International Journal of
Translational Medicine

MDPI

Article

Identifying High-Risk Bacteria with Active Nasal Swab Surveillance in Intensive Care Units to Prevent Ventilator-Associated Pneumonia

Yu Kuramasu [1], Yu Suzuki [2,3], Daisuke Akaneya [2,3], Yoshikazu Okuma [4], Yuta Tsujimoto [1], Daisuke Ishizawa [4], Kazunori Moriya [2], Parichart Hongsing [5,6], Mohan Amarasiri [7], Cameron Hurst [8], Paul G. Higgins [9,10], Kenji Shibuya [11], Anthony Kicic [12,13,14,15], Yoshitaka Shimotai [5], Hiroshi Hamamoto [5], Dhammika Leshan Wannigama [2,5,6,16,17,18,*] and Shuichi Abe [2,6,*]

1 Department of Emergency Medicine, Yamagata Prefectural Central Hospital, Yamagata 990-2292, Japan; yukuramasu1010@gmail.com (Y.K.); loadandgoyuta22@me.com (Y.T.)
2 Department of Infectious Diseases and Infection Control, Yamagata Prefectural Central Hospital, Yamagata 990-2292, Japan; suzukiyu1@ypch.gr.jp (Y.S.); daiakane@gmail.com (D.A.); kmoriya@ypch.gr.jp (K.M.)
3 Department of Clinical Laboratory Medicine, Yamagata Prefectural Central Hospital, Yamagata 990-2292, Japan
4 Department of Pharmacy, Yamagata Prefectural Central Hospital, Yamagata 990-2292, Japan; yookuma@ypch.gr.jp (Y.O.); ishizawad@ypch.gr.jp (D.I.)
5 Department of Infectious Diseases, Faculty of Medicine, Yamagata University Hospital, Yamagata University, Yamagata 990-2292, Japan; parichart.hongsing@gmail.com (P.H.); yoshimo@med.id.yamagata-u.ac.jp (Y.S.); hamamoto@med.id.yamagata-u.ac.jp (H.H.)
6 Pathogen Hunter's Research Collaborative Team, Department of Infectious Diseases and Infection Control, Yamagata Prefectural Central Hospital, Yamagata 990-2292, Japan
7 Department of Civil and Environmental Engineering, Graduate School of Engineering, Tohoku University, Sendai 980-8579, Miyagi, Japan; mohan.amarasiri.b5@tohoku.ac.jp
8 Molly Wardaguga Research Centre, Charles Darwin University, Brisbane, QLD 4000, Australia; cphurst@gmail.com
9 Institute for Medical Microbiology, Immunology and Hygiene, Faculty of Medicine, University Hospital Cologne, University of Cologne, 50935 Cologne, Germany; paul.higgins@uni-koeln.de
10 German Centre for Infection Research, Partner Site Bonn-Cologne, 50935 Cologne, Germany
11 Tokyo Foundation for Policy Research, Minato-ku, Tokyo 105-0001, Japan; kenjishibuya1@gmail.com
12 Wal-Yan Respiratory Research Centre, Telethon Kids Institute, University of Western Australia, Nedlands, WA 6009, Australia; anthony.kicic@thekids.org.au
13 Centre for Cell Therapy and Regenerative Medicine, Medical School, The University of Western Australia, Nedlands, WA 6009, Australia
14 Department of Respiratory and Sleep Medicine, Perth Children's Hospital, Nedlands, WA 6009, Australia
15 School of Population Health, Curtin University, Bentley, WA 6102, Australia
16 Graduate School, Yamagata Prefectural University of Health Sciences, Kamiyanagi, Yamagata 990-2212, Japan
17 School of Medicine, Faculty of Health and Medical Sciences, The University of Western Australia, Nedlands, WA 6009, Australia
18 Biofilms and Antimicrobial Resistance Consortium of ODA Receiving Countries, The University of Sheffield, Sheffield S10 2TN, UK
* Correspondence: leshanwannigama@ypch.gr.jp or leshanwannigama@med.id.yamagata-u.ac.jp (D.L.W.); shuichiabe@ypch.gr.jp (S.A.)

check for updates

Academic Editor: Haim Levy

Received: 11 March 2025
Revised: 19 April 2025
Accepted: 23 April 2025
Published: 25 April 2025

Citation: Kuramasu, Y.; Suzuki, Y.; Akaneya, D.; Okuma, Y.; Tsujimoto, Y.; Ishizawa, D.; Moriya, K.; Hongsing, P.; Amarasiri, M.; Hurst, C.; et al. Identifying High-Risk Bacteria with Active Nasal Swab Surveillance in Intensive Care Units to Prevent Ventilator-Associated Pneumonia. *Int. J. Transl. Med.* **2025**, *5*, 17. https://doi.org/10.3390/ijtm5020017

Abstract: Background: Active nasal surveillance culture (ANSC) is recognized to enable rapid detection of antibiotic-resistant bacteria in the intensive care unit (ICU), which can contribute to the prevention of Ventilator-associated pneumonia (VAP). This study aims to evaluate the usefulness of ANSC in assessing the development of VAP in ICU patients. Methods: Patients admitted to the Yamagata Prefectural Central Hospital ICU from January 2017 to 2018 (Term 1) or January 2020 to December 2021 (Term 2) and underwent invasive mechanical ventilation supports were eligible for this study. Nasal swab samples were collected from the patients upon their admission to the ICU. The diagnosis of VAP was made according to the criteria set by the Centers for Disease Control and Prevention.

Results: A total of 467 patients (156 women) in term 1, and 312 patients (113 women) in term 2 were enrolled. The incidence of VAP in term 2 was higher than in term 1 (7.1% vs. 12.8%, respectively). ANSC isolated several causative pathogens from the patients on admission who later developed VAP. *Haemophilus influenza*, *Streptococcus pneumoniae*, *Stenotrophomonas maltophilia*, *and Pseudomonas aeruginosa* had a 100% match rate with the sputum culture, indicating a perfect relation between ANSC results and sputum culture in VAP (+) cases. Conclusions: The isolation of high-risk bacterial species by ANSC could foresee the development of VAP in ICU patients and efficiently prevent VAP in critically ill patients.

