Study Title: Implementation of a Diagnostic Stewardship Bundle for Ventilator-associated Pneumonia among Mechanically-ventilated patients: a Pilot/Feasibility trial

National Clinical Trial (NCT) Identified Number: NCT05176353

Principal Investigator: Owen Albin, MD

Protocol Version IRB Approval Date: 3/4/2024

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Protocol Number: 1

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Principal Investigator: Owen Albin, MD

Sponsor: University of Michigan Medical School

Grant Title: CATALYST award

Grant Number: N/A

Funded by: Michigan Institute for Clinical & Health Research

Version Number: v1.2

2022-03-22

AMENDMENTS

Date	Version	Section(s)	Changes
22-Mar-2022	1.2	5, 1.3	Modified study timeline to reflect phased roll out of study interventions. Removal of study endpoints.

STATEMENT OF COMPLIANCE

This trial will be conducted in accordance with the protocol, Michigan Institute for Clinical & Health Research (MiCHR) Terms and Conditions of Award, applicable local and federal regulatory requirements and best research practices. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

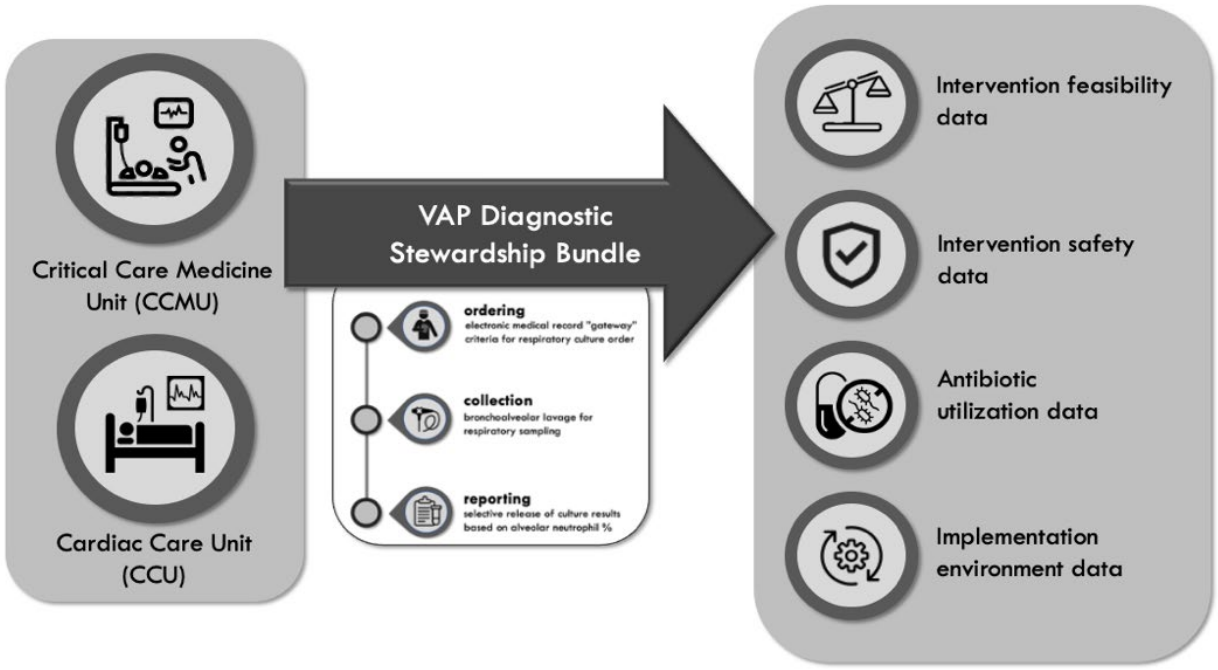
1 PROTOCOL SUMMARY

1.1 SYNOPSIS

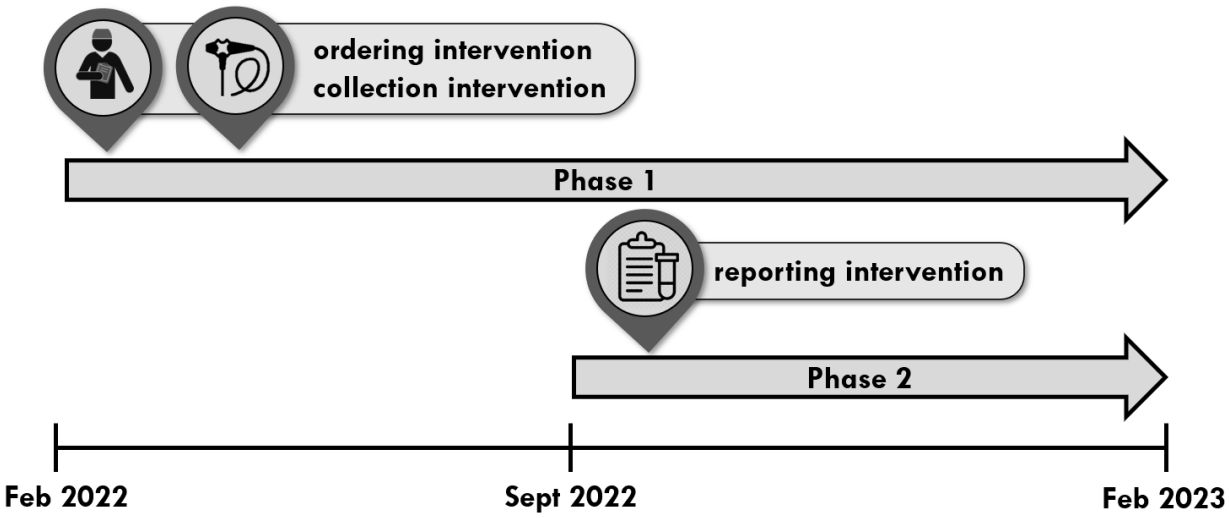
Title:	Implementation of a Diagnostic Stewardship Bundle for Ventilator-associated Pneumonia among Mechanically-ventilated patients: a pilot/feasibility trial.
Grant Number:	Not applicable
Study Description:	A pilot/feasibility trial to evaluate the safety and efficacy of a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle. Trial ICUs will sequentially implement interventions targetting the respiratory culture diagnostic testing pathway to minimize diagnostic error and overtreatment of ventilator-associated pneumonia.
Objectives:	Primary Objective: To determine the safety of a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle. Secondary Objectives: - To determine the association between a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle and ICU antibiotic utilization rates. - To determine the associated between a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle and rates of positive respiratory cultures. To assess study feasibility and adherence to protocolized intervention.
Endpoints:	Primary Endpoints: - Mortality per 1000 mechanically-ventilated patient days - Ventilator-associated events (using Centers for Disease Control/National Healthcare Safety Network definitions) per 1000 patient days - Median duration of mechanical ventilation per patient. Secondary Endpoints: - Positive respiratory cultures per 1000 mechanically-ventilated patient days. - Total ICU antibiotic utilization rates (total antibiotic days of therapy per 1000 mechanically-ventilated patient days). - Broad-spectrum ICU antibiotic utilization rates (broad-spectrum antibiotic days of therapy per 1000 mechanically-ventilated patient days). - Respiratory cultures ordered per 1000 patient days. - Percentage of respiratory cultures obtained by BAL. - Percentage of respiratory cultures from BAL samples with alveolar neutrophils <50% (for Phase 2 only)
