18.9%)	18 (20%)	8 (8.9%)	-----	-----	-----	-----	2 (2.2%)	-----	7,7.8%	-----	-----
Gupta et al.	77	12 (15.6%)	26 (33.8%)	15 (19.5%)	8 (10.4%)	-----	7 (9.1%)	-----	-----	4 (5.2%)	-----	-----	-----	5 (6.5%)
Wang et al.	48.7%	19 (25%)	18 (23.6%)	11 (14.5%)	6 (7.89%)	4 (5.26%)	-----	2 (2.63%)	-----	-----	6,7.9%	-----	4(5.26%)	-----
Patro et al.	35%	10 (31.25%)	5 (15.62%)	-----	-----	-----	-----	13 (40.61%)	-----	1 (3.3%)	-----	-----	1 (3.3%)	-----
Tran et al.	220	75 (42%)	29 (16.3%)	39 (22%)	9 (5%)	3 (1.66%)	-----	1 (0.56%)	1 (0.56%)	9 (5%)	----	7.34%	-----	-----
Japoni et al.	72%	20 (34.5%)	9 (15.5%)	4 (6.90)	2 (3.40%)	5.20%	-----	-----	-----	8.60%	10 (17.2%	3.40%	-----	-----
Namiduru et al.	140	60 (26.1%)	78 (33.9%)	5 (2.2%)	5 (2.2%)	10 (4.3%)	-----	3 (1.3%)	-----	69 (30%)	-----	-----	-----	-----
Balkhy et al.	297	87 (35.1%)	63 (25.4%)	15 (6%)	6 (2.4%)	10 (4%)	-----	-----	9 (3.6%)	43,17.3%	-----	-----	-----	-----
Joseph et al	30.67% 15.87%	32%	39%	-----	-----	-----	-----	14%	-----	15%	-----	-----	-----	-----
Tehrani et al.	29	11 (38%)	8 (27.5%)	4 (13.8%)	-----	-----	-----	-----	-----	-----	-----	-----	6((20.7%	-----
Xie et al.	20.9%	169 (19.7%)	623 (72.7%)	69 (8.1%)	60 (7.0%)	31 (3.7%)	-----	66 (7.7%)	-----	92 (10.7%)	-----	-----	88 (10.2%)	5 (0.6%)
Golia et al.	35.14%	8(13.56%)	20(33.9%)	5(8.47%)	15(25.42%)	1(1.69%)	-----	1(1.69%)	-----	1(1.69%)	6(10%)	-----	-----	-----
Farag et al.	50	6 (11.3%)	11(20.8%)	18 (34%)	3 (5.6%)	-----	-----	-----	-----	3 (5.6%)	-----	6%	4 (7.5%)	-----
Resende et al.	26.2%	11 (34.4%)	11 (34.4%)	5 (15.6%)	1 (3.1%)	2(6.2%)	-----	-----	-----	5 (15%)	-----	-----	-----	-----
Injac et al.	47.3	73 (59.8%)	14 (11.5%)	10 (8.2%)	-----	-----	-----	-----	-----	-----	5(4.1%	19 (15.6%	-----	-----
Kapaganty et al.	41.8%	7 (9.5%)	21 (28.4%)	9 (12.3%)	18 (24.3%)	1 (1.35%)	4 (5.40%)	-----	-----	11 (14.9%)	-----	-----	-----	-----
Mishra et al.	41.6%	8 (27.6%)	4 (13.2%)	10 (34.5%)	3 (10.3%)	-----	-----	-----	-----	-----	-----	13.8%	-----	-----
Turkovic et al.	24.9%	20 (13.6%)	28 (19%)	9 (6.2%)	16 (10.9%)	12 (8.1%)	2 (1.4%)	3 (2.1%)	13 (8.7%)	31 (21.1%)	-----	-----	18	03
Ali et al.	5 per 1000 ventilators days	23	39 (40.6%)	25	5	24	-----	-----	16	21	-----	-----	-----	-----

The five most commonly found microorganisms (*Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp. *Escherichia coli*, and *Staphylococcus aureus*) were compared between the 3 groups including HICs, UMICs, and LMICs. The final analysis suggested that these pathogens were more prevalent in developing countries as compared to the high-income countries (Figure 2).

