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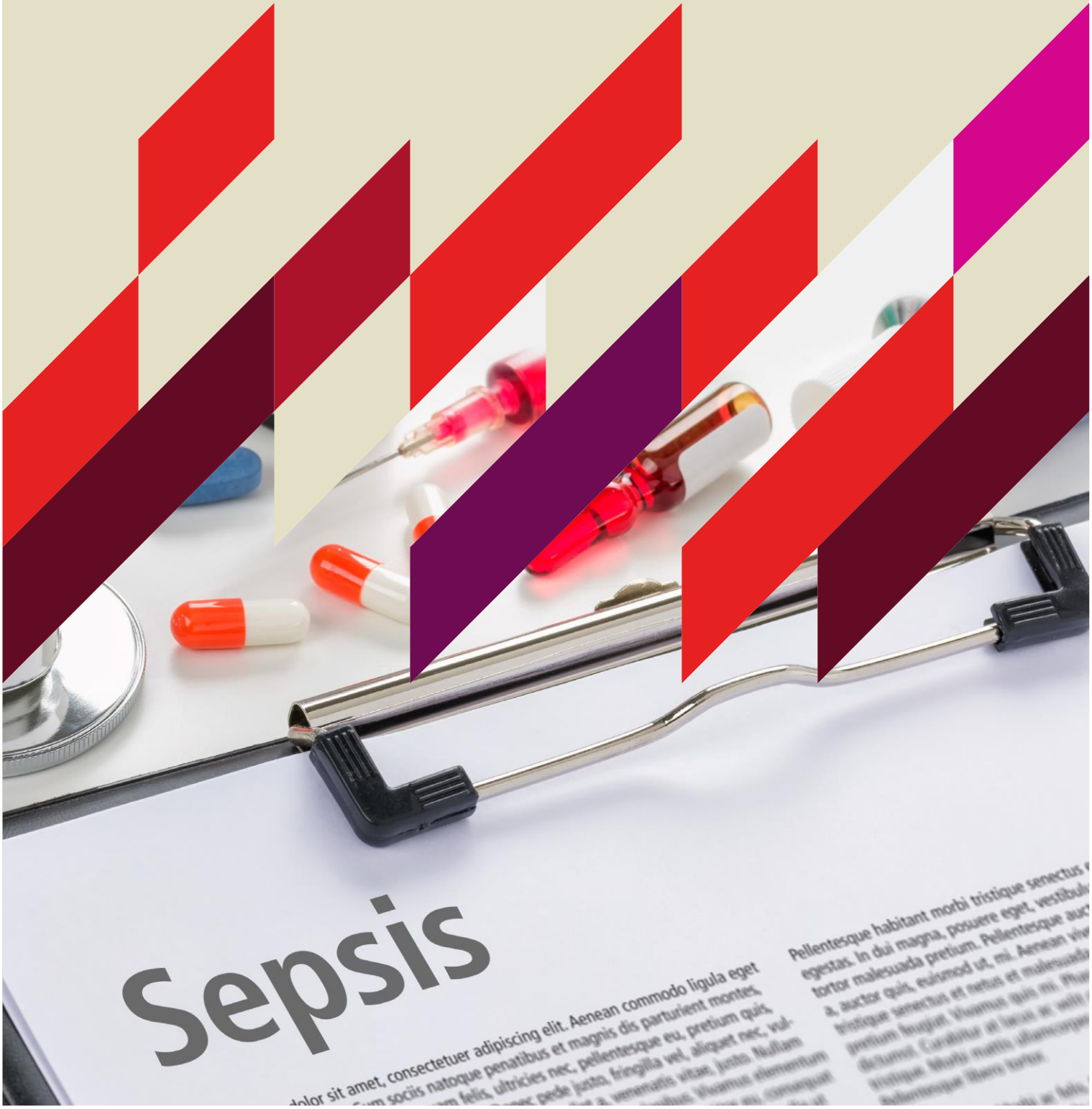
Evaluation and optimisation of risk identification tools for the early detection of sepsis in adult inpatients



PROJECT RESEARCH TEAM

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- Design and apply innovative approaches to understand the complex nature of health care delivery systems and make assessments of health care safety.
- Disseminate evidence to inform policy, system design, practice change and the integration and safe and effective use of ICT in healthcare.

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EXECUTIVE SUMMARY

Sepsis is a life-threatening condition that contributes considerably to the burden of disease in the population. However, poor patient outcomes related to sepsis can be significantly ameliorated by early identification of at-risk patients. This project assessed the performance of three sepsis risk identification tools to detect sepsis cases during hospital admissions. The three tools assessed were the quick Sequential (Sepsis-related) Organ Failure Assessment (qSOFA) score, the Adult Sepsis Pathway, and the Modified St. John Rule.

This project is the first to evaluate the Adult Sepsis Pathway and the Modified St. John Rule in New South Wales (NSW), and to compare the performance between these two tools and the qSOFA score. We used more than 130,000 patient admissions from 34 healthcare facilities across metropolitan, rural and regional localities to evaluate these tools and explore improved alternatives.

The project included data on adult patients (aged 18 and over) admitted to study sites in NSW during the study period in either of two study arms: 1) 36,065 patient admissions at Blacktown Hospital and 2) 100,087 admissions from facilities across four rural and regional NSW local health districts (LHDs). Sepsis cases were identified based on sepsis-related ICD-10-AM diagnosis codes. We compared the performance of the three sepsis risk identification tools by comparing the occurrence of any sepsis alert during an admission to an ICD-10-AM coded sepsis case. Tool performance was assessed with metrics from confusion matrices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the receiver operating characteristic curve (AUROC).

Sepsis alert data, extracted from the Cerner electronic Medical Record (eMR) system, for the Modified St. John Rule was available at Blacktown Hospital. Three separate algorithms were developed to generate sepsis alerts based on the three risk identification tools. These algorithms were then applied to the data from two study arms (Blacktown Hospital and rural and regional NSW LHD facilities) for analyses.

At Blacktown Hospital, 3.5% of admissions had a coded case of sepsis compared to 1.2% for rural facilities. The crude mortality rate of sepsis patients at Blacktown Hospital was 11.7%, which was nearly 12 times higher than that for patients without sepsis (1.0%).

Based on the Blacktown hospital data, sensitivity (65.1%) and AUROC (0.76 with 95% CI: 0.75-0.78) were highest for the Modified St. John Rule (eMR) when compared with qSOFA and the Adult Sepsis Pathway. The qSOFA score provided higher specificity (98.0%) and higher PPV (20.1%) than the other two risk identification tools. When used for predicting in-hospital mortality for non-ICU admissions, both the Modified St. John Rule and the Adult Sepsis Pathway provided relatively high sensitivity and AUROC; the qSOFA score had the lowest sensitivity and AUROC among the three tools, but higher specificity and PPV than the other two tools.

Overall, the Adult Sepsis Pathway and the Modified St. John Rule performed better when applied to the data from Blacktown Hospital than from the rural and regional NSW LHDs while the reverse was true for the qSOFA score. Rural and regional NSW LHD data generally had relatively more false positives than Blacktown Hospital, partly due to lower sepsis prevalence, which resulted in lower sensitivity, specificity and PPV for most scenarios.

We explored alternative versions of these tools to improve sensitivity, specificity, PPV and NPV compared to three existing tools. Seven options were developed as revised versions of the Modified St. John Rule (algorithm). Six of the seven options produced improved sensitivity and AUROC at the cost of reduced specificity for detecting coded sepsis cases and deteriorating patients. To develop the alternative bedside tools, we made use of the five most commonly available bedside measurements (systolic blood pressure, respiratory rate, heart rate, Glasgow coma scale and temperature) and used clinical thresholds from the three existing tools to assess 4,704 possible options. All 30 of the best performing options had better sensitivity than qSOFA and 29 of these options had better AUROC than qSOFA. Among the options with at least 98% specificity, the one with the highest sensitivity also had better specificity and PPV than qSOFA.

GLOSSARY

ASP	Adult Sepsis Pathway
AUROC	Area under the receiver operating characteristic curve
BC	Blood culture
CEC	Clinical Excellence Commission
CHADx	Classification of Hospital Acquired Diagnoses
CI	Confidence interval
eMR	Electronic medical record
ESRD	End-stage renal disease
FN	False negative
FP	False positive
GCS	Glasgow coma scale
HR	Heart rate
ICD-10-AM	International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification
IQR	Inter-quartile range
LHD	Local health district
LOS	Length of stay
MAP	Mean arterial pressure
MRN	Medical Record Number
NPV	Negative predictive value
PPV	Positive predictive value
qSOFA	Quick Sequential Organ Failure Assessment
RR	Respiratory rate
SBP	Systolic blood pressure
SIRS	Systemic inflammatory response syndrome
TN	True negative
TP	True positive
WBC	White blood cell count

1. INTRODUCTION

Sepsis is a life-threatening condition that arises when the body's response to an infection injures its own tissues and organs (1, 2). Despite advances in care, existing epidemiological studies suggest that sepsis remains a huge burden. A recent systematic review extrapolated data from high-income countries to suggest global estimates of 31.5 million sepsis and 19.4 million severe sepsis cases, with potentially 5.3 million deaths annually (3).

Sepsis is one of the most pervasive but poorly defined and recognised conditions. It has been called "one of the oldest and most elusive syndromes in medicine" (4). The first two consensus definitions (5, 6) introduced and included the systemic inflammatory response syndrome (SIRS), which was defined by four variables: temperature, heart rate, respiratory rate, and white blood cell count. However, SIRS criteria have been criticised for their poor specificity, with 90% of intensive care unit (ICU) patients and 50% of general ward patients meeting the criteria at some point during their hospitalisation (2, 7). The most recent sepsis definition was developed in 2016 using a more data-driven approach (8, 9). The 2016 guideline included a new tool that was derived specifically to prompt clinicians to consider the possibility of patients being septic (8). The tool was called the quick Sequential [Sepsis-related] Organ Failure Assessment (qSOFA) score, which was found to be more accurate than SIRS for predicting adverse events.

