Derivation and Internal Validation of a Health Administrative Data Algorithm for Identifying Sepsis

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Abstract

Objectives: The primary objective was to externally validate a Canadian ICD-coded sepsis case definition developed by Jolley et al. by examining its sensitivity and specificity in health administrative data among intensive care unit (ICU) patients at The Ottawa Hospital (TOH). We also evaluated whether two modifications (the addition of antimicrobial information and the removal of infection-related ICD codes) to the Jolley algorithm could improve sensitivity while maintaining specificity. The secondary objective was to examine the impact of these modifications on the algorithm's positive and negative predictive values.

Methods: We identified adults (18 years and older) admitted to TOH's Civic and General campus ICUs between April 1, 2014 and March 31, 2019. From this population, a random sample of 870 medical charts was selected for manual chart review, with sepsis positive and negative reference cases classified according to the Sepsis-3 criteria. Chart review data were linked to a health administrative dataset, containing pharmacy records, diagnosis and procedure codes. We then evaluated the sensitivity and specificity of the Jolley algorithm and its modified versions incorporating antimicrobial information and/or excluding infection codes.

Results: Among 10,407 eligible ICU patients, 833 of the 870 charts met the eligibility criteria. Of these, 391 patients met Sepsis-3 criteria through chart review, while 364 patients met Jolley sepsis criteria. The original Jolley algorithm had a sensitivity of 72.6% (95% CI: 69.6% - 75.7%) and specificity of 81.9% (95% CI: 79.3% - 84.5%). Incorporating antimicrobial information increased sensitivity to a range of 80.8% (95% CI: 78.1%- 83.5%) to 99.5% (95% CI: 99.0%-100.0%), but resulted in a marked decline in specificity, ranging from 12.2% (10.0%-14.4%) to 39.6% (95%

CI: 36.3%-42.9%). Removing infection-related ICD codes increased sensitivity to 83.4% (95% CI: 80.8%-85.9%) but further reduced specificity to 26.9% (95% CI: 23.9%-29.9%). Combining both modifications raised sensitivity to a range of 88.8% (95% CI: 86.6%- 90.9%) to 99.7% (95% CI: 99.4%-100.0%), while specificity dropped to 4.8% (95% CI: 3.3%- 6.2%) to 13.6% (95%CI: 11.2%-15.9%).

Conclusion: The Jolley algorithm demonstrated reasonable sensitivity and specificity in identifying sepsis patients among TOH ICU patients using administrative data. While adding antimicrobial information or removing infection codes substantially increased sensitivity, these modifications led to a marked decline in specificity. These findings highlight both the promise and limitations of using administrative data for sepsis surveillance and underscore the need for careful algorithm refinement to balance accuracy and utility.

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Abbreviations

WHO	World Health Organization
ICU	Intensive Care Unit
CIHI	Canadian Institute for Health Information
ICD	International Classification of Diseases
HAD	Health Administrative Data
ACCP/SCCM	American College of Chest Physicians and Society of Critical Care Medicine
SIRS	Systemic Inflammatory Response Syndrome
PaO_2	Partial pressure of oxygen in the arterial blood
FiO_2	Fraction of inspired oxygen
SaO_2	Arterial oxygen saturation
SOFA	Sequential Organ Failure Assessment
LMIC	Low and medium income countries
Sn	Sensitivity
Sp	Specificity
PPV	Positive Predictive Value
NPV	Negative Predictive Value
TOH	The Ottawa Hospital
TOHDW	The Ottawa Hospital Data Warehouse
MRN	Medical Record Number
IV	Intravenous
COPD	Chronic Obstructive Pulmonary Disease
CI	Confidence Interval

IQR	Interquartile Range
LOS	Length of Stay
ON	Ontario
QC	Quebec
CPAP	Continuous Positive Airway Pressure
BIPAP	Bilevel Positive Airway Pressure
MAP	Mean Arterial Pressure
P/F Ratio	Ratio of partial pressure of oxygen in arterial blood to the fraction of inspired oxygen
S/F Ratio	Ratio of arterial oxygen saturation to the fraction of inspired oxygen
TP	True Positive
FP	False Positive
TN	True Negative
FN	False Negative
rTPF	Relative True Positive Fraction
rFPF	Relative False Positive Fraction
AMA	Acute Monitoring Area

Chapter 1: Introduction

1.1 Overview of the Research Problem

Sepsis is life-threatening organ dysfunction caused by a dysregulated host response to an infection. As a major contributor to morbidity and mortality globally, sepsis has been listed as a key healthcare priority for the coming decade by the World Health Organization (WHO)[1]. A recently published meta-analysis of 51 population-level studies described the burden of sepsis on both community and hospital-acquired sepsis in 22 different countries and reported a pooled incidence of hospital-treated adult sepsis of 189 cases per 100,000 person-years and pooled incidence of ICU- treated sepsis of 58 per 100,000 person-years[2]. These estimates were derived from health administrative data (HAD), which has become the most increasingly utilized data source for epidemiological studies because it is readily available, population based, reasonably inexpensive and includes diagnosis codes assigned in different health care settings. However, the use of health administrative data requires thorough validation of case identification algorithms against a gold-standard method as these data are collected for the purpose of administering healthcare services or managing healthcare resources, and not specifically for disease surveillance or research purposes. Health administrative data are coded after a patient is discharged from the hospital; the medical chart is transferred to a health records department where trained non-clinical coders review the clinical notes and assign ICD (International Classification of Diseases) diagnostic codes and procedural codes based on the information documented in the medical chart.

Sepsis is a syndrome and includes a variety of symptoms, signs and laboratory features that occur over time as part of the clinical diagnosis. Hence coding for sepsis using health administrative data can be challenging since there is not one code to identify it.

Sepsis incidence estimates for Canada are outdated[3]. Utilizing a case definition for sepsis developed by CIHI (Canadian Institute for Health Information) in 2009, 30,587 sepsis hospitalizations were reported in Canada (excluding Quebec) in 2008-2009[3,4]. A validation study conducted in Canada by Jolley et al.[4] found that although the CIHI 2009 algorithm was highly specific for identifying ICU sepsis cases (98.7%), it lacked sensitivity (46.4%). These authors subsequently developed an optimized sepsis algorithm, which improved sensitivity by 25.5%, but reduced specificity by 13.3%[4]. Previously published validation studies show that there is a lack of consensus regarding which ICD codes should be used to define sepsis in health administrative data[5]. A wide range of sensitivities and specificities were reported, suggesting that existing ICD-coded sepsis definitions perform poorly in identifying sepsis. Additionally, the true incidence of sepsis was likely underestimated using ICD-coded case definitions, as sepsis is largely under-coded in administrative data[5].

Antimicrobials are administered to all patients who have a suspected infection clinically. Hence, the addition of antimicrobial usage information could potentially enhance the performance of ICD-based algorithms in identifying sepsis[6]. Despite existing studies evaluating the validity of ICD-coded sepsis definitions among the ICU patient population,[4,7–10] the specific contribution of antimicrobial information to these performance metrics has not been well established.

1.2 Objectives

The primary objectives of this thesis were to:

1. Validate the sensitivity and specificity of an existing sepsis identification algorithm developed by Jolley et al., using data from patients admitted to two academic ICUs in Ottawa.
2. Examine whether incorporating antimicrobial information into the existing Jolley algorithm improves the sensitivity while maintaining the specificity. Specifically, these included:

a) the presence of at least one antimicrobial order on a given day; and

b) the duration of antimicrobial orders

3. Assess whether further modification of the Jolley algorithm by adding antimicrobial information (as described in Objective 2) and removing ICD infection codes enhances sensitivity while maintaining specificity.

The secondary objective of this thesis was to:

1. Determine the impact of the above algorithm modifications (i.e., addition of antimicrobial information and/or the removal of infection codes) on the positive and negative predictive values of the Jolley algorithm (See appendix).

1.3 Hypotheses

1. The sepsis identification algorithm developed by Jolley et al will accurately identify sepsis cases among patients admitted to two academic ICUs in Ottawa with sensitivity and specificity comparable to those reported in its original validation study.
2. Incorporating antimicrobial information, including the presence of at least one antimicrobial order on a given day or a longer duration of antimicrobial orders, into the Jolley algorithm will improve the sensitivity without compromising specificity.

Chapter 2: Background and Literature Review

2.1 Sepsis Definitions

The first consensus definition for sepsis was published by the American College of Chest Physicians and Society of Critical Care Medicine (ACCP/ SCCM) in 1992, and described sepsis as the systemic inflammatory response to infection in a host. Infection was defined as "a pathological process caused by invasion of normally sterile tissue or fluid or body cavity by pathogenic or potentially pathogenic micro-organisms"[11]. Clinically, sepsis was identified by the presence of infection and two or more clinical features of systemic inflammatory response syndrome (SIRS), which include: a) body temperature greater than 38°Celsius or less than 36°Celsius, b) a heart rate greater than 90 beats per minute, c) a respiratory rate greater than 20 breaths per minute or arterial partial pressure of carbon dioxide of less than 32 mmHg, and d) a white blood cell count greater than 12000 per mm^3 or less than 4000 per mm^3 or more than 10% band cells on the blood count differential. To distinguish various levels of sepsis severity, severe sepsis was defined as sepsis associated with acute organ failure, hypoperfusion or hypotension and septic shock was defined as "sepsis-induced hypotension persisting despite adequate fluid resuscitation"[11].

As understanding of the pathophysiology of SIRS, sepsis and sepsis-related conditions improved, it was determined that the 1992 sepsis definition was overly sensitive and nonspecific, given that a variety of infectious and non-infectious processes have the potential to trigger SIRS[12]. Consequently, in 2001, the initial consensus definition was revised to include additional signs of inflammation in response to infection to diagnose sepsis[12,13]. The expanded list of signs and symptoms of sepsis were classified according to general, inflammatory, hemodynamic, organ

dysfunction and tissue perfusion parameters (Table 1). The definition of severe sepsis remained unchanged, while septic shock was defined as persistent hypotension with systolic blood pressure less than 90 mmHg or mean arterial blood pressure less than 70 mmHg, despite adequate fluid resuscitation[12].

Recognizing that suspected infection and two or more SIRS criteria combined did not reflect the increased risk of mortality associated with critical illness, the ACCP/SCCM convened to develop the third consensus definition (Sepsis-3) in 2015. The Sepsis-3 definition describes sepsis as "life-threatening organ dysfunction caused by dysregulated host response to infection". The classification of "severe sepsis" and the use of SIRS criteria were excluded from the diagnostic framework for sepsis, in accordance with this updated consensus definition[6].

Clinical criteria for diagnosing sepsis according to the Sepsis-3 consensus definition include the presence of infection and an acute increase in Sequential Organ Failure Assessment (SOFA) score of two or more points[6]. The SOFA score (Table 2) quantifies severity of organ dysfunction or failure according to clinical findings, laboratory data, or therapeutic interventions in critically ill patients. Each of six organ systems are scored from 0 (normal function) to 4 (most abnormal) based on the worse values for each day[14]. A higher SOFA score is therefore directly associated with an increased probability of in-hospital mortality[13,15]. Septic shock was also re-defined as "a subset of sepsis in which underlying circulatory and cellular or metabolic abnormalities are profound enough to substantially increase mortality". Septic shock was clinically diagnosed as sepsis with persisting hypotension requiring vasopressor therapy to maintain a mean arterial pressure (MAP) greater than or equal to 65 mmHg, and a serum lactate of at least 2 mmol/L despite adequate fluid

resuscitation. The Sepsis-3 criteria therefore adequately captures the increased mortality rate of more than 10% for sepsis and more than 40% for septic shock[13].

Table 1: Consensus Definitions for Sepsis

1992[11]	**2001**[12]	**2016**[6]
Sepsis: 1) Presence of infection; AND 2) Two or more of the following SIRS criteria: a) body temperature greater than 38°C or less than 36°C; b) a heart rate > 90 beats per minute; c) a respiratory rate > 20 breaths per minute or arterial partial pressure of carbon dioxide < 32 mmHg; d) a white blood cell count > 12000 per mm3 or < 4000 per mm3 or >10% band cells on the blood count differential **Severe Sepsis:** Sepsis associated with acute organ failure, hypoperfusion or hypotension, which may include, but are not limited to, lactic acidosis, oliguria, or acute alteration in mental status	**Sepsis:** 1) Documented or suspected infection; AND 2) Any of the following signs and symptoms: a) General parameters: o Fever (core temperature >38.3°C) o Hypothermia (core temperature <36°C) o Heart rate >90 bpm or >2 SD above the normal value for age o Tachypnea: >30 bpm o Altered mental status o Significant edema or positive fluid balance (>20 ml/kg over 24 h) o Hyperglycemia (plasma glucose >110 mg/dl or 7.7 mM/l) in the absence of diabetes b) Inflammatory parameters: o Leukocytosis (white blood cell count >12,000/μl) o Leukopenia (white blood cell count <4,000/μl) o Normal white blood cell count with >10% immature forms o Plasma C reactive protein >2 SD above the normal value o Plasma procalcitonin >2 SD above the normal value c) Hemodynamic parameters:	**Sepsis:** 1) Documented or suspected infection; AND 2) ΔSOFA score ≥ 2 **Severe Sepsis:** Deemed redundant and replaced with "Sepsis"

1992[11]	2001[12]	2016[6]
	○ Arterial hypotension (systolic blood pressure <90 mmHg, mean arterial pressure <70mmHg, or a systolic blood pressure decrease >40 mmHg in adults or <2 SD below normal for age) ○ Mixed venous oxygen saturation >70% ○ Cardiac index >3.5 min^{-1} m^{-2} d) Organ dysfunction parameters ○ Arterial hypoxemia (PaO_2/FIO_2 <300) ○ Acute oliguria (urine output <0.5 ml kg^{-1} h^{-1} or 45 mM/l for at least 2 h) ○ Creatinine increase ≥0.5 mg/dl ○ Coagulation abnormalities (international normalized ratio >1.5 or activated partial ○ thromboplastin time >60 s) ○ Ileus (absent bowel sounds) ○ Thrombocytopenia (platelet count <100,000/µl) ○ Hyperbilirubinemia (plasma total bilirubin >4 mg/dl or 70 mmol/l) e) Tissue perfusion parameters: ○ Hyperlactatemia (>3 mmol/l) ○ Decreased capillary refill or mottling **Severe Sepsis:** Same as 1991 consensus definition	

Table 2: Sequential Organ Failure Assessment (SOFA) Score

System	Score				
	0	1	2	3	4
Respiration PaO_2/FiO_2 (mmHg)	≥400	<400	<300	<200 with respiratory support	<100 with respiratory support
Coagulation Platelets ($x10^3/\mu L$)	≥150	<150	<100	<50	<20
Liver Bilirubin (μmol/L)	< 20	20-32	33-101	102-204	>204
Cardiovascular	MAP ≥ 70 mmHg	MAP < 70 mmHg	Dopamine < 5 or any dose dobutamine	Dopamine 5.1-15 or epinephrine ≤ 0.1 or norepinephrine ≤ 0.1	Dopamine > 15 or epinephrine >0.1 or norepinephrine >0.1
Central Nervous System Glasgow Coma Scale score	15	13-14	10-12	6-9	<6
Renal Creatinine (μmol/L) Urine output (mL/d)	<110	110-170	171-299	300-440 <500	>440 <200

*Table adopted from Singer et al. (2016)[6]

2.1.1 Challenges in Diagnosing Sepsis

As illustrated in Section 2.1, the clinical diagnosis of sepsis is a challenge as it is a syndrome without a specific diagnostic test to detect it. Sepsis definitions have been modified over time to improve its identification clinically, and for use in clinical trials and epidemiological studies. Sepsis is also heterogeneous, and can present differently across patients. This variability can further complicate its diagnosis.

2.2 Burden of Sepsis

2.2.1 Incidence of Sepsis

A recently published systematic review and meta-analysis by Fleischmann and colleagues of 51 population-level studies describing the burden of sepsis in 22 different countries reported the incidence of sepsis among hospital inpatients to be 189 cases per 100,000 person-years, and the incidence of ICU- treated sepsis to be 58 per 100,000 person-years[2]. Notably, there is a paucity of sepsis burden estimates from low and middle-income countries (LMICs), as high-income countries represented 46 out of the 51 included studies. However, Canada was not represented among the included studies from high-income countries. The most recent report on sepsis burden in Canada (excluding Quebec) by CIHI in 2009[3] indicated that sepsis hospitalizations increased from 26,803 hospitalizations in 2004–2005 to 30,587 hospitalizations in 2008-2009. Severe sepsis, including septic shock, was observed in 39.4%, or 12,063, of all sepsis hospitalizations in 2008-2009. These estimates were derived from health administrative data. However, a validation study conducted by Jolley et al. found that the CIHI ICD-coded sepsis case definition lacked sensitivity in both ICU and non-ICU patient populations. These authors subsequently developed an optimized sepsis case

definition with additional ICD codes for infection, which improved the sensitivity of the original CIHI sepsis definition by 17.9% to 65.1%[4].

2.2.2 Sepsis Mortality

Sepsis is recognized as a leading cause of death globally.[2,16] Fleischmann et al. also estimated that mortality for hospital-treated sepsis was 26.7%, while 41.9% of ICU-treated sepsis cases resulted in death prior to hospital discharge[2]. In 2009, CIHI reported severe sepsis mortality to be 38%, with sepsis accounting for 10.9% of all deaths occurring in Canadian hospitals (excluding Quebec)[3].

2.2.3 Economic Burden of Sepsis

Sepsis has been identified as a key contributor to healthcare expenditure worldwide.[17,18] The economic burden of sepsis in the United States (US) is estimated at over US$24 billion, accounting for 6.2% of total US hospitalization costs in 2013[1]. A recently published study estimated the yearly incremental cost of treating severe sepsis cases in Ontario at $29,238 per person, as compared to $9,475 for non-severe sepsis cases[17]. The epidemiological and economic burden of sepsis is likely much higher in LMICs, despite the lack of available data.

2.2.4 Quality of Life among Sepsis Survivors

Sepsis survivors often experience a significant decline in health-related quality of life (HRQoL) during ICU admission, with gradual improvement during the six-month period after ICU discharge, as compared to their pre-admission condition[18]. Sepsis survivors may experience a

quality of life similar to those who have survived other critical illnesses, and for some the impact of sepsis, could be even more severe. Older age, comorbidities and severity of sepsis are factors associated with a decline in quality of life among sepsis survivors.[3,19–22]

2.3 Identifying Sepsis in Health Administrative Data

2.3.1 Health Administrative Data

Sepsis burden estimates can be derived by utilizing various data sources, such as health administrative data or electronic medical records[5]. Health administrative data refers to information that are routinely created and collected whenever a service is rendered during patient encounters with healthcare services. Key information related to the encounter such as patient identifiers, diagnoses, services administered and date of service are captured. Health administrative data are not intended to be used for research, but for administrative purposes such as renumeration for doctors and hospitals for healthcare services provided, or for allowing hospitals to summarize each admission in compliance with legal requirements[23]. However, health administrative data are increasingly being used for surveillance purposes as it is less labour intensive than manual data abstraction, covers wide geographic areas, and captures all patient encounters within the healthcare system. Administrative data are also cost effective, minimize biases, and offer the opportunity to study rare outcomes[23,24]. Although administrative data may not contain important clinical and laboratory information such as the presence of positive microbiology cultures, it can be supplemented by linkage to other data sources such as the electronic medical record.