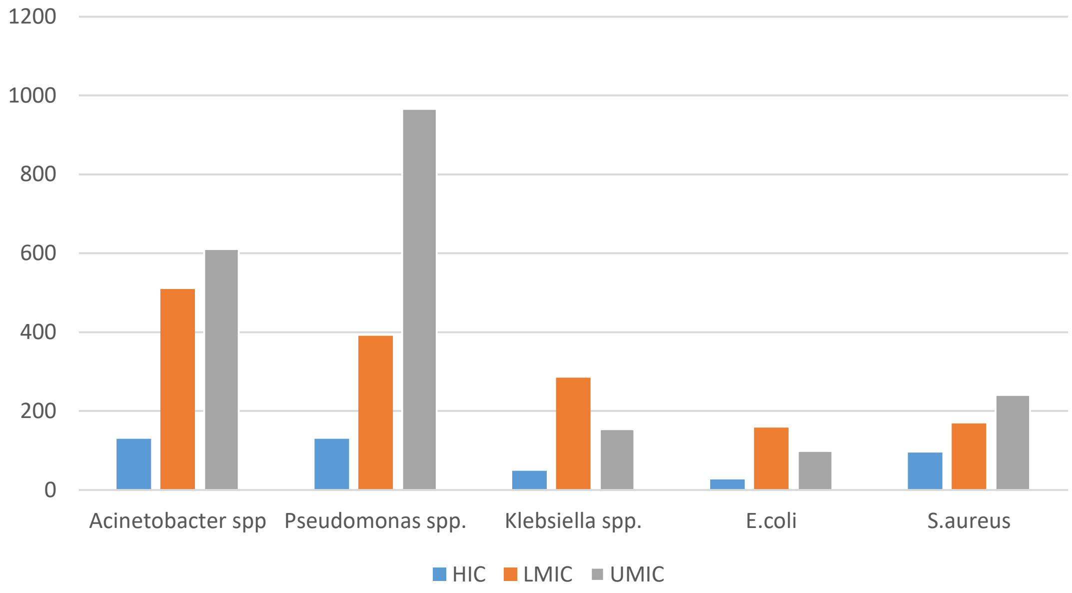

Figure 2. Comparison of highly resistant microorganisms between HICs, UMICs, and LMICs

Resistance pattern of organisms causing VAP

The resistance pattern of most commonly isolated organisms showed high resistance frequency against major antibiotics groups including carbapenem, cephalosporins, aminoglycosides, fluoroquinolones and beta-lactamase inhibitor combinations. The polymixin-B and colistin suggested the efficacy against all highly resistant pathogens (Table 3). Moreover, all the meticillin resistant *staphylococcus aureus* were sensitive to vancomycin. The study-wise comparison of 5 highly resistant microorganisms including *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp. *Escherichia coli*, and *Staphylococcus aureus* were further explained in Figure 3.

Table 3. Antibiotic resistance pattern of microorganisms involved in the pathogenesis of VAP

Author	**Bacteria**	**Antibiotics**										
		AK	CTR/CAZ	CIP	GEN	IMP	MRP	PTZ	PB	CS	VAN	PEN/OXA
Ahmed et al.	*A. baumannii*	91.67%	100%	95.83%	80%	95.65%	100%	90.48%	0%	-----	0%	-----
	E.coli	40%	100%	100%	60%	0%	20%	25%	0%	-----	0%	-----
	K.pneumoniae	80%	70%	50%	80%	50%	0%	0%	77.76%	-----	0%	-----
	P. aeruginosa	60%	0%	40%	40%	40%	100%	50%	0%	-----	0%	-----
	S.aureus	86.71%	100%	100%	100%	100%	0%	100%	0%	-----	0%	-----
Bahrami et al.	*A. baumannii*	78.26%	100%	97.82%	67.39%	84.78%	-----	-----	-----	0%	-----	-----
	P. aeruginosa	78.94%	100%	36.21%	57.89%	42.10%	-----	-----	-----	0%	-----	-----
	S.aureus	-----	-----	93.54%	90.32%	-----	-----	-----	-----	-----	0%	100% and 93.54%
Patil et al.	*Acinetobacter*	20%	-----	0%	-----	-----	20%	6.6%	-----	33.33%	-----	-----
	Klebsiella	33.33%	-----	27.77%	-----	-----	33.33%	33.3%	-----	50%	-----	-----
	Pseudomonas	31.57%	-----	26.31%	-----	-----	21.05%	36.8%	-----	42.1%	-----	-----
	E.coli	55.5%	-----	22.22%	-----	-----	33.33%	55.5%	-----	55.5%	-----	-----
	S.aureus	0%	-----	30.76%	-----	-----	0%	0%	-----	0%	-----	-----
Oliveira et al.	*P. aeruginosa*	-----	-----	-----	-----	47.6%	47.6%	-----	-----	-----	-----	-----
	S.aureus	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	OXA= 36.7%
	A. baumannii	-----	-----	-----	-----	69.2%	69.2%	-----	-----	-----	-----	-----
Lakhal et al.	*A. baumannii*	85%	CAZ=100%	100%	100%	100%	-----	100%	-----	0%	-----	-----
	P. aeruginosa	11%	CAZ=67%	48%	77%	44%	-----	0%	-----	0%	-----	-----