Study Population:	All mechanically-ventilated patients hospitalized within Michigan Medicine Cardiac Care Unit (CCU) and Critical Care Medicine Unit (CCMU).

Phase or Stage:	Pilot/feasibility trial of a population-based intervention.
Description of Sites/Facilities Enrolling Participants:	2 Michigan Medicine Intensive Care units.
Description of Study Intervention/Experimental Manipulation:	A multi-faceted diagnostic stewardship bundle targeting the ventilator-associated pneumonia respiratory culture testing pathway. Three interventions will be operationalized in sequential intervals at the following phases of the diagnostic testing pathway: ordering, collection, and reporting.
Study Duration:	2 years.
Participant Duration:	Not applicable.

1.2 SCHEMA



1.3 STUDY TIMELINE



2 INTRODUCTION

2.1 STUDY RATIONALE

Indiscriminate use of antibiotics is a leading cause of adverse drug events and a catalyst for emergence of multidrug-resistant organisms (MDROs), which account for 2.8 million infections and 37,000 deaths annually in the US.[1,2] Antimicrobial stewardship programs are instrumental in curbing antibiotic overuse, but their reach into intensive care units (ICUs)—where antibiotic resistance is most prevalent and problematic—is limited.[3-5] Treatment for suspected respiratory infection, in particular, ventilator-associated pneumonia (VAP), accounts for 50-70% of antibiotic use within ICUs.[6-9] Studies using multidisciplinary expert case review or autopsy findings as reference gold standards demonstrate that a majority of ICU patients treated for VAP are misdiagnosed, resulting in excessive and often unnecessary antimicrobial exposure, adverse drug events, and generation of MDROs.[10-13] **There is a pressing need to identify strategies to reduce unnecessary antibiotic use against misdiagnosed VAP in ICUs.**

2.2 STUDY BACKGROUND

Antibiotic overuse is an increasingly recognized problem in intensive care units (ICUs).[9,14] A recent multinational point-prevalence study of 1150 ICUs determined that 70% of patients surveyed were receiving antibiotics; only 54% of these patients had suspected or proven infection and only 35% had positive microbiologic cultures supporting a definitive diagnosis of infection.[15] Excess antibiotic use catalyzes the acquisition and spread of multidrug-resistant organisms (MDROs), which have risen precipitously within ICUs in recent decades and are associated with excess morbidity, mortality, and healthcare expense.[16-23] Antibiotic overuse is also associated with adverse patient outcomes, including *Clostridioides difficile* infection, drug toxicity, and incident sepsis, as well as increases in healthcare costs and length of stay.[24-28]