2.3.2 International Classification of Diseases (ICD) coding system

Diagnoses are captured in health administrative data using the International Classification of Diseases (ICD) coding system. The tenth revision of the ICD, ICD-10, was first released in 1994 and is currently used in Canadian hospital administrative databases to codify diseases, signs and symptoms, pathogens as well as external factors which may cause injury or disease. Unlike the numeric coding used in the previous version, ICD-10 uses alphanumeric coding with up to 6 characters and contains 12,420 codes compared to 6,969 in ICD-9[23]. This allows enhanced international comparability and enables more accurate and thorough capture of clinical information. Additionally, there are international variations of the standard ICD versions, which allow countries to make changes at the fifth and sixth digit level, in order to better capture and classify conditions that may be of special interest to that country. The Canadian version of ICD-10 developed by CIHI is denoted ICD-10-CA and was adopted in 2001[23].

2.3.3 Coding in Electronic Health Records

Upon admission to hospital, patients receive diagnoses that can be categorized as either the principal reason for admission (primary admission diagnosis) or additional health conditions identified at, or during the admission process (secondary admission diagnoses), which are documented in the patient's medical chart[23]. After the patient is discharged, the chart is transferred to a health records department, where non-clinical trained coders review the clinical notes and assign ICD-10-CA diagnosis codes and procedure codes in accordance with the data recorded in the chart.

2.3.4 Measuring the Validity of Code-Based Algorithms for Identifying Health Conditions

Sensitivity (Sn), specificity (Sp), positive predictive value (PPV) and negative predictive value (NPV) are measures of diagnostic accuracy used to describe the validity of ICD-coded case definitions in health administrative data. To determine the validity of a case definition, reference standard criteria must also be applied to identify patients with and without the disease. Results can then be classified as true positive, true negative, false positive and false negative cases within a contingency table (Table 3). True positive cases are classified as having the disease according to the reference standard and health administrative data, whereas patients who do not meet the reference standard criteria and are also correctly identified as not having the disease using health administrative data are classified as true negatives. Patients who are identified as not having the disease according to the reference standard, but are incorrectly classified as positive according to health administrative data, are false positives. Those who are identified as positive according to the reference standard, but are incorrectly classified as negative according to health administrative data, are false negatives.

Table 3: Contingency Table for Calculating Diagnostic Accuracy

ICD-coded Definition	**Reference Standard**	
	Sepsis-Positive	Sepsis-Negative
Sepsis-Positive	True Positive	False Positive
Sepsis-Negative	False Negative	True Negative

Sensitivity (Sn) measures the ability of an ICD-coded case definition to correctly identify the proportion of patients with the disease in health administrative data.

Sensitivity is calculated as:

$$\text{Sn} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Negative}}$$

A case definition with high sensitivity would therefore capture patients who truly have the disease very accurately, whereas a case definition with low sensitivity would underestimate the true number of cases in health administrative data.

Specificity (Sp) measures the ability of an ICD-coded case definition to correctly identify the proportion of patients who do not have the disease.

Specificity is calculated as:

$$\text{Sp} = \frac{\text{True Negative}}{\text{True Negative} + \text{False Positive}}$$

A highly specific definition would capture patients without the disease effectively. Alternatively, a case definition with low specificity would capture a greater number of patients who are incorrectly identified as having the disease in health administrative data.

To illustrate this, consider a hypothetical population of 1,000 patients, of whom 100 meet the reference standard criteria, Definition A, for a disease and 900 do not. A second case definition, Definition B, is applied in health administrative data to distinguish patients who have the disease

from those who do not. The results obtained by applying both case definitions to this population of 1,000 patients are shown below in Table 4.

Table 4: Classification of a Hypothetical Population by Definition A Compared with Definition B

Definition B (HAD)	**Definition A (Reference Standard)**		
	Positive	Negative	**Totals**
Positive	75	200	275
Negative	25	700	725
Totals	100	900	**1000**

Of the 100 patients with the disease, Definition B was able to correctly classify 75 as positive and misclassified 25 as negative in HAD. The sensitivity of this definition, or the proportion of true positives among all patients with the disease, is 75/100, or 75%. The specificity of Definition B, or the proportion of patients correctly identified as not having the disease in HAD, is 700/900 or 78%.

Sensitivity and specificity can therefore be considered population-level measures, such that sensitivity measures the proportion of true positives out of all actual positives in the population, and specificity measures the proportion of true negatives out of all actual negatives in the population for a case definition. These measures do not depend on the prevalence of the disease in the population, and are indicative of a definition's accuracy in a specific population, under specific conditions[25].

Positive and negative predictive values address the question: if a patient is identified as positive or negative for a disease in health administrative data, what is the probability that this patient truly has or does not have the disease?

PPV is calculated:

$$\text{PPV} = \frac{\text{True Positive}}{\text{True Positive} + \text{False Positive}}$$

NPV is calculated:

$$\text{NPV} = \frac{\text{True Negative}}{\text{True Negative} + \text{False Negative}}$$

Returning to the example in Table 4, 275 patients out of a population of 1000 patients were positive according to Definition B, of whom 75 patients truly had the disease. PPV of Definition B is therefore 75/275, or 27%, and so if a patient is identified as positive in health administrative data according to Definition B, the probability that this patient truly has the disease is 27%.

Similarly, 725 patients were classified a negative according to Definition B, of whom 700 patients were correctly identified as not having the disease. NPV of Definition B is therefore 700/725, or 96%. If a patient is identified as negative in health administrative data according to Definition B, the probability that this patient truly does not have the disease is 96%.

Whereas sensitivity and specificity are intrinsic characteristics of a case definition when compared to a particular reference standard, predictive values are dependent on both the sensitivity and specificity. As the sensitivity of a case definition improves, the negative predictive value also

improves (the definition becomes better at ruling out persons who do not have the disease). Alternatively, as the specificity of a case definition improves, the positive predictive value also improves (the definition becomes better at ruling in persons who have the disease). The predictive value of case definitions are also dependent on the prevalence of the disease in the patient population. As the prevalence of the disease decreases, PPV also decreases (a higher proportion of positive tests are false positives) and NPV increases. Predictive values are therefore relevant at the patient level, as they estimate the reliability of positive and negative results, but also require population level data for their calculation[25].

This thesis focuses on the sensitivity and specificity of sepsis definitions as we seek to apply these definitions to determine their suitability for population-level surveillance, rather than their utility in real-time clinical diagnosis or treatment decisions for individual patients.

True positive fraction (TPF), equivalent to sensitivity and false positive fraction (FPF), equivalent to 1-specificity, define how well a case definition reflects true disease status, and thus the inherent accuracy of a case definition. An ideal case definition would therefore have FPF=0 and TPF=1[26]. TPF and FPF can also be used to compare the accuracy of one case definition B, to another, Definition A, by deriving the relative true positive fraction (rTPF) and relative false positive fraction (rFPF)[26].

rTPF is calculated:

$$rTPF = \frac{TP_{Definition\ B}}{TP_{Definition\ A}}$$

rFPF is calculated:

$$rFPF = \frac{FP_{Definition\ B}}{FP_{Definition\ A}}$$

The interpretation of rTPF and rFPF is as follows: if rTPF is 0.5, the TPF according to Definition B is only 50% of that of Definition A. Similarly, if rFPF is 2.0, the FPF for Definition B is twice that of Definition A.

2.3.5 Validity of Code-Based Algorithms for Identifying Sepsis

Despite the increased utilization of health administrative data for sepsis surveillance and measuring economic burden, there is no consensus regarding which case definitions should be used, as multiple ICD codes for infection and organ dysfunction exist[2,5,7,27–30]. Researchers may use an implicit coding strategy, with a combination of infection and organ dysfunction codes, or an explicit coding strategy, with a single code such as ICD code R57.2 for septic shock, to identify sepsis cases. [31]Of note, the CIHI 2009 sepsis case definition uses 49 ICD-10-CA codes for infection in adults and neonates, and 28 ICD-10-CA codes for organ dysfunction[3,4].

A multi-centre validation study by Jolley et al[4], reported a sensitivity of 47.2% and specificity of 97.5% in the ICU setting using the CIHI 2009 sepsis algorithm. These authors derived an optimized ICD-coded sepsis definition containing seven additional ICD codes for infection and a code for septic shock (Table 5), which improved the sensitivity of the CIHI algorithm to 65.1%, whereas specificity decreased to 88.2%. Although the Jolley sepsis definition captures more cases, it is still only moderately sensitive, suggesting that sepsis in the ICU setting is highly under-coded

in health administrative data[4]. Additionally, the reference standard used by Jolley et al to classify patients as true sepsis-positive and true sepsis-negative in this validation study is the outdated SIRS-based criteria for identifying sepsis.

Table 5: Sepsis Identification Algorithm developed by Jolley et al.

ICD-10-CA Code	Code Definition
Jolley Sepsis Codes:	
R57.2 *	Septic Shock **OR** any Jolley infection code(s), **AND** at least one code for organ dysfunction in any one of the six systems, or any procedure code(s)
Jolley Infection Codes:	
A03.9	Shigellosis, unspecified
A02.1	Salmonella sepsis
A20.7	Septicaemic plague
A21.7	Generalized tularaemia
A22.7	Anthrax sepsis
A23.9	Brucellosis, unspecified
A24.1	Acute and fulminating melioidosis
A26.7	Erysipelothrix sepsis
A28.0	Pasteurellosis
A28.2	Extraintestinal yersiniosis
A32.7	Listerial sepsis
A39.2	Acute meningococcaemia
A39.3	Chronic meningococcaemia
A39.4	Meningococcaemia, unspecified
A40	Streptococcal sepsis
A40.0	Sepsis due to Streptococcus, group A
A40.1	Sepsis due to Streptococcus, group B
A40.2	Sepsis due to Streptococcus, group D
A40.3	Sepsis due to Streptococcus pneumoniae
A40.8	Other streptococcal sepsis
A40.9	Streptococcal sepsis, unspecified
A41	Other sepsis
A41.0	Sepsis due to Staphylococcus aureus
A41.1	Other sepsis
A41.2	Sepsis due to unspecified Staphylococcus
A41.3	Sepsis due to Haemophilus influenzae
A41.4	Sepsis due to anaerobes
A41.5	Sepsis due to other Gram-negative organisms
A41.50	Sepsis due to Escherichia coli
A41.51	Sepsis due to Pseudomonas
A41.52	Sepsis due to Serratia
A41.58	Sepsis due to other Gram-negative organisms, NOS

A41.8	Other specified sepsis
A41.80	Sepsis due to Enterococcus
A41.88	Other specified sepsis
A41.9	Sepsis, unspecified, includes: septicaemia
A42.7	Actinomycotic sepsis
B00.7	Disseminated herpes viral disease, includes: herpes viral sepsis
B37.7	Candidal sepsis
P36.0	Sepsis of newborn due to Streptococcus, group B
P36.1	Sepsis of newborn due to other and unspecified streptococci
P36.2	Sepsis of newborn due to Staphylococcus aureus
P36.3	Sepsis of newborn due to other and unspecified staphylococci
P36.4	Sepsis of newborn due to Escherichia coli
P36.5	Sepsis of newborn due to anaerobes
P36.8	Other bacterial sepsis of newborn
P36.9	Bacterial sepsis of newborn, unspecified
P35.2	Congenital herpes viral (herpes simplex) infection
P37.2	Neonatal (disseminated) listeriosis
P37.5	Neonatal candidiasis
A04.7*	Enterocolitis due to Clostridium difficile
B95.48*	Other Streptococcus as the cause of diseases classified to other chapters
B95.6*	Staphylococcus aureus as the cause of diseases classified elsewhere
B96.2*	Escherichia coli as the cause of diseases classified elsewhere
J18.9*	Pneumonia, unspecified organism
J44.0*	Chronic obstructive pulmonary disease with acute lower respiratory infection
N39.0*	Urinary tract infection, site not specified
Jolley Organ Dysfunction Codes:	
Respiratory	
J96.0	Acute respiratory failure
J96.9	Respiratory failure, unspecified
J80	Diseases of bronchus, not elsewhere classified
R09.2	Respiratory arrest
Cardiovascular	
R57.0	Cardiogenic shock
R57.1	Hypovolemic shock
R57.8	Other shock
R57.9	Shock, unspecified
I95.1	Orthostatic hypotension

I95.9	Hypotension, unspecified
Renal	
N17.0	Acute renal failure with tubular necrosis
N17.1	Acute renal failure with acute cortical necrosis
N17.2	Acute renal failure with medullary necrosis
N17.8	Other acute renal failure
N17.9	Acute renal failure, unspecified
Hepatic	
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K76.3	Infarction of liver
Neurologic	
F05.0	Delirium not superimposed on dementia, so described
F05.9	Delirium, unspecified
G93.1	Anoxic brain damage, not elsewhere classified
G93.4	Encephalopathy, unspecified
G93.80	Metabolic encephalopathy
Hematologic	
D69.5	Secondary thrombocytopenia
D69.6	Thrombocytopenia, unspecified
D65	Disseminated intravascular coagulation (defibrination syndrome)
Procedure codes (CCI)	
1.GZ.31.CA-ND 1.GZ.31.CR-ND 1.GZ.31.GP-ND	Ventilation, respiratory system NEC, invasive per orifice approach by endotracheal intubation, positive pressure (e.g. CPAP, BIPAP)

Table adopted from Jolley et al. (2015)[4]

*ICD-10-CA codes added to the CIHI sepsis definition by Jolley et al

Legend: CCI- Canadian Classification of Health Interventions

A 2015 systematic review identified 12 studies which examined the validity of ICD-coded sepsis definitions in health administrative data from 1992 to 2014[5]. Across the included studies, 38 sepsis algorithms comprising over 130 different ICD codes were assessed among hospital and ICU patients. While the published ICD-coded sepsis definitions were moderately specific (range: 78.3% to 100%, median: 98.5%), sensitivity was poor (range: 5.9% to 82.3%, median: 42.4%). Positive predictive value ranged from 5.6% to 100% (median: 50%) and negative predictive value, from 62.1% to 99.7% (median: 97.4%).

Our team conducted a search of the Embase database as previously described by Jolley et al.[5], to identify sepsis validation studies published after the 2015 systematic review, and up to October 5, 2021. 14 additional studies that compared the performance characteristics of ICD-9 or ICD-10 coded definitions for sepsis to a reference standard using administrative data and reported any diagnostic accuracy measures (i.e., sensitivity, specificity, positive predictive value or negative predictive value) were identified. Characteristics of the included studies are summarized in Appendix 1.

A total of 21 studies tested 16 different sepsis algorithms on general hospital admissions[28,32,41–50,33–40]. Two of these studies were conducted in Canada.[4,38] Five studies selected a random sample of all hospital admissions, as compared to pre-selected sepsis admissions[46–50]. Chart review was considered the reference standard to confirm true positive and true negative sepsis cases in 18 studies[28,34,44,45,47–52,35,37–43]. Two studies used an infection database as the reference standard to identify true positive and true negative sepsis cases[32,46] and one study used sepsis clinical trial patients[33].12 of the included studies used unique or modified published algorithms, of which five

included the addition of antimicrobial data[28,34,45,48,50]. The combination of an antibiotic order and a blood culture order was used to pre-select patients with infection who were admitted to hospital (not the ICU), in these studies. Sensitivity ranged from 5.9% to 93% across all validation studies conducted among hospital admissions. The highest sensitivity was derived from a study by Liu et al[45], which included a pre-selected sepsis sample from hospital admissions. Sepsis patients were selected using Sepsis-3 criteria. Specificities ranged from 37.2% to 100%, with the greatest specificity reported by a study that examined explicit, or exact ICD codes for sepsis and septic shock only. Among studies with sepsis definitions that included antimicrobial data, sensitivity ranged from 12% to 93%, and specificity ranged from 86% to 99.3%. Studies which assessed definitions without antimicrobial data reported sensitivities ranging from 5.9% to 90%, and specificities ranging from 37.2% to 99.8%.

Five studies assessed different sepsis algorithms' performance among patients admitted to the ICU[4,7–10]. Of these, one study was conducted in Canada.[4] Two of these studies were conducted on pre-selected sample of all ICU admissions[7,8]. Chart review was used to confirm true positive and true negative sepsis cases in one study[4]. Three studies used an ICU infection database as the sepsis reference standard[7,8,10], and one study used a laboratory results database[9]. Three studies tested unique or modified published algorithms, none of which included antimicrobial data in the sepsis algorithms. Sensitivity ranged from 6.7% to 71.9% and specificity from 85.4% to 100%.

We adapted the Jolley sepsis algorithm[4] for this study as it demonstrated moderate sensitivity (65.1%) and high specificity (88.2%) in ICU populations, outperforming other algorithms identified in our updated systematic review. The algorithm was also developed and validated

specifically in a Canadian healthcare setting, making it compatible with our data sources and clinical context.

2.3.6 Addition of Antimicrobial Information to ICD-Coded Sepsis Definitions

Only 30% to 40% of patients with sepsis have organisms identified in microbiological culture results[6]. Therefore, capturing infection based on confirmed microbiology results will likely underestimate the true incidence of infection. A Dutch study found that 33% of patients initially treated for sepsis at ICU admission were subsequently confirmed as true sepsis cases after manual adjudication[53]. This study proposed the addition of antimicrobial initiation and duration information as a means to retrospectively differentiate patients with true sepsis from those in which the initial suspicion of sepsis was not confirmed. While antimicrobial initiation is a strong indicator for suspected infection, antimicrobials are often prescribed empirically in critically ill patients as the source of the infection and the cause of the severe illness is not always clear. Furthermore, in the surgical setting, antimicrobials may be administered prophylactically for shorter time frames (24 to 48 hours) to prevent infection, and prescription rates may differ by unit policies and individual clinician behavior[54–56]. In the ICU, it remains unknown whether adding antimicrobial data to a sepsis algorithm can help improve its performance characteristics. [4,7–10]

Chapter 3: Methods

3.1 Study Design

A retrospective cohort study was conducted at two ICUs at TOH (Figure 1). Data were obtained from manual chart reviews and health administrative data. Manual chart review was conducted to identify patients with and without sepsis according to Sepsis-3 criteria[6], which served as the reference standard. These data were then linked to health administrative data containing antimicrobial usage information. We first evaluated the sensitivity and specificity of the existing Jolley sepsis algorithm[4] and subsequently assessed how modifying the algorithm affected its performance by:

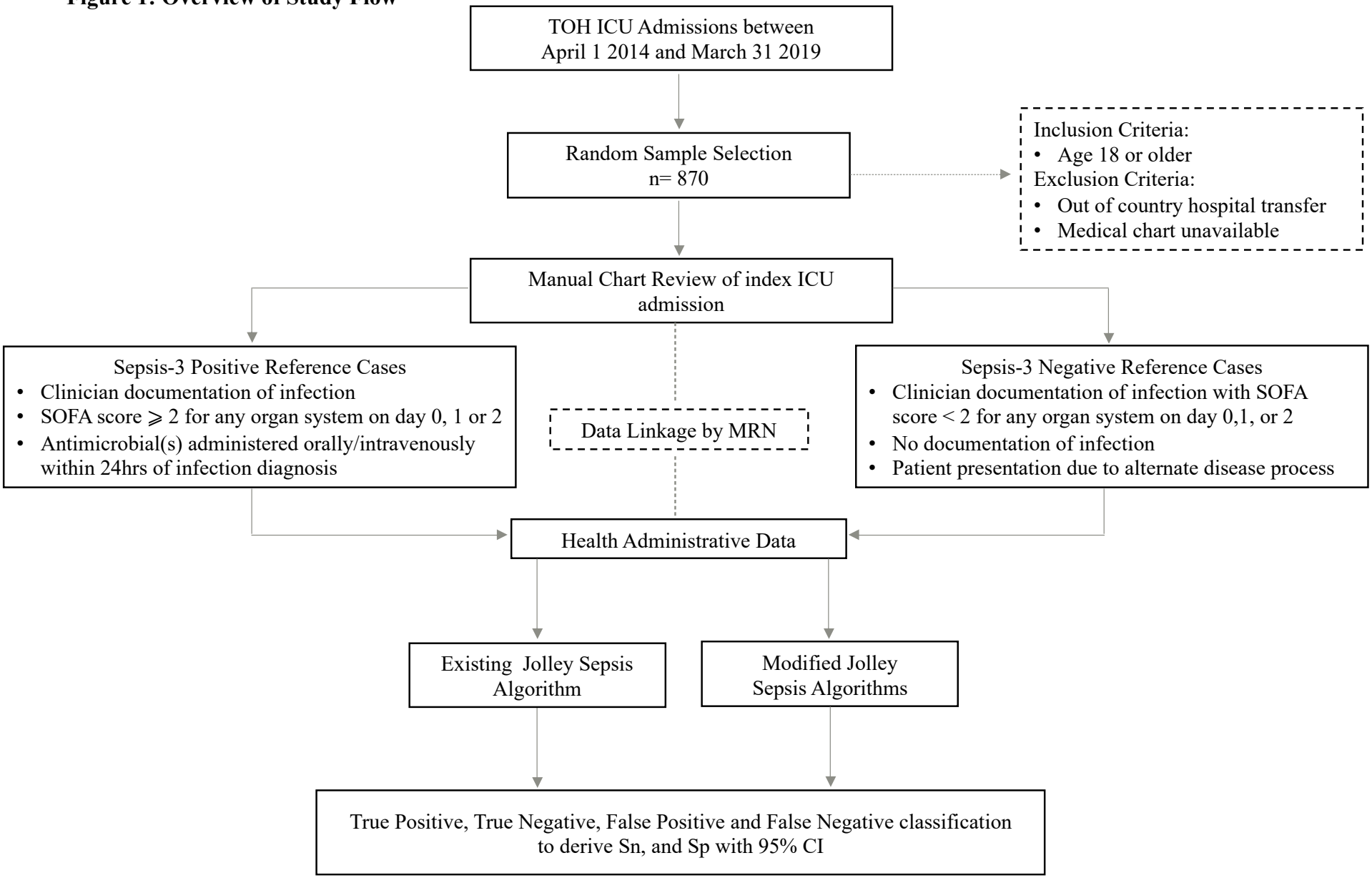
1. Incorporation of antimicrobial information (i.e., antimicrobial ordering and the duration of administration)
2. Removal of all infection-related ICD codes from the Jolley algorithm

3.2 Study Setting

The study was conducted at two ICUs, at TOH's General and Civic campuses. TOH is a multi-campus, academic tertiary-care hospital that serves approximately 1.3 million people in Ottawa, Eastern Ontario, Western Quebec and parts of Nunavut in Canada. The General and Civic Campus ICUs have a total of 63 beds, and receive an estimated 2300 admissions per year. TOH's General campus ICU is a medical/surgical ICU, which also admits oncology patients, such as bone marrow transplant patients. The Civic campus ICU receives surgical and neurology admissions, such as vascular surgery and neurosurgery patients. It is also a trauma centre. The University of Ottawa

Heart Institute (UOHI) ICU, which is also affiliated with TOH admits cardiac patients, and was excluded from this study.