	Enterobacterales	14%	CAZ=71%	14%	28%	0%	-----	71%	-----	-----	-----	-----
	S.aureus	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	MSSA=66.6% MRSA=33.3%
Chaudhury et al.	*E.coli*	30.5%	25.4%	84.7%	47.4%	8.4%	-----	20.3%	1.7%	-----	-----	-----
	Klebsiella spp.	23.2%	31.3%	52.5%	39.4%	18.1%	-----	29.3%	0%	-----	-----	-----
	Enterobacter spp.	43.7%	41.4%	56.3%	56.3%	17.2%	-----	31%	0%	-----	-----	-----
	Other *Enterobacteriaceae*	66.7%	37%	70.4%	74.1%	18.5%	-----	11.1%	0%	-----	-----	-----
	Pseudomonas spp.	18.6%	31.8%	24.8%	23.9%	13.3%	-----	15.9%	5.3%	-----	-----	-----
	NFGNB	67.7%	56.7%	77.9%	72.4%	33.1%	-----	55.9%	2.4%	-----	-----	-----
	S.aureus	-----	-----	65.5%	51.7%	-----	-----	-----	-----	-----	0%	93.1%
	CONS	-----	-----	50%	37.5%	-----	-----	-----	-----	-----	0%	91.7%
	Streptococcus spp.	-----	-----	11.1%	-----	-----	-----	-----	-----	-----	0%	33.3%
	Enterococcus spp.	-----	-----	66.7%	-----	-----	-----	-----	-----	-----	8.3%	33.3% (PEN)
Chittawtanarat et al.	Gram-negative bacteria	-----	-----	-----	-----	-----	-----	-----	-----	0%	-----	-----
	Gram-positive bacteria	-----	-----	-----	-----	-----	-----	-----	-----	-----	0%	-----
Rocha et al.	*Acinetobacter* spp	-----	82.3%	81.3%	-----	11.2%	-----	60%	-----	-----	-----	-----
	P. aeruginosa	-----	66.7%	50%	-----	52%	-----	33.3%	-----	-----	-----	-----
	Citrobacter freundii	-----	0%	0%	-----	0%	-----	-----	-----	-----	-----	-----
	Enterobacteriaceae	-----	43.7%	57.1%	-----	13.3%	-----	-----	-----	-----	-----	-----
	Burkholderia cepacea	-----	100%	0%	-----	0%	-----	0%	-----	-----	-----	-----
	S.aureus	-----	-----	52.2%	-----	-----	-----	-----	-----	-----	-----	65.4%
	Other Gram-positive bacteria	-----	-----	0%	-----	-----	-----	-----	-----	-----	-----	100% (OXA)
Medell et al.	*A. baumannii*	69.8%	100%	100%	100%	-----	90.6%	-----	-----	1.9%	-----	-----
	P. aeruginosa	44.1%	82.3%	47.1%	58.8%	-----	35.3%	-----	-----	0%	-----	-----
	E.coli	100%	100%	83.3%	100%	-----	0%	-----	-----	0%	-----	-----
	K.pneumoniae	25%	100%	41.7%	100%	-----	0%	-----	-----	25%	-----	-----
	S. marcescens	66.7%	33.3%	60%	40%	-----	20%	-----	-----	100%	-----	-----
Erdem et al.	*Acinetobacter* spp	43%	90%	80%	-----	64%	-----	-----	-----	-----	-----	-----
	P. aeruginosa	16%	59%	62%	-----	32%	-----	41%	-----	-----	-----	-----
	Enterobacteriaceae	18%	79%	26%	-----	0%	-----	-----	-----	-----	-----	-----