Early recognition and intervention are essential to optimize patient outcomes. In New South Wales (NSW), failure to recognise and respond to sepsis has been regularly reported. In 2009, 167 incidents were highlighted in a clinical focus report published by the Clinical Excellence Commission (CEC) (10). The CEC has developed the SEPSIS KILLS program with the aim of reducing preventable harm to patients through improved recognition and management of severe infection and sepsis in emergency departments and inpatient wards throughout NSW (11, 12). Four sepsis pathways, including the adult, paediatric, maternal or newborn pathway, are available online (11). The SEPSIS KILLS program promoted intervention within 60 minutes of recognition, including taking of blood cultures, measuring serum lactate levels, administration of intravenous antibiotics, and fluid resuscitation.

Both the qSOFA score and the CEC Adult Sepsis Pathway are used as bedside prompts to identify patients at risk of sepsis. To improve early sepsis detection, several automated sepsis alert systems using electronic medical record (eMR) data have been developed for use in hospital intensive care units (ICU) and in non-critical care settings (13). The St. John Sepsis Surveillance Agent is one such system. It was developed by Cerner Corporation, an American supplier of health information technology solutions, services, devices and hardware. The St. John Sepsis Surveillance Agent has been implemented in more than 550 hospitals in the United States (14). The CEC has worked with eHealth NSW to develop an updated version, the Modified St. John Rule, which has been piloted at Blacktown Hospital, NSW, in the inpatient, acute care setting.

The third task force, which developed the third consensus definition, strongly recommended international validation in different study settings (9). In this project, we evaluated the ability of three sepsis risk identification tools - qSOFA, the Adult Sepsis Pathway and the Modified St. John Rule - to predict sepsis and in-hospital mortality for adult patients during their hospital stays in a range of NSW hospitals.

These sepsis risk identification tools are designed to accurately identify patients on the sepsis trajectory, which requires the alerts to have high levels of both sensitivity and specificity. In this project, we also used retrospective data to develop a set of optimised alternative bedside risk identification tools and revised versions of the Modified St. John Rule with improved levels of sensitivity or specificity relative to the existing tools.

2. PROJECT AIMS

The aims of the project were:

1) To assess the performance of three sepsis risk identification tools based on data from Blacktown Hospital:
   a. The Modified St. John Sepsis Rule, which was built in the eMR and only active at Blacktown Hospital during the study period;
   b. The Clinical Excellence Commission (CEC) Adult Sepsis Pathway; and
   c. The quick Sequential Organ Failure Assessment (qSOFA) score.
2) To assess three sepsis risk identification tools based on data from facilities across four rural and regional NSW LHDs - Far West, Murrumbidgee, Southern NSW and Western NSW.
3) To develop two sets of tools:
   a. Revised versions of the Modified St. John Sepsis Rule; and
   b. Optimised risk identification tools applicable at the bedside, based on clinical thresholds from three existing sepsis risk identification tools.

3. PROJECT AND DATA

3.1 STUDY DESIGN AND SETTING

This is a retrospective longitudinal study with *two study arms*:
1) a cohort study at Blacktown Hospital (Aim 1 and Aim 3); and
2) a cohort study in facilities across four rural and regional NSW local health districts (LHDs), including Far West LHD, Murrumbidgee LHD, Southern NSW LHD, and Western NSW LHD (Aim 2 for all LHDs, and Aim 3 for Western NSW LHD). None of these rural facilities had active eMR sepsis alert systems during the study period.

3.2 STUDY POPULATION

The study included all data for adult patients (aged 18 and over) admitted to study sites in either of two study arms during the study period (as defined in sections 6 and 7). Admissions where the principal diagnosis was related to pregnancy and/or childbirth were excluded from the patient admissions data (all ICD-10-AM codes beginning with O) because a specific sepsis risk identification tool was developed by CEC for identifying maternal sepsis cases.

3.3 ETHICS APPROVAL

Ethics approval was obtained from Macquarie University Human Research Ethics Committee (Reference No: 5201600265).

3.4 DATA SOURCES AND DATA QUALITY ASSESSMENT

The data came from four sources:
1) **Hospital admissions data** from the Health Information Exchange (HIE), which comprises all patient admissions during the study period;
2) **Measurement data** from the eMR system containing measurements on vital signs and pathology results extracted for all records within the study period;
3) **Blood culture data** containing date and time of all blood culture orders during the study period; and
4) **Alert data** generated by the Modified St. John Rule from the eMR system. These data are only available for Blacktown Hospital.

Data sets from these sources were assessed internally and externally across different dimensions (15):
- Uniqueness: Nothing will be recorded more than once based upon how that thing is identified;
- Timeliness: The degree to which data represent reality from the required point in time;
- Validity: Data are valid if it conforms to the syntax (format, type, range) of its definition;
- Accuracy: The degree to which data correctly describes the "real world" object or event being described; and
- Consistency: How well data agree across different data sets, and the extent of agreement between different data sets that are measuring the same thing.

Details of the data quality checking conducted for the two study arms, Blacktown Hospital and four NSW LHDs, are presented in sections 6 and 7.

3.5 TERMS USED IN THE REPORT

The following terms are used consistently throughout the report:

- A measurement refers to a vital sign or a pathology test, such as temperature, systolic blood pressure (SBP), heart rate (HR), or lactate etc;
- A clinical threshold specifies a range of values for a measurement, e.g. “<90” or “≤50”;
- A clinical criterion describes a threshold applied to a measurement, e.g. “SBP<90” or “HR≤50”;
- A sepsis risk identification tool refers to a logical set of clinical criteria for the early detection of sepsis, such as the qSOFA score, the Adult Sepsis Pathway or the Modified St. John Rule (as shown in section 4.2);
- Rural facility refers to the hospitals/facilities in four rural and regional NSW LHDs in the second study arm (section 3.1, point 2);
- Modified St. John Rule (algorithm) is used to indicate alerts generated from the algorithm, and Modified St. John Rule (eMR) to indicate alerts extracted from the Cerner eMR system (as explained in section 5.1);
- SIRS stands for systemic inflammatory response syndrome; and
- Alerts were grouped into 1) SIRS alerts or 2) severe sepsis alerts under CEC Adult Sepsis Pathway and Modified St. John Sepsis Rule.

4. SEPSIS

4.1 INTERNATIONAL CLASSIFICATION OF DISEASES (ICD-10-AM) CODES FOR SEPSIS

For the purpose of this project, sepsis cases were identified based on sepsis-related ICD-10-AM diagnosis codes. **Two definitions were applied** (Table 4.1):

- Sundararajan *et al.* in a 2005 study (16); and
- the Classification of Hospital Acquired Diagnoses (CHADx) approach (Category 4) (17).

If any of these ICD-10-AM codes appeared in any of the diagnosis fields in a patient's hospital admission record, as either a primary or other diagnosis, this patient admission was recorded as a sepsis admission. Note that codes for identifying systemic inflammatory response syndrome (SIRS) are included within the CHADx sepsis definition: codes R65.0 and R65.1. According to Australian Coding Standard, SIRS would have not been coded in addition to sepsis if patients progressed to sepsis or if SIRS was of an infectious origin (e.g. urinary tract infection, or pneumonia).

TABLE 4.1: ICD-10-AM CODES FOR IDENTIFYING SEPSIS CASES

ICD-10-AM DIAGNOSIS CODE	DIAGNOSIS DESCRIPTION	2005 STUDY SEPSIS DEFINITION	CHADX SEPSIS DEFINITION
A01.0	Typhoid fever	•	
A02.1	Salmonella sepsis	•	•
A19	Miliary tuberculosis	•	
A24.1	Acute and fulminating melioidosis	•	
A32.7	Listerial sepsis	•	•
A39.4	Meningococemia, unspecified	•	
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	•	•
A41.0	Sepsis due to Staphylococcus aureus	•	•
A41.1	Sepsis due to coagulate-negative staphylococcus	•	•
A41.2	Sepsis clue to unspecified staphylococcus	•	•
A41.3	Sepsis due to Haemophilus influenzae	•	•
A41.4	Sepsis due to anaerobes	•	•
A41.50	Gram-negative septicemia NOS	•	•
A41.51	Sepsis due to Escherichia coli	•	•
A41.52	Sepsis due to Pseudomonas	•	•
A41.58	Sepsis due to other Gram-negative organisms	•	•

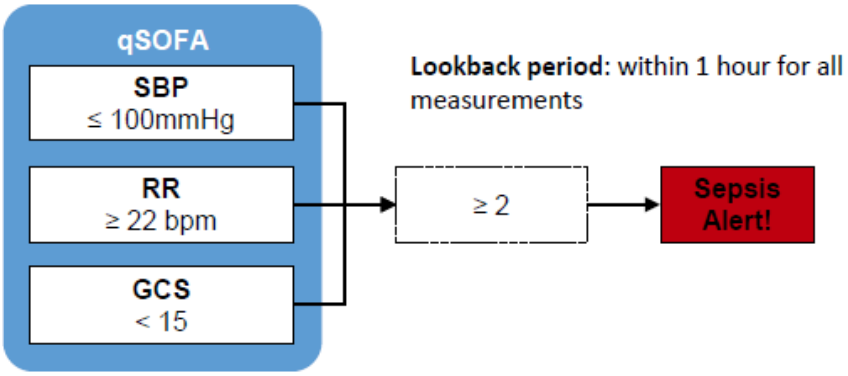
TABLE 4.1: ICD-10-AM CODES FOR IDENTIFYING SEPSIS CASES

ICD-10-AM DIAGNOSIS CODE	DIAGNOSIS DESCRIPTION	2005 STUDY SEPSIS DEFINITION	CHADX SEPSIS DEFINITION
A41.8	Other specified sepsis	•	•
A41.9	Sepsis unspecified, septicemia	•	•
A42.7	Actinomycotic sepsis	•	•
A43.0	Pulmonary nocardiosis	•	
A48.1	Legionnaires disease	•	
A48.3	Toxic shock syndrome	•	
A54.8	Other gonococcal infections	•	
A78	Q fever	•	
B37.7	Candidal sepsis	•	•
B38.7	Disseminated coccidioidomycosis	•	
B39.3	Disseminated histoplasmosis capsulati	•	
B40.7	Disseminated blastomycosis	•	
B41.7	Disseminated paracoccidioidomycosis	•	
B42.7	Disseminated sporotrichosis	•	
B44.7	Disseminated aspergillosis	•	
B45.7	Disseminated cryptococcosis	•	
B46.4	Disseminated mucormycosis	•	
R57.2	Septic shock		•
R65.0	[SIRS] of infectious origin without acute organ failure		•
R65.1	[SIRS] of infectious origin with acute organ failure		•
T81.42	Sepsis following a procedure		•