Figure 1: Overview of Study Flow



3.3 Study Population

The study population included adult patients, aged 18 years and older, admitted to TOH's Civic or General campus ICUs between April 1, 2014 and March 31, 2019. From this population, a random sample of 870 records were selected for manual chart review. Patients were included only if their medical charts contained sufficient data to determine a sepsis diagnosis based on Sepsis-3 criteria. Exclusion criteria included patients transferred to TOH Civic or General ICUs from hospitals outside Canada and cases with unavailable or incomplete medical records.

3.3.1 Sample Size and Justification

A sample size of 250 Sepsis-3 positive reference cases produced a two-sided 95% confidence interval for sensitivity with a width of 0.12, at worst (i.e. when the sensitivity is 0.5). Based upon a preliminary analysis of TOH data in 2013-2014, the prevalence of sepsis was approximately 30% (unpublished). Therefore, a minimum of 833 charts had to be reviewed. The sample size was increased to 870 charts to allow for potential missing, incomplete or corrupted medical charts.

3.4 Data Sources

3.4.1 Medical Chart Data

Each eligible ICU patient's medical chart was reviewed to identify sepsis-positive and sepsis-negative reference cases. Clinical notes (ICU admission notes, progress notes, nurse flowsheets, ICU transfer summaries and hospital discharge summaries), medication administration record, microbiology and laboratory results were reviewed and entered into an electronic data collection form (Appendix 2).

3.4.2 Health Administrative Data

A health administrative dataset housed at TOH Data Warehouse (TOHDW), comprising demographic data, hospital and ICU admission dates, ICD diagnosis codes, procedure codes, and administration of antimicrobial ordering information for each patient, was retrieved.

3.5 Sepsis Case Definitions

3.5.1 Definition of Sepsis in Manual Chart Review Data (Reference Standard)

A) Sepsis-Positive Reference Cases

For each patient, only index infections during the first ICU admission between April 1, 2014 and March 31, 2019 were included. To be classified as a sepsis-positive reference case according to manual chart review data, ICU patients were required to meet the following criteria:

a) Clinician documentation of the index infection in the medical chart that could have first been documented up to two days before the ICU admission, on the day of ICU admission or during ICU admission, AND;
b) Documentation of the infection in the ICU transfer summary or hospital discharge summary note.

   A two-day window before ICU admission for infection diagnosis was included to detect infections that may have preceded and contributed to the patient's acute organ dysfunction that required ICU admission since organ dysfunction often develops in the first few days following an infection.

Infections were further defined as confirmed or suspected according to the International Sepsis Forum Guidelines[57] during chart review as follows:

i. Confirmed infection cases included those where cultures that were taken from two days before to two days after infection diagnosis, yielded a positive microbiology result, and the patient received antimicrobials orally or intravenously within (+/-) one day of infection diagnosis as documented in the medication administration record. The source of the positive culture(s) (i.e. respiratory, bloodstream, intravascular catheter, intra-abdominal, urinary, skin and soft tissue, central nervous system), and the type of organism(s) grown were documented. The list of possible sites of infection and organisms included in our chart review are listed in Appendices 3 and 4, respectively.

ii. Suspected infection cases included those where an infection diagnosis was documented in the medical chart as described above, but cultures for that infection were negative. Additionally, these included cases where clinician impression that infection could not be ruled out was documented in the ICU transfer note and discharge summary, and had body fluids sampled for culture and received antimicrobials orally or intravenously within (+/-) one day of culture as documented in the medication administration record. [13]

AND

c) Presence of acute organ dysfunction, defined as a Sequential Organ Failure Assessment (SOFA) score of at least 2 points for one or more of the organ systems on Day 0 (day of infection), Day 1 and Day 2 following infection documentation in the medical chart on the day of ICU admission or during the ICU admission. For patients where the infection was diagnosed

up to two days prior to ICU admission, day 0 for organ dysfunction(s) was the day of ICU admission, with Days 1 and 2 defined as the first two days following ICU admission. Organ dysfunctions that were present for more than 2 days before infection diagnosis were not considered acute. The following describes how organ dysfunction data for each organ system was operationalized into corresponding SOFA scores:

i. Respiratory organ dysfunction score: P/F ratios (PaO_2/FiO_2) for days 0, 1 and 2 were calculated using the worst arterial blood gas values for each day. If no arterial blood gases were available, the worst oxygen saturation value (SaO_2) was used to estimate PaO_2 as shown in Appendix 5, as S/F ratios (SaO_2/FiO_2) have been shown to be reliable predictors of P/F ratios among critically ill patients.[58,59] For patients who were not intubated, FiO_2 was estimated according to oxygen delivery method as shown in Appendix 5. Patients with documented past medical history of chronic pulmonary disease, or on home oxygen in the ICU admission note were assigned a score of zero.

ii. Coagulation dysfunction score: the lowest platelet value on days 0, 1 and 2 was documented. Patients with documented past medical history of chronic thrombocytopenia in the ICU admission note were assigned a score of zero.

iii. Liver dysfunction score: the highest bilirubin value on days 0, 1 and 2 was documented. Patients with documented past medical history of end-stage liver disease or cirrhosis in the ICU admission note were assigned a score of zero.

iv. Cardiovascular organ dysfunction score: weight at ICU admission and the highest dose of each vasoactive agent given continuously for at least one hour in a 24-hour period on days 0, 1 and 2 from nurse flow sheets was documented.

Vasoactive agents included norepinephrine, phenylephrine, epinephrine, vasopressin, milrinone, dobutamine and dopamine. Phenylephrine, vasopressin and milrinone dosage equivalents were calculated using the conversions shown in Appendix 6. The vasoactive agent associated with the highest cardiovascular organ dysfunction score was documented for each day. The lowest MAP value for each day was documented for patients who were not given vasoactive agents.

v. Central nervous system dysfunction score: the lowest Glasgow Coma Score (GCS) for days 0, 1, and 2 from nurse flow sheets was documented. For intubated patients, the worst GCS prior to intubation was recorded and imputed for each day the patient was intubated. For sedated, non-intubated patients, the GCS prior to sedation was recorded and imputed for each day the patient was sedated.

vi. Renal dysfunction score: the highest creatinine value on days 0, 1 and 2 was documented. For patients who started renal replacement therapy (i.e. Slow Low Efficiency Dialysis, or dialysis) during this period, the renal SOFA score was determined based on the use of this therapy rather than creatinine values, since creatinine values are not reliable during dialysis. Urine output was not considered when assigning renal SOFA scores, as it is not consistently documented in nurse flowsheets. Patients with documented past medical history of end-stage renal disease requiring chronic dialysis use prior to ICU admission in the ICU admission note were assigned a score of zero.

AND

d) At least one or more antimicrobial(s) associated with the index ICU infection. All antimicrobials administered from one day prior to one day after the infection diagnosis were included.

B) Sepsis-Negative Reference Cases

ICU patients who met the following criteria were classified as sepsis-negative reference cases:

a) No documentation of infection up to two days prior to ICU admission, on the date of ICU admission or during the ICU admission AND no infection documented in the ICU transfer summary or hospital discharge summary;

   OR

b) Documentation in the ICU transfer note or hospital discharge summary that the patient's admission to the ICU was as a consequence of an alternative disease process other than infection, even if a course of antimicrobials was completed;

   OR

c) Infection diagnosis that could have occurred up to two days prior to ICU admission, on the date of ICU admission, or during the ICU admission, but without the development of acute organ dysfunction (a SOFA score of at least 2 points for any of the organ systems on Days 0, 1 or 2 from the date of ICU admission or during the ICU admission).

C) Sepsis Reference Case Adjudication

Given the complexity of capturing sepsis in a retrospective context, case adjudication meetings were held on a weekly basis to resolve unclear cases that arose during the chart review process. An ICU physician (LM), an internal medicine physician (EC) and a health service researcher (KT)

were members of the adjudicating team. The adjudication process was designed to systematically review cases where the role of infection in ICU admission was ambiguous. Specifically, clinical details from ICU admission notes, progress notes, ICU transfer summaries, discharge summaries, the medication administration record, microbiology and laboratory results were reviewed for patients with suspected infections or sepsis when the ICU transfer note or discharge summary did not clearly indicate whether the treating physician believed infection was a contributing factor to ICU admission. The adjudication process aimed to determine the causal and/or temporal relationship of infection to these patients' admission to the ICU.

3.5.2 Definition of Sepsis in Health Administrative Data

The Jolley sepsis identification algorithm is shown in Table 5. Since it was not possible in health administrative data to identify the exact date of infection or day(s) of organ dysfunction development, a patient was classified as having ICD-coded sepsis if any of the following ICD or procedure codes were recorded in the health administrative database for the period corresponding to the entire index ICU admission:

a) ICD-10 code R57.2, for septic shock.

OR

b) i. At least one ICD-10 infection code;

AND

ii. At least one ICD-10 organ dysfunction code or Canadian Classification of Health Interventions (CCI) procedure code;

3.6 Antimicrobial Information Associated with Infection Diagnosis

3.6.1 Antimicrobial Information in Chart Review

Antimicrobial information from chart review was used as part of the criteria for identifying sepsis-positive reference cases. While antimicrobial administration is not part of Sepsis-3 diagnostic criteria, we required evidence of antimicrobial use to strengthen the ascertainment of infection within our reference standard. For patients with a documented index ICU infection diagnosis in the medical chart, any antimicrobial, defined as antibiotics, antivirals, antifungals, or antiparasitics, administered orally or intravenously from one day before to one day after the infection diagnosis date was considered part of the initial treatment for the index ICU infection. All eligible antimicrobials are listed in Appendix 7. Antimicrobials given as chronic suppressive antimicrobial therapy prior to ICU admission, as described in the ICU admission note and those listed among patients' home medications were not considered as part of the initial treatment for the index ICU infection. For example, antimicrobials taken at home for chronic diabetic ulcers prior to ICU admission were excluded. Additionally, prophylactic pre-operative and post-operative antimicrobials described as such in the ICU clinical notes were also excluded as treatment for infection.

3.6.2 Antimicrobial Information in Health Administrative Data

A second objective of this thesis was to examine whether the addition of antimicrobial information as captured in HAD at TOHDW could maintain the sensitivity and improve the specificity of the Jolley sepsis algorithm. Since we could not ascertain the exact date of infection diagnosis using the Jolley sepsis algorithm (Table 5) in HAD, all oral and intravenous antimicrobials from HAD ordered up to two days before the date of ICU admission and throughout the ICU admission were

included. The time window for antimicrobial ordering in HAD mirrored the infection diagnosis window in chart review (starting from two days prior to ICU admission).

3.7 Data Collection

3.7.1 Data Collection in Chart Review

We developed a standardized electronic data collection form for medical chart data extraction using Microsoft Excel (Appendix 2). The form was piloted by conducting an independent and duplicate (AAB, EC) chart review of a random sample of 15 patient charts to assess concordance between the two reviewers, and to develop the standard operations manual, which served to operationalize the reference standard definition of sepsis as well as other variables for the chart review. Independent chart review commenced after 100% concordance was observed between reviewers. Clinical notes, nurse flow sheets, medication administration records and laboratory values were reviewed to capture the following data:

i. ICU and hospital admission date

ii. For patients identified with an index infection up to two days before ICU admission, on the day of ICU admission or during the ICU admission, the date of infection diagnosis, type(s) of antimicrobial(s) started within (+/-) one day of infection diagnosis, collected from first antimicrobial given during this period and all antimicrobials prescribed on that day and acute organ dysfunctions for each of the six organ systems associated with the infection diagnosis, were collected as described in Section 3.5.1. In case of missing clinical data for organ dysfunction, a score of zero was assigned to the corresponding SOFA score component.

iii. For patients who were admitted to the ICU without an index infection or who did not develop one during the ICU admission, we collected all antimicrobials administered on the first day that antimicrobials were initiated during the ICU admission.

iv. For patients who were admitted to the ICU without an index infection, or did not develop one during the ICU admission, we collected acute organ dysfunction(s) information as described in Section 3.5.1 for the first organ dysfunction day during the ICU admission (i.e. the first day where non-infected patients required the initiation of at least one organ support intervention such as mechanical ventilation, dialysis or vasoactive therapy). This approach identified clinically significant organ dysfunctions, comparable in severity to those commonly associated with sepsis.

3.7.2 Data Collection in Health Administrative Data

Data obtained from TOHDW for the entire cohort included:

i. Demographic data: age and sex

ii. Hospital and ICU admission data: admission and discharge date, Charlson comorbidities, discharge disposition, ICD diagnosis codes and;

iii. Antimicrobial information: type, dose, administration route, dates of initiation and cessation of orally and intravenously administered antimicrobials ordered up to two days before, and during ICU admission.

3.8 Data Linkage

Each randomly selected patient from TOHDW's health administrative database was assigned a unique study identifier (study ID) which was documented on the study master list. Clinical data obtained from the medical chart review was linked with health administrative data obtained from TOHDW. The study ID was used to link de-identified administrative data with the data obtained from manual chart review. To ensure accurate linkage, the date of ICU admission and medical record number (MRN) were also obtained from TOHDW and verified by reviewers throughout the data extraction process.

3.9 Analysis

Descriptive statistics were used to characterize patient demographics, index sepsis cases as defined by the Sepsis-3 reference standard definition and the Jolley sepsis algorithm, in terms of number and proportions for categorical variables, and means with standard deviations (SD) or medians and interquartile ranges (IQRs) as appropriate. The sensitivity and specificity of the Jolley sepsis algorithm were calculated as described in Section 2.3.4, together with 95% confidence intervals (CIs) (Primary Objective 1).

3.9.1 Incorporation of Antimicrobial Information in the Jolley Sepsis Algorithm

The duration of ordering for each type of antimicrobial was defined as the total number of consecutive calendar days of an antimicrobial order in HAD, from the start date to the end date, inclusively. The start and end dates in HAD were defined as the date on which an antimicrobial was ordered to begin and then to be discontinued as ordered by the treating physician, respectively.

For example, if piperacillin/tazobactam was ordered to be initiated and discontinued on the same day, then ceftriaxone ordered for the following five days in HAD, the duration for each antimicrobial would be one day and five days, respectively. For patients who received different doses of the same antimicrobial on consecutive days, the duration was calculated by counting each day of administration, regardless of antimicrobial dosage.

To assess whether incorporating antimicrobial information could maintain sensitivity while improving specificity of the Jolley sepsis algorithm, we conducted the following analyses:

i. First, the Jolley algorithm was modified by adding the first order of at least one antimicrobial recorded in HAD, as we reasoned that the ordering of any antimicrobial(s) would mean that the treating physician had an increased suspicion for infection (Primary Objective 2a).

ii. Second, the duration of antimicrobial administration was added to the Jolley sepsis algorithm (Primary Objective 2b). We reasoned that longer durations of antimicrobial ordering might better reflect true infection cases. In contrast, shorter duration of antimicrobial ordering may indicate prophylaxis (e.g., in post-operative patients) rather than treatment of sepsis, or initial clinical suspicion for infection that was subsequently ruled out.

iii. Given that antimicrobial administration often reflects clinical suspicion of infection, in a separate analysis, we modified the Jolley sepsis algorithm by removing all infection-related ICD codes, with retention of only organ dysfunction codes (Table 5) and antimicrobial information as described above (Primary Objective 3). We then recalculated the sensitivity and specificity, along with 95% CIs for these modified algorithms.

3.9.2 Relative Accuracy of the Modified Sepsis Algorithms

To compare the accuracy of the modified algorithms with the existing Jolley sepsis algorithm, we estimated the relative true positive fraction (rTPF) and relative false positive fraction (rFPF) for paired classifications, along with 95% CIs. This calculation followed the method previously described by Pepe[26], which accounts for correlations in paired accuracy data. Improvement in classification was concluded if the lower limit of the 95% CI for the relative accuracy measures excluded the null value of 1. All statistical analyses were performed using STATA V.17 (Stata Corp., College Station, Texas, USA)[60].

3.10 Ethics Approval

This study was approved by the Ottawa Hospital Sciences Network Research Ethics Board (Study ID#: 20200786-01H). To reduce the risk of patient re-identification from study records, the data collection form and study master list, which links patient identifiers and study ID were password-protected and accessible to chart reviewers only. All study data (health administrative data and chart review data) were password-protected and stored on a secure cloud server.

Chapter 4: Results

4.1 Overview and Study Cohort Identification

4.1.1 Study Cohort Identification and Linkage

A total of 10,407 patients were admitted to TOH's Civic or General campus ICUs during the period April 1, 2014 to March 31, 2019 according to administrative data from TOHDW (Figure 2). Of the 870 ICU patients randomly selected for manual chart review, 15 patients were excluded because of incomplete charts with insufficient data to derive organ dysfunction scores (n=2), could not be retrieved for review as they were corrupted or missing (n=12), or were inaccessible to reviewers for privacy reasons (n=1). Additionally, 22 patients were excluded for the following reasons: patients admitted to a step-down unit only (n= 14), international transfers (n = 4), patients admitted to ICU briefly for a specific procedure (n=2), patient not admitted to ICU during study period (n=1) and internal repatriation (n=1). All 833 patient charts that were included for manual review were successfully linked to TOHDW administrative data.

