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Coronavirus Pandemic

The impact of the COVID-19 pandemic on the trend of ventilator associated pneumonia incidence in a non-COVID-19 dedicated hospital

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Abstract
Introduction: Ventilator associated pneumonia (VAP) is one of the most common hospital-acquired infections for intensive care units in China. Since the COVID-19 outbreak, "Lockdown Wuhan" and other infection control strategies had been implemented in China. The impact of the policies on VAP prevention was estimated in a non-COVID-19 dedicated hospital.
Methodology: We analyzed the VAP trends of 6 intensive care units in a non-COVID-19 dedicated hospital from 2018 to 2020 by Joinpoint regression analysis. The information related to infected VAP patients, VAP surveillance were retrieved from an active surveillance system.
Results: There was an obvious decrease in the overall admissions and inpatients of ICUs since January 2020. The overall incidence of VAP was 6.1 episodes per 1000 IMV days. The 30-day case fatality was 16.8%. Generally, the utility rate of IMV ranged from 18.2% to 38.9% respectively, raising with the monthly percent change (MPC): 1.5% [95% confidence interval (CI): 0.8%, 2.2%] from January 2018 to February 2020 by Joinpoint regression analysis. A continuous decline with the MPC: -1.9% (95% CI: -3.2%, -0.5%) of VAP incidence was demonstrated. However, this trend varied among the different ICUs. We found no significant difference neither in 30-day case fatality nor pathogens of VAP patients.
Conclusions: By Joinpoint regression analysis, we can see February 2020 was an important time point. The surveillance indicators were changed, which influenced the VAP incidence.

Key words: Ventilator associated pneumonia; trend; COVID-19; impact.

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Introduction
Ventilator associated pneumonia (VAP) is defined as pneumonia occurring in patients with initiation of invasive mechanical ventilation (IMV) for more than 48 hours or withdrawal less than 48 hours [1-3]. VAP poses a global challenge. As one of the most common hospital-acquired infections (HAI) in ICU, VAP results in prolonged hospital stays, heavy economic burden, high mortality. Recent studies estimated VAP prolonged length of IMV by 7.6-11.5 days and hospitalization by 11.5-13.1 days compared to similar patients without VAP [4,5]. A systematic review of 334 Chinese publications found the mean length of stay (LOS) for intensive care unit (ICU) acquired VAP patients was 31 days, which was absolutely longer than ICU acquired pneumonia [6] patients. Studies estimated the mortality of VAP to be 20%-50% [4,7,8].

VAP rates vary with different socioeconomic backgrounds. It ranged from 0.9 to 16.3 per 1000 ventilator days [9-12]. In China, the VAP incidence used to be high for the first several years when the standard for nosocomial infection surveillance was released in 2009 [13]. A meta-analysis around China presented a VAP incidence of 24.14 per 1000 ventilator days from 2010 to 2015 [14]. Great importance has been attached to the prevention of VAP since then. Bundles for the prevention of VAP have been implemented. Some research illustrated a sharp reduction [14-17]. However, the SARS-CoV-2 virus broke in December 2019. Resources were primarily focused on mitigating viruses spread over the world. Attention to traditional VAP prevention efforts was inadvertently reduced. It was reported the VAP incidence has already increased in some countries [18,19]. The trend of VAP incidence in China remained unclear.

Virtually every country has stood with ongoing large-scale Coronavirus disease 2019 (COVID-19) infections except China in 2020. The Chinese government quickly controlled the outbreak by implementing a complete lockdown in Wuhan between January 23rd, 2020 and April 8th, 2020 [20]. After that, the government has stringently insisted on the "COVID-19 ZERO" quarantine policy across the country

IMV is crucial for critically ill patients because the SARS-CoV-2 virus is mainly transmitted by respiratory droplets. Patients with hypoxemia and respiratory failure are in urgent need of IMV during the pandemic [21,22]. To our knowledge, few studies have reported the impact on the trend of VAP incidence in China in the last three years. A retrospective study was conducted to clarify the trend of VAP incidence during the pandemic.