4.2 SEPSIS RISK IDENTIFICATION TOOLS

4.2.1 QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (QSOFA)

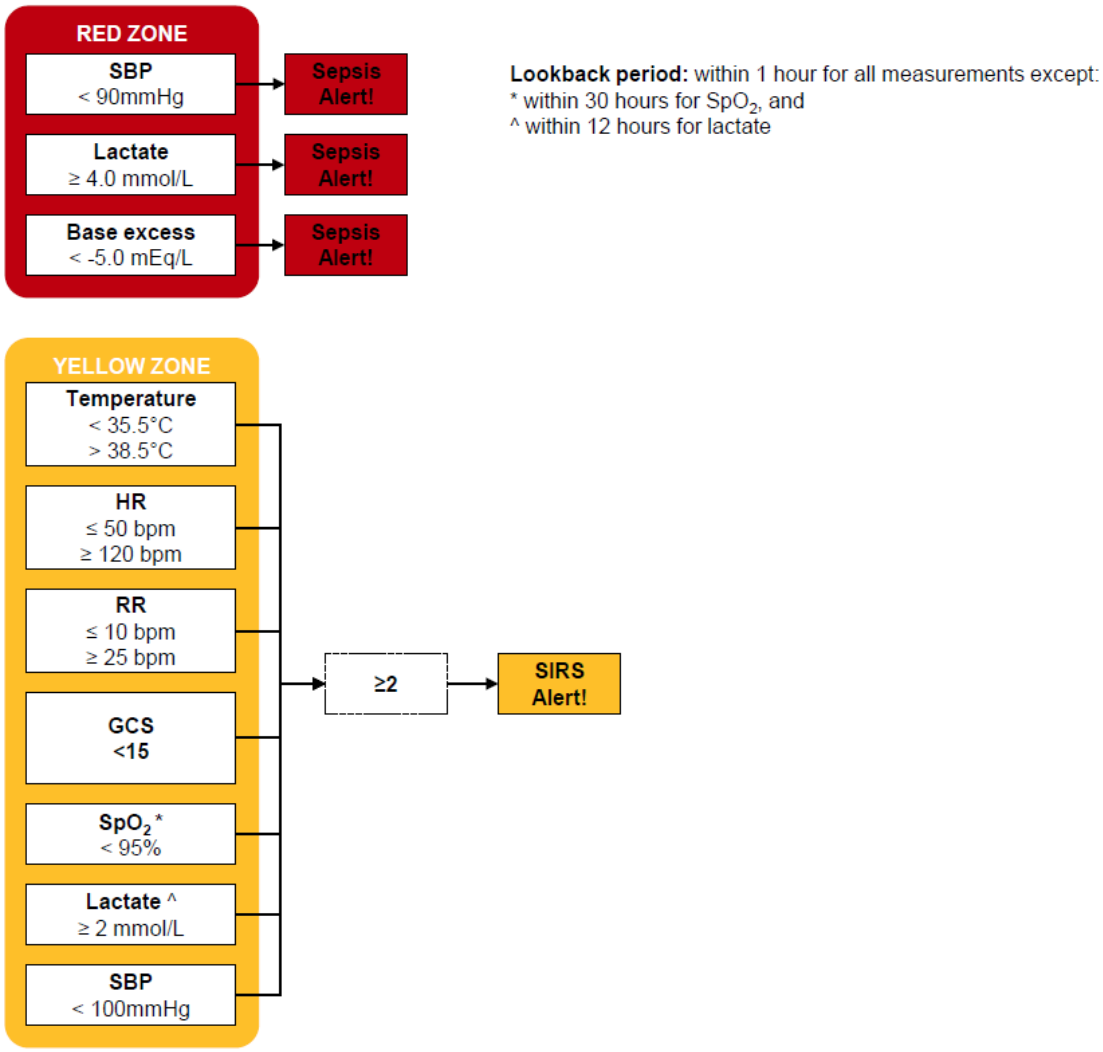
FIGURE 4.1: FLOW DIAGRAM FOR THE QUICK SEQUENTIAL ORGAN FAILURE ASSESSMENT (QSOFA) (SEE REFERENCE (9)).



The qSOFA score (also known as quickSOFA) was first proposed in 2016 (9). It is a bedside prompt that may identify patients with suspected infection who are at greater risk of a poor outcome, i.e. high mortality. Adult patients with suspected infection can be rapidly identified as being more likely to have poor outcomes typical of sepsis if they have at least 2 of the following clinical criteria that together constitute a qSOFA score as shown in Figure 4.1: respiratory rate (RR) of 22 breaths per minute or greater, altered consciousness (Glasgow coma scale [GCS] less than 15), or systolic blood pressure (SBP) of 100 mmHg or less. None of the study sites currently use the qSOFA score.

4.2.2 CEC ADULT SEPSIS PATHWAY

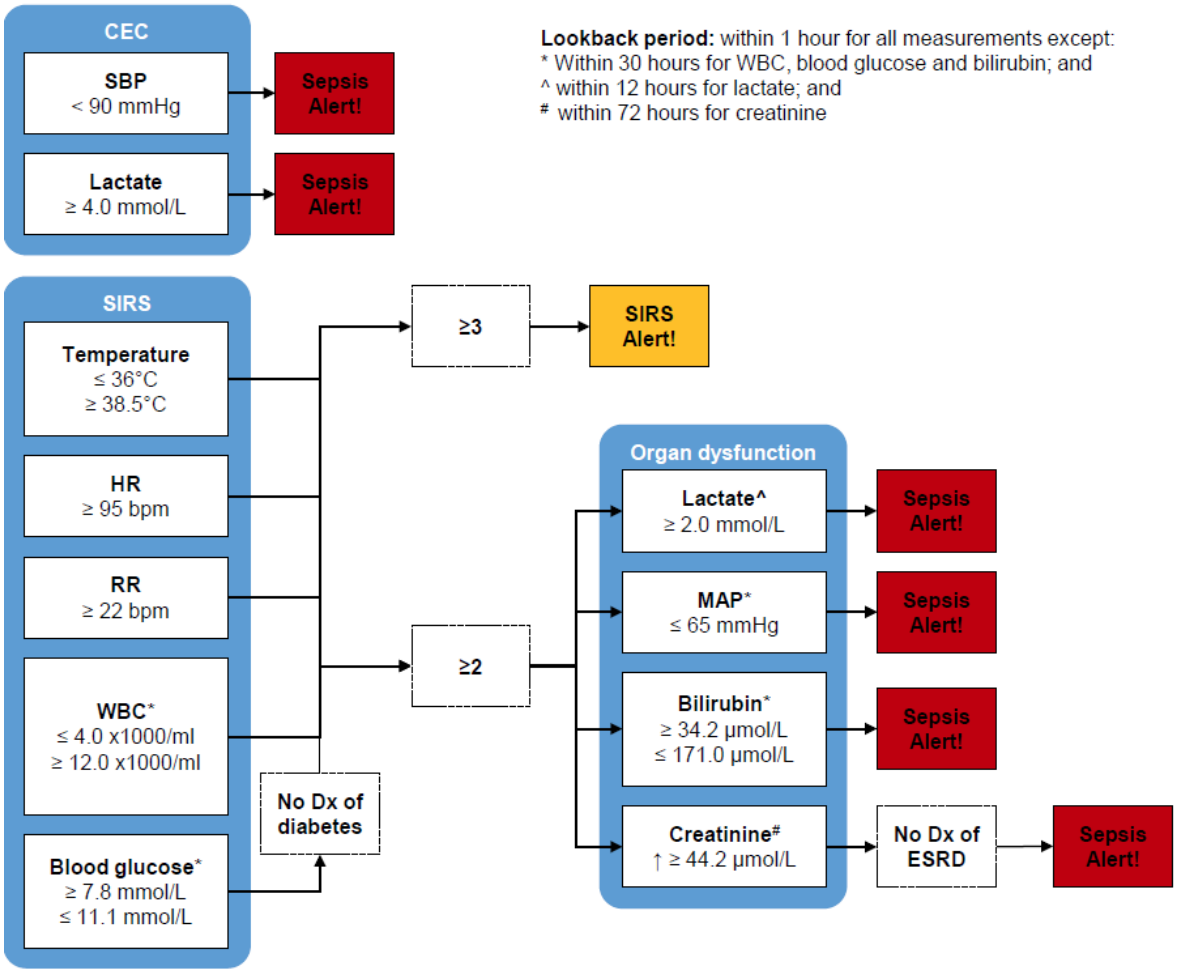
FIGURE 4.2: FLOW DIAGRAM FOR THE ADULT SEPSIS PATHWAY



The SEPSIS KILLS program, run by the NSW Clinical Excellence Commission (CEC), aims to reduce preventable harm to patients through improved recognition and management of severe infection and sepsis in emergency departments and inpatient wards throughout NSW (11). The Adult Sepsis Pathway is a tool developed for adult patients and is currently used in NSW hospitals, including the hospitals across four rural and regional NSW LHDs in the second study arm (as defined in section 3.1). A simplified flow diagram for this pathway is shown in Figure 4.2 and the detailed pathway is in Appendix A.