4.1.2 Characteristics of the Entire Study Cohort

Of the 833 patients included in the study cohort, 323 (38.8%) patients were female, and the mean age was 62 years (standard deviation (SD): 17.3 years) (Table 6). 464 patients (55.7%) were admitted to the Civic campus ICU and 410 (49.5%) patients had at least one Charlson comorbidity. The most common comorbidities among the study cohort were diabetes (n=287 (34.6%)), cancer (n=189 (22.8%)), peripheral vascular disease (n=82 (9.9%)) and cerebrovascular disease (n=76 (9.2%)). The median ICU and hospital length of stay were 3.8 days (IQR:1.9 days – 7.4 days) and

10.2 days (IQR: 4.5 days – 22.2 days), respectively. Hospital mortality among the study cohort was 25.8%.

Characteristics of Sepsis-Positive Reference Cases Identified in Chart Review Data

Of the 833 patient charts reviewed, 391(46.9%) patients were determined to have sepsis according to the reference standard Sepsis-3 definition (Table 6). 326 (83.4%) patients had their index infection(s) diagnosed up to two days prior to ICU admission or on the day of ICU admission. 167 (42.7%) sepsis-positive patients were female, and the mean age was 64 years (SD:16 years). 229 (58.4%) sepsis-positive patients were admitted to the General campus ICU and 233(60.0%) patients had at least one comorbid condition. The most common comorbidities among sepsis-positive patients were diabetes (n=161 (41.4%)), cancer (n=120 (30.8%)), chronic obstructive pulmonary disease (n=43 (11.1%)) and congestive heart failure (n=37 (9.6%)). The median ICU length of stay was 4.9 days (IQR: 2.4 days – 9.9 days) and the median hospital length of stay was 13 days (IQR: 5.7 days – 26.3 days). Hospital mortality was 31.0%.

Characteristics of Sepsis-Negative Reference Cases Identified in Chart Review Data

Of the 442 sepsis-negative patients identified by chart review, 156 (35.3%) patients were female, and the mean age was 61 years (SD:18 years) (Table 6). 140 (31.7%) patients were admitted to the General campus ICU and 170 (38.5%) patients had at least one comorbidity. The most common comorbidities were diabetes (n = 126 (28.6%)), cancer (n=69 (15.7%)), peripheral vascular disease (n=69 (15.7%)) and cerebrovascular disease (n=64 (14.9%)). Median length of stay in the ICU was 2.9 days (IQR: 1.6 days – 5.8 days) and the median hospital length of stay was 8.2 days (IQR: 3.8 days – 18 days). Hospital mortality was 21.3%.

Figure 2: Flow Diagram of Study Population

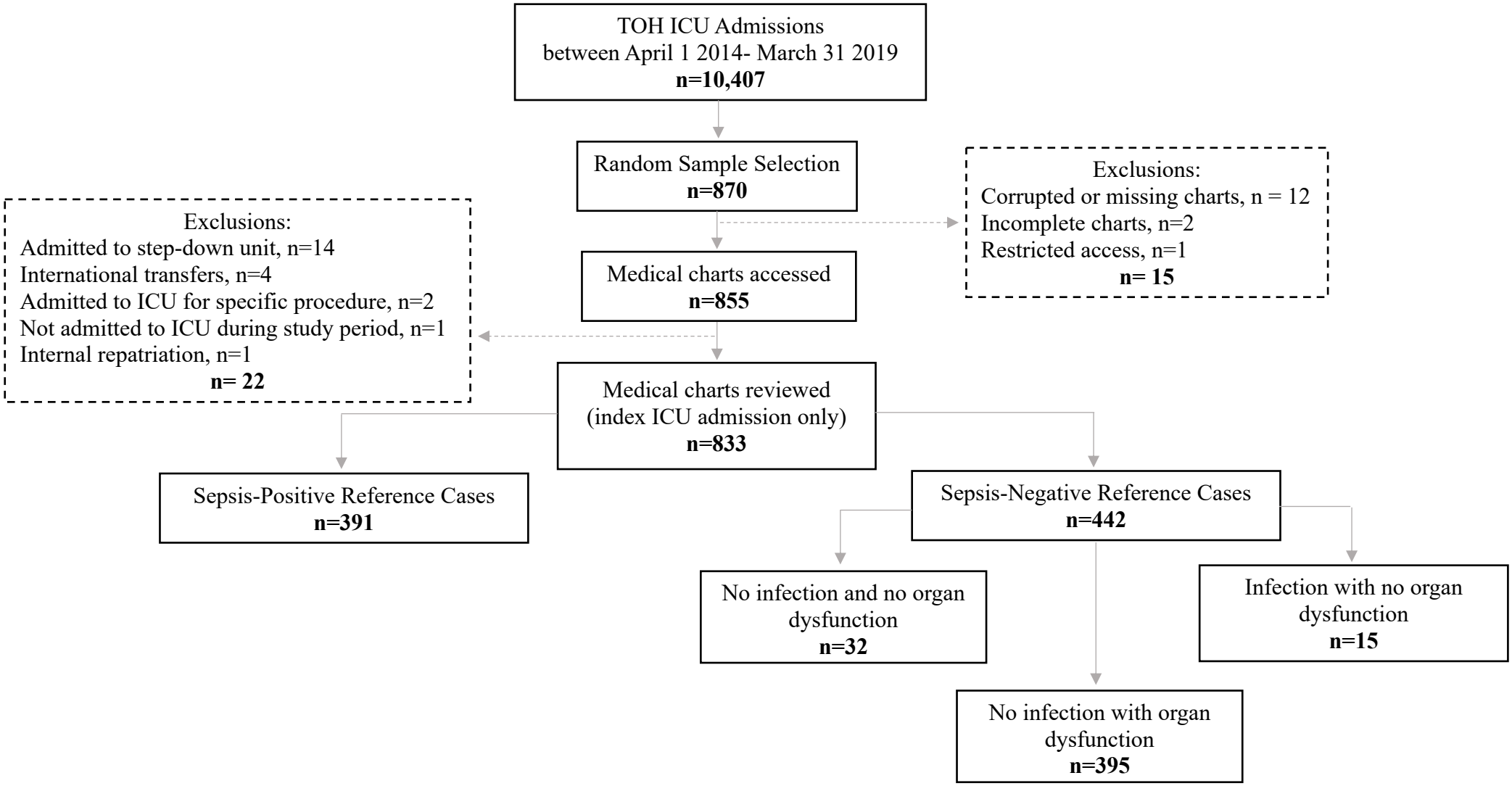


Table 6: Clinical and Demographic Characteristics of the Study Cohort defined by Sepsis-3 criteria in Chart Review Data and Jolley Criteria in HAD

Characteristics	Study cohort (n=833)	Sepsis-Positive		Sepsis-Negative	
		Chart Review (n=391)	HAD (n=364)	Chart Review (n=442)	HAD (n=469)
Age, mean (SD)	62 (17.3)	64 (16.3)	65 (15.7)	61 (18.1)	61 (18.3)
Sex (female), n (%)	323 (38.8)	167 (42.7)	156 (42.9)	156 (35.3)	167 (35.6)
Campus, n (%)					
Civic	464 (55.7)	162 (41.4)	157 (43.1)	302 (68.3)	307 (65.5)
General	369 (44.3)	229 (58.6)	207 (56.9)	140 (31.7)	162 (34.5)
Transfers from Peripheral Hospitals, n (%)	128 (15.5)	70 (17.9)	65 (17.9)	58 (13.3)	63 (13.6)
Charlson Comorbidities, n (%)					
0	419 (50.6)	154 (39.8)	124 (34.3)	265 (60.5)	295 (63.2)
1-2	252 (30.4)	134 (34.6)	144 (39.8)	115 (26.7)	108 (23.1)
3 or more	158 (19.1)	99 (25.5)	94 (26.0)	55 (12.7)	64 (13.7)
Charlson Condition, n (%)					
Congestive Heart Failure	62 (7.5)	37 (9.6)	36 (9.9)	22 (5.1)	26 (5.6)
Myocardial Infarction	23 (2.8)	9 (2.3)	11 (3.0)	14 (3.2)	12 (2.6)
Cerebrovascular Disease	76 (9.2)	9 (2.3)	21 (5.8)	64 (14.9)	55 (11.8)
Peripheral Vascular Disease	82 (9.9)	13 (3.3)	15 (4.1)	69 (15.7)	67 (14.3)
Chronic Obstructive Pulmonary Disease	65 (7.8)	43 (11.1)	57 (15.8)	22 (5.0)	8 (1.7)
Connective Tissue/Rheumatic Disease	7 (0.8)	3 (0.8)	3(0.8)	4 (0.9)	4 (0.9)
Dementia	16 (1.9)	12 (3.1)	13 (3.6)	4 (0.9)	3 (0.6)
Diabetes	287 (34.6)	161 (41.4)	154 (42.5)	126 (28.6)	133 (28.5)
HIV/AIDS	4 (0.5)	2 (0.5)	1 (0.3)	2 (0.5)	3 (0.6)
Hemi/Paraplegia	20 (2.4)	8 (2.1)	12 (3.3)	12 (2.7)	8 (1.7)
Liver Disease	28 (3.4)	15 (3.9)	13 (3.6)	13 (3.0)	15 (3.2)
Peptic Ulcer Disease	15 (1.8)	9 (2.3)	7 (1.9)	6 (1.4)	8 (1.7)
Cancer	189 (22.8)	120 (30.8)	110 (30.4)	69 (15.7)	79 (16.9)
Renal Disease	37 (4.5)	23 (5.9)	23 (6.4)	14 (3.2)	14 (3.0)
Hospital LOS, median (IQR)	10.2 (4.5, 22.2)	13.0 (5.7, 26.3)	17.3 (7.3, 30.8)	8.2 (3.8, 18.0)	7.4 (3.3, 14.5)
ICU LOS, median (IQR)	3.8 (1.9, 7.4)	4.9 (2.4, 9.9)	6.1 (2.9, 12.1)	2.9 (1.6, 5.8)	2.7 (1.5, 5.0)
Hospital Mortality, n (%)	215 (25.8)	121 (31.0)	115 (31.6)	94 (21.3)	100 (21.3)

Legend: HAD: health administrative data; LOS: length of stay; IQR: interquartile range; SD: standard deviation

Characteristics of Sepsis-Positive Cases identified in Health Administrative Data

When the Jolley sepsis algorithm was applied to health administrative data for the entire ICU cohort of 833 patients, it identified 364 (43.7%) patients with sepsis (Table 6). The mean age was 65 years (SD: 15.7 years) and 42.9% were female. 238 (65.8%) ICD-coded sepsis patients had at least one comorbidity. Diabetes (n=154 (42.5%)), cancer (n=110 (30.4%)), COPD (n=57 (15.8%)) and congestive heart failure (n=36 (9.9%)) were the most common comorbidities among these patients. Patients with ICD-coded sepsis had a median length of stay in ICU of 6.1 days (IQR: 2.9 days – 12.1 days) and a median length of stay in hospital of 17.3 days (IQR: 7.3 days – 30.8 days). Hospital mortality was 31.6% (Table 6).

Characteristics of Sepsis-Negative Cases identified in Health Administrative Data

469 (56.3%) patients did not have sepsis according to the Jolley definition in HAD (Table 6). The mean age was 61 years (SD: 18.3 years) and 167 (35.6%) were female. 172 (36.7%) had at least one comorbidity, where diabetes (n=133 (28.5%)), cancer (n=79 (16.9%)), peripheral vascular disease (n=67 (14.3%)) and cerebrovascular disease (n= 55 (11.8%)) were most common. The median length of stay in ICU and hospital were 2.7 days (IQR: 1.5 days -5.0 days) and 7.4 days IQR: 3.3 days- 14.5 days), respectively. Hospital mortality was 21.3%.

4.1.3 Infection in Chart Review and Health Administrative Data

Index Infection among Sepsis-Positive Reference Cases based on Chart Review Data

Among the 391 patients with sepsis by chart review, 177 (45.3%) patients had suspected infections with no positive confirmatory microbiology result. Sites of infection included: 216 (55.2%) respiratory infections, 74 (18.9%) bloodstream infections, 68 (17.4%) intra-abdominal infections,

58 (14.8%) urinary infections, 44 (11.2%) skin/soft tissue infections, 11 (2.8%) central nervous system infections, 3 (0.8%) intra-vascular catheter related infections and 7 (1.8%) infections from an unclear source (Table 7). Among the 214 (54.7%) patients who had confirmed infection in chart review, Staphylococcus aureus (n=69 (17.6%)), Escherichia coli (n=61 (15.6%)), Streptococcus (including pneumonia, pyogenes, etc.) (n=34 (8.7%)) and Pseudomonas (including aeruginosa, cloacae) (n=22 (5.6%)) were the most common isolates grown from their cultures (Appendix 8).

Index Infection among Sepsis-Negative Reference Cases based on Chart Review Data

Of the 442 sepsis-negative patients by chart review, 15 (3.4%) had a confirmed or suspected infection, without organ dysfunction (Figure 2). Respiratory (n=8 (1.8%)), urinary (n=5 (1.1%)), intra-abdominal (n=4 (0.9%)), skin/soft tissue (n=3(0.7%)), bloodstream (n=2 (0.5%)) and central nervous system infections (n=1 (0.2%)) were documented among these 15 patients (Table 7). Furthermore, 3 (0.6%) patients with positive cultures grew Streptococcus, while 2 (0.5%) patients each grew E.coli, Klebsiella and Clostridium, according to microbiology results (Appendix 8).

Frequency of Infection Codes among Sepsis-Positive Cases based on Health Administrative Data

Among the 364 (43.7%) patients with ICD-coded sepsis in HAD, 98 (26.9%) patients with ICD-coded sepsis had the septic shock code (R57.2) recorded in the health administrative dataset (Appendix 9). A41.9 (sepsis unspecified, including septicemia) was the most common infection-related ICD code, and was assigned to 108 (29.7%) patients. 221 (60.7%) patients had an ICD code specifying the site of infection where 119 (32.7%) respiratory infections, 77 (21.2%) urinary infections and 25 (6.9%) intra-abdominal infections were recorded. 113 (31.0%) patients had an

ICD code specifying the infectious organism. The most common pathogen-specific codes identified using the Jolley sepsis algorithm were Escherichia coli (n=43 (11.0%)), Clostridium difficile (n=23 (5.9%)), Staphylococcus (n=19 (4.9%)) and Streptococcus (n=9 (2.3%)).

Frequency of Infection Codes among Sepsis-Negative Cases based on Health Administrative Data

Among 469 (56.3%) patients identified as sepsis-negative by HAD, 21 (4.5%) of them had an ICD- coded infectious site. 12 (2.6%) urinary, 6 (1.3%) respiratory and 3 (0.6%) intra-abdominal infections were recorded. 11 (2.3%) patients had an ICD code specifying the infectious organism recorded in HAD. Escherichia coli (n=3 (0.6%)), Clostridium (n=3 (0.6%)), Staphylococcus (n=3 (0.6%)) and Streptococcal (n=2 (0.4%)) were among the most commonly recorded pathogen-specific infection codes (Appendix 9).

Table 7: Identified Sites of Infection among Sepsis-Positive and Negative Patients in Chart Review Data[i] and HAD[ii]

Infectious Site	Sepsis-Positive		Sepsis-Negative	
	Chart Review* (n=391) n (%)	**HAD (n=364) n (%)**	**Chart Review (n=442) n (%)**	**HAD (n=469) n (%)**
Respiratory	216 (55.2)	119 (32.7)	8 (1.8)	6 (1.3)
Bloodstream	74 (18.9)	-	2 (0.5)	-
Intra-abdominal	68 (17.4)	25 (6.9)	4 (0.9)	3 (0.6)
Urinary	58 (14.8)	77 (21.2)	5 (1.1)	12 (2.6)
Skin/Soft Tissue	44 (11.2)	-	3 (0.7)	-
Central Nervous System	11 (2.8)	-	1 (0.2)	-
Intravascular-catheter related	3 (0.8)	-	0	-

i- Chart review data- documented sites of confirmed or suspected infection in the medical chart
HAD- ICD codes included in the Jolley algorithm (Table 5) which describe the site of infection, including: Respiratory infection- J18.9, J44.0; Urinary infection- N39.0; and Intra-abdominal infection- A04.7

* Cumulative proportion exceeds 100% because sepsis-positive patients in the study cohort may have had more than one site of infection.

4.1.4 Acute Organ Dysfunction in Chart Review and Health Administrative Data

Acute Organ Dysfunction among Sepsis-Positive Reference Cases based on Chart Review Data

Patients with sepsis by chart review had a mean composite SOFA score of 8.2 (SD: 3.4). The mean cardiovascular SOFA score was the highest at 3.0 (SD 1.4), followed by respiratory at 2.1 (SD: 1.3), neurological at 1.2 (SD: 1.3), renal at 0.9 (SD: 1.1), hematologic at 0.7 (SD: 1.0) and hepatic score at 0.4 (SD: 0.8). Of the 391 sepsis-positive patients, 280 (71.6%) had more than one acute organ dysfunction. The three most common organ dysfunctions among patients with sepsis in chart review data were cardiovascular dysfunction (n=290 (74.1%)), respiratory dysfunction (n= 260 (66.4%)) and neurological dysfunction (n=115 (29.4%)) (Table 8).

Acute Organ Dysfunction among Sepsis-Negative Reference Cases based on Chart Review Data

Of the 442 patients who were sepsis-negative by chart review data, 395 (89.4%) had at least one organ dysfunction. The mean composite SOFA score for these patients was 6.1 (SD: 3.4). Cardiovascular SOFA scores were the highest, with a mean score of 3.0 (SD:1.4). Respiratory and neurological scores followed, both averaging 1.3 (SD: 1.2 and SD: 1.5, respectively). Renal and hematologic scores had a mean of 0.5 (SD: 0.9 and SD: 0.8, respectively), while hepatic scores were the lowest at 0.2 (SD 0.5). 353 (79.9%) sepsis-negative patients had more than one acute organ dysfunction. The three most common organ dysfunctions among sepsis-negative patients based on chart review data were cardiovascular dysfunction (n=217 (49.1%)), respiratory dysfunction (n=176 (39.8%)) and neurologic dysfunction (n=154 (34.8%)) (Table 8).

Acute Organ Dysfunction among Sepsis-Positive Cases based on Health Administrative Data

Among 364 (43.7%) patients with ICD-coded sepsis in HAD, the most common organ dysfunctions were respiratory dysfunction (n=299 (82.1%)), renal dysfunction (n=155 (42.6%)) and cardiovascular dysfunction (n=92 (25.2%)) (Table 8).

Acute Organ Dysfunction among Sepsis-Negative Cases based on Health Administrative Data

Among 469 (56.3%) patients who did not have ICD-coded sepsis, a total of 370 (78.9%) had at least one organ dysfunction code or procedure code (mechanical ventilation codes for respiratory dysfunction) according to the Jolley sepsis algorithm. Respiratory dysfunction (n= 280 (63.3%)), cardiovascular dysfunction (n=90 (20.4%)) and renal dysfunction (n=86 (19.4%)) were the most common organ dysfunctions recorded in HAD (Table 8).