Table 3. *continued*

Nusrat et al.	*A. baumannii*	70.7%	87.8%,	82.9%	92.7%	56.1%	-----	73.2%	-----	19.5%	-----	-----
	Pseudomonas	52.9%	80.5%	88.8%	61.1%	33.3%	-----	23.5%	-----	0%	-----	-----
	spp	44.4%	72.2%,	100%	55.6%	33.3%	-----	67%	-----	0%	-----	-----
	E.coli	50%	61.1%	87.5%	54.2%	54.2%	-----	11.1%	-----	0%	-----	-----
	Klebsiella spp	0%	100%,	100%	50%	25%	-----	-----	-----	75%	-----	-----
	Proteus	0%	89%	100%	0%	-----	-----	-----	-----	-----	0%	50% (OXA)
	S.aureus	25%	83.3%,	100%	25%	-----	-----	-----	-----	-----	0%	25% (OXA)
	CONS		50%									
			50%, 0%									
			50%, 0%									
			75%, 0%									
Gupta et al.	*A. baumannii*	65%	82, 78%	-----	71%	29%	-----	70%	S	S	-----	-----
	Pseudomonas	60%	74%, 65%	-----	64%	22%	-----	65%	S	S	-----	-----
	spp	68%	73%, 72%	-----	71%	21%	-----	70%	S	S	-----	-----
	E.coli	60%	78%, 75%	-----	61%	18%	-----	61%	S	S	-----	-----
	Klebsiella spp	-----	-----	-----		-----	-----	-----	-----	-----	-----	63.3% (OXA)
	S.aureus				67.8%							
Wang et al.	*A. baumannii*	21.1%	47.4%	63.2%	-----	63.2%	-----	57.9%	-----	-----	-----	-----
	P. aeruginosa	20%	26.7%	40%	-----	33.3%	-----	33.3%	-----	-----	-----	-----
	K.pneumoniae	27.3%	45.4%	27.3%	-----	9.1%	-----	18.2%	-----	-----	-----	-----
Patro et al.	*A. baumannii*	100%	100%	100%	-----	-----	29%	100%	0%	-----	-----	-----
	P. aeruginosa	100%	100%	100%	-----	-----	50%	67%	0%	-----	-----	-----
	K.pneumoniae	60%	100%	100%	-----	-----	40%	60%	0%	-----	-----	-----
	E.coli	100%	33%	100%	-----	-----	0%	33%	0%	-----	-----	-----
	MRSA	-----	-----	100%	100%	-----	-----	-----	-----	-----	0%	-----
	Enterococcus	-----	-----	0%	100%	-----	-----	-----	-----	-----	0%	-----
Tran et al.	*Acinetobacter*	77.8%	95.2%,	95.2%	84.1%	93.2%	90.5%	95%	-----	1.5%	-----	-----
	spp	65.5%	93.2%	80%	80%	79.3%	86.2%	32.1%	-----	3.4%	-----	-----
	Pseudomonas	5.1%	100%,	52.6%	27.8%	25.6%	20%	64.1%	-----	-----	-----	-----
	spp		72.4%									
	Klebsiella spp		82.7%,									
			76.3%									
Japoni et al.	*Acinetobacter*	85%	85%, 80%	85%	-----	20%	20%	-----	-----	0%	-----	-----
	spp	33.3%	0%,	11.1%	-----	0%	0%	-----	-----	0%	-----	-----
	Pseudomonas	50%	11.1%	50%	-----	0%	0%	-----	-----	0%	-----	-----
	spp	0%	50%, 50%	50%	-----	0%	0%	-----	-----	0%	-----	-----
	Klebsiella spp	66.7%	50%, 50%	0%	-----	0%	0%	-----	-----	0%	-----	-----
	E.coli	-----	100%,	-----	-----	-----	-----	-----	-----	-----	0%	10%
	Enterobacter		66.7%									
	spp.		-----									
	S.aureus											
Namiduru et al.	*Acinetobacter*	83.34%	100%,	70%	93.34	16.7%	-----	-----	-----	-----	-----	-----
	spp	33.4%	100%	84.62%	%	74.36%	-----	-----	-----	-----	-----	-----
	Pseudomonas	0%	92.3%,	60%	93.59	40%	-----	-----	-----	-----	-----	-----
	spp	-----	92.3%	80%	%	-----	-----	20%	-----	-----	0%	82% [OXA]
	Enterobacter		60%, -----		60%							
	spp.		-----		-----							
	S.aureus											
Balkhy et al.	*Acinetobacter*	89%	97%	98%	97%	98%	75%	83%	-----	-----	-----	-----
	spp	32%	97%	97%	100%	97%	57%	92%	-----	-----	-----	-----
	Pseudomonas	-----	93%,87%	100%	100%	100%	53%	93%	-----	-----	-----	-----
	spp	-----	100%,	100%	100%	83%	50%	67%	-----	-----	-----	-----
	Klebsiella spp	-----	100%	100%	100%	90%	-----	90%	-----	-----	-----	-----
	E.coli	-----	90%, 90%	65%	44%	-----	-----	-----	-----	-----	100%	100% [OXA], 63% [PEN]
	Enterobacter		-----									
	spp.											
	S.aureus											
Joseph et al.	*Acinetobacter*	86%	100%	100%	100%	-----	57%	43%	-----	14%	-----	-----
	spp	67%	67%	78%	89%	-----	22%	22%	-----	78%	-----	-----
	Pseudomonas	0%	100%	100%	100%	-----	0%	-----	-----	-----	-----	-----
	spp	0%	100%	100%	100%	-----	0%	-----	-----	-----	-----	-----
	Klebsiella spp	-----	-----	100%	100%	-----	-----	-----	-----	-----	0%	100% [OXA], 100% [PEN]
	E.coli											
	S.aureus											
Tehrani et al.	*Acinetobacter*	96.5%	93%,	100%	-----	-----	100%	100%	-----	0%	-----	-----
	spp	50%	96.5%	62.5%	-----	-----	37.5%	100%	-----	0%	-----	-----
	Pseudomonas	50%	87.5%,87.	50%	-----	-----	50%	25%	-----	0%	-----	-----
	spp		5%									
	Klebsiella spp		100%									
Xie et al.	*Acinetobacter*	80%	86.8%	91.2%	93.4%	64.9%	-----	-----	-----	-----	-----	-----
	spp	38.6%	48.5%	49.1%	69.2%	36.6%	-----	-----	-----	-----	-----	-----
	Pseudomonas	23.6%	65.2%	55.8%	62.3%	0%	-----	-----	-----	-----	-----	-----
	spp	34.4%	78.3%	78.3%	68.3%	0%	-----	-----	-----	-----	-----	-----
	Klebsiella spp	-----	-----	78.2%	94.5%	-----	-----	-----	-----	-----	0%	-----
	E.coli											
	S.aureus											