Keywords: ventilator-associated pneumonia; active nasal surveillance culture; intensive care unit

1. Introduction

Ventilator-associated pneumonia (VAP) is a serious infection of the lung parenchyma that typically develops more than two days after a patient begins invasive positive pressure ventilation [1]. This condition is among the most common infections in patients receiving such ventilation, significantly impacting patient outcomes and healthcare resources [1]. The incidence of VAP varies widely, affecting between 5% and 40% of patients undergoing invasive positive pressure ventilation, and leading to a cascade of clinical complications including increased antibiotic usage, heightened treatment costs, prolonged ventilator dependency, and extended hospital stays [2–7].

The pathogens most frequently responsible for VAP include a mix of Gram-negative bacteria such as *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Acinetobacter* species, alongside Gram-positive bacteria such as *Staphylococcus aureus* [1,6,8–15]. The timing of VAP onset is crucial in determining its etiology [1,4]. Early-onset VAP, which occurs within the first four days of hospitalization, generally involves bacteria from the patient's normal oropharyngeal flora, especially in those without prior antibiotic exposure [2,3,16]. In contrast, late-onset VAP, occurring after five days of hospitalization, is more likely to be caused by multidrug-resistant organisms, especially in patients with prolonged hospital stays or prior antibiotic treatments [2,16].

Efforts to prevent VAP in the ICU encompass several strategies, including maintaining appropriate sedation and analgesia, adjusting patient positioning, controlling tracheal tube cuff pressure, and providing rigorous oral care [16]. Despite these measures, the incidence of VAP remains a significant challenge, imposing a considerable burden on ICU resources and patient health [17].

Active nasal surveillance culture (ANSC) represents a proactive approach to managing the risk of VAP [18–20]. ANSC involves regularly screening patients for asymptomatic colonization with antibiotic resistant bacteria, thus enabling early identification and timely intervention. For example, ANSC has been instrumental in the surveillance and prevention of Methicillin-resistant *Staphylococcus aureus* (MRSA) infections, significantly reducing postoperative wound infections in orthopedic and cardiovascular surgery patients [20–22]. In the ICU setting, ANSC can identify multidrug-resistant bacteria responsible for VAP, thereby allowing clinicians to administer targeted antibiotics early, which helps to limit the use of broad-spectrum antibiotics and improve patient outcomes [2,16,23–25].

Based on these principles, we hypothesized that ANSC could be utilized to detect bacteria with a high likelihood of causing VAP at an early stage. This early detection would enable the implementation of more effective preventive measures tailored to the specific pathogens identified, ultimately reducing the incidence and severity of VAP. To test this

hypothesis, we conducted research to evaluate the efficacy of ANSC in the early detection and prevention of VAP, focusing on its impact on patient outcomes and healthcare resource utilization.

2. Methods

2.1. Study Cohort

We conducted a retrospective review of medical records from patients admitted to the intensive care unit (ICU) of Yamagata Prefectural Central Hospital (Yamagata, Japan) between January 2017 and December 2021. Eligible patients included those who required invasive positive pressure ventilation during their ICU stay. Clinical data were collected, including the primary reasons for ICU admission and details of antibiotic administration following admission. To assess the impact of the COVID-19 pandemic on ventilator-associated pneumonia (VAP) trends and clinical practices, participants were stratified into two temporal cohorts: Term 1 (pre-pandemic period, January 2017 to December 2018) and Term 2 (pandemic period, January 2020 to December 2021). All patients received standard-of-care VAP prophylaxis in accordance with institutional protocols throughout the study period [26]. Decisions regarding ventilator management, sedation, and antimicrobial therapy were made at the discretion of the attending physicians. The study was conducted using anonymized data and was approved by the Institutional Review Board of Yamagata Prefectural Central Hospital.

2.2. ANSC Sample Collection and Processing

ANSC samples were collected at the time of admission to the ICU and every week thereafter during the patient's ICU stay. Specimens were collected on the nearest weekday if admission was on a holiday. The collected samples were cultured for 48 h on blood agar, Candida medium, MRSA screen medium, and BTB agar, and the bacterial species of positive samples were identified using a mass spectrometer (MALDI biotyper/BECKMAN COULTER, Nagaizumi, Japan). A drug susceptibility test was then performed (MicroScan WalkAway D × M/BECKMAN COULTER). The susceptibility testing was performed for clinical purposes, and the findings were not included in this analysis as they fell outside the primary objectives of the study.

2.3. Definition of VAP

VAP was defined using the guidelines for ventilator-associated events established by the Centers for Disease Control and Prevention [27]. In this guideline, a condition in which an increase in F_IO_2 or PEEP indicating deterioration of oxygenation is observed after 48 h have passed without an increase in FIO_2 or PEEP after starting invasive pressure evocation is defined as a Ventilator-Associated Condition (VAC). Beyond VAC status, having a fever higher than 38 degrees Celsius, hypothermia lower than 36 degrees Celsius, or a white blood cell count of 12,000/mm^3 or higher or 4000/mm^3 or lower, and 4 days have elapsed since starting a new antibiotic, is defined as Infection related Ventilator-Associated Complication (IVAC). Possible Ventilator-Associated Pneumonia (PVAP) is defined when bacteria are pathologically detected in the lung parenchyma. When positive cultures from endotracheal aspirate, bronchoalveolar lavage fluid, lung tissue, specimen brush specimens, sputum or endotracheal aspirate containing neutrophils pleural effusion, lung parenchyma were detected, Possible Ventilator-Associated Pneumonia (PVAP) is defined.

2.4. Statistical Analysis

All statistical analyses were conducted using the R statistical package (R version 4.5) (https://www.r-project.org) [28]. Data were compared by using Analysis of Variance

(ANOVA). All data are presented as the mean ± SD. Differences were considered significant when $p < 0.05$.

3. Results

3.1. Patient Characteristics

In the ICU of Yamagata Prefectural Central Hospital, 467 patients required invasive positive pressure ventilation in Term 1 and 312 patients in Term 2. Table 1 shows the patient characteristics of the group that developed VAP and non-VAP in both periods (Supplementary Tables S1 and S2). The mean age of the VAP group was 66 years, 71% were male, the median body-mass index was 22.9%, and the smoking rate was 69%, which was no different from non-VAP. The most common reason for admission to ICU in both terms was post-surgery complications. In the VAP group, trauma, and poisoning, post-CPR recovery, and COVID-19 were significantly more common reasons for admission. Those who developed VAP had higher mortality rates and longer hospital stays. Sequential Organ Failure Assessment (SOFA) score had significantly higher values in respiration, circulation, and CNS. The two groups did not differ in using cefazolin for postoperative infection prevention. Still, the use of meropenem, tazobactam/piperacillin, fourth-generation cephalosporins, and vancomycin was significantly higher in the VAP group.