Table 8: Acute Organ Dysfunctions among Sepsis-Positive and Negative Patients in Chart Review Data[i] and HAD[ii]

Organ system	Sepsis-Positive		Sepsis-Negative	
	Chart Review (n=391) n(%)	**HAD (n=364) n (%)**	**Chart Review (n=442) n(%)**	**HAD (n=496) n(%)**
Respiratory	260 (66.4)	299 (82.1)	176 (39.8)	272 (58.0)
Cardiovascular	290 (74.1)	92 (25.2)	217 (49.1)	80 (17.1)
Neurologic	115 (29.4)	40 (11.0)	154 (34.8)	23 (4.9)
Renal	108 (27.6)	155 (42.6)	56 (12.7)	74 (15.8)
Hematologic	78 (20.0)	24 (6.6)	57 (12.9)	8 (1.7)
Hepatic	45 (11.5)	12 (3.3)	24 (5.4)	8 (1.7)

i- Chart review data- highest daily SOFA score of at least two for one or more organ systems during the first two days after infection diagnosis or ICU admission for all sepsis-positive patients (n=391) and sepsis-negative patients with infection (n=15) , For sepsis-negative patients without infection (n=427), highest SOFA scores were for the first ICU day with organ dysfunction for one or more organ systems

ii- HAD- presence of any ICD code for organ dysfunction or procedure code from the Jolley algorithm (see Table 5) in HAD. Respiratory organ dysfunction included any of the procedure codes for mechanical ventilation (1.GZ.31.CA-ND, 1.GZ.31.CR-ND or 1.GZ.31.GP-ND)

4.1.5 Antimicrobial Information from Chart Review Data and Health Administrative Data

Antimicrobial Administration within one day of Infection Diagnosis for Sepsis-Positive Reference Cases in Chart Review Data

All 391 patients with sepsis, as determined by chart review, were administered at least one dose of an antimicrobial within one day of infection diagnosis as this was part of infection diagnosis criteria. Five antibiotics- piperacillin/tazobactam (n=214 (54.7%)), vancomycin (n=167 (42.7%)), ceftriaxone (n=147 (37.6%)), azithromycin (n=80 (20.5%)) and meropenem (n= 51 (13.0%)) were the most commonly administered antimicrobials within one day of infection diagnosis (Table 9). 323 (82.6%) sepsis-positive patients received their first dose of an antimicrobial during the period from two days before ICU admission to the day of ICU admission.

Antimicrobial Administration for Sepsis-Negative Reference Cases in Chart Review Data

Of the 442 sepsis-negative patients in chart review, all 15 (3.4%) patients with infection but no organ dysfunction received at least one dose of an antimicrobial within one day of infection diagnosis. Of the remaining 427 sepsis-negative patients without an infection diagnosis, 136 (30.8%) were administered at least one dose of an antimicrobial. During the ICU admission. These included 133 (30.1%) patients with no infection and at least one organ dysfunction and 3 (0.7%) patients with neither infection nor organ dysfunction.

Antimicrobial Orders in Health Administrative Data

Antimicrobial Orders for Sepsis-Positive Cases in Health Administrative Data

358 (98.3%) patients with ICD-coded sepsis had at least one antimicrobial order in HAD. Of these, 166 (45.6%) patients had their first antimicrobial order up to two days prior, or on the day of ICU admission.

Antimicrobial Orders for Sepsis-Negative Cases in Health Administrative Data

307 (65.5%) patients without ICD-coded sepsis had at least one antimicrobial order in HAD. Of these, 194 (41.3%) without ICD-coded sepsis had their first antimicrobial order in HAD up to two days prior, or on the day of ICU admission.

Table 9: Types of Antimicrobials administered or ordered for Sepsis-Positive and Negative Patients in Chart Review Data[i] and HAD[ii], respectively

Sepsis-Positive				Sepsis-Negative			
Type of Antimicrobial In Chart Review	**n (%) (n=391)**	**Type of Antimicrobial in HAD**	**n (%) (n=364)**	**Type of Antimicrobial in Chart Review**	**n (%) (n=442)**	**Type of Antimicrobial In HAD**	**n (%) (n=469)**
Piperacillin/tazobactam	214 (54.7)	Piperacillin/tazobactam	113 (31.0)	Piperacillin/tazobactam	50 (11.3)	Cefazolin	95 (20.3)
Vancomycin	167 (42.7)	Ceftriaxone	99 (27.2)	Ceftriaxone	50 (11.3)	Piperacillin/tazobactam	47 (10.0)
Ceftriaxone	147 (37.6)	Vancomycin	61 (16.8)	Vancomycin	28 (6.3)	Ceftriaxone	45 (9.6)
Azithromycin	80 (20.5)	Cefazolin	41 (11.3)	Ancef	23 (5.2)	Vancomycin	19 (4.1)
Meropenem	51 (13.0)	Azithromycin	25 (6.9)	Flagyl	22(5.0)	Metronidazole	18 (3.8)

i- Chart review data- antimicrobials given within ±1 day of infection diagnosis for infected patients (all sepsis-positive patients (n=391) and sepsis-negative patients with infection (n=15)) or on first day of antimicrobial therapy for non-infected patients (sepsis-negative patients without infection (n=427)

ii- HAD- antimicrobials from the first day of antimicrobial ordering during the ICU admission

Concordance between Antimicrobial Information from Chart Review Data versus Health Administrative Data

We assessed whether each initial order of an antimicrobial agent (by type) identified in the chart review was also captured in HAD. 291 (74.4%) sepsis-positive patients had antimicrobials administered within one day of infection diagnosis documented in the chart review with corresponding orders also recorded in HAD (Table 10). However, 100 (25.6%) patients with sepsis had discordant antimicrobial records across the two data sources for the following reasons: no record of ordering in HAD for at least one of the antimicrobials collected in chart review (n= 45 (45.0%)), different antimicrobial(s) recorded in HAD than what was recorded in chart review (n=32 (32.0%)) and antimicrobial order(s) present in HAD but outside of the time window corresponding to chart review collection period (n=23 (23.0%)).

There was concordance between antimicrobials administered in chart review data and antimicrobials ordered in HAD among 416 (94.1%) sepsis-negative patients. For these patients the antimicrobials collected in chart review data were also recorded in HAD, or no antimicrobials were recorded in either data source. 26 (5.9%) patients had discordant records for the following reasons: no record of ordering for at least one of the antimicrobials collected in chart review in HAD (n= 13 (50.0%)), at least one antimicrobial order in HAD with none collected during chart review (n=6 (23.1%)), antimicrobial order(s) present in HAD but outside of time window corresponding to chart review collection period (n=4 (15.4%)) and different antimicrobial(s) recorded in HAD than collected in chart review (n=3 (11.5%)).

Table 10: Concordance between Antimicrobials administered according to Chart Review Data and Antimicrobials ordered according to HAD

	Sepsis-Positive by chart review (n= 391) n (%)	**Sepsis-Negative by chart review (n=442) n (%)**
Concordant [i]	291 (74.4)	416 (94.1)
Discordant [ii]	100 (25.6)	26 (5.9)

i- Concordant-all antimicrobials collected during chart review also recorded in HAD, or no antimicrobials recorded in both chart review data and HAD

ii- Discordant- some or none of the antimicrobials collected during chart review recorded in HAD

Duration of Antimicrobial Therapy based on Health Administrative Data

Duration of Antimicrobial Therapy among Sepsis-Positive Reference Cases in Health Administrative Data

The median duration of an antimicrobial order among sepsis-positive patients identified by chart review was 6 days (IQR: 3 days–- 10 days).

Duration of Antimicrobial Therapy among Sepsis-Negative Reference Cases in Health Administrative Data

The median duration of an antimicrobial order among sepsis-negative patients identified by chart review was 3 days (IQR:1 day – 6 days).

Duration of Antimicrobial Therapy among Sepsis-Positive Cases in Health Administrative Data

Patients with ICD-coded sepsis had an antimicrobial order consecutively for a median duration of 6 days (IQR: 4 days -12 days).

Duration of Antimicrobial Therapy among Sepsis-Negative Cases in Health Administrative Data

Among patients who did not meet ICD-coded sepsis criteria, the median duration of consecutive days of an antimicrobial order was 3 days (IQR: 1 day-6 days).

Table 11: Duration[i] of Antimicrobial administration for Sepsis-Positive and Negative Patients recorded in HAD

Duration (days)	Sepsis-Positive		Sepsis-Negative	
	Chart Review (n=391) n (%)	HAD (n=364) n (%)	Chart Review (n=442) n (%)	HAD (n=469) n (%)
0	5 (1.3)	23 (6.3)	162 (36.7)	230 (49.0)
1	54 (13.8)	19 (5.2)	98 (22.2)	47 (10.0)
2	30 (7.7)	25 (6.9)	30 (6.8)	35 (7.5)
3	21 (5.4)	25 (6.9)	29 (6.6)	25 (5.3)
4	51 (13.0)	42 (11.5)	20 (4.5)	29 (6.2)
5	23 (5.9)	20 (5.5)	16 (3.6)	19 (4.1)
6	47 (12.0)	42 (11.5)	22 (5.0)	27 (5.8)
7+	160 (40.9)	168 (46.2)	65 (14.7)	57 (12.2)

i- Consecutive number of days of administration for each antimicrobial defined as the number of calendar days from start date to end date recorded in HAD.

4.2 Primary Objective 1: External Validation of the Jolley Sepsis Algorithm

4.2.1 Summary of Sensitivity and Specificity

284 patients were correctly classified as sepsis-positive (true positives) and 362 patients were correctly classified as sepsis-negative (true negatives) by the existing Jolley sepsis algorithm in HAD. There were 107 patients with sepsis according to chart review data, who were misclassified as sepsis-negative (false negatives) in HAD, and 80 patients who did not have sepsis in the chart review were misclassified as sepsis-positive (false positives) in HAD (Table 12). The Jolley sepsis algorithm had a sensitivity of 72.6% (95% CI: 69.6% - 75.7%) and a specificity of 81.9% (95% CI: 79.3% - 84.5%) when applied to our TOH ICU cohort.

4.2.2 Misclassification with the Jolley Sepsis Algorithm

We examined the ICD codes recorded for patients misclassified by the Jolley sepsis algorithm in HAD, specifically among false negatives (n=107) and false positives (n=80) (Appendix 9). The most frequently recorded code from the Jolley algorithm in both groups was 1.GZ.31.CA-ND (invasive ventilation), present in 50 (46.7%) false negatives and 55 (68.8%) false positives. Among false positives, 68 patients (85.0%) were judged as non-infectious based on chart review. Notably, the ICD code A41.9 for unspecified sepsis appeared among 7 (8.8%) patients who were classified as sepsis-positive by chart review, but were not identified by the algorithm due to the absence of an organ dysfunction code in health administrative data.

4.3 Primary Objective 2: Modification of the Jolley Sepsis Algorithm by adding antimicrobial information from Health Administrative Data

4.3.1 Primary Objective 2a: Sensitivity and Specificity of the Modified Jolley Sepsis Algorithm with the Addition of at Least One Order of any Antimicrobial from Health Administrative Data

First, we measured the sensitivity and specificity of a modified Jolley sepsis algorithm by adding records of at least one order of any antimicrobial. Figure 3 illustrates the performance characteristics of these algorithms. Sensitivity of the algorithm increased from 72.6% (95% CI: 69.6%-75.7%) to 99.5% (95% CI: 99.0%-100.0%), whereas specificity decreased from 81.9% (95% CI: 79.3%-84.5%) to 36.2% (95% CI: 32.9%-39.5%).

4.3.2 Primary Objective 2b: Sensitivity and Specificity of the Modified Jolley Sepsis Algorithm with the Addition of Antimicrobial Duration Information from Health Administrative Data

The consecutive number of days of antimicrobial therapy was then added to the Jolley sepsis algorithm. The combination of the Jolley sepsis algorithm and use of any antimicrobial for at least one day produced the greatest sensitivity of 96.4% (95% CI: 95.2%-97.7%) and reduced specificity to 12.2% (95% CI: 10.0%-14.4%). As the duration of antimicrobial therapy increased to seven days, algorithm sensitivity progressively decreased to 80.8% (95% CI: 78.1%-83.5%), whereas specificity increased to 39.6% (95% CI: 36.3%-42.9%).

4.3.3 Comparative Performance of the Modified Jolley Sepsis Algorithms with the Addition of Antimicrobial Information from Health Administrative Data

The addition of at least one order of any antimicrobial over any duration produced a relative true positive fraction (rTPF) of 1.04 (95% CI: 1.01-1.08) and false positive fraction (rFPF) of 3.52 (95% CI: 2.80-4.43) (Table 12). When consecutive days of antimicrobial administration was included, rTPF decreased from 1.32 (95% CI: 1.32-1.32) for antimicrobials for at least one day to 0.91 (95% CI: 0.87-0.95) for antimicrobials for at least seven days. Similarly, rFPF also decreased from 4.85 (95% CI: 3.89-6.05) to 3.34 (95% CI: 2.65-4.20) with these modifications to the algorithm.

4.4 Primary Objective 3: Sensitivity and Specificity of the modified Jolley Sepsis Algorithm with the Addition of Antimicrobial Information from Health Administrative Data and Removal Infection Codes

When applied to HAD for our study cohort, the algorithm with organ dysfunction codes and no infection codes improved sensitivity to 83.4% (95% CI: 80.8% - 85.9%) but decreased specificity to 26.9% (95% CI: 23.9% - 29.9%) (Figure 3). Additionally, we estimated the performance characteristics of the Jolley algorithm with the removal of infection codes with any dose of any antimicrobial given over any duration. This algorithm had a sensitivity of 99.7% (95% CI: 99.4%-100.0%) and a specificity of 13.6% (95% CI: 11.2%-15.9%). The combination of organ dysfunction ICD codes and any antimicrobial for at least one day produced a sensitivity of 98.7% (95% CI: 98.0%-99.5%) and a specificity of 4.8% (95% CI: 3.3%- 6.2%). The consecutive number of days of antimicrobial therapy was then added to this modified version of the Jolley sepsis

algorithm. As the duration of antimicrobial therapy increased to seven days, algorithm sensitivity progressively decreased to 88.8% (95% CI: 86.6%-90.9%), whereas specificity increased to 11.1% (95% CI: 9.0%-13.2%).

4.4.1 Comparative Performance of the Modified Jolley Sepsis Algorithms with the Addition of Antimicrobial Information from Health Administrative Data and Removal of Infection Codes

Removal of infection codes produced an rTPF of 1.01 (95% CI: 0.97-1.05 and rFPF of 4.04 (95% CI: 3.22-5.06). Both measures of relative accuracy increased to 1.33 (95% CI: 1.32-1.34) and 4.78 (95% CI: 3.83-5.96), respectively with the addition of at least one order of any antimicrobial over any duration (Table 12). rTPF for all algorithms which included consecutive days of antimicrobial administration was within the range 1.31 (95% CI: 1.30-1.32) to 1.34 (95% CI: 1.33-1.35), while rFPF increased from 5.26 (95% CI: 4.23-6.55) to 4.91(95% CI: 3.94-6.12) as duration increased from one day to seven days.

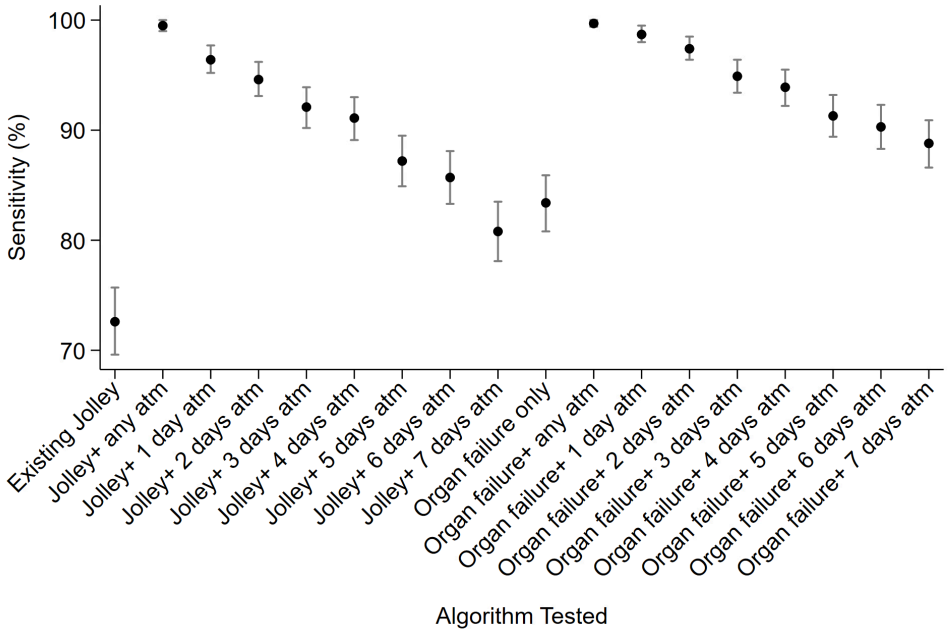
4.5 Secondary Objective: Effect of Modifying the Jolley sepsis algorithm by Adding Antimicrobial Order and Duration Data from Health Administrative Data on Predictive Values

4.5.1 Positive and Negative Predictive Values across Modified Algorithms

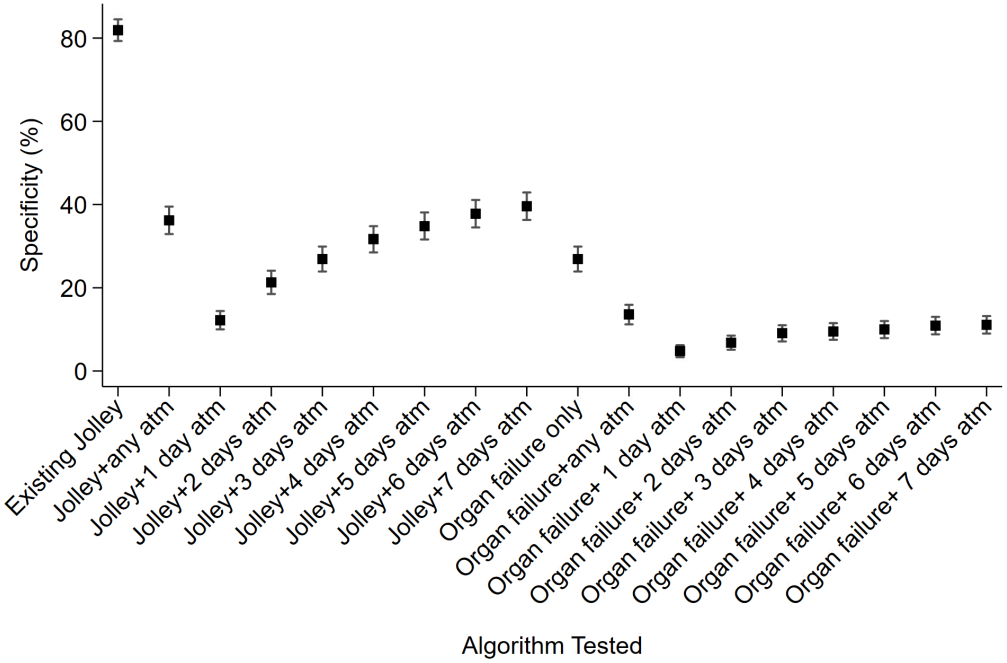
Positive and negative predictive values for each of the modified algorithms were derived as described in Section 2.3.4 and are summarized in Appendix 10.