Treatment for suspected respiratory infection—in particular, ventilator-associated pneumonia (VAP)—accounts for 50-70% of antibiotic use within ICUs.[6-9] **Multidisciplinary case review and autopsy studies demonstrate that a substantial number of ICU patients treated for VAP are misdiagnosed, resulting in significant antimicrobial overuse**.[10-13,29,30] For example, a multidisciplinary review of 231 cases diagnosed and treated as VAP in 6 ICUs at Johns Hopkins Hospital determined that antibiotics were not indicated in 59% of cases at the time of diagnosis, resulting in 1,183 days of unnecessary antibiotic use over 1 year.[10] A similar multidisciplinary review of surgical ICUs at Johns Hopkins Hospital found that fewer than 25% of patients empirically treated for postoperative VAP met standardized criteria for infection, accounting for 1,460 days of inappropriate antibiotic therapy over 1 year.[11] At Michigan Medicine University Hospital, a review of patients with positive respiratory cultures who were treated for nosocomial pneumonia determined that 34% were misdiagnosed, account for a median of 12 excess days of unnecessary antibiotics per patient.[30]

Most efforts to curb inappropriate VAP-directed antibiotic use have focused on therapeutic processes, namely antibiotic discontinuation or de-escalation strategies, for patients with an established VAP diagnosis.[31-39] These strategies have been largely unsuccessful in curbing antibiotic overuse. To date, no efforts have instead addressed the diagnostic process for VAP—interventions targeting the pathway of ordering, collection, and reporting of diagnostic tests to proactively avert unnecessary antibiotic use in patients with low pretest probabilities of infection (Figure 1).[40] Interventions targeting the diagnostic testing pathway for infectious syndromes—collectively termed diagnostic stewardship approaches—have been shown to avert unnecessary antibiotic treatment of conditions such as asymptomatic bacteriuria and *Clostridioides difficile* colonization but remain unexplored in VAP.[40-49]

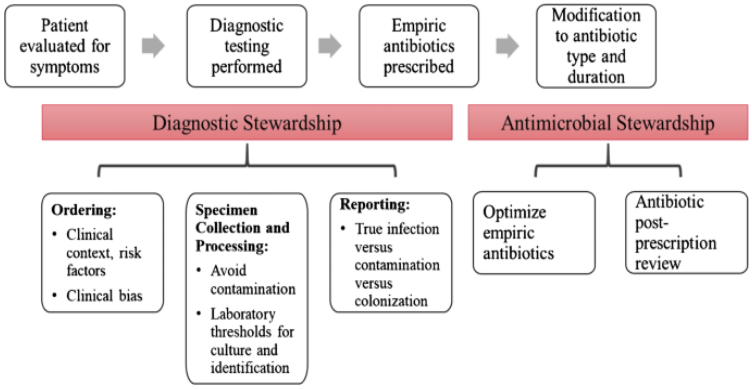


Figure 1: Schematic Representation of Diagnostic vs Antimicrobial Stewardship.

A foundational component of the VAP diagnostic pathway is the collection and interpretation of respiratory cultures. Positive respiratory cultures inform the diagnostic probability of VAP, but by themselves are not synonymous with infection, owing to the high burden of bacterial colonization of endotracheal tubing and distal lung parenchyma in critically ill patients.[50-53] Respiratory bacterial colonization with pathogenic organisms has been reported in over 50% of patients requiring intensive care and in up to 90% of patients with prolonged ventilator-dependence.[52,53] Indeed, advances in microbiologic techniques have shown that the lungs, once considered sterile, in fact house diverse bacterial communities.[54] **Contemporary respiratory culturing practices frequently identify bacteria from the respiratory tract of critically-ill patients without pneumonia and are a major factor in incenting unnecessary antibiotic use**.[10,39,55] Novel interventions targeting the respiratory culture testing pathway therefore represent an attractive and, to date, unexplored target for stewardship interventions to proactively decrease antibiotic use.