Table 1. Baseline characteristics of patients with and without ventilator-associated pneumonia (VAP).

Characteristic	VAP (*n* = 73)	Non-VAP (*n* = 706)	*p*-Value
Median age—year	66	67	0.17
Male sex—number (%)	52 (71)	458 (65)	0.28
Median body–mass index	23.4	22.9	0.38
Smoking (%)	55%	69%	0.29
Primary reason for ICU admission			
State after surgical operation	13	314	<0.0001
Sepsis	4	87	0.08
Heart failure	8	80	0.92
Trauma/Poisoning	16	39	<0.0001
CPR recovery	10	13	<0.0001
COVID-19	10	4	<0.0001
Others	12	169	
Duration of hospital stay—days	64.3	32	<0.0001
Mortality (%)	19%	8%	<0.0002
SOFA SCORE			
Respiration	2.49	2.08	<0.0001
Coagulation	0.90	1.01	0.32
Liver function	0.50	0.52	0.98
Circulation	2.57	2.11	0.01
CNS	1.79	0.94	<0.0001
Renal function	0.91	0.70	0.095
Total	9.14	7.36	<0.0001
Antimicrobials—no. (%)			
Cefazolin (CEZ)	45 (62)	516 (73)	0.038
Meropenem (MEM)	19 (27)	54 (8)	<0.0001
Tazobactam/piperacillin (TZP)	20 (27)	32 (5)	<0.0001
Cefepime (FEP) or cefozopran (CZOP)	21 (28)	15 (2)	<0.0001
Vancomycin (VAN)	16 (22)	15 (2)	<0.0001
Others	46 (63)	161 (23)	<0.0001

3.2. Incidence of VAP and Antimicrobial Usage

The incidence of VAP was 7.1% in Term 1 and 13% in Term 2, with a significant increase ($p = 0.0069$) in Term 2 (Figure 1a). Antimicrobial usage in non-VAP and VAP patients was different before and during the COVID-19 outbreak (Table 2). Total antimicrobial usage decreased in Term 2. Antibiotic usage did not change in non-VAP patients. In the VAP group, the use of fourth-generation cephalosporins significantly increased ($p = 0.0200$) in term 2, but no differences were observed in the use of other antibiotics.

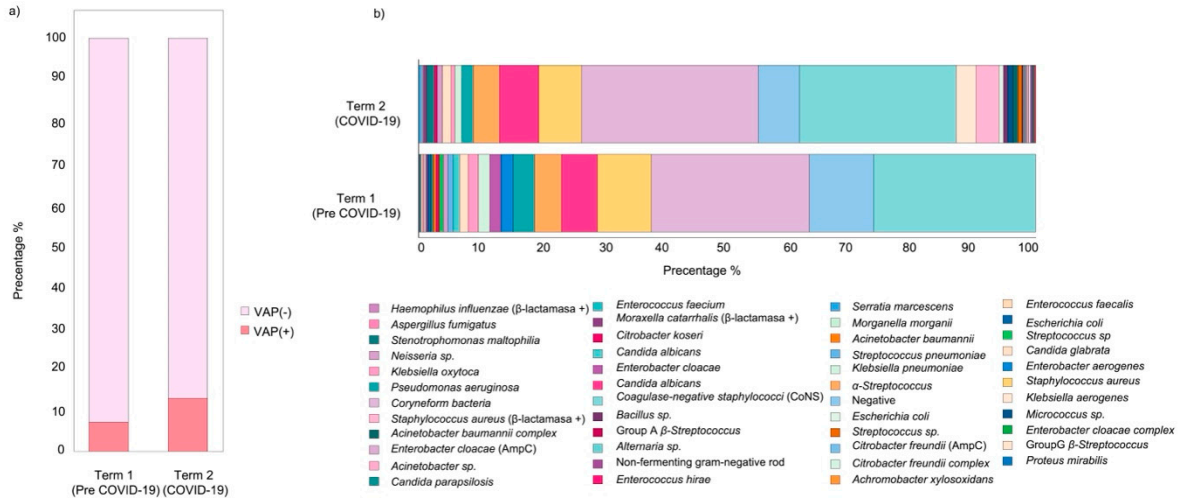

Figure 1. (**a**) Incidence of ventilator-associated pneumonia (VAP) among patients admitted to the ICU requiring invasive mechanical ventilation, stratified by study period (Term 1: January 2017–December 2018; Term 2: January 2020–December 2021). (**b**) Distribution of bacterial species detected through active nasal swab culture (ANSC) surveillance during the same periods. Data reflect the most commonly isolated organisms associated with potential VAP risk.

Table 2. Comparison of antimicrobial usage patterns in VAP and non-VAP patients before and during the COVID-19 pandemic. Term 1: January 2017–December 2018; Term 2: January 2020–December 2021.

	Characteristic					
Antimicrobialsno (%)	**non-VAP Term 1 (Pre COVID-19)**	**Term 2 (COVID-19)**	***p*-Value**	**VAP Term 1 (Pre COVID-19)**	**Term 2 (COVID-19)**	***p*-Value**
Cefazolin (CEZ)	322 (74)	194 (71)	0.49	21 (64)	24 (60)	0.75
Meropenem (MEM)	49 (11)	39 (14)	0.22	7 (21)	12 (30)	0.39
Piperacillin–Tazobactam (TZP)	29 (6.6)	23 (8.5)	0.37	10 (30)	10 (25)	0.61
Cefepime (FEP)/Cefoperazone (CZOP)	11 (2.5)	14 (5.2)	0.065	5 (15)	16 (40)	0.020
Vancomycin (VAN)	14 (3.2)	13 (4.8)	0.29	5 (15)	11 (28)	0.20
Others	156 (36)	45 (17)	<0.0001	24 (72)	22 (55)	0.12

3.3. Bacterial Species Diversity in ANSC

Figure 1b shows the bacterial species detected in ANSC during Term 1 and Term 2. In both Term 1 and Term 2, normal nasal flora, such as Coagulase-negative staphylococcus (CoNS), *Coryneform* bacteria, and *S. aureus*, were commonly detected. On the other hand, Gram-negative bacteria such as *Enterobacter*, *Klebsiella* spp., and *P. aeruginosa* were rarely detected. Comparing Term 1 and Term 2, *Enterobacter* ($p < 0.0001$) and *P. aeruginosa* ($p = 0.0370$) significantly decreased in Term 2, while *Stenotrophomons maltophilia* ($p = 0.0440$) significantly increased.