Figure 3: A) Sensitivity of the Existing and Modified Jolley Sepsis Algorithms with 95% Confidence Intervals. B) Specificity of the Existing and Modified Jolley Sepsis Algorithms with 95% Confidence Intervals

A)



B)



Legend: atm-antimicrobials

Table 12: Performance Characteristics of the Existing and Modified Jolley Sepsis Algorithms

Algorithm Tested	TP (n)	FN (n)	FP (n)	TN (n)	rTPF n (95% CI)	rFPF n (95% CI)
Existing Jolley algorithm	284	107	80	362	*Reference*	*Reference*
Jolley with any antimicrobial for any duration	389	2	282	160	1.04 (1.01-1.08)	3.52 (2.80-4.43)
Jolley criteria or any antimicrobial for at least 1 day	377	14	388	54	1.32 (1.32-1.32)	4.85 (3.89-6.05)
Jolley criteria or any antimicrobial for at least 2 days	370	21	348	94	1.30 (1.29-1.31)	4.35 (3.48-5.44)
Jolley criteria or any antimicrobial for at least 3 days	360	31	323	119	1.06 (1.03-1.10)	4.04 (3.22-5.06)
Jolley criteria or any antimicrobial for at least 4 days	356	35	302	140	1.02 (0.99-1.06)	3.77 (3.01-4.74)
Jolley criteria or any antimicrobials for at least 5 days	341	50	288	154	0.98 (0.94-1.02)	3.60 (2.86-4.52)
Jolley criteria or any antimicrobial for at least 6 days	335	56	275	167	0.95 (0.91-0.99)	3.44 (2.73-4.32)
Jolley criteria or any antimicrobial for at least 7 days	316	75	267	175	0.91 (0.87-0.95)	3.34 (2.65-4.20)
Organ failure codes only	326	65	323	119	1.01 (0.97-1.05)	4.04 (3.22-5.06)
Organ failure codes or any antimicrobial for any duration	390	1	382	60	1.33 (1.32-1.34)	4.78 (3.83-5.96)
Organ failure codes or antimicrobial for at least 1 day	386	5	421	21	1.34 (1.33-1.35)	5.26 (4.23-6.55)
Organ failure codes or antimicrobial for at least 2 days	381	10	412	30	1.34 (1.33-1.35)	5.15 (4.14-6.41)
Organ failure codes or antimicrobial for at least 3 days	371	20	402	40	1.33 (1.32-1.34)	5.02 (4.03-6.26)
Organ failure codes or antimicrobial for at least 4 days	367	24	400	42	1.32 (1.31-1.33)	5.00 (4.01-6.23)
Organ failure codes or antimicrobial for at least 5 days	357	34	398	44	1.32 (1.31-1.33)	4.97 (3.99-6.20)
Organ failure codes or antimicrobial for at least 6 days	353	38	394	48	1.31 (1.30-1.32)	4.92 (3.95-6.14)
Organ failure codes or antimicrobial for at least 7 days	347	44	393	49	1.31 (1.30-1.32)	4.91 (3.94-6.12)

Chapter 5: Discussion

5.1 Validation of the Existing Jolley Sepsis Algorithm in the TOH ICU Cohort

Our results showed that the sepsis algorithm derived by Jolley et al performs reasonably well in identifying sepsis cases among critically ill patients admitted to TOH Civic and General campus ICUs. Of the 833 patients included in the study, 391 patients (46.9%) met the Sepsis-3 criteria based on the manual chart review data, closely approximating the 51.8% prevalence reported in the Jolley validation study[4] conducted in Calgary ICUs. This consistency supports the broader applicability of the algorithm across geographically and structurally distinct healthcare settings. However, differences in patient case mix may explain subtle discrepancies in algorithm performance. In the Jolley's cohort, 70.6% had at least one Charlson comorbidity, as compared to 49.5% of our TOH cohort. This suggests a higher burden of chronic illness and possibly greater acuity in the original validation sample, which may partially account for the higher sepsis prevalence observed in Calgary.

The Jolley algorithm defines sepsis in HAD as the presence of the ICD code R57.2 for septic shock, or a combination of ICD codes for infection and organ dysfunction[4]. Although the R57.2 ICD code captured 92 (23.5%) true positive cases in our cohort, the majority of true positives were identified using the combination of infection and organ dysfunction codes. However, this method also produced several misclassified cases. Among both true positives and false positives, the procedure code for invasive mechanical ventilation (1.GZ.31.CA-ND) was commonly present. This reflects the fact that organ dysfunction requiring ventilation in ICU is not specific to sepsis and may be driven by diverse etiologies, including trauma, heart failure, or non-infectious

inflammatory conditions. Additionally, organ dysfunctions identified in chart review, except respiratory and renal dysfunction, were significantly undercoded in HAD. Cardiovascular dysfunction was the most undercoded, among sepsis-positive cases (74.1% in chart review versus 25.2% in HAD) and sepsis-negative cases (49.1% chart review versus 17.1% in HAD). This undercoding likely stems from limitations inherent in administrative coding practices. Coders are less likely to capture the full extent of cardiovascular dysfunction in the ICU, as coding is done retrospectively after hospital discharge and does not incorporate real-time clinical parameters such as mean arterial pressure, vasopressor use, or cardiac output, all of which are integral to clinical diagnoses of cardiovascular compromise but are not well-reflected in ICD coding standards.

While index infections were captured during chart review, HAD captured infection-related codes for the entire ICU admission. As these codes are not specific to the timing or clinical relevance of the infection, they may reflect secondary infections occurring later in the ICU stay rather than the index infection. This broader capture likely explains why 85.0% of false positives in our analysis had an infection code present in HAD that was not documented as an index infection in the chart review.. We also detected several infection codes in HAD corresponding to index infections identified during medical chart reviews, that are not part of Jolley criteria. These codes included: J15.1- Pneumonia due to Pseudomonas, G00.2- Streptococcal meningitis, T84.7- Infection and inflammatory reaction due to other internal orthopedic prosthesis, T84.53- Infection and inflammatory reaction due to hip prosthesis, T84.68- Infection and inflammatory reaction due to internal fixation device of bones at other site, T83.5- Infection and inflammatory reaction due to prosthetic device, implant and graft in urinary, T87.47- Infection of below knee amputation stump,

T87.48- Infection of other amputation stump, T81.4- Infection following a procedure, not elsewhere classified and K57.2- diverticular disease of large intestine with perforation and abscess. Incorporating these additional codes could improve algorithm sensitivity without sacrificing specificity, and may better reflect the range of infections encountered in ICU settings.

5.2 Derivation and Validation of the Modified Jolley Sepsis Algorithms

Ideally, a valid ICD-coded sepsis definition should maximize both sensitivity and specificity. However, when the goal is to identify cases of a particular disease in a population, an algorithm's sensitivity is a critical diagnostic accuracy measure because it determines the extent to which true cases are captured. Algorithms with poor sensitivity could substantially underestimate disease burden, which in turn risks misinforming health system planning, resource allocation or surveillance activities. Conversely, maintaining high specificity remains essential as it minimizes false positives that can inflate incidence estimates and ensures that observed variations reflect true differences in burden of disease rather than errors in classifying cases. In the context of this study, our main objective was to increase sensitivity and maintain specificity of the existing Jolley algorithm by adding antimicrobial usage data. This approach was intended to reduce missed cases without compromising the accuracy of classification.

Antimicrobial usage in the ICU is widespread given the risk of infection among critically ill patients. The severity of infections in the ICU also requires prompt initiation of antimicrobials, leaving little room for withdrawal or de-escalation of therapy[57]. Additionally, many non-infectious conditions mimic the clinical signs of infection, contributing further to high antimicrobial usage. Point prevalence studies reviewing global antimicrobial prescribing practices among adult ICU

patients report 47.7% to 71% receiving antimicrobials as prophylaxis or treatment[61,62]. In Canadian hospitals, the prevalence of antimicrobial use among adult ICU patients was estimated to range from 60% to 67% during the period 2002 to 2017[63]. 79.8% of patients among our study cohort had at least one antimicrobial order recorded in administrative data during or before ICU admission. 74.4% of sepsis-positive patients by chart review among our study cohort had at least one antimicrobial order recorded in administrative data before admission to the ICU. Additionally, the greater proportion of new antimicrobial orders observed in patients with sepsis by chart review versus those who did not (28.8% vs. 1.6%) reflects clinical patterns and further supports antimicrobial use as a meaningful proxy indicator for suspected infection.

All patients with sepsis by chart review data in our study cohort received at least one dose of an antimicrobial in the ICU, as it was part of the criteria for identifying sepsis-positive reference cases. Therefore, near perfect sensitivity of 99.5% (95% CI: 99.0%-100.0%) was achieved when the administration of any antimicrobial over any duration was added to the Jolley algorithm. Similarly, 99.7% (95% CI: 99.4%-100.0%) sensitivity was observed when any antimicrobial for any duration was combined with Jolley organ dysfunction codes. Overall, the addition of any antimicrobial data, including administration of any antimicrobial for at least one day, up to at least seven days can also improve sensitivities as compared to the existing Jolley sepsis algorithm. These results suggest that antimicrobial use is a powerful augmenting variable for detecting potential sepsis cases. However, this gain in sensitivity came at a considerable cost to specificity, which dropped as low as 4.8% (95% CI: 3.3%-6.2%) and never exceeded 36.2% (95% CI: 32.9%-39.5%) across all modified versions of the algorithm. Together, these metrics suggest that the modified algorithms lack accuracy and are likely to incorrectly classify patients as sepsis-positive.

Overestimating sepsis prevalence has serious implications. From a health system perspective, it may distort the burden of sepsis and lead to inefficient resource allocation. At the patient level, false-positive sepsis classification can result in overtreatment, unnecessary exposure to broad-spectrum antimicrobials, increased risk of antimicrobial resistance, and misdirection away from more accurate diagnoses. These consequences also carry economic costs and potential harm to patient safety.

Further analysis of the false positive results suggested that patients admitted to the ICU with suspected infections, where infection was never ruled out as a possible cause of the patient's presentation were responsible for these misclassifications. These were cases where cardiogenic versus septic shock were included in the differential diagnosis, as well as polytrauma patients who developed infection(s) during the ICU admission. The number of false positives progressively increased with the introduction of antimicrobial therapy duration data in the algorithm. These findings underscore a key challenge: administrative data capture the intention to treat infection (e.g., initiation of antimicrobials), but not the eventual clinical confirmation of sepsis. As we increased the antimicrobial duration threshold in the algorithm, the number of false positives increased correspondingly, reflecting the non-specific nature of antimicrobial exposure in critical care.

As a result, antimicrobial exposure in critical care, which is common and often precautionary, becomes a non-specific signal that inflates false positives when used without additional clinical context. These findings reinforce that antimicrobial use is an imperfect proxy for confirmed

infection and that relying solely on duration-based criteria introduces meaningful misclassification. . Future work should explore ways to differentiate empiric use from confirmed infection. Promising directions include linking administrative datasets to microbiology results, incorporating procedure or diagnostic codes that signal confirmed infection, integrating time-stamped clinical data (e.g., lactate trends, culture ordering patterns), or using treatment trajectories such as antimicrobial de-escalation or narrowing of spectrum as markers of confirmation..

Our modified algorithms demonstrated higher sensitivity than the Jolley algorithm and other administrative definitions identified in our systematic review (Appendix 1), including those from international studies such as Rhee et al. (U.S.) and the Angus criteria[64]. For example, Rhee et al.'s CDC surveillance definition based on EHR data reported a sensitivity of 70% and specificity of 72% when compared to Sepsis-3 chart review. In contrast, our modified algorithm achieved near-perfect sensitivity but at the expense of very low specificity.

The undercoding of sepsis in HAD, as observed in this and other studies, may stem from various factors, including lack of standardized documentation practices, retrospective coding disconnected from real-time clinical data, and variability in the recognition and documentation of organ dysfunction. These limitations further support the need for enhanced and standardized coding guidelines and, where possible, linkage of administrative data with richer clinical datasets.

5.3 Study Strengths

This study has a number of strengths. First, the sepsis algorithms were validated by establishing ICU patients' sepsis diagnosis by manual chart reviews. Sepsis-3 criteria, which is the most current consensus definition for sepsis, was applied to the study cohort. While Sepsis-3 criteria were not in clinical use during the first two years of the study period, applying it retrospectively does not compromise the validity of the reference standard. We used standardized clinical data elements, such as confirmed/suspected infection, SOFA-based organ dysfunction criteria, was routinely documented in the medical record regardless of which sepsis definition guided bedside management at the time. Because these data elements were abstracted directly from charts independent of clinicians' real-time diagnostic labeling, the retrospective application of Sepsis-3 ensured a consistent and clinically meaningful standard against which to evaluate administrative data algorithms. We also excluded any patients with insufficient data in their chart to determine sepsis diagnosis according to the Sepsis-3 criteria. In addition to laboratory values and microbiological results, we referenced additional clinical records during the medical chart review, such as admission notes, progress notes, consult notes, ICU transfer summaries, discharge summaries. This depth of review increases the accuracy of case classification. To further ensure diagnostic fidelity, the chart review process was conducted by a multidisciplinary team that included a physician reviewer. Ambiguous or borderline cases were adjudicated through team discussions involving both an intensivist and an epidemiologist, reducing the likelihood of misclassification and enhancing the internal validity of the sepsis determinations.

Additionally, the study sample was selected from TOH's General and Civic campus ICUs which admit patients from a large geographical area. These ICUs admit patients with a wide range of

medical and surgical conditions, increasing the representativeness and generalizability of the findings to other Canadian academic hospital ICUs and potentially to similar high-income healthcare settings.

5.4 Study Limitations

This study has several limitations. While we applied the Sepsis-3 definition consistently to chart review data, reliance on hand-written, paper notes from patients' medical charts may have introduced misclassification due to incomplete documentation, diagnostic uncertainty, or ambiguous clinical narratives. However, ICU patients typically undergo comprehensive work-ups, and our review process included multiple clinical sources, such as progress notes, consults, and discharge summaries, reducing the likelihood of systematic omissions.

Additionally, all patient medical records reviewed in this study were documented before the introduction of the EPIC electronic medical records system at TOH, in June 2019. This transition has important implications for both the internal validity of our algorithm and its external applicability. The absence of structured, time-stamped data meant that reviewers reconstructed organ dysfunction trajectories manually, which is inherently less precise than reviewing integrated EMR flowsheets. Future validations using EPIC data, with its standardized fields for laboratory values, vitals, and medication administration, may yield more reproducible application of Sepsis-3 criteria and could refine the estimates presented in this study.

The transition from SIRS-based to SOFA-based sepsis diagnostic criteria likely affected case identification and influenced the observed performance of ICD-coded sepsis definitions. Cases

coded as sepsis-positive in 2014–2015 may not all meet Sepsis-3 criteria, and vice versa. This definitional mismatch may lead to apparent under- or over-estimation of algorithm sensitivity and specificity compared with real-time case classification.

It is also difficult to ascertain whether antimicrobials ordered by a patient's treating physician documented in the physician's orders, which serves as the source document for pharmacy data captured in HAD, were administered to the patient. This is particularly challenging when physicians' orders may be given verbally, and antimicrobials which are already stocked in the ICU are initiated. These may not have been accurately captured in health administrative data before the EPIC electronic medical records system, which currently captures all pharmacy orders and medication administration electronically. Consequently, administration and order data may not be fully concordant, which could bias estimates of antimicrobial exposure and, by extension, the performance of sepsis algorithms incorporating this variable. For 84.9% of our study cohort, antimicrobials given according to chart review data were accurately captured as ordered in HAD. However, 25.6% of patients with sepsis according to Sepsis-3 criteria had only some or none of the antimicrobials collected during chart review recorded in HAD. Missing antimicrobial orders may cause sepsis cases meeting Sepsis-3 criteria to be incorrectly classified as sepsis negative by the modified algorithms. This reduces sensitivity and overall validity of the modified algorithms. Improving the completeness and accuracy of antimicrobial data in HAD would therefore strengthen the fidelity, sensitivity, and clinical relevance of sepsis algorithms.

Our use of both explicit and implicit coding strategies in HAD introduced additional complexity. The implicit strategy, which classifies sepsis based on the co-occurrence of infection and organ

dysfunction codes, risks misclassification, especially when these two diagnoses are clinically unrelated. With admission dates serving as proxies for diagnosis dates in HAD, distinguishing the temporal relationship between infection and organ dysfunction diagnoses is challenging. For instance, a patient with a urinary tract infection and unrelated acute kidney injury may be incorrectly flagged as having sepsis. While this approach improves sensitivity, it reduces specificity and can distort true sepsis burden estimates, especially in administrative datasets that lack temporal resolution.

Variation in both coding practices and antimicrobial prescribing patterns across institutions may limit the generalizability of our findings. The coding intensity and diagnostic behaviour of physicians, the availability of infectious disease services, and formulary differences across hospitals can all influence how sepsis and infection are recorded in administrative data. Our cohort, while representative of a large tertiary care academic center in Ontario, may not reflect practice patterns in smaller, rural, or non-academic settings.

Finally, the study was conducted using a single-center dataset drawn from two campuses within one hospital system. While this enhances internal consistency, it may constrain external validity. Multi-center validation across different health systems, EMR platforms, and jurisdictions would be necessary to determine whether the performance characteristics of both the existing and modified Jolley algorithms are stable in other contexts.

5.5 Clinical and Policy Implications and Areas for Future Research

The integration of antimicrobial data with existing ICD and procedure codes can enhance the identification and management of sepsis. Our research's specific contributions and implications are provided below.

5.5.1 Improved Sepsis Identification

Adding antimicrobial data to existing code-based definitions could significantly enhance the accuracy and specificity of sepsis identification. Currently, changes in coding practices have led to an apparent increase in sepsis incidence, which may not necessarily reflect true clinical changes[65]. This issue arises from the limitations in the specificity of ICD codes, which can sometimes lead to over-diagnosis or misclassification of sepsis. By integrating antimicrobial data, clinicians can more reliably differentiate between sepsis and other similar inflammatory or infectious conditions. This refinement in identification can help ensure appropriate treatment and management of patients, potentially reducing mortality rates associated with misdiagnosed or delayed treatment of sepsis.

5.5.2 More Precise Epidemiological Data

Refining sepsis definitions through the integration of antimicrobial data can provide more accurate and reliable epidemiological data concerning the incidence, prevalence, and outcomes of sepsis[66]. Improved data quality is vital for several reasons: it enhances the accuracy of public health surveillance, aids in resource allocation, and informs clinical practice. With more precise data, healthcare providers and policymakers can better understand the burden of sepsis and the quality

of life of sepsis survivors, evaluate the effectiveness of interventions, and prioritize healthcare services and funding accordingly. This leads to better-prepared health systems that can effectively manage sepsis cases and improve patient outcomes.

5.5.3 Enhanced Understanding of Antimicrobial Use

Incorporating antimicrobial data into the definitions of sepsis could also demonstrate antimicrobial prescribing patterns in sepsis cases[67]. This analysis is invaluable for antimicrobial stewardship programs, as it helps identify trends in the use of antimicrobials, including potential overuse or misuse. Understanding prescribing patterns can aid in assessing the appropriateness of empiric antibiotic choices and guide adjustments to treatment guidelines to combat antibiotic resistance. Furthermore, this insight can foster targeted educational initiatives to promote optimal antimicrobial usage among healthcare providers, ultimately leading to more effective and judicious use of these critical medications.

5.5.4 Recommendations for Future Research

This study highlights several important avenues for future research aimed at improving the identification of sepsis in HAD. A key priority is to refine sepsis detection algorithms to enhance specificity without compromising sensitivity. While the addition of antimicrobial usage data significantly increased sensitivity, it also introduced substantial false positives. Future efforts should explore integrating clinical context, such as infection site, diagnostic certainty, or severity markers, to better distinguish true sepsis cases from other critical illnesses that also involve organ dysfunction or empiric antimicrobial use.

A second important direction is the integration of richer clinical data sources with administrative data. The limitations of ICD-based coding could be addressed by linking HAD to EMRs, pharmacy administration data, laboratory results, and bedside clinical observations. This would allow algorithms to incorporate real-time clinical indicators, such as vasopressor requirements, lactate levels, or respiratory support, which are more specific to sepsis-related organ dysfunction than retrospective coding.

In addition, external validation across diverse settings is essential. The performance of sepsis algorithms may vary substantially depending on coding practices, ICU case mix, availability of infectious disease consultation, and institutional antimicrobial stewardship protocols. Multi-centre studies using data from different hospitals, regions, and health systems will be important to assess generalizability and refine algorithm parameters for local use.