4.2.3 MODIFIED ST. JOHN SEPSIS RULE

FIGURE 4.3: FLOW DIAGRAM FOR THE MODIFIED ST. JOHN SEPSIS RULE



The Modified St. John Rule was provided to the research team by CEC. It is based on the St. John Sepsis Rule, but includes additional clinical criteria for activating a severe sepsis alert. It was implemented in the Cerner eMR system at the Blacktown Hospital during the study period. A simplified flow diagram was approved by CEC and is presented in Figure 4.3.

5. DATA MANAGEMENT AND ANALYSIS METHODS

5.1 ALGORITHMS FOR SEPSIS RISK IDENTIFICATION TOOLS

Three separate algorithms were developed to generate sepsis alerts based on the three risk identification tools. These algorithms were then applied to Blacktown Hospital data and NSW hospital data for analyses described in sections 5.4 and 5.5. Clinical criteria (e.g. SBP > 90mmHg), and lookback time periods were used as shown in Figures 4.1, 4.2 and 4.3 for the three sepsis risk identification tools.

In this report, the term *Modified St. John Rule (algorithm)* is used to indicate alerts generated from the algorithm, and *Modified St. John Rule (eMR)* to indicate alerts extracted from the Cerner eMR system. The algorithms were written in R statistical software (18). For further details, annotated R scripts are available in Appendix B.

5.1.1 ALGORITHM FOR QSOFA

The qSOFA algorithm was developed in the following steps:

1) We extracted records for the three qSOFA measurements (SBP, RR and GCS), including the date/time when these measurements were taken and their numerical readings as shown in Figure 4.1;
2) An iterative procedure was used for each measurement to produce a sepsis risk score, from 0 to 3. This procedure included two loops:
   a. The *outer loop* applied at patient level and iterated once per patient. Assume that there were n unique patients, then outer loop would run n times.
   b. The *inner loop* considered the patients' measurements. Assume that the i^{th} patient had k records, then the inner loop would run k times for that patient. For a measurement of this i^{th} patient, say the j^{th} measurement, we first identified all the measurements for the i^{th} patient which were taken before or at the same time as the j^{th} measurement. If the j^{th} measurement satisfied its clinical threshold, we recorded the sepsis risk score as 1. We then used the time of the j^{th}measurement as the reference time to check the other two measurements. If any of these measurements satisfied the corresponding clinical thresholds within the lookback periods (one hour for all measurements in qSOFA in Figure 4.1), we updated the sepsis risk score accordingly. Otherwise, if the j^{th} measurement failed to satisfy its clinical threshold, the sepsis risk score would be recorded as 0. For instance, if the j^{th} measurement was SBP=88mmHg, we would record the sepsis risk score as 1 and then check the other two measurements, RR and GCS, within the lookback period of one-hour. If RR=24 bpm, the sepsis risk score would be updated to 2;
3) A sepsis status variable was created where a sepsis risk score greater than or equal to 2 was recorded as "Sepsis alert"; otherwise "No alert".

5.1.2 ALGORITHM FOR THE ADULT SEPSIS PATHWAY

The algorithm for the Adult Sepsis Pathway was more complex than for qSOFA as it produced severe sepsis alerts ("Red zone" in Figure 4.2) and SIRS alerts ("Yellow zone"). This algorithm was developed in the following steps:

1) We extracted records for the eight measurements used in the Adult Sepsis Pathway, including the time when these measurements were taken and their numerical readings as shown in Figure 4.2;
2) An iterative procedure was used for each measurement to produce a SIRS risk score from 0 to 7 using a similar approach to the qSOFA algorithm (see section 5.1.1);
3) A sepsis status variable was created where if a SIRS risk score was greater than or equal to 2, a "SIRS alert" would be recorded; otherwise "No alert";
4) Measurements including SBP, lactate and base excess, were reassessed for severe sepsis alerts. The procedure started if any of these measurements appeared in the inner loop (i.e. j^{th} measurement of i^{th} patient). For example, if the j^{th} measurement was SBP, its reading was checked against the corresponding clinical threshold in the "Red zone" (Figure 4.2), which was <90 mmHg. If the clinical criterion was satisfied, a "Severe sepsis" status would be recorded in the sepsis status variable. Similarly, the same procedure was performed for lactate and base excess readings where the clinical thresholds were given as ≥4 mmol/L and < -5 mEq/L, respectively.

5.1.3 ALGORITHM FOR THE MODIFIED ST. JOHN RULE

The algorithm for the Modified St. John Rule was the most complicated to develop as it produced two alert types (severe sepsis alerts and SIRS alerts) and involved three separate procedure groups ("CEC", "SIRS" and "Organ dysfunction") as shown in Figure 4.3. The algorithm was implemented by the following steps:

1) We extracted records for the ten relevant measurements, including the time when these measurements were taken and their numerical readings as shown in Figure 4.3;
2) We calculated the changes in creatinine readings over time for each patient, and then created a flag if there was an increase of 44.2 μmol/L or more in a patient's creatinine level within the past 72 hours;
3) We created flags for blood glucose and creatinine measurements. These flags were then used later in defining the sepsis status for patients coded with diabetes and end-stage renal disease (ESRD) when linking with the hospital admissions data (as explained in section 5.2);
4) An iterative procedure was used for each measurement to produce a SIRS risk score, from 0 to 5 based on the five SIRS clinical criteria, and using a similar approach to the qSOFA algorithm as explained in section 5.1.1;
5) This step was used to define sepsis status based on the procedure groups under "SIRS" and "Organ dysfunction" in Figure 4.3. The number of measurements satisfying the organ dysfunction clinical thresholds were recorded as a count for organ dysfunction, from 0 to 4. If a SIRS risk score was 2 or more and a count for organ dysfunction was 1 or more, a "Severe sepsis" status would be recorded in the sepsis status variable. If the SIRS risk score was 3 or more and no organ dysfunction was identified, a "SIRS alert" would be recorded; and otherwise "No alert";
6) Measurements under the "CEC" procedure group including SBP and lactate were reassessed for severe sepsis alerts. This step was similar to that described in step 4 for the Adult Sepsis Pathway algorithm.

5.2 DATA MANAGEMENT RELATED TO ICD-10-AM CODES

Coded Sepsis cases related to pregnancy and childbirth (ICD-10-AM code: P36) were excluded, and accordingly admissions where the principal diagnosis was related to pregnancy and childbirth were excluded from the patient admissions data (all ICD-10-AM codes beginning with O).

The Modified St. John Rule required coded diagnoses of diabetes and end-stage renal disease (ESRD) as part of its logic. To facilitate the application of the rule, diabetes was defined in the hospital admissions data as any diagnosis code in the range E10 to E14 appearing in any diagnosis field, and ESRD was defined by ICD-10-AM code N18.5 in any diagnosis field. If a patient was coded with diabetes or ESRD, the sepsis alert status generated from the algorithm (as explained in section 5.1.3) would be updated accordingly as shown in Figure 4.3.

5.3 DATA LINKAGE

De-identified Medical Record Numbers (MRNs) were used to link the multiple data extracts for each patient. Sepsis alert data from Blacktown Hospital and blood culture data were further matched with patients' corresponding admissions during study periods.

All available measurement data for the study population were used to generate alerts based on three risk identification tools using the algorithms explained in section 5.1. These alerts were then linked with corresponding hospital admissions data during study periods. Further details on data linkage related to each study arm are described in section 6 for Blacktown Hospital data and section 7 for rural and regional NSW LHD data.

5.4 ANALYSIS METHODS FOR AIM 1 AND AIM 2

The linked patient data extracts were analysed based on periods-of-care for a patient (i.e. all continuous episodes-of-care related to the index admission until discharge from the hospital). We refer to such a period of care as an *admission*, and note that one admission may involve multiple episodes. The analyses of this project were conducted at the admission level.

5.4.1 ASSESSING THE PERFORMANCE OF THREE SEPSIS RISK IDENTIFICATION TOOLS

The definition of sepsis cases, including SIRS cases, based on the ICD-10-AM codes defined in section 4.1 was used as the proxy gold standard for analyses. We assessed the performance of three sepsis risk identification tools by comparing the occurrence of any sepsis alert during an admission to ICD-10-AM coded sepsis cases. The performance was assessed with metrics from confusion matrices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the receiver operating characteristic curve (AUROC) (see Box 1).

BOX 1: CONFUSION MATRIX AND PREDICTIVE ACCURACY

Performance metrics from a confusion matrix, including sensitivity, specificity, the positive predictive value (PPV), and negative predictive value (NPV) were calculated (as shown in the Table 5.1) for patient admissions where the sepsis alert was provided against the proxy gold standard for sepsis.

TABLE 5.1: CONFUSION MATRIX AND PERFORMANCE METRICS

		ANY SEPSIS ALERT DURING ADMISSION?	
		NO	**YES**
Sepsis coded during admission	**NO**	True negative (TN)	False positive (FP)
	YES	False negative (FN)	True positive (TP)
Derivations		Sensitivity (%)=100*TP/ (FN+TP) Specificity (%)=100*TN/(TN+FP) PPV (%)= 100*TP/ (FP+TP) NPV (%) =100*TN/(TN+FN)	

- Sensitivity is the proportion of coded sepsis cases that are correctly identified by alerts.
- Specificity is the proportion of non-coded sepsis cases that are correctly identified by not generating any alerts.
- PPV is the proportion of admissions with alerts that are correctly identified as coded sepsis cases.
- NPV is the proportion of admissions without alerts that are correctly identify non-sepsis cases.
- The area under the receiver operating characteristic curve (AUROC) was generated to assess the overall predictive accuracy of the sepsis alerts. In general, the higher the area under the curve the better prediction power the model has. AUROC in this study represents a combination of sensitivity and specificity.

Two types of alerts, SIRS alerts and severe sepsis alerts, were triggered based on the Adult Sepsis Pathway and the Modified St. John Rule. We conducted assessments using 1) any alert against ICD-10-AM coded sepsis cases; 2) any severe sepsis alert against ICD-10-AM coded sepsis cases and 3) any SIRS alert against ICD-10-AM coded SIRS cases.