3.4. ANSC Bacteria Diversity and Relation to VAP

MRSA was the most common causative pathogen of VAP in both Term 1 and Term 2 (Figure 2). *Enterobacteriaceae*, such as *Klebsiella aerogenes*, *Klebsiella oxitca*, *Klebsiella pneumoniae*, *Enterobacter*, *Citrobacter*, and *P. aeruginosa* were also detected. There was no significant difference in the number of bacteria detected in Term 1 and Term 2. *Haemophilus influenza*, *Streptococcus pneumoniae*, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa* had a 100% match rate with sputum culture, indicating a perfect correlation between ANSC results and sputum culture in VAP(+) cases (Table 3). *Serratia marcescens* also showed a high match percentage (100%) between ANSC results and sputum culture but had lower incidences of VAP. *Staphylococcus aureus* had a relatively high match percentage (83%) with a considerable number of cases. For some species, like *Moraxella catarrhalis*, *Escherichia coli*, *Acinetobacter sp.*, *Coagulase-negative staphylococci*, and *Coryneform bacteria*, cases had a 0% match rate, indicating no correlation between ANSC and sputum culture results.

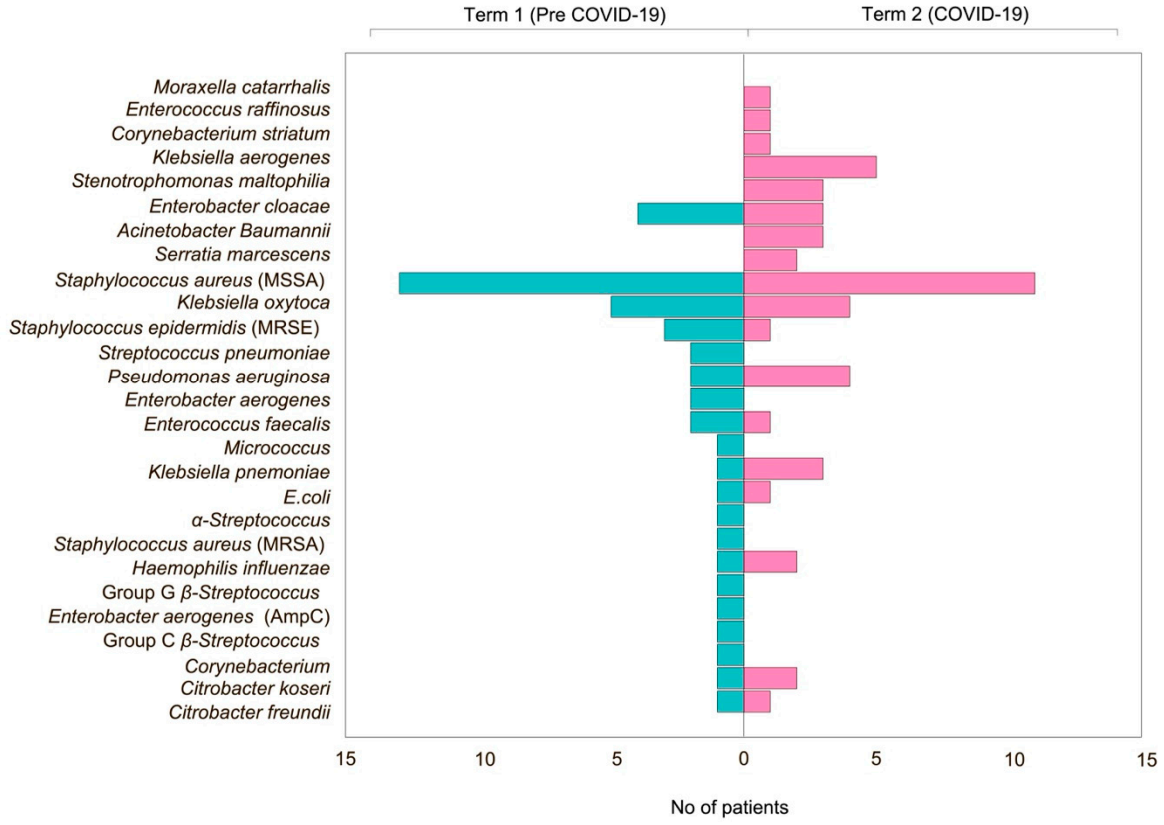

Figure 2. Causative pathogens identified in ventilator-associated pneumonia (VAP) cases.

Table 3. Incidence of ventilator-associated pneumonia (VAP) by major causative pathogen and concordance with active nasal swab culture (ANSC).

	ANSC	VAP(+)	VAP(−)	Incidences	Match with ANSC and Sputum Culture	Match %
Haemophilus influenz	1	1	0	100%	1	100%
Serratia marcescens	4	2	2	50%	2	100%
Moraxella catarrhalis	8	1	7	13%	0	0%
Klebsiella spp.	75	8	67	10.7%	5	63%
Staphylococcus aureus	176	18	158	10.2%	15	83%
Streptococcus pneumoniae	10	1	9	10.0%	1	100%

Table 3. *Cont.*

	ANSC	VAP(+)	VAP(−)	Incidences	Match with ANSC and Sputum Culture	Match %
Escherichia coli	10	1	9	10%	0	0%
Enterobacter spp.	46	4	42	8.7%	1	25%
Acinetobacter sp.	13	1	12	8%	0	0%
Stenotrophomonas maltophilia	13	1	13	8%	1	100%
Pseudomonas aeruginosa	53	3	50	6%	3	100%
Coagulase-negative staphylococci	302	25	456	5.2%	0	0%
Coryneform bacteria	295	5	494	1.0%	0	0%
Negative	120	2	118	1.7%	0	0%

4. Discussion

This single-center retrospective study found that patients with ventilator-associated pneumonia (VAP) experienced longer hospital stays, increased mortality rates, and heightened usage of broad-spectrum antimicrobials. Thus, VAP poses a significant threat in the intensive care unit (ICU) and potentially promotes the spread of antimicrobial resistance. The incidence of VAP was higher among patients with detected pathogens such as *H. influenzae*, *S.*, *S. pneumoniae*, *S. maltophilia*, and *P. aeruginosa* compared to other bacteria identified through active nasal surveillance cultures (ANSC). Notably, the pathogens causing VAP matched those identified by ANSC in these patients.