Efforts to standardize sepsis and organ dysfunction coding practices would also improve the reliability of administrative data for surveillance. Collaboration with health information professionals and medical coders may help identify barriers to accurate coding and inform the development of updated coding guidance or targeted training to better reflect Sepsis-3 criteria in practice.

Furthermore, in-depth characterization of false positives and false negatives is needed to understand why misclassification occurs and how to prevent it. Qualitative or mixed-methods investigations of discordant cases could uncover patterns in clinical presentation, diagnostic

ambiguity, or data entry that influence algorithm performance. These insights could guide algorithm refinement or suggest additional data elements worth capturing.

Finally, as datasets grow in size and complexity, there is significant potential to leverage machine learning and natural language processing to improve sepsis identification. These advanced analytic methods can model non-linear relationships and incorporate unstructured data, such as free-text clinical notes, to detect sepsis more accurately than rule-based approaches alone.

By addressing these areas, future research can advance the development of robust, scalable, and clinically meaningful tools for sepsis surveillance using routinely collected health data, ultimately supporting more accurate burden estimation, quality monitoring, and health system planning.

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Appendix

Appendix 1: Characteristics of Studies Included in the Updated Systematic Review and Summary of Diagnostic Measures Reported

Author/Year	Country/ Number of Centers/ Sample Size	Type of Administrative Database	Sepsis Algorithm Used	Sepsis Reference Standard	Performance Characteristics	Antimicrobial Data Included in Sepsis Algorithm?	Sample Size Calculation?
Database: sepsis hospitalizations pre-selected							
Madsen et al 1998	Denmark Single center N=377	Pre-selected random sample of general admissions with sepsis from a hospital database	Madsen	Bacteremia database (no manual chart review)	Sn 5.9% PPV 21.7%	No	No
Ollendorf et al 2002	USA 10 centers N=122	Pre-selected sample of sepsis patients enrolled in a severe sepsis clinical trial from a claims database	Modified sepsis-1	Clinical trial patients with severe sepsis	PPV 75.4%	No	No
Schneeweiss et al 2007	USA Single center N=158	Pre-selected sample of all admissions with specific bacterial infections from a Veterans	Schneeweiss	Chart review	PPV 91%	Yes (per their algorithm – type, route, duration for the specific infections)	No

		Affairs database					
Grijalva et al 2008	USA All hospitals in Tennessee N=336	Pre-selected sample of patients with RA from a hospital database	Grijalva	Chart review	PPV 80%	No	No
Cevasco et al 2011	USA 28 centers N=112	Pre-selected sample of general surgical admissions from Veterans Affairs database	Patient safety index (PSI) for post-operative sepsis	Chart review	PPV 53%	No	Yes
Whittaker et al 2013	USA Single center N=100	Pre-selected sample of ED admitted patients with sepsis from a hospital database	Explicit Angus	Chart review	Explicit (severe sepsis) Sn 20.5% Angus (severe sepsis) Sn 47.2% Explicit (septic shock) Sn 42.4% Angus (septic shock) Sn 75.1%	No	No
Quan et al 2013	Canada 3 centers N=490	Pre-selected random sample of general	Patient safety index (PSI) for post-	Chart review	Including PSI present on admission	No	Yes

		surgical admissions with post-operative complications from a hospital database	operative sepsis		PPV 9.8% <u>Excluding PSI present on admission</u> PPV 12.5%		
Iwashyna et al 2014	USA Single center N=3,146	Pre-selected sample of all sepsis admissions from a hospital database	Angus Explicit Martin	Chart review	<u>Angus</u> Sn 50.3% Sp 96.3% PPV 70.7% NPV 91.5% <u>ICD-9 explicit</u> Sn 9.3% Sp 100% PPV 100% NPV 86.0% <u>Martin</u> Sn 16.8% Sp 99.8% PPV 97.6% NPV 87.0%	No	No
Ramanathan et al 2014	USA Single center N=243	Pre-selected sample of surgical admissions who died in-hospital mortality from a hospital surgical mortality database	Explicit	Chart review	<u>Explicit</u> Sn 82.3% Sp 78.3% PPV 91.1% NPV 62.1%	No	No

Lauridsen et al 2015	Denmark Single center N=190	Pre-selected sample of shock patients (hypovolemic, cardiogenic and septic) from a national patient registry	Explicit (codes for septic shock only) Combined (shock code with inotrope/ vasopressor codes)	Chart review	<u>Explicit</u> PPV 69.2% <u>Combined</u> PPV 82.4%	No	Yes
Wang et al 2015	USA Multicenter (unspecified) N=379	Pre-selected hospital patients with suspected infection from a longitudinal, population-based study cohort (REGARDS study)	Angus Martin	Chart review	<u>Angus</u> Sn 27.6% Sp 94.6% PPV 78.2% NPV 65.1% <u>Martin</u> Sn 42.6% Sp 85.6% PPV 58.4% NPV 75.9%	No	No
Rhee et al 2016	USA 2 centers N=1000 (600 charts from admissions between 2003-2009 and 400 charts from admissions in 2012)	Pre-selected random sample of hospital patients with at least one blood culture order	Modified Angus Explicit (severe sepsis or septic shock codes only)	Chart review	<u>Modified Angus (2003-2009)</u> Sn 51.6% PPV 52.3% <u>Explicit (2003-2009)</u> Sn 9.4% PPV 100% <u>Modified Angus (2012)</u>	No	No

					Sn 67.4% PPV 55.4% <u>Explicit (2012)</u> Sn 26.1% PPV 96.0%		
Shahraz et al 2017	USA 5% of national hospital data N=1,991,830	Pre-selected random sample of all sepsis admissions from a hospital database	Dombrovsky Martin Wang Angus	Chart review	<u>Dombrovsky</u> Sn 90% Sp 99.7% <u>Martin</u> Sn 87.4% Sp 96.5% <u>Wang</u> Sn 84.7% Sp 38.5% <u>Angus</u> Sn 84.6% Sp 37.2%	No	No
Weise et al 2018	USA 28 centers N=716	Pre-selected hospital patients with serious infection from a hospital database	Schneeweiss/ Grijalva	Chart review	PPV 82.6%	No	No
Liu et al 2020	Hong Kong Single center N=490	Pre-selected hospital patients with suspected infection from a	Sepsis-3 Angus Martin	Chart review	<u>Sepsis-3</u> Sn 93% Sp 86% PPV 85% NPV 93%	Yes (per Sepsis-3 algorithm- timing of administration to collection of body fluid culture)	Yes

		hospital database			<u>Angus</u> Sn 12% Sp 99% PPV 90% NPV 57% <u>Martin</u> Sn 19% Sp 92% PPV 66% NPV 57%		
Churpek et al 2021	USA 3 centers N=2,874	Pre-selected random sample of all sepsis admissions from a hospital database	Sepsis-3 Angus Rhee	Chart review	<u>Sepsis-3:</u> Sn 81% Sp 89% PPV 73.8% NPV 89.7% <u>Angus:</u> Sn 77% Sp 90% PPV 78.2% NPV 87.8% <u>Rhee:</u> Sn 52% Sp 97% PPV 86.2% NPV 79.1%	Yes (used with Rhee and Sepsis-3 algorithms – timing of administration to collection of body fluid culture)	No*
Database: sepsis hospitalizations not pre-selected							
Lawson et al 2012	USA 214 centers N=117,752	Unselected sample of all general surgical	Lawson (post-operative	American College of Surgeons	Sn 46.3% Sp 94.0%	No	No

		admissions from a claims database	complications that included sepsis)	National Surgical Quality Improvement Program (ACS-NSQIP) database (no manual chart review)			
Brandt et al 2015	USA Single center N=2352	Unselected random sample from a hospital database	Explicit	Chart review	Sn 51.6% Sp 99.5% PPV 88.5% NPV 96.8%	No	No
Rhee et al 2017	USA 409 centers N=510	Unselected random sample from a hospital database	Rhee Explicit (codes only for sepsis, septic shock) Angus	Chart review	<u>Rhee</u> Sn 69.7% Sp 98.1% PPV 70.4% NPV 98.0% <u>Angus</u> Sn 66% Sp 90.4% PPV 31.0% NPV 97.6% <u>Explicit</u> Sn 32.3% Sp 99.3% PPV 75.2% NPV 95.7%	Yes (with Rhee algorithm - timing of administration to collection of body fluid culture)	No
Fleishmann-Struzek et al	Germany Single center	Unselected random sample	Explicit Angus	Chart review	<u>Explicit Angus</u> Sn 42%	No	Yes

2018	N=937	of all admissions from a hospital database	Implicit Angus		Sp 99.4% PPV 60% NPV 98.8% <u>Implicit Angus</u> Sn 59% Sp 96% PPV 22% NPV 99%		
Valik et al 2020	Sweden Single center N=1000	Unselected random sample of all admissions from a hospital database	Sepsis-3	Chart review	Sn 88.7% Sp 98.5% PPV 88.1% NPV 98.6 %	Yes (per Sepsis-3 algorithm – timing of administration to collection of body fluid culture)	No
Database: sepsis ICU admissions pre-selected							
Gedeborg et al 2007	Sweden Single center N=7,615	Selected random sample of ICU admissions from a hospital database and intensivist-coded ICU database	Gedeborg (including sepsis wide definition, sepsis narrow definition, community acquired sepsis, pneumonia, CNS infection)	ICU database	<u>Sepsis (wide) ICD-9:</u> Sn 45.7% Sp 97.5% PPV 45.9% NPV 97.5% <u>Sepsis (wide) ICD-10:</u> Sn 52.5% Sp 92.6% PPV 28.0% NPV 97.5% <u>Sepsis (narrow) ICD-9:</u> Sn 17.2%	No	No

					Sp 99.4% PPV 56.1% NPV 96.3% <u>Sepsis (narrow)</u> <u>ICD-10:</u> Sn 20.1% Sp 98.4% PPV 40.9% NPV 95.7% <u>Community acquired sepsis</u> <u>ICD-9:</u> Sn 42.2% Sp 95.5% PPV 7.4% NPV 99.5% <u>Community acquire sepsis</u> <u>ICD-10:</u> Sn 51.5% Sp 92.6% PPV 5.6% NPV 99.6%		
Ibrahim et al 2012	Australia Single center N=254	Pre-selected sample of ICU admissions admitted direct from the ED	Modified Angus	ICU database	<u>Angus (sepsis codes only)</u> Sn 16.5% Sp 99.8% PPV 93.9% NPV 86.8%	No	No

		from a hospital database			Angus (combined) Sn 44.1% Sp 98.9% PPV 88.2% NPV 89.7%		
Database: sepsis ICU admissions unselected							
Jolley et al 2015	Canada 3 centers N=1001	Unselected random sample of both general and ICU admissions from a hospital and ICU database	Modified Angus	Chart review	*ICU population* CIHI (sepsis) Sn 46.4% Sp 98.7% PPV 98.2% NPV 54.7% CIHI (severe Sepsis) Sn 47.2% Sp 97.5% PPV 95.3% NPV 63.2% Optimized (sepsis) Sn 71.9% Sp 85.4% PPV 88.2% NPV 66.6% Optimized (severe sepsis) Sn 65.1%	No	Yes

					Sp 88.2% PPV 85.6% NPV 70.1% *Non-ICU population* <u>CIHI (sepsis)</u> Sn 6.7% Sp 100% PPV 100% NPV 93% <u>CIHI (severe sepsis)</u> Sn 25% Sp 100% PPV 100% NPV 98.5% <u>Optimized (sepsis)</u> Sn 60% Sp 94.7% PPV 52.6% NPV 96.7% <u>Optimized (severe sepsis)</u> Sn 25% Sp 99.5% PPV 50% NPV 98.5%		

Yamana et al 2016	Japan 3 centers N=595	Unselected sample of ICU admissions from a hospital database	Angus Martin	Laboratory results database	<u>Angus</u> Sn 21.7% Sp 98.7% <u>Martin</u> Sn 14.6% Sp 99.5%	No	No
Vermassen et al 2020	Belgium Single center N=8911	Unselected random sample of ICU patients	Explicit (ICD-9 codes for septic shock)	COSARA (an ICU infection database) No chart review performed	Sn 56.0% Sp 97.5% PPV 62.1% NPV 96.8%	No	No

Appendix 2: Data Extraction Forms

A) Admission Data Form

Study ID	Case ID	Hospital Admission Date	ICU Admission Date	Place of Hospital Admission	Place of ICU Admission	Meets Eligibility Criteria?	Multiple ICU Admissions	Transfer summary	Discharge summary	Notes

B) Infection Data Form

Study ID	Case ID	Documentation of Infection	Infection Date	Infection Source 1	Organism Source 1	Organism 1	Antimicrobial Initiation?	Number of Antimicrobials initiated	Antimicrobial Type 1	Antimicrobial Type 2

C) Organ Dysfunction Data Forms

i) Respiratory Dysfunction

Study ID	Case ID	Respiratory Comorbidity	PaO2	SaO2	FiO2	Calculated PF Ratio	Calculated SF Ratio	PF Ratio SOFA Score	SF Ratio SOFA Score

ii) Cardiovascular Dysfunction

Study ID	Case ID	Weight	Vasopressor Use	MAP ≥ 70?	Infusion Type 1	Infusion Dose 1	Infusion Rate 1	CVS SOFA Score 1	Infusion Type 2	Infusion Dose 2	Infusion Rate 2	CVS SOFA Score 2	Infusion Type 3	Infusion Dose 3	Infusion Rate 3	CVS SOFA Score 3	Vasopress >12 Hrs?

iii) Coagulation Dysfunction

Study ID	Case ID	Comorbid Thrombocytopenia	Platelets	Platelets SOFA Score	Comorbid Liver Disease	Bilirubin	Bilirubin SOFA

iv) Central Nervous System Dysfunction

Study ID	Case ID	GCS	GCS SOFA Score

v) Renal Dysfunction

Study ID	Case ID	Chronic ESRD	RRT	Creatinine	Creatinine SOFA Score

vi) Lactate

Study ID	Case ID	Lactate	Lactate Score

Appendix 3: Infectious Sites Included in Chart Review

Source	Samples
Lung	Any organism grown from positive cultures from lung or pleural space including: -Sputum, bronchoscopy samples, tracheal aspirates, direct tissue biopsy -Pleural fluid, pleural biopsy -Positive nasopharyngeal swab
Bloodstream	Any organism grown from positive culture from the blood
Intravascular catheter-related	Any organism grown from positive culture from intravascular catheter: -Catheter tip culture -Positive blood culture from intravascular catheter
Intra-abdominal	Any organism grown from positive culture from the intra-abdominal cavity, including: -Surgical specimens (culture intra-operatively, or direct tissue) -Percutaneous drain fluid (i.e. from intra-abdominal abscess, biliary tree) -Positive peritoneal fluid culture -Positive stool cultures or C. difficile antigen
Urinary	Any organism grown from positive culture from the urinary tract, including: -Urine sample -Percutaneous drainage from upper urinary tract (i.e. nephrostomy tubes) -Direct surgical culture or tissue from urinary tract
Skin /soft tissue	Any organism from positive soft tissue culture, including: -Surgical culture/tissue sample (i.e. from surgical debridement) -Wound culture
Central Nervous System	Any organism from positive CSF fluid or tissue culture, including: -From lumbar puncture, or other means of sampling CSF (i.e.: extra ventricular drain) -Surgical culture/tissue sample (i.e. from surgical debridement or other invasive neurosurgical procedure)

Appendix 4: Types of Organisms Included in Chart Review

#	**Organism**		#	**Organism**
3	Acinetobacter		44	Prevotella
4	Actinomyces		45	Proteus
5	Aeromonas		46	Providencia
6	Alcaligenes		47	Pseudomonas
7	Bacillus		48	Rhodococcus
8	Bacteroides		49	Rickettsia
9	Babesia		50	Salmonella
10	Bartonella		51	Serratia
11	Borrellia		52	Shigella
12	Bortetella		53	Staph
13	Burkholderia		54	Stenotrophomas
14	Campylobacter		55	Strep
15	Capnocytophaga		56	Streptobacillus
16	Chlamydia		57	Yersinia
17	Citrobacter		58	Vibrio
18	Clostridium		59	Aspergillus
19	Coryneoobacteria		60	Bipolaris
20	Coxiella		61	Candida
21	Diphteroids		62	Coccidiomycosis
22	Eikenella		63	Pneumocystis
23	Ehrlichia		64	Yeast, Unspecified
24	Enterobacter		65	Adenovirus
25	Enterococcus		66	Cytomegalovirus
26	Escherichia		67	Herpes
27	Erysipelothrix		68	HIV
28	Fransisella		69	Hepatitis
29	Fusobacterium		70	Influenza
30	Hafnia Alvei		71	Other Virus
31	Helicobacter		72	Avium-Intracellulare
32	Hemophilus Influenza		73	Tuberculosis
33	Klebsiella		74	Other Mycobacteria
34	Legionella		75	Malaria
35	Listeria		76	Other Parasite
36	Moraxella			
37	Morganella			
38	Mycoplasma			
39	Neisseria			
40	Nisseria			
41	Nocardia			
42	Pasteurella			
43	Peptostreptococcus/Peptococcus			

Appendix 5: Conversion Tables for SaO2 and Oxygen Flow Rate

Estimating PaO_2 from SaO_2 (If no arterial blood gases available)	
SaO_2 (%)	PaO_2 (mmHg)
80	44
81	45
82	46
83	47
84	49
85	50
86	52
87	53
88	55
89	57
90	60
91	62
92	65
93	69
94	73
95	79
96	86
97	96
98	112
99	145

Estimating FiO_2 from Oxygen Flow rate (If patient is not intubated)	
Nasal canula	
100% O_2 Flow rate (L/min)	FiO_2 (%)
1	24
2	28
3	32
4	36
5	40
6	44
Oxygen mask	
100% O_2 Flow rate (L/min)	FiO_2 (%)
5-6	40
6-7	50
7-8	60
9	90
10	99+
Oxygen mask with reservoir bag	
100% O_2 Flow rate (L/min)	FiO_2 (%)
6	60
7	70
8	80

Appendix 6: Cardiovascular SOFA Scores-MAP Values and Vasoactive Agent Doses

SOFA Score	MAP value/Vasoactive agent dose[68]
0	MAP ≥70, no vasoactive agent
1	MAP <70, no vasoactive agent
2	Dopamine ≤5 μg/kg/min OR Dobutamine or milrinone (any dose)
3	Dopamine >5 μg/kg/min OR Norepinephrine ≤ 0.1 μg/kg/min OR Epinephrine ≤ 0.1 μg/kg/min OR Phenylephrine ≤1.0 μg/kg/min OR Vasopressin ≤0.04 μg/kg/min U/min
4	Dopamine >15 μg/kg/min OR Norepinephrine >0.1 μg/kg/min OR Epinephrine >0.1 μg/kg/min OR Phenylephrine >1.0 μg/kg/min OR Vasopressin >0.04 U/min

Appendix 7: Types of Antimicrobials Included in Chart Review

#	Type of Antimicrobial		#	Type of Antimicrobial
1	Abacavir		42	Tobramycin
2	Acyclovir		43	Valacyclovir
3	Amoxicillin		44	Valganciclovir
4	Amphotericin B		45	Vancomycin
5	Ampicillin		46	Voriconazole
6	Azithromycin			
7	Caspofungin			
8	Cefazolin			
9	Ceftazidime			
10	Ceftriaxone			
11	Cefuroxime			
12	Cephalexin			
13	Ciprofloxacin			
14	Clarithromycin			
15	Clavulin			
16	Clindamycin			
17	Cloxacillin			
18	Daptomycin			
19	Doxycycline			
20	Ertapenem			
21	Erythromycin			
22	Famciclovir			
23	Fluconazole			
24	Ganciclovir			
25	Gentamicin			
26	Ketoconazole			
27	Lamivudine			
28	Levofloxacin			
29	Linezolid			
30	Lopinavir/Ritonavir (Kaletra)			
31	Meropenem			
32	Metronizadole			
33	Micafungin			
34	Moxifloxacin			
35	Oseltamivir			
36	Penicillin			
37	Piperacillin/Tazobactam			
38	Rifaximin			
39	Septra			
40	Tenofovir			
41	Tetracycline			