Methodology

Setting and population

The study was conducted in a 3200-bed tertiary hospital in Chongqing. There was no pediatric department in our hospital. There were surgical ICU (SICU), cardiothoracic ICU (CTICU), neurosurgical ICU (NSICU), respiratory ICU (RICU), neurological ICU (NICU), general ICU (GICU) and coronary care units (CCU). The coronary care unit (CCU) was excluded because of the extremely low utility rate of IMV. The other six ICUs are supplied with 130 beds. The patients admitted to SICU, CTICU, NSICU, RICU, NICU, GICU were included. A real-time surveillance system has been used to monitor nosocomial infection for a decade. The system has joined the hospital information system (HIS), laboratory information system (LIS), picture archiving and communication system (PACS), and surgical anesthesia system (SAS) together. All information related to infection, the number of ICU inpatients, IMV days, and inpatient days were retrieved from this system.

Scenario at the hospital

The government carried out a strict quarantine policy at the border adjacent to Hubei province. Few COVID-19 patients from Hubei province entered Chongqing due to lockdown in Wuhan. They would be quarantined in appointed hotels or hospitals for almost two weeks based on the suspected results of epidemiological investigations. Our hospital is not a dedicated hospital for COVID-19 cases. As of December 31, 2020, a number of suspected COVID-19 cases were admitted to a dedicated quarantine area of our hospital with four patients confirmed by real-time polymerase chain reaction (RT-PCR). None of them attended the ICU. Some aggressive measures were adopted. Strict admission policies, two vacant wards in each department, no elective surgery, wearing personal protective equipment (PPE), timely hand hygiene, restricted visits by relatives, regular environmental cleaning and disinfection, and frequent audits by preventionists.

Ethical approval

The study eliminated the sensitive information of patients like names and identification numbers for privacy. The study was approved by the Ethical Committee of the first affiliated hospital of Chongqing Medical University (2022-155). The procedures have been performed in accordance with the Declaration of Helsinki. Since this study is a retrospective study, subjects do not need to sign informed consent.

Data collection

There was an infection prevention (IP) team in each ICU responsible for nosocomial infection surveillance and prevention. A preventionist from the hospital infection control department educated the team at least once a year. IP teams of doctors and nurses were trained on the definition of VAP, surveillance methods, and prevention bundles. The information related to the VAP surveillance (the number of ICU admissions, inpatients, IMV days, inpatient days) was recorded by the surveillance system daily and calculated monthly. VAP was confirmed by both preventionist from the hospital infection control department and IP doctors according to the definition of VAP. The information related to infected VAP patients (age, gender, ID number, pathogens) was extracted from the surveillance system.

Diagnosis

VAP was identified according to guidelines published in 2013 by Critical Care Medicine Society of China [3]. Pneumonia should occur in patients with initiation of IMV for more than 48 hours or withdrawal less than 48 hours. Patients considered to be VAP should have a new or progressive radiographic infiltrate, plus at least two of the following: a. temperature > 38°C or < 36°C; b. leukocytosis, $> 10 \times 10^9$/L or leukopenia $< 4 \times 10^9$/L; c. purulent tracheal secretions or change in character of sputum, pulmonary edema, tuberculosis, and embolism excluded. Microbiology results can further confirm VAP by sputum culture, endotracheal aspirates (ETA), protective specimen brush (PSB), bronchoalveolar lavage (BAL). A qualified sputum culture must meet the demand after smeared: epithelial cells < 10/LP, WBC > 25/LP. The quantitative test includes: a. ETA ≥

10^5 CFU/mL; b. PSB ≥ 10^3 CFU/mL; c. BAL ≥ 10^4 CFU/mL.

Microbiology tests

Preliminary bacterial species identification and antimicrobial susceptibility were determined by using VITEK2 compact system (BioMérieux, Lyon, France). The carbapenem-resistant isolates were confirmed manually by the standard broth microdilution method and were defined as resistant to at least one carbapenem (imipenem ≥ 4 μg/mL, or meropenem ≥ 4 μg/mL, or ertapenem ≥ 2 μg/mL). All drug sensitivity results were interpreted based on the American Institute for "Clinical and Laboratory Standards Institute" (CLSI) document [23]. *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC25923, and *Pseudomonas aeruginosa* ATCC27853 were used as quality control strains for susceptibility testing. *Aspergillus* was mainly detected by sputum culture in Sabouraud Medium. *Candida* was identified by chromatography with MALDI-TOF MS and semi-quantized by sputum culture.