The mortality rate associated with VAP is influenced by the severity of the disease at diagnosis, the specific pathogen involved, and the adequacy of the initial empiric antimicrobial therapy [2,17,29–32]. Nasal surveillance cultures are crucial in identifying potential VAP-causing microorganisms colonized in the nasal cavity, which can lead to infections. such as VAP. Specifically, *P. aeruginosa* and *S. aureus* are known to colonize the nasal cavity and trachea and are associated with VAP [33,34]. Patients with positive surveillance cultures are at a higher risk of developing infections due to the identified bacteria [25]. Surveillance cultures enable clinicians to assess the risk of infection and predict the involvement of multidrug-resistant bacteria, thereby reducing the unnecessary use of broad-spectrum antibiotics [35,36].

In this study, ANSC detected numerous normal nasal flora, such as CoNS and Coryneform bacteria, and a few Gram-negative rods (GNRs) like Enterobacteriaceae. The bacteria identified during ANSC were associated with a higher incidence of VAP, and it was confirmed that the pathogens responsible for VAP matched those found in the nasal surveillance cultures at ICU admission, including their antimicrobial susceptibility profiles. Implementing VAP prevention bundles, which include appropriate sedation/analgesia, early extubation, and rigorous hand hygiene, has been reported to reduce the incidence of VAP [37]. Recognizing the risk of VAP based on ANSC results allows for timely administration of appropriate antibiotics, potentially improving patient outcomes.

The study also explored the impact of the COVID-19 pandemic on VAP incidence. During the pandemic, VAP incidence increased significantly to 12.8%, although there was no change in the detection status of VAP-causing pathogens between the pre-pandemic and pandemic periods. The unchanged microbial profile of VAP cases during Term 2, despite increased antibiotic use, may be explained by several factors. First, the rise in empirical broad-spectrum antibiotic use during the COVID-19 outbreak likely reflected heightened clinical uncertainty and patient severity; however, if these antibiotics were

not specifically effective against the dominant VAP pathogens, their use may not have significantly impacted the microbial landscape. Second, the consistent organism profile may indicate a stable hospital microbiome and effective infection control practices across terms, which could have limited the emergence or selection of new or resistant pathogens. Lastly, the duration of increased antibiotic pressure may have been too short to drive notable changes in pathogen distribution, as such shifts typically occur over longer periods of sustained selection pressure.

There was a significant increase in COVID-19 cases among VAP patients during the pandemic, and the Sequential Organ Failure Assessment (SOFA) score for respiration also rose. Previous studies have indicated that COVID-19 patients are at a higher risk of developing VAP and have higher mortality rates compared to non-COVID-19 patients [38,39]. Factors contributing to this increased risk include poor adherence to VAP prevention bundles, immune disorders related to COVID-19 or its treatment, prolonged mechanical ventilation, and long-term sedative use [40]. Immune abnormalities in COVID-19 patients can lead to excessive inflammatory responses, organ damage, and reduced antibacterial activity, increasing VAP incidence. Severe COVID-19, characterized by acute respiratory distress syndrome (ARDS) and severe hypoxemia, further contributes to the increased VAP risk [41–44]. Our ICU prioritized severe COVID-19 patients during the pandemic, limiting admissions for other critical illnesses. This likely contributed to the higher proportion of VAP cases. Additionally, ARDS findings on chest X-rays and CT scans in COVID-19 patients led to severe hypoxemia and increased SOFA scores.

In non-VAP patients, antimicrobial usage decreased during the pandemic, while VAP patients saw an increase in antimicrobial use, particularly fourth-generation cephalosporins. Infection control measures during the pandemic, such as social distancing, mask-wearing, and home isolation, reduced other respiratory tract infections and primary care antibiotic use [45]. However, in the ICU, antimicrobial usage increased due to the higher risk of nosocomial infections among COVID-19 patients [46–48], although our hospital saw a decrease in total antimicrobial usage in the ICU due to fewer admissions of non-COVID-19 patients. Conversely, increased antimicrobial usage in VAP patients was observed due to the higher number of VAP cases among COVID-19 patients.

This study has several limitations. As a retrospective, single-center analysis, the findings may not be fully generalizable to other institutions with different ICU protocols, patient populations, or infection control practices. Additionally, the inclusion of the COVID-19 pandemic period introduces potential confounding factors, such as shifts in ICU workflows, staffing, and patient demographics, which may have influenced VAP incidence and antimicrobial usage patterns. Despite these limitations, a major strength of this study lies in its comprehensive evaluation of active nasal swab culture (ANSC) surveillance and VAP trends during a critical period. The findings offer valuable insight into the utility of routine colonization screening to identify high-risk patients, while also highlighting the need for sustained infection control and antimicrobial stewardship—especially during times of increased healthcare strain such as pandemics.

5. Conclusions

This study highlights the potential value of active nasal swab culture (ANSC) surveillance in identifying patients at increased risk of developing ventilator-associated pneumonia (VAP) in the intensive care unit. Despite a significant rise in VAP cases and antibiotic usage during the COVID-19 outbreak, the microbial profile of VAP pathogens remained largely unchanged, underscoring the importance of ongoing surveillance, stringent infection control, and robust antimicrobial stewardship practices. These findings support the integration of targeted bacterial colonization screening as part of VAP prevention strategies

and emphasize the need for sustained vigilance, particularly during periods of heightened clinical burden such as pandemics.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ijtm5020017/s1, Table S1: Characteristics of the non-VAP Patients at Baseline in Term and term 2; Table S2: Characteristics of the VAP Patients at Baseline in term1 and term 2.