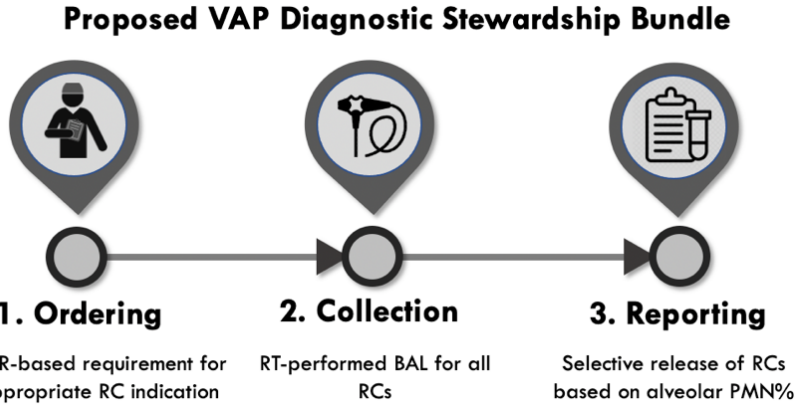


Figure 2. VAP Diagnostic Stewardship Bundle. EMR=electronic medical record, RC=respiratory culture, RT=respiratory therapist, PMN%=polymorphonuclear cell percentage of alveolar cytology

Using an approach patterned on validated diagnostic stewardship interventions for asymptomatic bacteriuria, **our group has identified interventions at each of the three phases of the VAP microbiologic diagnostic pathway (test ordering, sample collection and result reporting) to lower antibiotic overuse among mechanically-ventilated patients (Figure 2, see details below):**

1. Ordering (preanalytic) phase:

- *Current state:* At present, there are no preconditions for ordering respiratory cultures; as a result, respiratory cultures are often ordered indiscriminately and in scenarios of uncertain or low utility: for surveillance purposes following tracheostomy placement, following transient clinical decompensations which resolve expediently with supportive care (i.e. mucous plugging events), for isolated changes in endotracheal secretion character, as as part of a "pan-culture" workup in response to fever or leukocytosis.[30,56,57,58] We have demonstrated that these practices incent unnecessary antibiotic use and are common at our institution.[30] Additionally, approximately 10% of respiratory cultures ordered in ICUs are "repeat cultures"—tests that are drawn within 72 hours of an identical test (internal data).

  While a positive respiratory culture in the context of fever informs the diagnostic probability of pneumonia, it is exceedingly unlikely to indicate VAP in patients without localizing pulmonary features of infection. For example, if one assumes a VAP prevalence of 10% among mechanically-ventilated patients,[21] those with fever but without new radiographic infiltrates, alterations in gas exchange or purulent sputum have a pretest probability of VAP prior to respiratory culture of 2.6%; a positive respiratory culture would increase the posttest probability of VAP to 3.7%, rendering the test minimally beneficial at best.[50] Our group has shown that procuring respiratory cultures in patients identified above is associated with excessive antibiotic utilization within just one week of respiratory culture collection.[59]

2. Collection (analytic) phase:

- *Current state:* There is wide variability in ICU practice patterns for acquiring respiratory specimens. 60% of respiratory cultures in ICUs at our institutional are obtained from proximal lung samples, most frequently via endotracheal aspiration (ETA). ETAs are convenient to acquire, but growth of microorganisms from ETA adds little to the diagnostic specificity of VAP, as pathogenic organisms often colonize endotracheal material within hours of intubation.[60-62] ETA samples demonstrate low concordance with organisms isolated from the lung itself in both animal models and human studies.[62,63] Distal lung sampling, via bronchoalveolar lavage (BAL), offers the advantage of directly sampling the alveolar space and can be performed without bronchoscopic guidance by Respiratory Therapists at Michigan Medicine for equivalent supply and labor cost to ETAs. In multiple randomized controlled trials, use of BAL rather than ETA for respiratory collection in suspected VAP has been associated with lower rates of antibiotic use, without increased rates of mortality or ventilator-dependence.[64-67]

3. Reporting (postanalytic) phase:

- *Current state:* Physicians routinely utilize the number and proportion of white blood cells recovered from bodily fluid to determine the significant of positive culture results (for example, this is considered standard of care in ascites fluid, pleural fluid and urine). Using this data from clinical specimens helps providers to differentiate infection from contamination when a clinical culture grows bacteria. For example, if a patient grows bacteria from a urine specimen, but the patient's urine has few to no white blood cells present, it virtually assures that the bacteria recovered is not causing a clinical infection. In a VAP enriched population of 851 ICU patients, our collaborators have demonstrated that BAL neutrophil percentage <50% has a negative predictive value of 92% for ruling out VAP.[68] Autopsy studies have similarly shown that BAL neutrophil percentage <50% approaches a sensitivity of 100% in ruling out infection.[69] Despite this, alveolar neutrophilia has never been adopted for diagnostic stewardship purposes. Similarly, all respiratory cultures include

a gram stain to identify bacteria under a microscope. If one assumes a VAP prevalence of 20-30%, the negative predictive value of a negative gram stain for VAP diagnosis is 91%. Despite this, negative gram stains are not routinely used by providers to inform interpretation of respiratory cultures.