Table 3. *continued.*

Golia et al.	*Acinetobacter*	62.5%	75%	62.5%	62.5%	37.5%	37.5%	75%	-----	-----	-----	-----
	spp	70%	55%	60%	80%	40%	40%	55%	-----	-----	-----	-----
	Pseudomonas	40%	100%	66.6%	66.6%	0%	0%	0%	-----	-----	-----	-----
	spp	53.3%	100%	66.6%	66.6%	0%	0%	0%	-----	-----	-----	-----
	Klebsiella spp	100%	100%	100%	100%	0%	0%	0%	-----	-----	-----	-----
	E.coli	-----	-----	-----	-----	-----	-----	-----	-----	-----	0%	100%
	S. marcescens											
	S.aureus											
Farag et al.	*Acinetobacter*	33%	100%,	67%	-----	-----	83%	83%	-----	0%	-----	-----
	spp	46%	100%	67%	73%	-----	55%	73%	-----	0%	-----	-----
	Pseudomonas	28%	100%,	67%	61%	-----	28%	67%	-----	0%	-----	-----
	spp	33%	100%	67%	-----	-----	33%	67%	-----	0%	-----	-----
	Klebsiella spp	100%	72%, 89%	67%	-----	-----	-----	67%	-----	-----	33%	67%
	E.coli		100%,									
	S.aureus		100%									
			100%									
Resende et	*Acinetobacter*	27.3%	63.6%	63.6%	45.4%	54.5%	63.6%	45.4%	-----	-----	-----	-----
al.	spp	18.2%	54.5%	45.4%	36.4%	45.4%	45.4%	36.4%	-----	-----	-----	-----
	Pseudomonas	12.5%	25%	37.5%	50%	12.5%	12.5%	12.5%	-----	-----	-----	-----
	spp											
	Enterobacteriac											
	eae											
Injac et al.	*Acinetobacter*	42%	92%	97%	87%	95%	96%	99%	-----	-----	-----	-----
	spp	41%	52%	67%	73%	35%	57%	42%	-----	-----	-----	-----
	Pseudomonas	22%	93%, 94%	94%	44%	11%	11%	47%	-----	-----	-----	-----
	spp	-----	-----	-----	-----	-----	-----	-----	-----	-----	0%	-----
	Klebsiella spp											
	MRSA											
Kapaganty	*Acinetobacter*	57%	43%	71%	57%	-----	43%	43%	-----	-----	-----	-----
et al.	spp	43%	48%	52%	43%	-----	38%	43%	-----	-----	-----	-----
	Pseudomonas	33%	-----	78%	44%	-----	11%	11%	-----	-----	-----	-----
	spp	33%	-----	67%	33%	-----	11%	22%	-----	-----	-----	-----
	Klebsiella spp	-----	-----	-----	-----	-----	-----	-----	-----	-----	0%	100% [PEN]
	E.coli											
	S.aureus											
Mishra et al.	*Acinetobacter*	80%	-----	-----	-----	83%	100%	-----	33	0%	-----	-----
	spp	25%	-----	-----	-----	75%	100%	-----	%	0%	-----	-----
	Pseudomonas	20%	-----	-----	-----	44%	44%	-----	-----	50%	-----	-----
	spp	0%	-----	-----	-----	67%	100%	-----	33	100%	-----	-----
	Klebsiella spp								%			
	E.coli								100			
									%			
Turkovic et	*Acinetobacter*	-----	-----	94%	-----	20%	63%	-----	-----	-----	-----	-----
al.	spp	-----	7%	11%	-----	58%	9%	4%	-----	-----	-----	-----
	Pseudomonas	-----	13%	15%	-----	0%	0%	25%	-----	-----	-----	-----
	spp	-----	-----	56%	-----	-----	-----	-----	-----	-----	0%	-----
	Enterobacteriac											
	eae											
	S.aureus											
Ali et al.	*Acinetobacter*	-----	91.3%,82.	78.3%	78.3%	-----	78.3%	78.3%	-----	0%	-----	-----
	spp	-----	6%	7.7%	7.7%	-----	7.7%	7.7%	-----	0%	-----	-----
	Pseudomonas	-----	15.4%	4%	0%	-----	0%	20%	-----	-----	-----	-----
	spp	-----	28%	80%	60%	-----	0%	20%	-----	-----	-----	-----
	Klebsiella spp	-----	80%, 80%	0%	0%	-----	4.2%	29.2%	-----	-----	-----	-----
	E.coli	-----	25%	-----	-----	-----	-----	-----	-----	-----	0%	66.7% [PEN], 38.1%
	Enterobacter		-----									[OXA]
	S.aureus											

Abbreviations: AK: Amikacin; CTR: Ceftriaxone, CAZ: Ceftazidime, CIP: Ciprofloxacin, GEN: Gentamicin, IMP: Imipenem, MRP: Meropenem, PTZ: Piperacillin-Tazobactam, PB: Polymixin-B, CS: Colistin, VAN: Vancomycin, PEN/OXA: Penicillin/Oxacillin; S: Sensitive