For the Modified St. John Rule, we used eMR sepsis alert data in section 6 to address Aim 1, and used alert data generated using algorithms to address aims 2 and 3. The cross-checking between the alert data generated from the Cerner eMR system and our algorithm was conducted in section 6.10.3.

5.4.2 ASSESSING THE DETECTION OF DETERIORATING PATIENTS

Blacktown Hospital data were used to assess the performance of three sepsis risk identification tools for detecting patients' deterioration. Two outcomes were used:

1) Patients' in-hospital mortality was used as *the primary outcome* to conduct assessments. The qSOFA score was developed to identify patients with suspected infection who are at greater risk for a poor outcome outside the ICU (8, 9). In this report, we assessed the performance of three sepsis risk identification tools in detecting non-ICU patients' risk of dying. A second set of assessments was performed using a cohort of non-ICU patient admissions with the blood cultures ordered during their hospital stays. The ordering of the blood culture was considered as an indication of suspected infection; and
2) Patients' in-hospital mortality and/or ICU admission during the stay was used as *the secondary outcome*. We used two cohorts of patient admissions: a) all admissions and b) admissions with a blood culture order.

5.4.3 ANALYSIS FOR SEPSIS ALERTS AND SUSPICION OF INFECTIONS

The blood culture order time was used as a proxy time when a patient was suspected to be septic. For example, in the Blacktown Hospital blood culture data, there were 4,161 admissions with at least one blood culture. Forty-two percent of admissions had more than one blood culture ordered. For these patient admissions, we used the time of the first ordered blood culture as the proxy time for suspected sepsis.

To examine the relationship between sepsis alerts and suspicion of infection, we divided patient admissions having at least one alert into three groups: 1) first alert fired before the first blood culture was ordered, 2) first alert fired after the patient's first blood culture was ordered, and 3) patient admission with alert, but no blood culture ordered.

The risk identification tool in use at each study site was used for the relevant analysis section. Sepsis alerts from the Modified St. John Rule (eMR) were used for the Blacktown Hospital analysis (section 6.8) and alerts from the Adult Sepsis Pathway were used for the rural and regional NSW LHD data analysis (section 7.5).

For admissions with both an alert and blood culture order, we calculated the median time difference between the first alert and the first blood culture order time by patient groups and by alert type (SIRS alert, severe sepsis alert and any alert).

Cumulative proportions of admissions with the blood culture ordered after the first alert were presented by alert type, within 6 hours for the Blacktown Hospital analysis and within 2 hours for the rural and regional NSW LHD data analysis.

Patient outcomes, including mortality and median length of stay (LOS) available in the Blacktown Hospital data, were summarised by patient group and coded sepsis (yes/no) for those patients experiencing at least one alert.

5.5 ANALYSIS METHODS FOR AIM 3

Two new optimisation approaches were developed based on the existing sepsis identification tools. These two approaches were applied with a focus on improving the sensitivity, specificity, PPV and NPV compared to existing sepsis alerts, and each aimed to:

1) identify high performing tools that could be implemented via the existing Cerner eMR system by considering revised versions of the Modified St. John Rule (algorithm); and
2) develop high performing tools that could be applied at the bedside in a similar way to the qSOFA score.

5.5.1 REVISED MODIFIED ST. JOHN RULE (ALGORITHM)

One major aim of optimising the existing sepsis risk identification tools was to reduce the number of SIRS alerts and increase the number of severe sepsis alerts. To increase the chance of triggering a severe sepsis alert, several revisions of the Modified St. John Rule were considered, including adding a new measurement (base excess), updating thresholds for some of the existing measurements and relaxing the number of clinical thresholds under the "SIRS" heading (procedure group) in Figure 4.3. These alternative clinical threshold values were based on the thresholds from qSOFA and the Adult Sepsis Pathway. For example, instead of using a clinical threshold of "≥ 95" for HR as per the Modified St. John Rule, we used the clinical thresholds of "≥ 95 or ≤50" for HR, which were used in the Adult Sepsis Pathway.

The combinations of these possibilities resulted in the following seven optimisation options:

Option 1: In the original St. John Rule, two out of five SIRS clinical criteria must be satisfied before any organ dysfunction clinical criteria can be considered. We relaxed this to one out of five SIRS clinical criteria.

Option 2: Base excess less than -5.0 mEq/L was added as a new measurement to the existing CEC clinical criteria.

Option 3: Updated threshold values of the existing clinical criteria as follows:

MEASUREMENT	EXISTING THRESHOLD	UPDATED THRESHOLD
SBP (mmHg)	< 90	≤ 100
Lactate(mmol/L)	≥ 4 (CEC)	≥ 2 (CEC)
HR (beats/minute)	≥ 95	≥ 95 or ≤ 50
RR (breaths/minute)	≥ 22	≥ 22 or ≤ 10

Option 4: Combining option 1 and option 2.
Option 5: Combining option 1 and option 3.
Option 6: Combining option 2 and option 3.
Option 7: Combining option 1, option 2 and option 3.

These seven options were applied to Blacktown Hospital data and Western NSW LHD data for detecting ICD-10-AM coded sepsis cases. Data from other LHDs was not used in this part of the analysis as there were issues with the bilirubin and creatinine measurements necessary for the seven options. In addition, Blacktown data were used to assess the performance of these revised options for detecting patients' deterioration using two outcomes: 1) mortality and 2) mortality and/or ICU admission.

5.5.2 OPTIMISATION OF RISK IDENTIFICATION TOOLS APPLICABLE AT THE BEDSIDE

Another aspect of optimising sepsis risk identification tools was to develop a rule that can be applied quickly and easily at the bedside based on measurements that can similarly be obtained at the bedside without having to wait for pathology results. Specifically, we considered rules that use some combination of SBP, RR, GCS, temperature and/or HR, with a particular set of thresholds for each. A large set of logical combinations of clinical criteria based on these measurements was examined to determine the best performing rules. This approach was then extended by also considering blood lactate as an additional measurement.

The rules considered took the same basic form as qSOFA. While qSOFA has three measurements, each with a particular clinical criterion (SBP≤ 100, RR≥ 22, or GCS<15), we considered six measurements with up to three possible thresholds resulting in 14 clinical criteria considered. Those are as follows:

SBP (mmHg)	a. ≤ 100	b. < 100	c. < 90
RR (breaths/minute)	a. ≥ 22	b. ≤ 10 or ≥ 25	c. ≤ 10 or ≥ 22
GCS	a. < 15		
Temperature (°C)	a. ≤ 36 or ≥ 38.5	b. < 35.5 or > 38.5	
HR (beats/minute)	a. ≤ 50 or ≥ 95	b. ≤ 50 or ≥ 120	c. ≥ 95
Lactate (mmol/L)	a. ≥ 2.0	b. ≥ 4.0	

These threshold values were based on those in the existing risk identification tools: qSOFA, the Adult Sepsis Pathway and the Modified St. John Rule. In contrast to qSOFA's three clinical criteria, we allowed combinations of between one and six clinical criteria. Also, where qSOFA triggers an alert when at least two of the three clinical criteria are satisfied, we considered different numbers of clinical criteria to be satisfied to trigger an alert. For example, if there were four clinical criteria, then "one or more satisfied" represents one possible risk identification tool, and similarly "two or more", "three or more" and "all four" are the other possibilities. All of these variations on the basic qSOFA logic resulted in 4,704 different possible risk identification tools. Then, a set of selected high performing tools by specificity or sensitivity were applied to a test data set: Western NSW LHD.

6. AIM 1: ASSESSING THREE SEPSIS RISK IDENTIFICATION TOOLS – BLACKTOWN HOSPITAL

KEY FINDINGS:

- Out of all 36,065 admissions in the study period, 1,279 (3.5%) had a coded case of sepsis. Among these sepsis patients, there were only 36 SIRS cases.
- The crude mortality rate of sepsis patients was 11.7%, which was nearly 12 times higher than for patients without sepsis (1.0%).
- These sepsis patients were also more likely to be admitted to ICUs and stay longer than those patient without sepsis.
- A total of 12,131 sepsis alerts (eMR) were triggered for 5,096 patient admissions (14.1%) during the study period.
- Although only 36 SIRS cases were coded, there were 6,674 SIRS alerts.
- Out of all patient admissions, 8.4% (n=3,034 admissions) had at least one blood culture ordered.
- A higher proportion of admissions had blood cultures ordered after any severe sepsis alert than that after any SIRS alert. However, overall only a small proportion of admissions with alerts had a follow-up blood culture ordered.
- Patients coded with sepsis and experiencing any sepsis alert, but no blood cultures, had a high mortality rate (14.0%).
- Sensitivity and AUROC were highest for the Modified St. John Rule (eMR) when compared with qSOFA and the Adult Sepsis Pathway.
- The qSOFA score provided higher specificity (98.0%) and higher PPV (20.1%) than the other two risk identification tools.
- Both the Modified St. John Rule and the Adult Sepsis Pathway provided relatively high sensitivity and AUROC when used to detect dying patients in non-ICU wards.
- There were 15,730 alerts generated based on the Modified St. John Rule (algorithm), which was 3,599 more alerts compared to alerts from the eMR system.
- Two main reasons for the difference between the alerts from the algorithm versus the EMR system are 1) different lookback periods and 2) overall more measurements used in the algorithm.

6.1 STUDY POPULATION

This part of the study included all adult patients (aged 18 and over at the time of admission) admitted to Blacktown Hospital during the study period (from 9 Dec 2014 to 30 June 2016), excluding admissions where the principal diagnosis was related to pregnancy and/or childbirth (all ICD-10-AM codes beginning with O).