Calculation of indicators

The indicators were calculated as the following:

$$\text{Utility rate of ventilation} = \frac{\begin{matrix}\text{IMV days in a given time}\\ \text{for certain ICU}\end{matrix}}{\begin{matrix}\textit{inpatient days in a given time}\\ \textit{for certain ICU}\end{matrix}} \times 100\%$$

$$\text{VAP incidence} = \frac{\begin{matrix}\textit{VAP episodes in a given time}\\ \textit{for certain ICU}\end{matrix}}{\begin{matrix}\textit{IMV days in a given time}\\ \textit{for certain ICU}\end{matrix}} \times 1000‰$$

$$\text{Fatality} = \frac{\begin{matrix}\textit{all the deaths in a given time after}\\ \textit{VAP occurred for certain ICU}\end{matrix}}{\begin{matrix}\textit{number of VAP patients in a given time}\\ \textit{for certain ICU}\end{matrix}} \times 100\%$$

$$30-\text{day case fatality} = \frac{\begin{matrix}\textit{number of deaths within 30 days in a given time after}\\ \textit{VAP occurred for certain ICU}\end{matrix}}{\begin{matrix}\textit{number of VAP patients in a given time}\\ \textit{for certain ICU}\end{matrix}} \times 100\%$$

$$\text{MDRO incidence density} = \frac{\textit{MDRO of VAP in a certain year}}{\textit{inpatien days of a certain year}} \times 1000‰$$

Statistical analysis

Joinpoint regression program (version 4.9.0.0 March 2021, National Cancer Institute, USA) was applied to calculate the tendency of utility rate and the trend of VAP incidence for the past 36 months. The crude rates of VAP were assumed as dependent variables and months as independent variables. The same in the analysis of utility rates. When the rate was 0, we replaced it with 0.5. Poisson variance was selected to estimate the homoscedasticity for the analysis of VAP incidence, while standard error (calculated) was used for utility rate analysis. The permutation test was used to select the final model. To analyze the 30-day case fatality change and MDR pathogen variation, the Fisher's test was used with SPSS software (version 25, IBM Corp., USA). All tests of significance were two-sided and set at p value of less than 0.05.

Results

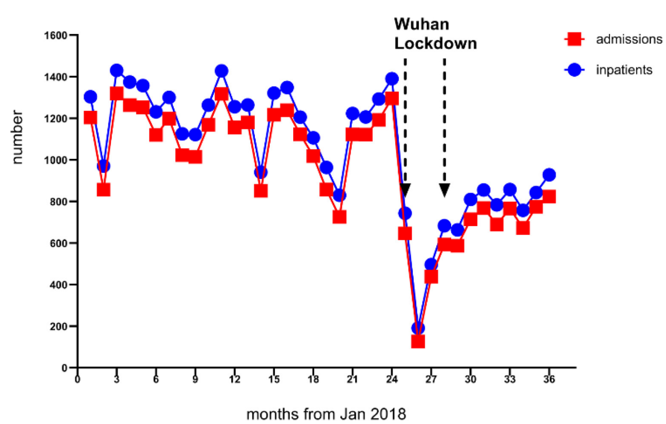
Demographic characteristics

Between January 1st 2018 and December 31st 2020, 29,067 patients were hospitalized. There was an obvious decrease in the overall number of ICU inpatients and admissions since January 2020 (Figure 1). 163 patients (182 episodes) were confirmed as VAP. Males accounted for the larger proportion (71.6%) among them. The average age of VAP patients was 61.1 (Standard Deviation (SD) = 18.1). 66.9% of VAP patients had over one month of hospital stay and 60.7% of VAP were late onset. The time between IMV initiation and onset was longer than 7 days.

Utility rate of IMV

The pooled utility rates of IMV ranged from 18.2% to 38.9%, with a mean of 25.7% and 95% CI (24.1%, 27.2%) (Table 1).

Figure 1. Tendencies for the number of ICU inpatients and admissions from January 2018 to December 2020.