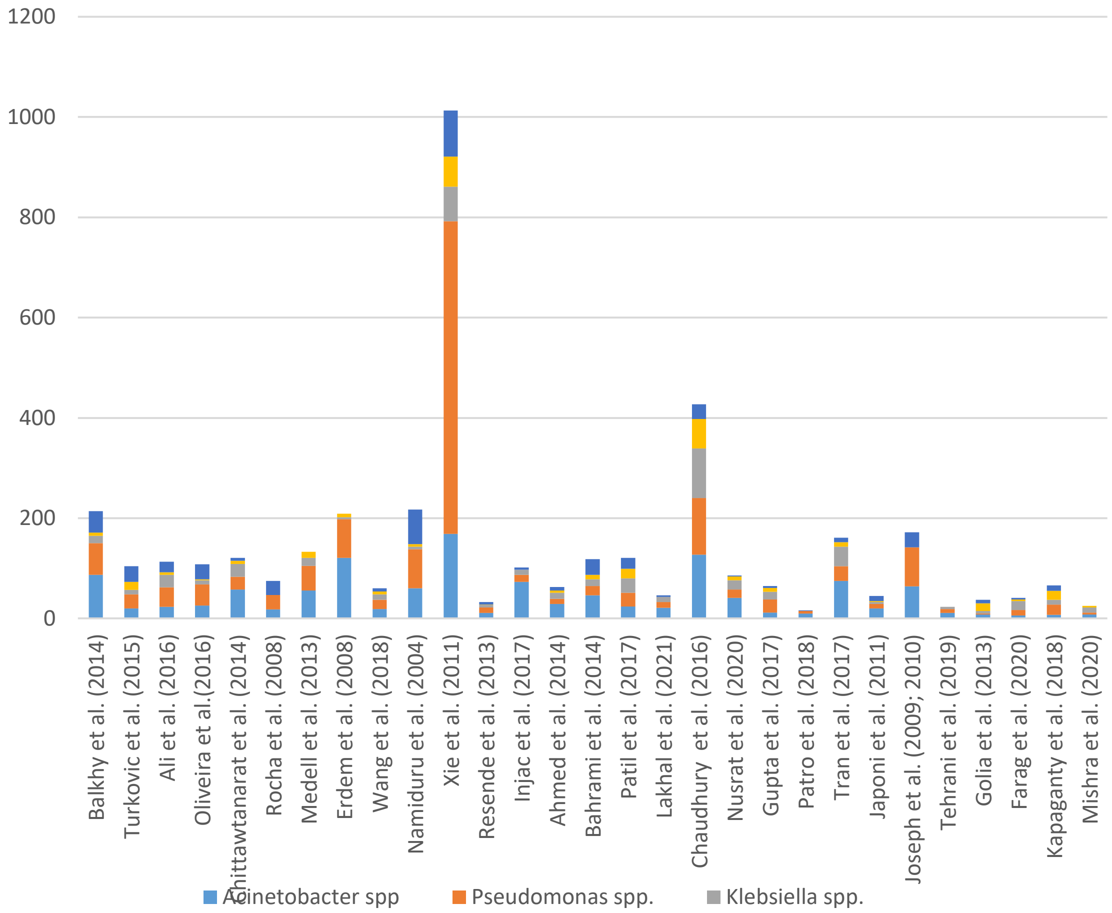

Figure 3. Comparison of microbiological profiles in final selected studies

DISCUSSION

Although many studies have determined the role of multi-drug resistant bacteria in ventilator-associated pneumonia, but the current review is the comprehensive assessment of microorganisms involved in VAP and the resistance pattern of these hospital-acquired pathogens that can help in better therapeutic strategies against these MDR bacteria. Moreover, this review focuses on baseline parameters including incidence, and comorbidities associated with VAP. In our study the incidence of ventilator-associated pneumonia in high-income to lower-middle incomes countries ranged from 20-49%, it was predominant in male patients and elderly patients. Similarly, a study conducted by Mathai et al. in India reported 38% VAP incidence, with 53.60 mean age, and 59.6% patients were males (43). In addition, this study results suggested the VAP was more prevalent in immunocompromised patients such as in cardiovascular diseases, diabetes, COPD, and hypertension. The results of a study conducted in the European population also suggested the high prevalence of VAP in male patients with a high number of various comorbidities including heart diseases (49%), COPD (8.7%), diabetes (11.7%), and peripheral vascular diseases (18.4%) (44).

In this present study, the most common MDR bugs were Gram-negative bacilli. The most frequent bacteria in VAP were *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp., and *Escherichia coli* while among Gram-positive pathogens *Staphylococcus aureus* was the most common. The *candida* spp were also observed in eight studies candida while the 3 studies also reported the Aspergillus. The Gram-negative bacteria showed resistance to all tested antibiotics except polymixin-B and colistin. While vancomycin was the most effective antibiotic for MRSA.

This study's findings were consistent with those reported by Chung et al. in the Asian population. The most frequent isolated pathogen in this study was *Acinetobacter* spp., *Pseudomonas* spp., *Klebsiella* spp., and *Staphylococcus aureus*. Moreover, the resistance pattern analysis showed that these bacteria were highly resistant to antibiotics used for treatment (45). Djordjevic et al. also isolated 95.2% Gram-negative microorganisms from VAP. The *Acinetobacter* spp. ranked first followed by *Pseudomonas* spp (>60%). The resistance pattern showed high resistance to cephalosporins, aminoglycosides, and fluoroquinolones. Colistin was the most effective antibiotic against *Acinetobacter* spp. While vancomycin proved beneficial against MRSA (46).

In conclusion, the findings of the current review suggest that the Gram-negative bacteria were the most prevalent pathogens in ventilator-associated pneumonia patients particularly in low-income and upper-middle-income countries. These isolated bacteria showed multi-drug resistance to all the tested antibiotics except polymixin-B and colistin for Gram-negative bacteria while vancomycin for MRSA. In the future, there is a need to conduct more studies with a larger sample size that can provide us more insight into the disease incidence, pathogenesis, and better therapeutic strategies.

Conflict of interest

No conflict of interest was declared by the authors.

REFERENCES

1. Papazian L, Klompas M, Luyt CE. Ventilator-associated pneumonia in adults: a narrative review. Intensive Care Med 2020; 46(5): 888-906.