Author Contributions: Y.K., D.L.W. and S.A. conceived the study, conducted the investigation and contributed to data curation, formal analysis and writing the original draft of the manuscript. D.L.W. and S.A. acquired funding and provided supervision. Clinical sample collection and analysis were performed by Y.S. (Yu Suzuki), D.A., K.M., Y.O. and D.I., P.H., C.H., P.G.H., K.S., Y.S. (Yoshitaka Shimotai), H.H. M.A., A.K. and Y.T. provided supervision, critical review and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding: Dhammika Leshan Wannigama was supported by Balvi Filantropic Fund, Barry Satz and Ronald Satz Memorial Fund, and the Japan Society for the Promotion of Science JSPS KAKENHI Grant Number JP24KF0177). Anthony Kicic is a Rothwell Family Fellow.

Institutional Review Board Statement: This study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice guidelines, and other applicable laws and regulations, including STROBE guidelines. The study is part of the ANSC surveillance study and was reviewed and approved by the institutional review board at Yamagata Prefectural Central Hospital, Yamagata, Japan (SW5/2021-08-12).

Informed Consent Statement: Nasal swab samples were collected as part of the hospital's standard infection control strategy, and therefore, the requirement for informed consent.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its additional information.

Acknowledgments: We thank all the hospital staff who kindly supported us with sample collection.

Conflicts of Interest: The authors declare that they have no known potential conflict of interest or competing financial or non-financial interest in relation to the manuscript.

References

1. Torres, A.; Cilloniz, C.; Niederman, M.S.; Menéndez, R.; Chalmers, J.D.; Wunderink, R.G.; van der Poll, T. Pneumonia. *Nat. Rev. Dis. Primers* **2021**, *7*, 25. [CrossRef] [PubMed]
2. Daghmouri, M.A.; Dudoignon, E.; Chaouch, M.A.; Baekgaard, J.; Bougle, A.; Leone, M.; Deniau, B.; Depret, F. Comparison of a short versus long-course antibiotic therapy for ventilator-associated pneumonia: A systematic review and meta-analysis of randomized controlled trials. *eClinicalMedicine* **2023**, *58*, 101880. [CrossRef] [PubMed]
3. Ladbrook, E.; Khaw, D.; Bouchoucha, S.; Hutchinson, A. A systematic scoping review of the cost-impact of ventilator-associated pneumonia (VAP) intervention bundles in intensive care. *Am. J. Infect. Control* **2021**, *49*, 928–936. [CrossRef] [PubMed]
4. Kalil, A.C.; Metersky, M.L.; Klompas, M.; Muscedere, J.; Sweeney, D.A.; Palmer, L.B.; Napolitano, L.M.; O'Grady, N.P.; Bartlett, J.G.; Carratalà, J.; et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin. Infect. Dis.* **2016**, *63*, e61–e111. [CrossRef]
5. Melsen, W.G.; Rovers, M.M.; Groenwold, R.H.; Bergmans, D.C.; Camus, C.; Bauer, T.T.; Hanisch, E.W.; Klarin, B.; Koeman, M.; Krueger, W.A.; et al. Attributable mortality of ventilator-associated pneumonia: A meta-analysis of individual patient data from randomised prevention studies. *Lancet Infect. Dis.* **2013**, *13*, 665–671. [CrossRef]
6. Gil-Perotin, S.; Ramirez, P.; Marti, V.; Sahuquillo, J.M.; Gonzalez, E.; Calleja, I.; Menendez, R.; Bonastre, J. Implications of endotracheal tube biofilm in ventilator-associated pneumonia response: A state of concept. *Crit. Care* **2012**, *16*, R93. [CrossRef]
7. Shein, A.M.S.; Hongsing, P.; Smith, O.R.K.; Phattharapornjaroen, P.; Miyanaga, K.; Cui, L.; Ishikawa, H.; Amarasiri, M.; Monk, P.N.; Kicic, A.; et al. Current and novel therapies for management of Acinetobacter baumannii-associated pneumonia. *Crit. Rev. Microbiol.* **2024**, 1–22. [CrossRef]
8. Chirabhundhu, N.; Luk-In, S.; Phuadraksa, T.; Wichit, S.; Chatsuwan, T.; Wannigama, D.L.; Yainoy, S. Occurrence and mechanisms of tigecycline resistance in carbapenem- and colistin-resistant Klebsiella pneumoniae in Thailand. *Sci. Rep.* **2024**, *14*, 5215. [CrossRef]