The manner in which test results are reported by microbiology labs has been shown to significantly impact antibiotic use. Strategies such as "cascading" and selective reporting of antimicrobial susceptibility results, adding comments to microbiologic test results (to "nudge" providers towards appropriate antimicrobial prescriptions), and censoring tests results in certain clinical scenarios (such as growth of likely contaminant organisms from blood cultures or growth of pathogenic bacteria in urine without pyuria) have all shown success as diagnostic stewardship strategies.[41,70]

Our goal is to conduct a pilot/feasibility trial of this VAP diagnostic stewardship bundle within Michigan Medicine ICUs to 1) demonstrate concept feasibility, 2) gauge and address protocol adherence, and 3) collect preliminary data pertaining to intervention efficacy and safety. **A successful VAP diagnostic stewardship bundle has the potential to significantly lower inappropriate ICU antibiotic use and consequent rates of antimicrobial resistance while simultaneously providing an innovative blueprint for future ICU stewardship interventions.**

3 RISK/BENEFIT ASSESSMENT

3.1.1 Known Potential Risks

This study's intervention is aimed at reducing overtesting/overdiagnosis and their consequent harms to patients. A potential concern for any intervention aimed at lowering overdiagnosis is the possibility of *underdiagnosis*. This is of particularly importance for VAP which is a condition associated with substantial morbidity and mortality.[21] Expedient performance of respiratory cultures and receipt of susceptibility test results is a key component of VAP management and delays in effective antimicrobial therapy are important determinants of outcomes.[71,72]

3.1.2 Known Potential Benefits

Reduction of unnecessary antibiotic use has been associated with significant benefits to patients and healthcare systems. For patients, these include lower rates of *Clostridioides difficile* infection, adverse drug events and incident sepsis. For healthcare systems, reduction of unnecessary antibiotic use has been consistently associated with decreases in hospital-wide rates of multi-drug resistant organisms, as well as hospital costs and inpatient lengths of stay.

3.1.3 Assessment of Potential Risks and Benefits

While the possibility of underdiagnosis VAP is a theoretical concern, this trial does **not** prohibit ordering of diagnostic tests, prescription of antibiotics or microbiology lab culture workflows. Rather, it 1) utilizes behavioral "nudges" to disincentivize ordering diagnostic tests which do not meaningfully alter Bayesian diagnostic probability; 2) improves/standardizes sampling methods for respiratory cultures to decrease the frequency of false positive test results; and 3) provides frontline providers with data (degree of alveolar neutrophilia) to better inform culture interpretation and management decisions. All of these interventions components are within what is considered the standard of care and supported by expert consensus guidelines to inform clinical decision making, however they have not been

operationalized/implemented in a standardized fashion as proposed by this study.[9,10] Counterbalanced with the significant harms of overuse of antibiotics, on the whole the potential benefits of this study intervention significantly outweigh its potential risks.

This study's endpoints have been calibrated to reflect safety concerns and will track rates of mortality, ventilator usage and ventilator-associated events to monitor for important safety signals. Importantly, systematic reviews of other antimicrobial stewardship interventions in ICUs (predominantly prospective audit and feedback) have shown stewardship interventions to be safe.[73] In total, there are multiple *immediate* potential benefits to patients exposed to this intervention and the potential *long-term* benefits to patients from information gained from this trial are significant.

4 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To determine the safety of a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle.	*Mortality per 1000 mechanically-ventilated patient days* *Ventilator-associated events (using Centers for Disease Control/National Healthcare Safety Network definitions) per 1000 patient days* *Median duration of mechanical ventilation per patient.*	*The goal of this study is to demonstrate preliminary safety of a diagnostic stewardship bundle for ventilator-associated pneumonia.*
Secondary		
To determine the association between a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle and ICU antibiotic utilization rates.	*Total ICU antibiotic utilization rates (total antibiotic days of therapy per 1000 mechanically-ventilated patient days).* *Broad-spectrum ICU antibiotic utilization rates (broad-spectrum antibiotic days of therapy per 1000*	*Our preliminary data suggests that a bundled diagnostic stewardship intervention can successfully reduce antibiotic use in mechanically-ventilated patients.*

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
	mechancially-ventilated patient days).	
To determine the association between a multi-faceted ventilator-associated pneumonia diagnostic stewardship bundle and rates of positive respiratory cultures.	*Positive respiratory cultures per 1000 mechanically-ventilated patient days.*	
To assess study feasibility and adherence to protocolized intervention.	*Respiratory cultures ordered per 1000 mechcanically-ventilated patient days* *Percentage of respiratory cultures obtained by BAL* *Percentage of respiratory cultures from BAL samples with alveolar neutrophils <50%*	Adherence to study intervention is crucial to evaluating study efficacy and potentially recalibrating approach to intervention prior to multi-center implementation.