2. Koenig SM, Truwit JD. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. Clin Microbiol Rev 2006; 19: 637-57.
3. Bor C, Demirag K, Okcu O, Cankayali I, Uyar M. Ventilator-associated pneumonia in critically ill patients with intensive antibiotic usage. Pak J Med Sci 2015; 31: 1441-46. Spalding MC, Cripps MW, Minshall CT. Ventilator-associated pneumonia: new definitions. Crit Care Clin 2017; 33: 277-92.
4. Tejerina E, Frutos-Vivar F, Restrepo MI, Anzueto A, Abroug F, Palizas F, et al. Incidence, risk factors, and outcome of ventilator-associated pneumonia. J Crit Care 2006; 21: 56-65.
5. Fihman V, Messika J, Hajage D, Tournier V, Gaudry S, Magdoud F, et al. Five-year trends for ventilator-associated pneumonia: correlation between microbiological findings and antimicrobial drug consumption. Int J Antimicrob Agents 2015; 46: 518-25.
6. Wu D, Wu C, Zhang S, Zhong Y. Risk factors of ventilator-associated pneumonia in critically III patients. Front Pharmacol 2019; 10: 482..
7. Cotoia A, Spadaro S, Gambetti G, Koulenti D, Cinnella G. Pathogenesis-targeted preventive strategies for multidrug resistant ventilator-associated pneumonia: a narrative review. Microorganisms 2020; 8: 821. Altinsoy S, Catalca S, Sayin MM, Tutuncu EE. The risk factors of ventilator Associated Pneumonia and relationship with type of tracheostomy. Trends Anaesth Crit Care 2020; 35: 38-43.
8. Sosa-Hernández O, Matías-Téllez B, Estrada-Hernández A, Cureño-Díaz MA, Bello-López JM. Incidence and costs of ventilator-associated pneumonia in the adult intensive care unit of a tertiary referral hospital in Mexico. Am J Infect Control 2019; 47: e21-5.
9. Farag AM, Tawfick MM, Abozeed MY, Shaban EA, Abo-Shadi MA. Microbiological profile of ventilator-associated pneumonia among intensive care unit patients in tertiary Egyptian hospitals. J Infect Dev Ctries 2020; 14: 153-61.
10. Thakuria B, Singh P, Agrawal S, Asthana V. Profile of infective microorganisms causing ventilator-associated pneumonia: a clinical study from resource limited intensive care unit. J Anaesthesiol Clin Pharmacol 2013; 29: 361-66.
11. Rhodes NJ, Cruce CE, O’Donnell JN, Wunderink RG, Hauser AR. Resistance trends and treatment options in gram-negative ventilator-associated pneumonia. Curr Infect Dis Rep 2018; 20: 1-5.
12. Ahmed W. Microorganisms related with ventilator Associated pneumonia (VAP) and their antibiotic sensitivity pattern. J Rawalpindi Med Coll 2014; 18:45-8.
13. Bahrami H, Rahbar M, Rahimifard N, Mehdipour HH, Rastegar H, Ashtiani HA, et al. Etiology and drug resistance pattern of ventilator associated pneumonia in an Iranian 1000-bed tertiary care hospital. Microbiol Res J Int 2014; 4: 1211-8.
14. Patil HV, Patil VC. Incidence, bacteriology, and clinical outcome of ventilator-associated pneumonia at tertiary care hospital. J Nat Sci Biol Med 2017; 8: 46-55.
15. Souza-Oliveira AC, Cunha TM, Passos LB, Lopes GC, Gomes FA, Röder DV. Ventilator-associated pneumonia: the influence of bacterial resistance, prescription errors, and de-escalation of antimicrobial therapy on mortality rates. Braz J Infect Dis 2016; 20: 437-43.
16. Ben Lakhal H, M’Rad A, Naas T, Brahmi N. Antimicrobial susceptibility among pathogens isolated in early-versus late-onset ventilator-associated pneumonia. Infect Dis Rep 2021; 13: 401-10.
17. Chaudhury A, Rani AS, Kalawat U, Sumant S, Verma A, Venkataramana B. Antibiotic resistance & pathogen profile in ventilator-associated pneumonia in a tertiary care hospital in India. Indian J Med Res 2016; 144: 440-46.
18. Chittawatanarat K, Jaipakdee W, Chotirosniramit N, Chandacham K, Jirapongcharoenlap T. Microbiology, resistance patterns, and risk factors of mortality in ventilator-associated bacterial pneumonia in a Northern Thai tertiary-care university based general surgical intensive care unit. Infect Drug Resist 2014; 7: 203-10.
19. Rocha LD, Vilela CA, Cezário RC, Almeida AB, Gontijo Filho P. Ventilator-associated pneumonia in an adult clinical-surgical intensive care unit of a Brazilian university hospital: incidence, risk factors, etiology, and antibiotic resistance. Braz J Infect Dis 2008; 12: 80-5.
20. Medell M, Hart M, Duquesne A, Espinosa F, Valdés R. Nosocomial ventilator-associated pneumonia in Cuban intensive care units: bacterial species and antibiotic resistance. MEDICC Review 2013; 15: 26-9.
21. Erdem I, Ozgultekin A, Inan AS, Dincer E, Turan G, Ceran N, et al. Incidence, etiology, and antibiotic resistance patterns of gram-negative microorganisms isolated from patients with ventilator-associated pneumonia in a medical-surgical intensive care unit of a teaching hospital in istanbul, Turkey (2004-2006). Jpn J Infect Dis 2008; 61: 339-42.
22. Nusrat T, Akter N, Rahman NA, Godman B, D. Rozario DT, Haque M. Antibiotic resistance and sensitivity pattern of metallo-β-lactamase Producing Gram-negative bacilli in ventilator-associated pneumonia in the intensive care unit of a public medical school hospital in Bangladesh. Hosp Pract 2020; 48: 128-36.