6.2 DATA EXTRACTED

Four sets of data from Blacktown Hospital were extracted for this part of the study:

1) **Hospital patient admissions data** from the Health Information Exchange, which comprised all patient admissions during the study period (admission date: 09/12/2014 - 30/06/2016 and discharge date: 09/12/2014 - 27/02/2017);
2) **Sepsis alert data** extracted from the Cerner eMR system containing all the sepsis alerts fired based on the Modified St. John Rule (encounter end date:03/12/2014 - 21/03/2017; alert triggered date: 01/12/2014 -07/02/2017);
3) **Measurement data** from the eMR system containing measurements on vital signs and pathology results (admission date: 01/12/2014 - 31/07/2016; measurement date: 01/12/2014-27/10/2016); and
4) **Blood culture data** containing blood culture orders (Admission date: 05/12/2014-31/07/2016; Blood culture order date: 05/12/2014 - 19/03/2017).

6.3 DATA QUALITY CONTROL AND LINKAGE

Data sets from each data source were examined internally for missing and invalid values.

1) Hospital admissions data

- 43,314 records were extracted.
- 10 records with missing separation dates were excluded.
- 6,801 pregnancy and childbirth-related admissions were excluded.

2) Alert data

- 66,847 records were extracted, of which 53,475 records without alert information were excluded.
- The last measurement of all relevant measurements used to trigger a sepsis alert should be recorded as the alert trigger time. We found that the alert trigger time for 11,042 records was different from the time when the last measurement was taken.
  - 10,864 (98.4%) records had the alert trigger time after the last measurement time. The lag was up to 29.4 hours. The majority of these records were lagged for less than one hour (85.1%, n=9,241).
  - 178 (1.6%) records had the alert trigger time before the last measurement time. The maximum time difference was almost one year (363 days). Of these records, 43.3% (n=77) had less than one-hour time differences.

3) Measurement data

- 4,301,658 de-identified records were extracted (supplied as 6 individual files).
- 722 records were removed because measurement results contained non-numerical values, such as “Cancel”, “cancel”, “Incorrect”, “Insufficient”, “Clotted”, “clotted”, “Contaminated”, “Alert” and “Not Indicated”.
- 71 Bilirubin readings in which the result given as “<2” were replaced with “2”. (Note that Bilirubin was used in the Modified St. John Rule (algorithm) for identifying an organ dysfunction the thresholds ≤ 34.2 or ≥171.0mol/L. A bilirubin reading less than 2 was outside these clinical thresholds).

4) Blood culture data

- 63,185 records were extracted.
- 54,585 records without blood culture orders were excluded.

Data linkage was performed and the following data sets were used for the analyses:

- 36,065 patient admissions for the study population during the study period;
- 12,131 alert records matched study population during the study period;
- 3,745,587 records were used for deriving alerts based on qSOFA, Adult Sepsis pathway and St. John Rule (algorithm); and
- 8,600 blood cultures matched to records in the study population during the study period.

6.4 PRELIMINARY STATISTICS FOR THE STUDY POPULATION

A total of 28,957 unique patients were included in the Blacktown Hospital part of the study. Their median age was 55 years (IQR: 38-71) and 46% (n=11,946) of these patients were male. Of all patients, 3.2% (n=824) reported themselves as being Aboriginal and/or Torres Strait Islander origin.

Out of all 36,065 patient admissions, 3.9% (n=1,402) were admitted to ICUs during their hospital stays and a total of 483 patients died in hospital during the study period. The median length of stay (LOS) was 1.9 days (IQR: 0.3 - 4.9).

6.5 BY SEPSIS DIAGNOSIS BASED ON ICD-10-AM

The two sepsis definitions described in section 4.1, were applied to identify sepsis cases. Out of all 36,065 patient admissions, 3.3% (n=1,192) involved a coded case of sepsis based on the definition used by Sundararajan et al. (2015). The number of sepsis cases at admission level was slightly higher when the CHADx definition was applied, with 1,279 (3.5%) admissions involving a sepsis code, including 36 SIRS cases.

Comparing patients at admission level with and without a sepsis coding (CHADx) during their hospital stay, we found that patients with sepsis were older, more likely to be male, to be admitted to ICU, and the overall hospital stay tended to be longer. The mortality rate of sepsis patients was nearly 12 times higher than those patients without sepsis (Table 6.1).

TABLE 6.1: PATIENT DEMOGRAPHICS BY SEPSIS CODING (CHADX) AT ADMISSION LEVEL

PARAMETERS	NON-SEPSIS CODED ADMISSIONS	SEPSIS CODED ADMISSIONS
Age in years - *median (IQR)*	58 (40 -73)	71 (59 – 82)
Male - *n (%)*	16,060 (46.2%)	647 (50.6%)
Female - *n (%)*	18,726 (53.8%)	632 (49.4%)
ATSI - *n (%)*	1,229 (3.5%)	39 (3.1%)
ICU admissions - *n (%)*	948 (2.7%)	454 (35.5%)
LOS in days - *median (IQR)*	1.8 (0.3 – 4.6)	8.4 (4.8 – 16.3)
In-hospital mortality - *n (%)*	333 (1.0%)	150 (11.7%)
Total admission - *n (%)*	34,786 (96.5%)	1,279 (3.5%)

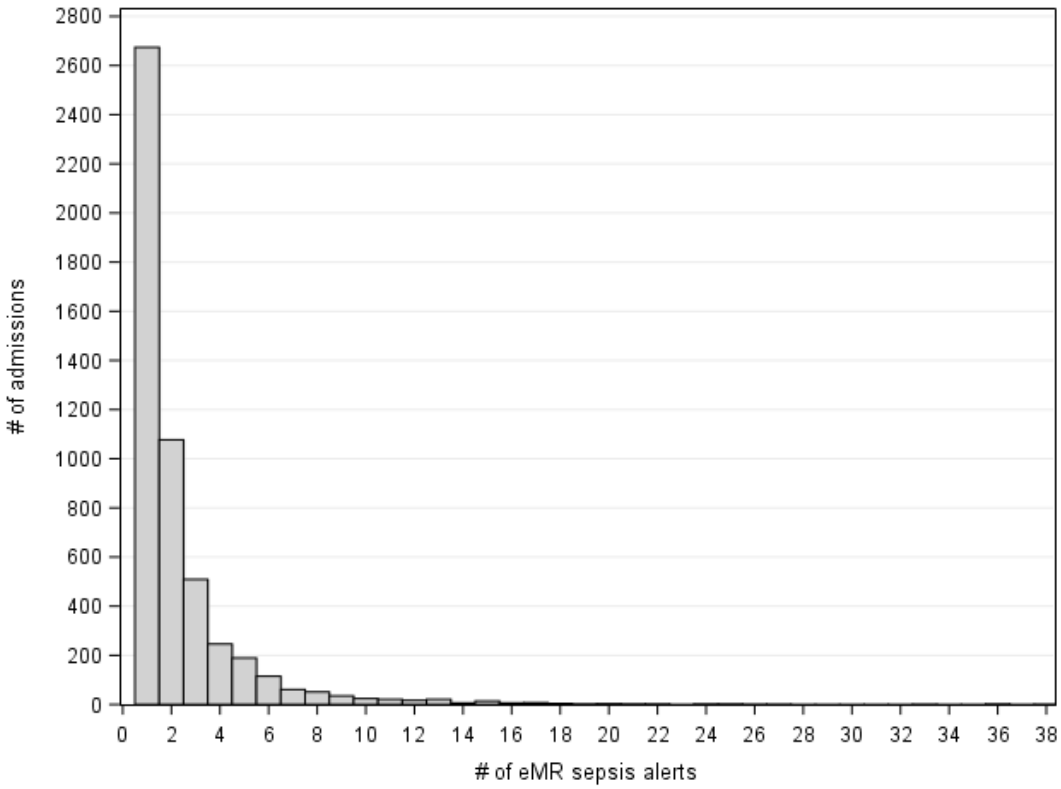
6.6 SEPSIS ALERTS BASED ON THE MODIFIED ST. JOHN RULE (EMR)

6.6.1 SEPSIS ALERTS EXTRACTED FROM EMR

A total of 12,131 sepsis alerts were triggered for 5,096 patient admissions (14.1%) during the study period: 5,457 severe sepsis alerts for 2,829 admissions (7.8%) and 6,674 SIRS alerts for 3,338 admissions (9.3%). Note that 1,071 admissions (3.0%) had both types of alerts.

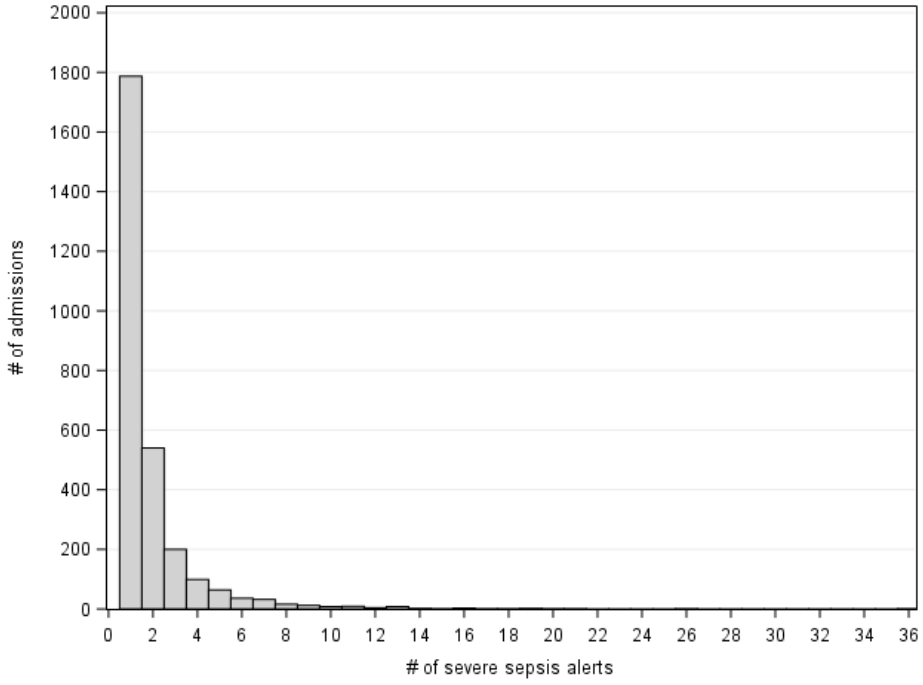
For the 5,096 admissions with any eMR sepsis alert (either a SIRS or severe sepsis alert), 52.5% had one alert during the stay period, 21.1% had two alerts, and 10.0% had three alerts (Figure 6.1). The maximum number of sepsis alerts was 38 during one patient admission.