Appendix 8: Isolates from Sepsis-Positive and Negative Patients with Infection in Chart Review and Health Administrative Data

Organism	Sepsis-Positive		Sepsis-Negative	
	Chart Review (n=391) n(%)	HAD (n=364) n (%)	Chart Review (n=442) n(%)	HAD (n=469) n (%)
Staphylococcus (aureus, etc.)	69 (17.6)	19 (5.2)	1 (0.2)	4 (0.9)
Escherichia coli	61 (15.6)	43 (11.8)	2 (0.5)	8 (1.7)
Streptococcus (pneumoniae, pyogenes, etc.)	34 (8.7)	9 (2.5)	3 (0.7)	1 (0.2)
Pseudomonas (aeruginosa, cloacae)	22 (5.6)	3 (0.8)	0	0
Candida	16 (4.1)	5 (1.4)	1 (0.2)	0
Klebsiella	15 (3.8)	0	2 (0.5)	0
Influenza	14 (3.6)	0	0	0
Clostridium difficile	12 (3.1)	23 (6.3)	2 (0.5)	5 (1.0)
Enterococcus	12 (3.1)	2 (0.5)	0	1 (0.2)
Enterobacter	11 2.8)	0	0	0
Hemophilus Influenza	7 (1.8)	1 (0.3)	0	0
Proteus	5 (1.3)	0	2 (0.5)	0
Other virus	4 (1.0)	0	1 (0.2)	0
Aspergillus	4 (1.0)	0	0	0
Coryneobacteria	3 (0.8)	0	1 (0.2)	0
Bacteroides	3 (0.8)	0	0	0
Morganella	3 (0.8)	0	0	0
Providencia	3 (0.8)	0	0	0
Serratia	3 (0.8)	0	0	0
Other parasite	3 (0.8)	0	0	0
Acinetobacter	2 (0.5)	0	0	0
Bacillus	2 (0.5)	0	0	0
Citrobacter	2 (0.5)	0	0	0
Moraxella	2 (0.5)	0	0	0
Stenotrophomas	2 (0.5)	0	0	0
Burkholderia	1 (0.3)	0	0	0
Capnocytophaga	1 (0.3)	0	0	0
Legionella	1 (0.3)	0	0	0
Neisseria	1 (0.3)	0	0	0
Pneumocystis	1 (0.3)	0	0	0
Cytomegalovirus	1 (0.3)	0	0	0
Fusobacterium	1 (0.3)	0	0	0
Peptostreptococcus/Peptococcus	1 (0.3)	0	0	0

Prevotella	1 (0.3)	0	0	0
Other mycobacteria	1 (0.3)	0	0	0
Aeromonas	0	0	1 (0.2)	0
Avium-Intracellulare	0	0	1 (0.2)	0

Legend: Cultures were documented +/- 2 days from date of infection during chart review. The isolates for Sepsis negative patients are those patients (n = 15) who had infection but no organ dysfunction in the ICU. Isolates in HAD were derived from the frequency of organism-specific infection codes included in the Jolley sepsis algorithm (Table 5).

Appendix 9: Prevalence of the ICD-10-CA Codes Included in the Optimized Algorithm Developed by Jolley et al to Identify Sepsis Cases in Health Administrative Data

ICD-10-CA Code	Code Definition	Sepsis-Positive		Sepsis-Negative		TP	FP	FN	TN
		Chart Review (n=391) n (%)	HAD (n=364) n (%)	Chart Review (n=442) n (%)	HAD (n=469) n (%)				
Jolley Sepsis Code									
R57.2	Septic Shock	92 (23.5)	98 (26.9)	6 (1.3)	0	92	6	0	0
Jolley Infection Codes									
A03.9	Shigellosis, unspecified	0	0	0	0	0	0	0	0
A02.1	Salmonella sepsis	0	0	0	0	0	0	0	0
A20.7	Septicaemic plague	0	0	0	0	0	0	0	0
A21.7	Generalized tularaemia	0	0	0	0	0	0	0	0
A22.7	Anthrax sepsis	0	0	0	0	0	0	0	0
A23.9	Brucellosis, unspecified	0	0	0	0	0	0	0	0
A24.1	Acute and fulminating melioidosis	0	0	0	0	0	0	0	0
A26.7	Erysipelothrix sepsis	0	0	0	0	0	0	0	0
A28.0	Pasteurellosis	0	0	0	0	0	0	0	0
A28.2	Extraintestinal yersiniosis	0	0	0	0	0	0	0	0
A32.7	Listerial sepsis	0	0	0	0	0	0	0	0
A39.2	Acute meningococcaemia	0	0	0	0	0	0	0	0
A39.3	Chronic meningococcaemia	0	0	0	0	0	0	0	0
A39.4	Meningococcaemia, unspecified	0	0	0	0	0	0	0	0
A40	Streptococcal sepsis	0	0	0	0	0	0	0	0
A40.0	Sepsis due to Streptococcus, group A	1 (0.3)	0	0	1(0.2)	0	0	1	0

A40.1	Sepsis due to Streptococcus, group B	0	0	0	0	0	0	0	0
A40.2	Sepsis due to Streptococcus, group D	0	0	0	0	0	0	0	0
A40.3	Sepsis due to Streptococcus pneumoniae	1 (0.3)	1 (0.3)	0	0	1	0	0	0
A40.8	Other streptococcal sepsis	0	0	0	0	0	0	0	0
A40.9	Streptococcal sepsis, unspecified	1 (0.3)	1 (0.3)	0	0	1	0	0	0
A41	Other sepsis	0	0	0	0	0	0	0	0
A41.0	Sepsis due to Staphylococcus aureus	5 (1.3)	4 (1.1)	0	1 (0.2)	4	0	1	0
A41.1	Other sepsis	3 (0.8)	3 (0.8)	0	0	3	0	0	0
A41.2	Sepsis due to unspecified Staphylococcus	0	0	0	0	0	0	0	0
A41.3	Sepsis due to Haemophilus influenzae	1 (0.3)	1 (0.3)	0	0	1	0	0	0
A41.4	Sepsis due to anaerobes	2 (0.5)	2 (0.5)	0	0	2	0	0	0
A41.5	Sepsis due to other Gram-negative organisms	2 (0.5)	2 (0.5)	0	0	2	0	0	0
A41.50	Sepsis due to Escherichia coli	10 (2.6)	10 (2.7)	0	0	10	0	0	0
A41.51	Sepsis due to Pseudomonas	3 (0.8)	3 (0.8)	0	0	3	0	0	0
A41.52	Sepsis due to Serratia	0	0	0	0	0	0	0	0
A41.58	Sepsis due to other Gram-negative organisms, NOS	2 (0.5)	2 (0.5)	0	0	2	0	0	0
A41.8	Other specified sepsis	3 (0.8)	4 (1.1)	1 (0.2)	0	3	1	0	0
A41.80	Sepsis due to Enterococcus	2 (0.5)	3 (0.8)	1 (0.2)	0	2	1	0	0
A41.88	Other specified sepsis	3 (0.8)	3 (0.8)	1 (0.2)	1 (0.2)	3	1	0	0
A41.9	Sepsis, unspecified, includes: septicaemia	106 (27.1)	108 (29.7)	11 (2.5)	9 (1.9)	99	9	7	2
A42.7	Actinomycotic sepsis	0	0	0	0	0	0	0	0
B00.7	Disseminated herpes viral disease, includes herpes viral sepsis	0	0	0	0	0	0	0	0
B37.7	Candidal sepsis	5 (1.3)	5 (1.4)	0	0	5	0	0	0
P36.0	Sepsis of newborn due to Streptococcus, group B	0	0	0	0	0	0	0	0
P36.1	Sepsis of newborn due to other and unspecified streptococci	0	0	0	0	0	0	0	0
P36.2	Sepsis of newborn due to S. aureus	0	0	0	0	0	0	0	0

P36.3	Sepsis of newborn due to other and unspecified staphylococci	0	0	0	0	0	0	0	0
P36.4	Sepsis of newborn due to E. coli	0	0	0	0	0	0	0	0
P36.5	Sepsis of newborn due to anaerobes	0	0	0	0	0	0	0	0
P36.8	Other bacterial sepsis of newborn	0	0	0	0	0	0	0	0
P36.9	Bacterial sepsis of newborn, unspecified	0	0	0	0	0	0	0	0
P35.2	Congenital herpes viral (herpes simplex) infection	0	0	0	0	0	0	0	0
P37.2	Neonatal (disseminated) listeriosis	0	0	0	0	0	0	0	0
P37.5	Neonatal candidiasis	0	0	0	0	0	0	0	0
A04.7	Enterocolitis due to Clostridium difficile	23 (5.9)	25 (6.9)	5 (1.1)	3 (0.6)	20	5	3	0
B95.48	Other Streptococcus as the cause of diseases classified to other chapters	6 (1.5)	6 (1.6)	1 (0.2)	1 (0.2)	5	1	1	0
B95.6	S. aureus as the cause of diseases classified elsewhere	14 (3.6)	16 (4.4)	4 (0.9)	2 (0.4)	12	4	2	0
B96.2	E. coli as the cause of diseases classified elsewhere	33 (8.4)	38 (10.4)	8 (1.8)	3 (0.6)	30	8	3	0
J18.9	Pneumonia, unspecified organism	65 (16.6)	86 (23.6)	26 (5.9)	5 (1.1)	61	25	4	1
J44.0	Chronic obstructive pulmonary disease with acute lower respiratory infection	24 (6.1)	33 (9.1)	10 (2.3)	1 (0.2)	24	9	0	1
N39.0	Urinary tract infection, site not specified	61 (15.6)	77 (21.2)	28 (6.3)	12 (12.6)	55	22	6	6
Jolley Organ Dysfunction Codes									
Respiratory:									
J96.0	Acute respiratory failure	11 (2.8)	10 (2.7)	1 (0.2)	2 (0.4)	9	1	2	0
J96.9	Respiratory failure, unspecified	1(0.3)	1 (0.3)	0	0	1	0	0	0
J80	Diseases of bronchus, not elsewhere classified	9 (2.3)	9 (2.5)	4 (0.9)	4 (0.8)	8	1	1	3
R09.2	Respiratory arrest	1(0.3)	1(0.3)	1 (0.2)	1 (0.2)	1	0	0	1

Cardiovascular:									
R57.0	Cardiogenic shock	12 (3.1)	14 (3.8)	12 (2.7)	10 (2.1)	10	4	2	8
R57.1	Hypovolemic shock	4 (1.0)	2 (0.5)	6 (1.4)	8 (1.7)	2	0	2	6
R57.8	Other shock	3 (0.8)	4 (1.1)	7 (1.6)	6 (1.3)	3	1	0	6
R57.9	Shock, unspecified	6 (1.6)	4 (1.1)	7 (1.6)	9 (1.9)	2	2	4	5
I95.1	Orthostatic hypotension	1 (0.3)	3 (0.8)	3 (0.7)	1 (0.2)	1	2	0	1
I95.9	Hypotension, unspecified	56 (14.3)	65 (17.8)	55 (12.4)	46 (9.8)	45	20	11	35
Renal:									
N17.0	Acute renal failure with tubular necrosis	20 (5.1)	24 (6.6)	10 (2.3)	6 (1.3)	17	7	3	3
N17.1	Acute renal failure with acute cortical necrosis	0	0	0	0	0	0	0	0
N17.2	Acute renal failure with medullary necrosis	1 (0.3)	1 (0.3)	0	0	1	0	0	0
N17.8	Other acute renal failure	0	1 (0.3)	1 (0.2)	0	0	1	0	0
N17.9	Acute renal failure, unspecified	122 (31.2)	129 (35.4)	75 (17.0)	68 (14.5)	111	18	12	56
Hepatic:									
K72.0	Acute and subacute hepatic failure	8 (2.0)	8 (2.2)	5 (1.1)	5 (1.1)	7	1	1	4
K72.9	Hepatic failure, unspecified	3 (0.8)	4 (1.1)	3 (0.7)	2 (0.4)	3	1	0	2
K76.3	Infarction of liver	0	0	1 (0.2)	1 (0.2)	0	0	0	1
Neurologic:									
F05.0	Delirium not superimposed on dementia, so described	1 (0.3)	2 (0.5)	1 (0.2)	0	1	1	0	0
F05.9	Delirium, unspecified	36 (9.2)	33 (9.1)	10 (2.3)	13 (2.8)	30	3	6	7
G93.1	Anoxic brain damage, not elsewhere classified	2 (0.5)	1 (0.3)	8 (1.8)	9 (1.9)	1	0	1	8
G93.4	Encephalopathy, unspecified	0	1 (0.3)	2 (0.5)	1 (0.2)	0	1	0	1
G93.80	Metabolic encephalopathy	2 (0.5)	3 (0.8)	1 (0.2)	0	2	1	0	0

Hematologic:									
D69.5	Secondary thrombocytopenia	3 (0.8)	3 (0.8)	0	0	3	0	0	0
D69.6	Thrombocytopenia, unspecified	14 (3.6)	15 (4.1)	6 (1.4)	5 (1.1)	12	3	2	3
D65	Disseminated intravascular coagulation (defibrination syndrome)	4 (1.0)	6 (1.6)	5 (1.3)	3 (0.6)	4	2	0	3
Procedure codes (CCI) :									
1.GZ.31.CA-ND	Ventilation, respiratory system NEC, invasive per	249 (63.7)	254 (68.8)	248(56.1)	243 (51.8)	199	55	50	193
1.GZ.31.CR-ND	orifice approach by endotracheal intubation, positive	19 (4.9)	23 (6.2)	24 (5.4)	20 (4.3)	10	13	9	11
1.GZ.31.GP-ND	pressure (e.g. CPAP, BIPAP)	1 (0.3)	1(0.3)	2 (0.5)	2 (0.4)	0	1	1	1

Appendix 10a: Sepsis Algorithms Tested

Algorithm #	
1	Existing Jolley algorithm
2	Jolley with any antimicrobial for any duration
3	Jolley criteria or any antimicrobial for at least 1 day
4	Jolley criteria or any antimicrobial for at least 2 days
5	Jolley criteria or any antimicrobial for at least 3 days
6	Jolley criteria or any antimicrobial for at least 4 days
7	Jolley criteria or any antimicrobials for at least 5 days
8	Jolley criteria or any antimicrobial for at least 6 days
9	Jolley criteria or any antimicrobial for at least 7 days
10	Organ failure codes only
11	Organ failure codes or any antimicrobial for any duration
12	Organ failure codes or antimicrobial for at least 1 day
13	Organ failure codes or antimicrobial for at least 2 days
14	Organ failure codes or antimicrobial for at least 3 days
15	Organ failure codes or antimicrobial for at least 4 days
16	Organ failure codes or antimicrobial for at least 5 days
17	Organ failure codes or antimicrobial for at least 6 days
18	Organ failure codes or antimicrobial for at least 7 days

Appendix 10b: Performance Characteristics of the Existing and Modified Sepsis Algorithms with Predictive Values

Algorithm #	TP (n)	FN (n)	FP (n)	TN (n)	Sensitivity % (95% CI)	Specificity %(95% CI)	PPV % (95% CI)	NPV % (95% CI)	rTPF n (95% CI)	rFPF n (95% CI)
1	284	107	80	362	72.6 (69.6-75.7)	81.9 (79.3-84.5)	78.0 (75.2-80.8)	77.2 (74.3-80.0)	Reference	Reference
2	389	2	282	160	99.5 (99.0-100.0)	36.2 (32.9-39.5)	58.0 (54.6-61.3)	98.8 (98.0-99.5)	1.04 (1.01-1.08)	3.52 (2.80-4.43)
3	377	14	388	54	96.4 (95.2-97.7)	12.2 (10.0-14.4)	49.3(45.9-52.7)	79.4 (76.7-82.2)	1.32 (1.32-1.32)	4.85 (3.89-6.05)
4	370	21	348	94	94.6 (93.1-96.2)	21.3(18.5-24.1)	51.5 (48.1-54.9)	81.7 (79.1-84.4)	1.30 (1.29-1.31)	4.35 (3.48-5.44)
5	360	31	323	119	92.1 (90.2-93.9)	26.9 (23.9-29.9)	52.7(49.3-56.1)	79.3 (76.6-82.1)	1.06 (1.03-1.10)	4.04 (3.22-5.06)
6	356	35	302	140	91.1 (89.1-93.0)	31.7 (28.5-34.8)	54.1 (50.7-57.5)	80.0 (77.3-82.7)	1.02 (0.99-1.06)	3.77 (3.01-4.74)
7	341	50	288	154	87.2 (84.9-89.5)	34.8 (31.6-38.1)	54.2 (50.8-57.6)	75.5 (72.6-78.4)	0.98 (0.94-1.02)	3.60 (2.86-4.52)
8	335	56	275	167	85.7 (83.3-88.1)	37.8 (34.5-41.1)	54.9 (51.5-58.3)	74.9 (71.9-77.8)	0.95 (0.91-0.99)	3.44 (2.73-4.32)
9	316	75	267	175	80.8 (78.1-83.5)	39.6 (36.3-42.9)	54.2 (50.8-57.6)	70.0 (66.9-73.1)	0.91 (0.87-0.95)	3.34 (2.65-4.20)
10	326	65	323	119	83.4 (80.8- 85.9)	26.9 (23.9- 29.9)	50.2 (46.8- 53.6)	64.7 (61.4- 67.9)	1.01 (0.97-1.05)	4.04 (3.22-5.06)
11	390	1	382	60	99.7 (99.4-100.0)	13.6 (11.2-15.9)	50.5 (47.1-53.9)	98.4 (97.5-99.2)	1.33 (1.32-1.34)	4.78 (3.83-5.96)
12	386	5	421	21	98.7 (98.0-99.5)	4.8 (3.3-6.2)	47.8 (44.4-51.2)	80.8 (78.1-83.4)	1.34 (1.33-1.35)	5.26 (4.23-6.55)
13	381	10	412	30	97.4 (96.4-98.5)	6.8 (5.1-8.5)	48.1 (44.6-51.4)	75.0 (72.1-77.9)	1.34 (1.33-1.35)	5.15 (4.14-6.41)
14	371	20	402	40	94.9 (93.4-96.4)	9.1 (7.1-11.0)	48.0 (45.6-51.4)	66.7 (63.5-69.9)	1.33 (1.32-1.34)	5.02 (4.03-6.26)
15	367	24	400	42	93.9 (92.2-95.5)	9.5 (7.5-11.5)	47.8 (44.5-51.2)	63.6 (60.4-66.9)	1.32 (1.31-1.33)	5.00 (4.01-6.23)
16	357	34	398	44	91.3 (89.4-93.2)	10.0 (7.9-12.0)	47.3 (43.9-50.7)	56.4 (53.0-59.8)	1.32 (1.31-1.33)	4.97 (3.99-6.20)
17	353	38	394	48	90.3 (88.3-92.3)	10.9 (8.8-13.0)	47.3 (43.9-50.6)	55.8 (52.4-59.2)	1.31 (1.30-1.32)	4.92 (3.95-6.14)
18	347	44	393	49	88.8 (86.6-90.9)	11.1 (9.0-13.2)	46.9 (43.5-50.3)	52.7 (49.3-56.1)	1.31 (1.30-1.32)	4.91 (3.94-6.12)