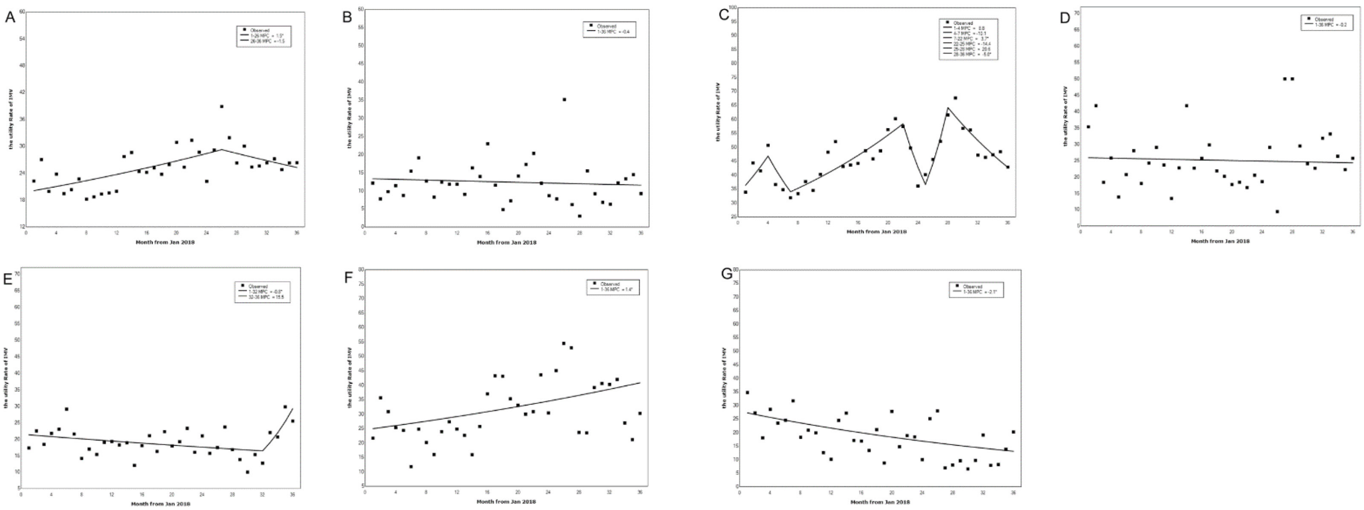


The red line presents a decline in the number of ICU inpatients. The blue line plots a decline in the number of ICU admissions. The black arrows point out the starting time and ending time for Wuhan Lockdown.

Table 1. Pooled utility rates of IMV (%) and Pooled VAP incidences (%).