5 STUDY DESIGN

5.1 OVERALL DESIGN

We plan to conduct a quasi-experimental, single-arm pilot/feasibility trial of a VAP diagnostic stewardship bundle in the MM Critical Care Medicine Unit (CCMU) and Cardiac Care Unit (CCU). This is a population-based rather than individual intervention. Both the CCMU and CCU will designate team leaders (one faculty member, fellow, and unit nurse), who will be instructed on study design and rationale, to disseminate study information and education in concert with study PI to colleagues through use of infographics and powerpoint-based sessions.

The study intervention will consist of interventions at all 3 phases of the diagnostic testing pathway (see Section 7 for full details). The bundle's first two interventions (ordering & collection phase interventions) will be implemented at the onset of the study period. The final bundled intervention (reporting phase) will be implemented 6 months after study onset (see Study Timeline (section 1.2)).

5.2 Scientific Rationale for Study Design

The majority of antimicrobial stewardship interventions are system-based interventions, operationalized at the level of individual hospital, hospital units or outpatient clinics. Thus, quasi-experimental pre/post study designs are a widely utilized and validated approach for studies of large-scale antimicrobial stewardship interventions.

5.3 Justification for Intervention

VAP is overdiagnosed and overtreated, resulting in ICU antibiotic overuse which degrades patient care. Novel antimicrobial stewardship approaches to combat ICU antimicrobial overuse are required.

5.4 End-of-Study Definition

The study will conclude after 1 year of intervention operationalization (February 2023).

6 STUDY POPULATION

6.1 Inclusion Criteria

This pilot/feasibility trial will occur within the Michigan Medicine Cardiac Care Unit (CCU, 7D) and the Michigan Medicine Critical Care Medicine Unit (CCMU, 6D). This study will not be screening or enrolling individual patients, but rather instituting system-based interventions in the diagnostic testing workflow that providers engage with as part of routine clinical care. Study subjects in this trial are therefore all patients hospitalized in the aforementioned Michigan Medicine ICUs during the study period requiring invasive mechanical ventilation, as well as healthcare providers providing care to said patients in the aforementioned ICUs during the study period.

6.2 Exclusion Criteria

For the study intervention requiring performance of bronchoalveolar lavage rather than endotracheal aspirate for respiratory culture collection, the following are exclusion criteria for performance of bronchoalveolar lavage: INR>2, platelet count <50, gross blood in endotracheal secretions, P/F ratio<80, major lung surgery in prior 30 days. There are no exclusion criteria for study interventions at the ordering and reporting phases of the diagnostic testing pathway.

7 STUDY INTERVENTION(S)

7.1 Study Intervention(s) Administration

7.1.1 Study Intervention Description

This study's VAP diagnostic stewardship bundle will include interventions that occur at discrete phases in the diagnostic testing pathway: 1) the *preanalytic phase,* in which tests are ordered; 2) the *analytic*

phase, in which diagnostic specimens are collected and laboratory tests are performed; and 3) the *postanalytic phase*.

Trial Interventions

Diagnostic Testing Phase	Intervention	Implementation method	Details
Respiratory culture ordering	CDS tool requiring providers to select a **valid indication for respiratory culture performance**: • New radiographic infiltrate on CXR or chest CT • Purulent endotracheal secretions • Worsening PEEP and/or FiO2	Interruptive EHR alert triggered upon respiratory culture order, tagged to custom CDS order set.	The following prompts were given to providers using the CDS order set: • *Fever or leukocytosis without aforementioned culture indications is unlikely to indicate pneumonia.* • *Radiographic infiltrates consistent with atelectasis or pulmonary edema do not require respiratory cultures.* • *Purulent secretions are different than thickened or increased nonpurulent secretions (the latter do not require cultures).* • *Transient worsening of PEEP or FiO2 that rapidly improves is unlikely to indicate pneumonia*
Respiratory culture collection	CDS tool requiring providers to **use non-bronchoscopic BAL** (performed by respiratory therapists) when no contraindications present. All BAL specimens automatically sent for **quantitative respiratory culture & cell count/differential**.	Interruptive EHR alert triggered upon respiratory culture order, tagged to custom CDS order set	Contraindications to BAL were as follows: • *major lung surgery in prior 30 days* • *gross blood in endotracheal secretions* • *INR>2* • *platelet count <50k* • *P/F ratio <80.* Consideration of bronchoscopy was recommended for sampling upper lobe infiltrates.
Respiratory culture result reporting	Respiratory culture results **automatically released in EHR only for BAL samples with a PMN% of >50%**. Respiratory culture results for BAL samples with PMN% <50% released upon direct primary team request to Clinical Microbiology Lab.	Modification to Clinical Microbiology Laboratory workflows.	The following prompt was provided for suppressed respiratory culture results: • *"Culture results suppressed due to <50% PMNs seen in BAL, which has a sensitivity of 95% for diagnosis of bacterial pneumonia in non-neutropenic patients. Please call the Microbiology Laboratory within 7 days if identification/antimicrobial susceptibility testing are needed."*

CDS=clinical decision support; EHR=electronic health record; CXR=chest X-ray; CT=computed tomography; BAL=bronchoalveolar lavage; PMN%=percentage of polymorphonuclear neutrophils observes on BAL cell count/differential.