FIGURE 6.1: DISTRIBUTION OF EMR SEPSIS ALERTS PER ADMISSION



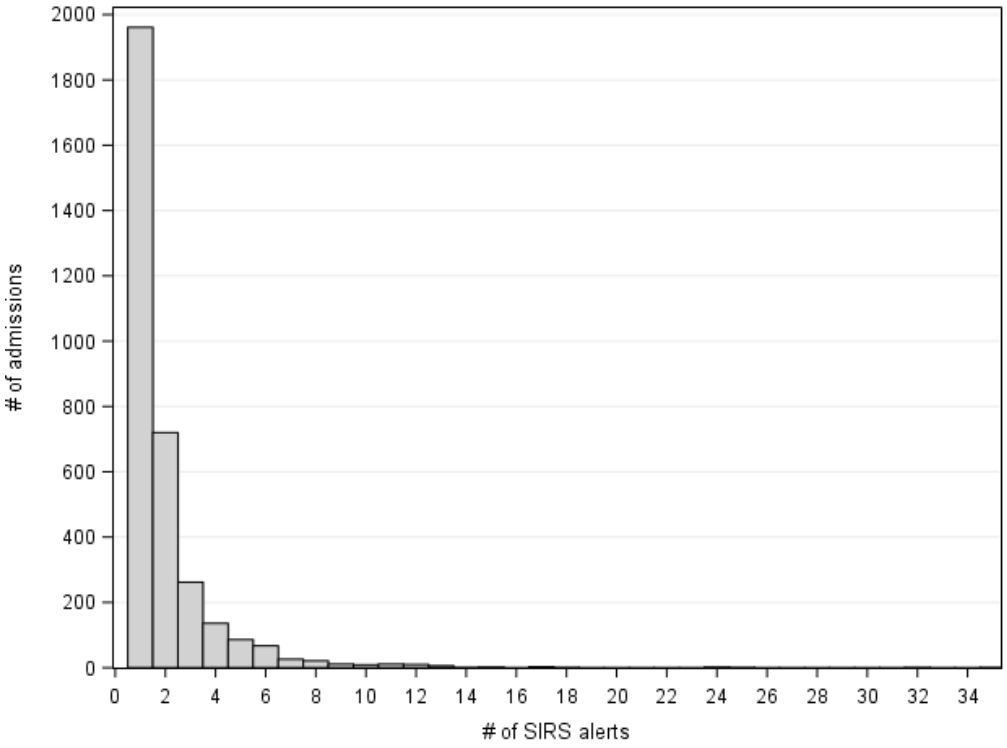
For the 2,829 patient admissions with any severe sepsis alert, 63.2% had one alert during the stay period, 19.1% had two alerts, and 7.1% had three alerts (Figure 6.2). The maximum number of severe sepsis alerts was 36 for one patient admission.

FIGURE 6.2: DISTRIBUTION OF SEVERE SEPSIS ALERTS PER ADMISSION



For the 3,338 patient admissions with any SIRS alert, 58.8% had one alert during the stay period, 21.6% had two alerts, and 7.9% had three alerts (Figure 6.3). The maximum number of SIRS alerts was 35 for one patient admission.

FIGURE 6.3: DISTRIBUTION OF SIRS ALERTS PER ADMISSION



6.6.2 ASSESSMENT OF THE MODIFIED ST. JOHN RULE (EMR) SEPSIS ALERTS

Sepsis alerts were assessed against sepsis cases identified using the two definitions described in section 4.1. Table 6.2 shows the assessment results based on any sepsis alert and Table 6.3 shows the results for any severe sepsis alert and any SIRS alert.

Out of 1,192 sepsis admissions identified using the definition from the 2005 paper by Sundararajan et al. (16), 771 had at least one sepsis alert, and the overall sensitivity was 64.7% (Table 6.2). Comparable results were obtained based on the CHADx definition with 833 out of 1,279 sepsis cases having at least one alert, and a sensitivity of 65.1%. Overall, the assessment results based on the two ICD-10-AM definitions were very similar as shown in Table 6.2 and Table 6.3. We used the CHADx definition for subsequent analyses in this project.

When assessing severe sepsis alerts only, the sensitivity dropped to 45.5% when comparing to CHADx-defined sepsis, while the specificity increased to 93.5% and PPV increased to 20.6% (Table 6.3). Based on the CHADx definition for sepsis cases, the predictive validity for all eMR Sepsis alerts (Area under the receiver operating characteristic curve [AUROC] =0.76) was higher than for severe sepsis alerts only (AUROC=0.70).

Although only 36 SIRS cases were coded, there were 6,674 SIRS alerts. A total of 2,267 patient admissions had both SIRS alerts and severe sepsis alerts. This finding provided a foundation for us to improve the alert performance in Aim 3 by removing SIRS alerts while relaxing the measurement threshold for severe sepsis alerts (see section 8).

TABLE 6.2: ASSESSING ANY EMR SEPSIS ALERT COMPARED TO ICD-10-AM CODED SEPSIS BY TWO DEFINITIONS

SEPSIS CODING DEFINITIONS	ANY ICD-10 CODED SEPSIS	ANY SEPSIS ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		No	Yes	Total					
Sundararajan et al., 2005	No	30,548	4,325	34,873	64.7	87.6	15.1	98.6	0.76 (0.75-0.78)
	Yes	421	771	1,192					
	Total	30,969	5,096	36,065					
CHADx	No	30,523	4,263	34,786	65.1	87.8	16.4	98.6	0.76 (0.75-0.78)
	Yes	446	833	1,279					
	Total	30,969	5,096	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

TABLE 6.3: ASSESSING ANY EMR SEVERE SEPSIS ALERT AND ANY EMR SIRS ALERT COMPARED TO ICD-10-AM CODED SEPSIS/SIRS BY TWO DEFINITIONS IF APPLICABLE

SEPSIS CODING DEFINITIONS	ANY ICD-10 CODED SEPSIS	ANY SEVERE SEPSIS ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		No	Yes	Total					
Sundararajan et al., 2005	No	32,580	2,293	348,73	45.0	93.4	19.0	98.0	0.69 (0.68 – 0.71)
	Yes	656	536	1,192					
	Total	33,236	2,829	36,065					
CHADx	No	32,539	2,247	34,786	45.5	93.5	20.6	97.9	0.70 (0.68 - 0.71)
	Yes	697	582	1,279					
	Total	33,236	2,829	36,065					
	Any ICD-10 coded SIRS^	**Any SIRS alert**							
CHADx (SIRS)	No	32,714	3,315	36,029	63.9	90.8	0.7	100.0	0.77 (0.69 - 0.85)
	Yes	13	23	36					
	Total	32,727	3,338	36,065					

**PPV=positive predictive value; NPV=negative predictive value ^ Note that there were only 36 coded SIRS cases*

6.7 DETECTION OF DETERIORATING PATIENTS (DEATHS/ICU ADMISSIONS)

6.7.1 DETECTION OF IN-HOSPITAL MORTALITY

Of 34,663 non-ICU admissions, 318 patients died in hospital. Table 6.4 presents the performance accuracy of the three sepsis risk identification tools in detecting dying patients. When assessed using all sepsis alerts, the Modified St. John Rule (eMR) had the highest sensitivity (74.2%) closely followed by the Adult Sepsis Pathway (70.4%). These two tools produced the same AUROC of 0.81, which was much higher than the qSOFA score (0.66). However, qSOFA achieved the highest PPV with 15.1% and the highest specificity with 98.2%.

When severe sepsis alerts were used as a predictor of mortality, the Modified St. John Rule (eMR) had much higher sensitivity (54.4%) and AUROC (0.74) than the Adult Sepsis Pathway (sensitivity 36.8% and 0.67 AUROC).

For 2,253 non-ICU admissions with blood cultures ordered, 103 patients (4.6%) died in hospital. The performance of all three sepsis risk identification tools in identifying dying patients is presented in Table 6.5. Using all sepsis alerts, the sensitivity for the Modified St. John Rule (eMR) was 90.3%, which was the same as that for the Adult Sepsis Pathway, while the Adult Sepsis Pathway had the highest AUROC (0.79) among three tools. Using severe sepsis alerts, the Modified St. John Rule (eMR) had higher sensitivity and similar AUROC in comparison to the Adult Sepsis Pathway.

6.7.2 DETECTION OF IN-HOSPITAL MORTALITY AND/OR ICU ADMISSIONS

Table 6.6 presents the performance accuracy of the three sepsis risk identification tools in detecting negative outcomes (deaths and/or ICU admissions) for all patient admissions. Of all 36,065 patient admissions, 1,720 (4.8%) involved deaths of patients and/or ICU admissions. When assessed using all sepsis alerts, both the Modified St. John Rule (eMR) and the Adult Sepsis Pathway had high sensitivity and AUROC while qSOFA had the highest specificity of 98.2%.

For 3,034 admissions with blood cultures ordered, 884 (29.1%) involved patient deaths and/or ICU admissions. Table 6.7 presents the performance accuracy of the three sepsis risk identification tools in detecting dying patients and/or ICU admissions for these 3,034 admissions. When assessed using all sepsis alerts, the Modified St. John Rule (eMR) and the Adult Sepsis Pathway had high sensitivity while qSOFA had the highest specificity of 91.5% and the Adult Sepsis Pathway had the highest PPV (50.1%) and AUROC (0.73) among three tools.