9. Shein, A.M.S.; Wannigama, D.L.; Hurst, C.; Monk, P.N.; Amarasiri, M.; Badavath, V.N.; Phattharapornjaroen, P.; Ditcham, W.G.F.; Ounjai, P.; Saethang, T.; et al. Novel intranasal phage-CaEDTA-ceftazidime/avibactam triple combination therapy demonstrates remarkable efficacy in treating Pseudomonas aeruginosa lung infection. *Biomed. Pharmacother.* **2023**, *168*, 115793. [CrossRef]
10. Srisakul, S.; Wannigama, D.L.; Higgins, P.G.; Hurst, C.; Abe, S.; Hongsing, P.; Saethang, T.; Luk-in, S.; Liao, T.; Kueakulpattana, N.; et al. Overcoming addition of phosphoethanolamine to lipid A mediated colistin resistance in Acinetobacter baumannii clinical isolates with colistin–sulbactam combination therapy. *Sci. Rep.* **2022**, *12*, 11390. [CrossRef]
11. Shein, A.M.S.; Wannigama, D.L.; Higgins, P.G.; Hurst, C.; Abe, S.; Hongsing, P.; Chantaravisoot, N.; Saethang, T.; Luk-in, S.; Liao, T.; et al. High prevalence of mgrB-mediated colistin resistance among carbapenem-resistant Klebsiella pneumoniae is associated with biofilm formation, and can be overcome by colistin-EDTA combination therapy. *Sci. Rep.* **2022**, *12*, 12939. [CrossRef] [PubMed]
12. Shein, A.M.S.; Wannigama, D.L.; Higgins, P.G.; Hurst, C.; Abe, S.; Hongsing, P.; Chantaravisoot, N.; Saethang, T.; Luk-in, S.; Liao, T.; et al. Novel colistin-EDTA combination for successful eradication of colistin-resistant Klebsiella pneumoniae catheter-related biofilm infections. *Sci. Rep.* **2021**, *11*, 21676. [CrossRef] [PubMed]
13. Singkham-in, U.; Higgins, P.G.; Wannigama, D.L.; Hongsing, P.; Chatsuwan, T. Rescued chlorhexidine activity by resveratrol against carbapenem-resistant Acinetobacter baumannii via down-regulation of AdeB efflux pump. *PLoS ONE* **2020**, *15*, e0243082. [CrossRef]
14. Wannigama, D.L.; Hurst, C.; Hongsing, P.; Pearson, L.; Saethang, T.; Chantaravisoot, N.; Singkham-in, U.; Luk-in, S.; Storer, R.J.; Chatsuwan, T. A rapid and simple method for routine determination of antibiotic sensitivity to biofilm populations of Pseudomonas aeruginosa. *Ann. Clin. Microbiol. Antimicrob.* **2020**, *19*, 8. [CrossRef]
15. Phuengmaung, P.; Somparn, P.; Panpetch, W.; Singkham-In, U.; Wannigama, D.L.; Chatsuwan, T.; Leelahavanichkul, A. Coexistence of Pseudomonas aeruginosa With Candida albicans Enhances Biofilm Thickness Through Alginate-Related Extracellular Matrix but Is Attenuated by N-acetyl-l-cysteine. *Front. Cell Infect. Microbiol.* **2020**, *10*, 594336. [CrossRef]
16. Klompas, M.; Branson, R.; Cawcutt, K.; Crist, M.; Eichenwald, E.C.; Greene, L.R.; Lee, G.; Maragakis, L.L.; Powell, K.; Priebe, G.P.; et al. Strategies to prevent ventilator-associated pneumonia, ventilator-associated events, and nonventilator hospital-acquired pneumonia in acute-care hospitals: 2022 Update. *Infect. Control Hosp. Epidemiol.* **2022**, *43*, 687–713. [CrossRef]
17. Semet, C. The ongoing challenge of ventilator-associated pneumonia: Epidemiology, prevention, and risk factors for mortality in a secondary care hospital intensive care unit. *Infect. Prev. Pract.* **2023**, *5*, 100320. [CrossRef]
18. Chaberny, I.F.; Schwab, F.; Ziesing, S.; Suerbaum, S.; Gastmeier, P. Impact of routine surgical ward and intensive care unit admission surveillance cultures on hospital-wide nosocomial methicillin-resistant Staphylococcus aureus infections in a university hospital: An interrupted time-series analysis. *J. Antimicrob. Chemother.* **2008**, *62*, 1422–1429. [CrossRef]
19. Holzmann-Pazgal, G.; Monney, C.; Davis, K.; Wanger, A.; Strobel, N.; Zhong, F. Active surveillance culturing impacts methicillin-resistant Staphylococcus aureus acquisition in a pediatric intensive care unit. *Pediatr. Crit. Care Med.* **2011**, *12*, e171–e175. [CrossRef]
20. Kondo, T.; Okabayashi, K.; Sugiura, K.; Obara, H.; Takeuchi, H.; Wada, N.; Takano, Y.; Iwata, S.; Hasegawa, N.; Kitagawa, Y. Effectiveness of active nasal surveillance culture for Methicillin-resistant Staphylococcus aureus in patients undergoing colorectal surgery. *J. Infect. Chemother.* **2020**, *26*, 1244–1248. [CrossRef]
21. Murphy, E.; Spencer, S.J.; Young, D.; Jones, B.; Blyth, M.J. MRSA colonisation and subsequent risk of infection despite effective eradication in orthopaedic elective surgery. *J. Bone Jt. Surg. Br.* **2011**, *93*, 548–551. [CrossRef] [PubMed]
22. Malde, D.J.; Hardern, L.; Welch, M. Is it possible to predict outcome in MRSA positive patients undergoing arterial reconstruction? *Int. Angiol.* **2006**, *25*, 78–83. [PubMed]
23. Depuydt, P.; Benoit, D.; Vogelaers, D.; Decruyenaere, J.; Vandijck, D.; Claeys, G.; Verschraegen, G.; Blot, S. Systematic surveillance cultures as a toolto predict involvement of multidrug antibiotic resistant bacteria in ventilator-associated pneumonia. *Intensive Care Med.* **2008**, *34*, 675–682. [CrossRef]
24. Depuydt, P.O.; Blot, S.I.; Benoit, D.D.; Claeys, G.W.; Verschraegen, G.L.; Vandewoude, K.H.; Vogelaers, D.P.; Decruyenaere, J.M.; Colardyn, F.A. Antimicrobial resistance in nosocomial bloodstream infection associated with pneumonia and the value of systematic surveillance cultures in an adult intensive care unit. *Crit. Care Med.* **2006**, *34*, 653–659. [CrossRef]
25. Depuydt, P.; Benoit, D.; Vogelaers, D.; Claeys, G.; Verschraegen, G.; Vandewoude, K.; Decruyenaere, J.; Blot, S. Outcome in bacteremia associated with nosocomial pneumonia and the impact of pathogen prediction by tracheal surveillance cultures. *Intensive Care Med.* **2006**, *32*, 1773–1781. [CrossRef]
26. Klompas, M. Prevention of Intensive Care Unit-Acquired Pneumonia. *Semin. Respir. Crit. Care Med.* **2019**, *40*, 548–557. [CrossRef]
27. CDC. Ventilator-Associated Event (VAE). 2023. Available online: www.cdc.gov/nhsn/pdfs/pscmanual/10-vae_final.pdf (accessed on 25 April 2024).
28. RcoreTeam. *R, a Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2016.