1. **Ordering (preanalytic) phase:**
    - *Study intervention:* In participating ICUs, all providers who order respiratory cultures will be automatically routed to a custom study order set within the electronic medical record. This order set will require providers to select a valid clinical indication for respiratory culture performance (worsening hypoxia, new infiltrate on chest imaging, purulent sputum production), but will not include aforementioned scenarios in which respiratory culture collection is *not* indicated (fever or leukocytosis without features localizing infection to the respiratory tract, changes in secretions that are *not* purulent, transient respiratory decompensations that rapidly improve without supportive care.
2. **Collection (analytic) phase:**
    - *Study intervention*: In participating ICUs, all providers who order respiratory cultures will be automatically routed to a custom study order set within the electronic medical record. This order set will require physician or RT-guided BAL for respiratory collection rather than endotracheal aspiration for mechanically-ventilated patients, provided there are no specific exclusion criteria for individual patients (see Section 4.1 for specific patient exclusion criteria). Importantly, Respiratory Therapists are trained in the use of BAL for respiratory collection and routinely perform these procedures hundreds of times a year for precisely

this purpose. Performance of BAL is considered standard of care by national and international VAP expert guidelines.[9,10]

3. **Reporting (postanalytic) phase:**
    - *Study intervention:* In participating ICUs, all providers who order respiratory cultures will be automatically routed to a custom study order set within the electronic medical record. This order set will require performance of BAL for all patients without exclusion criteria (see Section 4.1) in whom respiratory cultures are ordered. The order set will include not only an order for respiratory culture from BAL (performed by the Michigan Medicine Clinical Microbiology lab), but also a BAL cell count and differential. The Michigan Medicine Clinical Microbiology lab will work up all respiratory cultures according to current practices, but will not release the culture reports to providers for samples in which the BAL neutrophil % is less than 50%. When providers examine the culture result in the electronic medical record, an automated message will indicate that the BAL neutrophil % is low on the sample, making pneumonia exceedingly unlikely. Providers will be informed in this automated message that they can call the Michigan Medicine Clinical Microbiology lab and manually request release of the results if they feel it is indicated.

7.2 FIDELITY

7.2.1 Provider Training

Providers will be counseled on CDST use during bimonthly educational sessions over a 3-month trial rollout period and via subsequent monthly email reminders thereafter. Each ICU will designate a nursing and physician champion to facilitate implementation.

7.2.2 Intervention Delivery

Interventions 1 and 2 will be operationalized through an interruptive clinical decision support tool, triggered within the electronic health record whenever a respiratory culture is ordered in a mechanically-ventilated study ICU patient. Intervention 3 will be operationalized through modifications in Clinical Laboratory workflows.

8 END-OF-INTERVENTION/END-OF-STUDY

8.1 DISCONTINUATION OF INTERVENTION

The full diagnostic stewardship intervention will be discontinued at the primary study completion date (February 2023). The study interventions will also be halted for prespecified increases in adverse safety outcomes (noted previously).

9 STATISTICAL CONSIDERATIONS

9.1 GENERAL STATISTICAL APPROACH

9.1.1 Descriptives

We will compare categorical variables by reporting frequencies and percentages and assess statistical significance using a chi-square test. Subject-level continuous variables will be compared compared using Kruskal-Wallis tests. Rate variables (e.g., deaths per 1,000 MVPDs) will be compared using a z-score test.

9.1.2 Hypotheses

The primary study hypothesis was that implementation of a bundled DSI targeting the respiratory culturing pathway would not associate with significant increases in adverse safety outcomes.

The secondary study hypotheses were that implementation of a bundled DSI targeting the respiratory culturing pathway would associate with reductions in rates of respiratory culture positivity (RCP) and ICU-antimicrobial utilization rates (ICU-AURs).

9.2 ANALYSIS OF THE PRIMARY AND SECONDARY ENDPOINT(S)

Primary and secondary study outcomes will be compared between patient cohorts before and after DSI implementation. All primary/secondary study outcomes will compare patients admitted to study ICUs over the course of the year-long study intervention (Feb 2022-23) versus those admitted in the pre-intervention historical control period (Feb 2017-22). As above, rate variables will be compared using a z-score test. A p-value of 0.05 will be utilized for statistical significance.