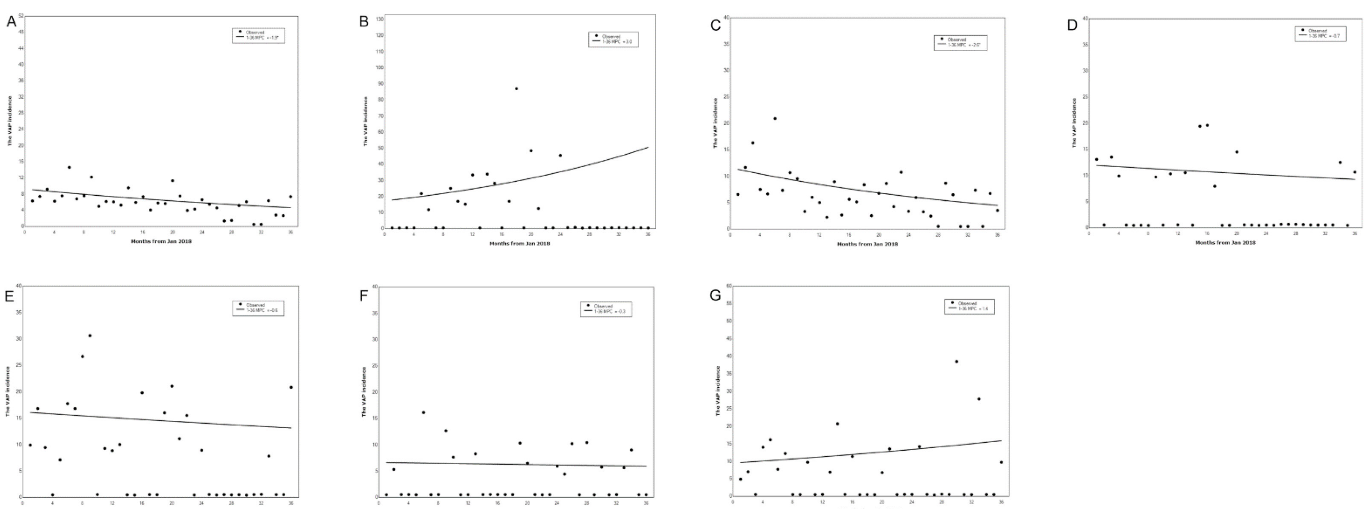
Year	Indicators	Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
2018	utility rate of IMV	22.2	27.0	19.9	23.8	19.4	20.3	22.7	18.2	18.7	19.4	19.6	20.0
	VAP incidence	6.3	7.4	9.2	6.2	7.6	14.6	6.8	7.6	12.2	5.0	6.2	6.1
2019	utility rate of IMV	27.7	28.6	24.4	28.8	29.7	27.5	25.9	30.9	30.0	31.3	28.7	22.2
	VAP incidence	5.3	9.5	5.9	7.3	4.1	5.8	5.7	11.3	7.5	3.9	4.3	6.6
2020	utility rate of IMV	29.2	38.9	31.9	26.3	30.0	25.4	25.6	26.3	27.2	24.8	26.3	26.3
	VAP incidence	5.5	4.6	1.3	1.5	5.2	6.1	0	0	6.4	2.8	2.7	7.4

Figure 2. Trends of utility rate of IMV by Joinpoint regression.



(A) trend of pooled utility rate, **(B)** trend of utility rate for CTICU, **(C)** trend of utility rate for GICU, **(D)** trend of utility rate for SICU, **(E)** trend of utility rate for NSICU, **(F)** trend of utility rate for NICU, **(G)** trend of utility rate for RICU. A black square indicates the utility rate of ventilation for ICU in different month. The black curves indicate fitted patterns for the black squares by permutation test. The segments indicate the fitting values of the Joinpoint regression. Legends give the Monthly Percent Change (MPC) value of each fitted curve for related months. *Indicates that the MPC is significantly different from zero at the alpha = 0.05 level.

Figure 3. trend of VAP incidence by Joinpoint regression.



(A) trend of pooled incidence, **(B)** trend of incidence for CTICU, **(C)** trend of incidence for GICU, **(D)** trend of incidence for SICU, **(E)** trend of incidence for NSICU, **(F)** trend of incidence for NICU, **(G)** trend of incidence for RICU. A black circle indicates the VAP incidence for ICU in different month. The black curves indicate fitted patterns for the black circles by permutation test. The segments indicate the fitting values of the Joinpoint regression. Legends give the Monthly Percent Change (MPC) value of each fitted curve for related months. *Indicates that the MPC is significantly different from zero at the 0.05 level.

It was shown a significant increase from January 2018 to February 2020, with monthly percent change (MPC): 1.5% (95% confidence interval (CI): 0.8%, 2.2%) (Figure 2a) by Joinpoint regression. However, this trend varied among the different ICUs. It presented a significant decline from January 2018 to August 2020, with MPC: -0.8% (95% CI: -1.6%, 0) (Figure 2e) for the trend of utility rate in NSICU. For RICU, the trend of utility rate kept falling with MPC: -2.1% (95% CI: -3.2%, -0.9%) (Figure 2g). As for GICU, there were bidirectional changes. From July 2018 to October 2019, it presented an increase with MPC: 3.7% (95% CI: 2.3%, 5.0%) (Figure 2c). A steep reduction was shown since April 2020 with MPC: 5.0% (95% CI: -7.9%, -1.9%) (Figure 2c). A continuous rise was shown in NICU with MPC: 1.4% (95% CI: 0.4%, 2.4%) (Figure 2f). No significant change in the utility rate was seen in other ICUs (Figure 2b, Figure 2d).