29. Wannigama, D.L.; Hurst, C.; Monk, P.N.; Hartel, G.; Ditcham, W.G.F.; Hongsing, P.; Phattharapornjaroen, P.; Ounjai, P.; Torvorapanit, P.; Jutivorakool, K.; et al. tesG expression as a potential clinical biomarker for chronic Pseudomonas aeruginosa pulmonary biofilm infections. *BMC Med.* **2025**, *23*, 191. [CrossRef]
30. Abe, S.; Wannigama, D.L. Quick Sequential Organ Failure Assessment (qSOFA) and Performance Status Scoring Systems as Prognostic Predictors in Pneumococcal Community-Acquired Pneumonia. *Cureus* **2024**, *16*, e73201. [CrossRef]
31. Maertens, B.; Blot, S.; Veld, D.H.I.; Blot, K.; Koch, A.; Mignolet, K.; Pannier, E.; Sarens, T.; Temmerman, W.; Swinnen, W. Stepwise implementation of prevention strategies and their impact on ventilator-associated pneumonia incidence: A 13-Year observational surveillance study. *Intensive Crit. Care Nurs.* **2025**, *86*, 103769. [CrossRef]
32. Motowski, H.; Ilges, D.; Hampton, N.; Kollef, M.H.; Micek, S.T. Determinants of Mortality for Ventilated Hospital-Acquired Pneumonia and Ventilator-Associated Pneumonia. *Crit. Care Explor.* **2023**, *5*, e0867. [CrossRef]
33. Rocha, L.A.; Marques Ribas, R.; da Costa Darini, A.L.; Gontijo Filho, P.P. Relationship between nasal colonization and ventilator-associated pneumonia and the role of the environment in transmission of Staphylococcus aureus in intensive care units. *Am. J. Infect. Control* **2013**, *41*, 1236–1240. [CrossRef] [PubMed]
34. Tsay, T.-B.; Jiang, Y.-Z.; Hsu, C.-M.; Chen, L.-W. Pseudomonas aeruginosa colonization enhances ventilator-associated pneumonia-induced lung injury. *Respir. Res.* **2016**, *17*, 101. [CrossRef]
35. Spoto, S.; Daniel Markley, J.; Valeriani, E.; Abbate, A.; Argemi, J.; Markley, R.; Fogolari, M.; Locorriere, L.; Anguissola, G.B.; Battifoglia, G.; et al. Active Surveillance Cultures and Procalcitonin in Combination With Clinical Data to Guide Empirical Antimicrobial Therapy in Hospitalized Medical Patients With Sepsis. *Front. Microbiol.* **2022**, *13*, 797932. [CrossRef]
36. Brusselaers, N.; Labeau, S.; Vogelaers, D.; Blot, S. Value of lower respiratory tract surveillance cultures to predict bacterial pathogens in ventilator-associated pneumonia: Systematic review and diagnostic test accuracy meta-analysis. *Intensive Care Med.* **2013**, *39*, 365–375. [CrossRef]
37. Righi, E.; Aggazzotti, G.; Ferrari, E.; Giovanardi, C.; Busani, S.; Rinaldi, L.; Girardis, M. Trends in ventilator-associated pneumonia: Impact of a ventilator care bundle in an Italian tertiary care hospital intensive care unit. *Am. J. Infect. Control* **2014**, *42*, 1312–1316. [CrossRef]
38. Vacheron, C.H.; Lepape, A.; Savey, A.; Machut, A.; Timsit, J.F.; Comparot, S.; Courno, G.; Vanhems, P.; Landel, V.; Lavigne, T.; et al. Attributable Mortality of Ventilator-associated Pneumonia Among Patients with COVID-19. *Am. J. Respir. Crit. Care Med.* **2022**, *206*, 161–169. [CrossRef]
39. Ippolito, M.; Misseri, G.; Catalisano, G.; Marino, C.; Ingoglia, G.; Alessi, M.; Consiglio, E.; Gregoretti, C.; Giarratano, A.; Cortegiani, A. Ventilator-Associated Pneumonia in Patients with COVID-19: A Systematic Review and Meta-Analysis. *Antibiotics* **2021**, *10*, 545. [CrossRef]
40. Wicky, P.H.; Niedermann, M.S.; Timsit, J.F. Ventilator-associated pneumonia in the era of COVID-19 pandemic: How common and what is the impact? *Crit. Care* **2021**, *25*, 153. [CrossRef]
41. Wannigama, D.L.; Jacquet, A. NOD2-dependent BCG-induced trained immunity: A way to regulate innate responses to SARS-CoV-2? *Int. J. Infect. Dis.* **2020**, *101*, 52–55. [CrossRef]
42. Rad, S.M.A.H.; Wannigama, D.L.; Hirankarn, N.; McLellan, A.D. The impact of non-synonymous mutations on miRNA binding sites within the SARS-CoV-2 NSP3 and NSP4 genes. *Sci. Rep.* **2023**, *13*, 16945. [CrossRef]
43. Laing, A.G.; Lorenc, A.; del Molino del Barrio, I.; Das, A.; Fish, M.; Monin, L.; Muñoz-Ruiz, M.; McKenzie, D.R.; Hayday, T.S.; Francos-Quijorna, I.; et al. A dynamic COVID-19 immune signature includes associations with poor prognosis. *Nat. Med.* **2020**, *26*, 1623–1635. [CrossRef] [PubMed]
44. Hotchkiss, R.S.; Monneret, G.; Payen, D. Immunosuppression in sepsis: A novel understanding of the disorder and a new therapeutic approach. *Lancet Infect. Dis.* **2013**, *13*, 260–268. [CrossRef] [PubMed]
45. Maes, M.; Higginson, E.; Pereira-Dias, J.; Curran, M.D.; Parmar, S.; Khokhar, F.; Cuchet-Lourenço, D.; Lux, J.; Sharma-Hajela, S.; Ravenhill, B.; et al. Ventilator-associated pneumonia in critically ill patients with COVID-19. *Crit. Care* **2021**, *25*, 25. [CrossRef]
46. Ayzac, L.; Girard, R.; Baboi, L.; Beuret, P.; Rabilloud, M.; Richard, J.C.; Guérin, C. Ventilator-associated pneumonia in ARDS patients: The impact of prone positioning. A secondary analysis of the PROSEVA trial. *Intensive Care Med.* **2016**, *42*, 871–878. [CrossRef]

47. Vermeulen, H.; Hens, N.; Catteau, L.; Catry, B.; Coenen, S. Impact of the COVID-19 pandemic on community antibiotic consumption in the EU/European Economic Area: A changepoint analysis. *J. Antimicrob. Chemother.* **2023**, *78*, 2572–2580. [CrossRef]
48. Önal, U.; Tüzemen, Ü.; Kazak, E.; Gençol, N.; Souleiman, E.; İmer, H.; Heper, Y.; Yılmaz, E.; Özakın, C.; Ener, B.; et al. Effects of COVID-19 pandemic on healthcare-associated infections, antibiotic resistance and consumption rates in intensive care units. *Le Infez. Med.* **2023**, *31*, 195–203. [CrossRef]