9.3 EXPLORATORY ANALYSES

In addition to unadjusted pre- vs post- outcome comparisons, we will utilize additional analytic approaches to explore exposure-outcome relationships between the study DSI and ICU antimicrobial use. These will include: 1) interrupted time series analyses of rates at the calendar month level to account for changes in temporal trends antecedent to the time of the intervention, 2) individual subject-level negative binomial analyses with a covariate for admitted pre vs. post intervention date.
For the interrupted time series analysis, will treat each calendar month (beginning as the unit of analysis. Each month will have an average antibiotic DOT per mechanically-ventilated patient per day. Linear regression will be used to model change over time, as well as an interaction for the change over time before and after the start of the trial intervention date.

Subject-level analyses will also be performed to account for confounding clinical variables impacting ICU antimicrobial use. We will utilize patient-level data from pre-intervention historical control data to construct a multivariate model predictive of ICU-AURs. For these analyses, all study subjects will have a calculated rate of ICU-AURs (e.g., total antibiotic DOTs on mechanical ventilation divided by total number of person days on mechanical ventilation). Multiple imputation using fully conditional specification will be performed to create 25 imputation data sets to account for missing data, and negative binomial regression models were constructed for each data set using backwards selection. Covariates will be retained in a final multivariate master model if they are retained in 100% of negative

binomial regression models, after evaluation for multicollinearity. Admission before or after the study intervention will then be to the final model as a covariate to determine the independent effect of the study intervention on antibiotic use.

9.4 OTHER ANALYSES

9.4.1 Safety Analyses

This study will utilize a Data and Safety Monitoring Board (DSMB) comprised of study personnel (the study PI, biostatistician, and ICU medical directors, Drs. Hyzy and Thomas), as well as an independent medical monitor (Dr. Keith Kaye, Chief of Division of Allergy, Immunology and Infectious Diseases at Robert Wood Johnson University Hospital). Dr. Kaye has served on data safety and monitoring committees for multiple federally- and industry-funded clinical trials, many of which have involved the study of ventilator-associated pneumonia.

The DSMB will meet every two months to review the following safety metrics: 1) Mortality per 1000 mechanically-ventilated patient days per ICU, Ventilator- associated events (using Centers for Disease Control/National Healthcare Safety Network definitions) per 1000 mechanically-ventilated patient days per ICU, Median duration of mechanical ventilation per patient per ICU. All safety outcomes will be compared to preintervention ICU data collected over the last 5 years to ensure that postintervention values fall within 2 standard deviations of preintervention controls. The study will be halted if any safety outcome is increased by more than 2 standard deviations relative preintervention control data. If safety outcomes are decreased by more than 2 standard deviations relative to preintervention control data (i.e. in a favorable direction following the intervention), the study intervention will be continued as this is a single-arm study trial design.

9.4.2 Sub-Group Analyses

We will also perform a series of prespecified confirmatory subgroup analyses for all study outcomes, stratified by individual study ICU and DSI implementation phase (for the latter, in order to account for seasonality, outcomes in the post-intervention cohort were compared to historical control patients admitted to study ICUs during analogous months in the pre-intervention control period).

10SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 CONFIDENTIALITY AND PRIVACY

10.1.1 Data sharing

Sharing of data generated by this project is an essential part of our proposed activities and will be carried out in several different ways. We would wish to make our results available both to the community of scientists interested in ventilator-associated pneumonia to avoid unintentional

duplication of research. Conversely, we would welcome collaboration with others who could make use of protocols developed in this project. Data generated from this projects will be shared at national meetings and conferences and in peer-reviewed publications.

We will share the final data in accordance with NIH policy. The final dataset will be stripped of patient identifiers prior to release for sharing. Because of the remote possibility of deductive disclosure of subjects' identities, we will make data available to interested parties under a data sharing agreement that includes commitments to the following: (a) use of data for research purposes only; (b) use of appropriate electronic safeguards to ensure information security; (c) destruction or return of the data after the analysis has been completed; (d) agreement to not use data for any commercial purposes; and (e) agreement to not redistribute the data to third parties. Interested parties will be able to request access to unpublished data from the Principal Investigators by email using the following contact information: oalbin@med.umich.edu.

10.2 SAFETY OVERSIGHT

10.2.1 Key Roles and Study Governance

Principal Investigator	**Medical Monitor or Independent Safety Monitor**
Owen Albin, MD, Assistant Professor of Medicine	*Keith Kaye, MD, MPH, Professor of Medicine and Chair of the Division of Allergy, Immunology & Infectious Diseases*
University of Michigan Medical School	*Robert Wood Johnson School of Medicine*
1500 E. Medical Center Drive, Ann Arbor, MI 48109	*125 Paterson St, New Brunswick, NJ 08901*
734-232-1871	*N/A*
oalbin@med.umich.edu	*Kk1116@rwjms.rutgers.edu*

10.3 QUALITY ASSURANCE AND QUALITY CONTROL

10.3.1 Data Handling and Record Keeping

All study data will be maintained on HIPPA-complaint, secure servers through the University of Michigan Advanced Research Computing (ARC) core.

11. REFERENCES

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