VAP incidence

On aggregate, the ventilator days were 29,976, with 182 episodes confirmed as VAP during the past three years. The VAP incidence was 6.1 episodes per 1000 IMV days. It varied from 0 to 14.6 (Table 1). The median and the interquartile range were 6.1 and 3. It kept falling off with MPC: -1.9% (95% CI: -3.2%, -0.5%) (Figure 3a). A significant decline was plotted for GICU (Figure 3c). There was no significant change for other ICUs (Figure 3b, 3d-3g).

Fatality

Out of 163 VAP patients, 46 died. The fatality was 28.2%. 31 patients died within 30 days. The 30-day case fatality was 19.02%. We found no obvious variation by the Chi-square test ($\chi^2 = 1.111$, $p = 0.574 > 0.05$).

Responsible pathogens

Generally, 143 patients (181 strains) were microbiological confirmed (Table 2). The multiple drug-resistant (MDR) pathogens accounted for 63.5% of the total. Mixed pathogens were detected in 40 people, 31 with two and 9 with three. Gram-negative bacteria (GNB) was at a predominance. They made up 89.5% of all. Gram-positive bacteria (GPB) seconded after it and followed by fungi. *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae* took up the top three GNB (Table 2). There was no variation in the constitution of pathogens by Fisher's test ($\chi^2 = 2.277$, $p = 0.713 > 0.05$). As for carbapenem resistant *Acinetobacter baumannii* (CRAB), carbapenem resistant *Pseudomonas aeruginosa* (CRPA), carbapenem resistant *Klebsiella pneumoniae* (CRKP), and methicillin-resistant *Staphylococcus aureus* (MRSA), no significant difference was found in the distribution of them through three years by Fisher's test ($\chi^2 = 2.896$, $p = 0.913 > 0.05$). The number of isolated MDROs cases had remarkably reduced compared to the previous two years. The likewise trend in the incidence density of them.

Discussion

A robust decrease in the number of ICU admissions since January 2020 (Figure 1) as well as inpatients. It declined almost 15% compared to the previous year, similar to the study mentioned by Huang [24]. The COVID-19 pandemic has seriously influenced admissions to hospitals across China according to data from the National Health Commission of China [25,26]. The shrinkage in ICU admissions may be related to the hospital's strict admission and ban on elective surgery

Table 2. Responsible pathogens of VAP.

Pathogen	Year			Pooled strains
	2018	2019	2020	
Gram negative bacteria				**162**
Acinetobacter baumannii	22	26	18	66
Pseudomonas aeruginosa	20	14	8	42
klebsiella pneumoniae	17	12	9	38
Escherichia coli	3	1	1	5
Stenotrophomonas maltophilia	0	4	0	4
others	4	3	1	7
Fungi				**7**
Candida albicans	2	2	0	4
Candida tropicalis	0	1	0	1
Aspergillus fumigatus	1	0	0	1
Asporgillus	0	1	0	1
Gram positive bacteria				**12**
Staphylococcus aureus	3	3	0	6
others	2	2	2	6
Total				**181**

policies during the SARS-CoV-2 outbreak. The SICU was even shut down for two months. Hospitals except for that in Hubei province didn't sustain admission pressure before February 2020.

Joinpoint regression program is a piecewise linear regression model that characterizes the trend behavior in the data by identifying the significant points where changes occur [27]. It can reflect the periodic change. The pulled utility rate of IMV varied from 18.2% to 38.9%, with a mean of 25.7% and 95% CI (24.1%, 27.2%). It was lower than some studies reported [12,14]. It showed a significant increase from January 2018 to February 2020 by Joinpoint regression analysis. No obvious change was seen after February 2020. Despite the increasing trend shown in NICU, there was a significant reduction or no variation for the rest of the ICUs through 2020. After the introduction of the hierarchical medical system since June 2016, more critically ill patients were sent to tertiary hospitals from secondary hospitals. Inevitably this brought a rise in the utility rate. Despite the overall decline in admissions, ICU admissions with respiratory symptoms rose in 2020. Non-COVID-19 patients with respiratory symptoms wouldn't come to ICUs unless they were critically ill. IMV is crucial for critically ill patients with hypoxemia and respiratory failure. Hence, the utility rate of IMV increased before February 2020. After the first surge in February 2020, the outbreak was controlled, and elective surgeries were gradually resumed. The prevention and control strategies attached more importance to standard precaution. IMV was assumed to be high-risk for virus exposure. Cautious using IMV would reduce the risk of exposure. When the ICU admissions gradually rose, oxygen masks and high-flow nasal cannula oxygen were chosen to replace IMV if permitted in terms of exposure risk, which indirectly reduced the utility rate [28,29].