23. Gupta R, Malik A, Rizvi M, Ahmed M, Singh A. Epidemiology of multidrug-resistant Gram-negative pathogens isolated from ventilator-associated pneumonia in ICU patients. J Glob Antimicrob Resist 2017; 9: 47-50. Wang Y, Zhang R, Liu W. Distribution and drug resistance of pathogenic bacteria in ventilator-associated pneumonia at a local hospital of North-eastern China. Infect Drug Resist 2018; 11: 2249-55.
24. Patro S, Sarangi G, Das P, Mahapatra A, Mohapatra D, Paty BP, et al. Bacteriological profile of ventilator-associated pneumonia in a tertiary care hospital. Indian J Pathol Microbiol 2018; 61: 375-79.
25. Tran GM, Ho-Le TP, Ha DT, Tran-Nguyen CH, Nguyen TS, Pham TT, et al. Patterns of antimicrobial resistance in intensive care unit patients: a study in Vietnam. BMC Infect Dis 2017; 17: 1-7.
26. Japoni A, Vazin A, Davarpanah MA, Ardakani MA, Alborzi A, Japoni S, et al. Ventilator-associated pneumonia in Iranian intensive care units. J Infect Dev Ctries 2011; 5: 286-93.
27. Namiduru M, Güngör G, Karaoğlan I, Dikensoy ÖN. Antibiotic resistance of bacterial ventilator-associated pneumonia in surgical intensive care units. J Int Med Res 2004; 32: 78-83.
28. Balkhy HH, El-Saed A, Maghraby R, Al-Dorzi HM, Khan R, Rishu AH, Arabi YM. Drug-resistant ventilator associated pneumonia in a tertiary care hospital in Saudi Arabia. Ann Thorac Med 2014; 9: 104-11.
29. Joseph NM, Sistla S, Dutta TK, Badhe AS, Parija SC. Ventilator-associated pneumonia in a tertiary care hospital in India: incidence and risk factors. J Infect Dev Ctries 2009; 3: 771-77.
30. Joseph NM, Sistla S, Dutta TK, Badhe AS, Rasitha D, Parija SC. Ventilator-associated pneumonia in a tertiary care hospital in India: role of multi-drug resistant pathogens. J Infect Dev Ctries 2010; 4: 218-25.
31. Tehrani S, Saffarfar V, Hashemi A, Abolghasemi S. A survey of genotype and resistance patterns of ventilator-associated pneumonia organisms in ICU patients. Tanaffos 2019; 18: 215-22.
32. Xie DS, Xiong W, Lai RP, Liu L, Gan XM, Wang XH, et al. Ventilator-associated pneumonia in intensive care units in Hubei province, China: a multicentre prospective cohort survey. J Hosp Infect 2011; 78: 284-88.
33. Golia S, Sangeetha KT, Vasudha CL. Microbial profile of early and late onset ventilator associated pneumonia in the intensive care unit of a tertiary care hospital in Bangalore, India. J Clin Diagn Res 2013; 7: 2462-66.
34. Resende MM, Monteiro SG, Callegari B, Figueiredo PM, Monteiro CR, Monteiro-Neto V. Epidemiology and outcomes of ventilator-associated pneumonia in northern Brazil: an analytical descriptive prospective cohort study. BMC Infect Dis 2013; 13: 1-6.
35. Injac V, Batranović U, Matijašević J, Vukoja M, Hadnađev M, Bukumirić Z, et al. Etiology and resistance patterns of bacteria causing ventilator-associated pneumonia in a respiratory intensive care unit. Vojnosanit pregl 2017; 74: 954-62.
36. Kapaganty VC, Pilli R. Microbiological profile of ventilator-associated pneumonia in the intensive care unit of a tertiary hospital in Visakhapatnam, India. Indian J Microbiol Res 2018; 5: 252-57.
37. Mishra DR, Shah DS, Shah N, Prasad JN, Gupta PP, Agrawaal KK. Study of microbiological and antibiotic sensitivity pattern of ventilator associated pneumonia (VAP) in ICU of a tertiary care hospital in Nepal. J Family Med Prim Care 2020; 9: 6171-76.
38. Magdić Turković T, Gverić Grginić A, Đuras Cuculić B, Gašpar B, Širanović M, et al. Microbial profile and antibiotic susceptibility patterns of pathogens causing ventilator-associated pneumonia at intensive care unit, sestre milosrdnice university hospital center, Zagreb, Croatia. Acta Clin Croat 2015; 54: 127-35.
39. Ali HS, Khan FY, George S, Shaikh N, Al-Ajmi J. Epidemiology and outcome of ventilator-associated pneumonia in a heterogeneous ICU population in Qatar. BioMed Res Int 2016; 2016.
40. Mathai AS, Phillips A, Kaur P, Isaac R. Incidence and attributable costs of ventilator-associated pneumonia (VAP) in a tertiary-level intensive care unit (ICU) in northern India. J Infect Public Health 2015; 8: 127-35.
41. Hortal J, Muñoz P, Cuerpo G, Litvan H, Rosseel PM, Bouza E. Ventilator-associated pneumonia in patients undergoing major heart surgery: an incidence study in Europe. Crit Care 2009; 13: 1-0.
42. Chung DR, Song JH, Kim SH, Thamlikitkul V, Huang SG, Wang H, et al. High prevalence of multidrug-resistant nonfermenters in hospital-acquired pneumonia in Asia. Am J Respir Crit Care Med 2011; 184: 1409-17.
43. Djordjevic ZM, Folic MM, Jankovic SM. Distribution and antibiotic susceptibility of pathogens isolated from adults with hospital-acquired and ventilator-associated pneumonia in intensive care unit. J Infect Public Health 2017; 10: 740-44.