The pooled incidence of VAP was 6.1 per 1000 IMV days. The median and the interquartile range were 6.1 and 3 per 1000 IMV days. It was lower than European and International Nosocomial Infection Control Consortium (INICC) 's reports [11,15]. It was almost consistent with a multicenter study conducted among 14 ICUs around China before the pandemic [8]. A consecutive decrease of the overall VAP incidence presented with MPC: -1.9% by Joinpoint regression analysis (Figure 3a). Before the pandemic, the declining VAP trend by implementation of prevention strategies had been documented in many studies [13,16,17]. Major reason for decreasing incidence undoubtedly came to effective implementation of prevention bundles. However, the VAP rates increased in some countries since January 2020 [19,21]. Unlike these countries, the VAP incidence demonstrated a progressive decrease (Figure 3a) in our study. Our hospital wasn't dedicated to COVID-19 patients. Because of the strong and rigid "Lockdown Wuhan" [30], sharply dropped inpatients number (Figure 1) for the first two months of 2020, which resulted in lower VAP infections. After February 2020, the SARS-CoV-2 outbreak in Wuhan was contained. No patient had been confirmed as a COVID-19 patient at our hospital since February 3, 2020. Due to sporadic outbreaks in other cities, Strategies such as proper PPE, hand hygiene, restricted visits, cleaning and disinfection, and frequent audits remained, which was helpful for prevention of VAP. Unobvious change in utility rate and more cautious use of IMV after February 2020. IMV was thought to be a high-risk intervention for exposure because of aerosol generation. Therefore, daily evaluation and early extubation were considered frequently. Fewer ventilator days, less risk for VAP infection.

On the other hand, the average length of stay decreased for ICUs with high IMV utility rates. As a result, the incidence of VAP has maintained a downward tendency. The fatality for VAP was 28.2%. The 30-day case fatality rate was 19.02%. This was in congruence to the published studies [31,32]. There was no noted change for 30-day case fatality of VAP these years. Risk factors for mortality were mainly associated with the severity of the clinical situation at admission and with other iatrogenic procedures [7]. This may reflect the fact that there is no difference in the severity of illness among VAP patients over the years. The Pathogens can be found in 78.6% of VAP infections. The GNB accounted for 89.5% of the total. The dominant causative organisms were *Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Klebsiella pneumoniae*. This was consistent with the outcome published by China Antimicrobial Resistance Surveillance System [33-35]. Of these, 63.5% were MDROs. No significant change was found in the distribution of MDROs. An obvious decline of CRAB, CRPA, CRKP, and MRSA isolates was demonstrated after 2020 as well as the incidence density of them. This was most likely caused by a steep reduction in admissions to the ICU. In parallel, a bundle of contact precautions, enhanced hand hygiene, and surface cleaning should reduce the spread of circulating MDROs in these settings [36,37].

On the other hand, social distancing in the community prevents human-to-human contact, hindering the spread of SARS-CoV-2, but potentially also of community bacterial pathogens such as *Streptococcus pneumoniae* [36]. However, this was a single-center retrospective study which may not reflect the general trend in China. Because the compliance rate of VAP prevention strategies was not recorded. The implementation of the strategies was not referred to.

Conclusions

Under the stringent quarantine and control policies during the COVID-19 pandemic, both the number of ICU admissions and inpatients dropped obviously since January 2020. The overall utility rate of ventilation presented a rise tendency before February 2020. The pooled VAP incidence kept decreasing. We can see that the period during the first wave of the pandemic (the first two months in 2020) was an important time point. The tendency demonstrated an apparent change.

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