TABLE 6.4: ASSESSMENT OF THREE SEPSIS RISK IDENTIFICATION TOOLS USED FOR PREDICTING IN-HOSPITAL MORTALITY FOR 34,663 NON-ICU ADMISSIONS

ALERT TYPE	SEPSIS RISK IDENTIFICATION TOOL	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
All	qSOFA	34.6	98.2	15.1	99.4	0.66 (0.64 - 0.69)
	Adult Sepsis Pathway	70.4	92.5	8.0	99.7	0.81 (0.79 - 0.84)
	Modified St. John Rule (eMR)	74.2	88.6	5.7	99.7	0.81 (0.79 - 0.84)
Severe sepsis	Adult Sepsis Pathway	36.8	97.8	13.5	99.4	0.67 (0.65 - 0.70)
	Modified St. John Rule (eMR)	54.4	94.5	8.4	99.6	0.74 (0.72 - 0.77)

TABLE 6.5: ASSESSMENT OF THREE SEPSIS RISK IDENTIFICATION TOOLS USED FOR PREDICTING IN-HOSPITAL MORTALITY FOR 2,253 NON-ICU ADMISSIONS WITH BLOOD CULTURE ORDERS

ALERT TYPE	SEPSIS RISK IDENTIFICATION TOOL	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
All	qSOFA	49.5	91.5	21.9	97.4	0.71 (0.66 - 0.75)
	Adult Sepsis Pathway	90.3	68.5	12.1	99.3	0.79 (0.76 - 0.82)
	Modified St. John Rule (eMR)	90.3	54.1	8.6	99.1	0.72 (0.69 - 0.75)
Severe sepsis	Adult Sepsis Pathway	55.3	90.4	21.7	97.7	0.73 (0.68 - 0.78)
	Modified St. John Rule (eMR)	70.9	77.4	13.1	98.2	0.74 (0.70 - 0.79)

TABLE 6.6: ASSESSMENT OF THREE SEPSIS RISK IDENTIFICATION TOOLS USED FOR PREDICTING IN-HOSPITAL MORTALITY AND/OR ICU ADMISSION FOR ALL 36,065 ADMISSIONS

ALERT TYPE	SEPSIS RISK IDENTIFICATION TOOL	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
All	qSOFA	14.0	98.2	28.0	95.8	0.56 (0.55 - 0.57)
	Adult Sepsis Pathway	65.5	92.5	30.6	98.2	0.79 (0.78 - 0.80)
	Modified St. John Rule (eMR)	68.0	88.6	23.0	98.2	0.78 (0.77 - 0.79)
Severe sepsis	Adult Sepsis Pathway	41.5	97.8	48.7	97.1	0.70 (0.68 - 0.71)
	Modified St. John Rule (eMR)	54.1	94.5	32.9	97.6	0.74 (0.73 - 0.75)

TABLE 6.7: ASSESSMENT OF THREE SEPSIS RISK IDENTIFICATION TOOLS USED FOR PREDICTING IN-HOSPITAL MORTALITY AND/OR ICU ADMISSION FOR 3,034 ADMISSIONS WITH BLOOD CULTURE ORDER.

ALERT TYPE	SEPSIS RISK IDENTIFICATION TOOL	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
All	qSOFA	17.0	91.5	45.2	72.8	0.54 (0.53 - 0.56)
	Adult Sepsis Pathway	76.8	68.5	50.1	87.8	0.73 (0.71 - 0.74)
	Modified St. John Rule (eMR)	78.8	54.1	41.4	86.2	0.66 (0.65 - 0.68)
Severe sepsis	Adult Sepsis Pathway	52.8	90.4	69.4	82.3	0.72 (0.70 - 0.73)
	Modified St. John Rule (eMR)	65.0	77.4	54.2	84.3	0.71 (0.69 - 0.73)

6.8 SUSPECTED INFECTION FOR THOSE ADMISSIONS WITH ANY SEPSIS ALERT

The first blood culture (BC) order time was used as a proxy time for a patient suspected to be septic. A total of 8,600 blood cultures were ordered for 4,164 patient admissions. Out of all patient admissions, 8.4% (n=3,034 admissions) had at least one blood culture ordered. A total of 1,683 admissions (55.5% out of these 3,034 admissions) has at least one sepsis alert.

6.8.1 ALERT TRIGGER TIME AND BLOOD CULTURE ORDERING TIME

Out of 5,096 admissions with any sepsis alert, two thirds (67.0%, n=3,413) had no blood cultures ordered, while one third had at least one blood culture ordered either before or after the first sepsis alert triggered (Table 6.8). These proportions were roughly similar for admissions with any SIRS alert or with any severe sepsis alert.

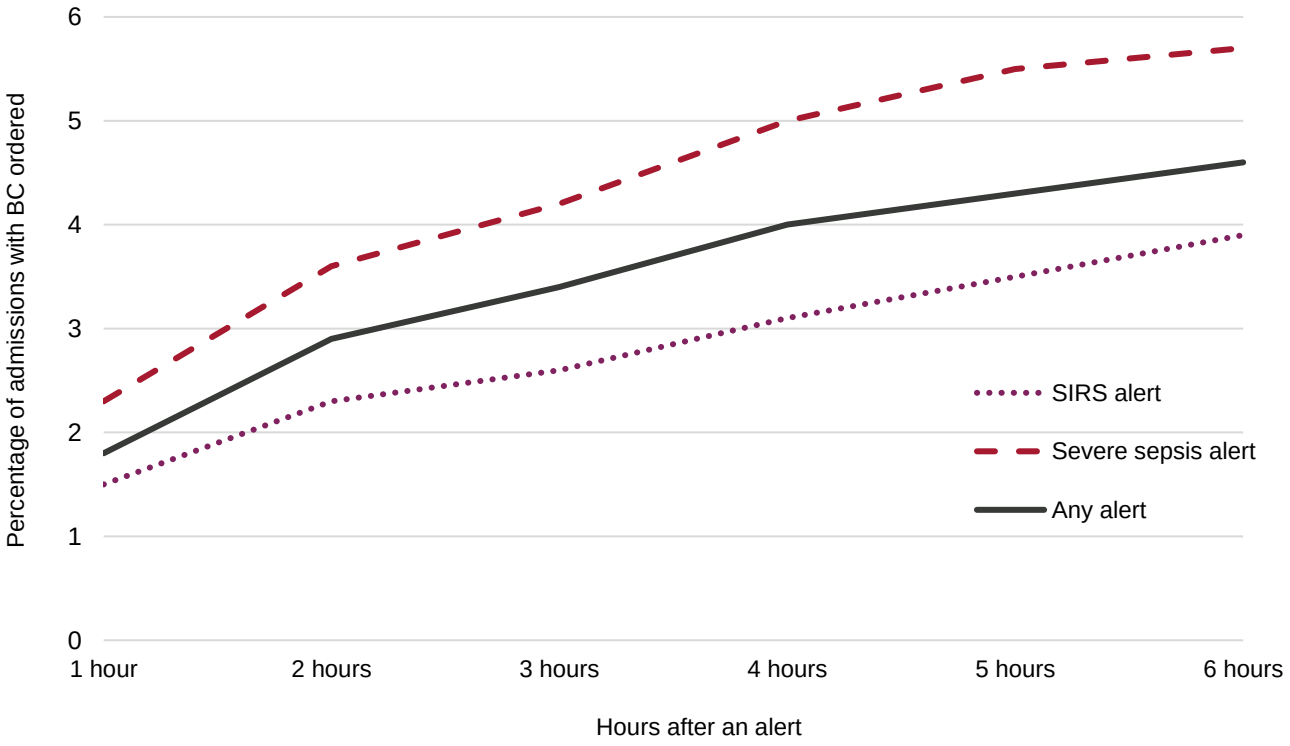
If a blood culture was ordered after an alert was triggered, 50% of these tests were ordered within 15.3 hours of the alert trigger time, however, the IQR varied from 2.8 hours to 70.8 hours. The median time difference from the first severe sepsis alert to time for the first blood culture order was much shorter than that for SIRS alerts (17.2 hours versus 26.6 hours). This could mean that clinicians responded more quickly to severe sepsis alerts compared to SIRS alerts.

If an alert was triggered after a blood culture was ordered, 50% of these alerts were triggered within 18.9 hours of test ordering time. This time difference for any severe sepsis alert was 16.8 hours, which is shorter than for any SIRS alert (23.3 hours).

6.8.2 A BLOOD CULTURE ORDERED WITHIN SIX HOURS AFTER THE FIRST SEPSIS ALERT

Figure 6.4 shows the cumulative proportion of the first blood cultures ordered within 6 hours after the first alert by alert type. Over this 6-hour period, a consistently higher proportion of admissions had blood cultures ordered after any severe sepsis alert than that after any SIRS alert. However, of all admissions with an alert, only small proportion of had follow-up blood cultures ordered (For more details see Table C.1 in Appendix C).

FIGURE 6.4: THE FIRST BLOOD CULTURE (BC) ORDERED WITHIN SIX HOURS AFTER THE FIRST ALERT BY ALERT TYPE (PERCENTAGE WAS CALCULATED OUT OF ALL ADMISSIONS WITH AT LEAST ONE ALERT. FOR MORE DETAILS SEE TABLE C.1 IN APPENDIX C).



6.8.3 PATIENT OUTCOMES

We examined patient outcomes for those admissions with any sepsis alert by their sepsis coding and patient group (Table 6.9). If an alert was triggered before a blood culture order, about one third (32.4%, n=202) of patient admissions involved a coded case of sepsis. A similar proportion (35.5%, n=356) was seen if an alert was triggered after a blood culture order. However, only 7.5% of patients (n=257) were coded with sepsis if there was at least one sepsis alert but no blood culture order during their admissions.

Across all three patient groups, patients coded with sepsis stayed longer and were more likely to die in hospital than those without sepsis. The LOS patterns for patients who experienced any alert and had a blood culture were similar. Patients who were coded with sepsis and had any sepsis alert, but no blood cultures, had a higher mortality rate (14.0%) and longer stay (median LOS 6.8 days) than those who were not coded with sepsis (mortality 4.7% and median LOS 5.2 days).

TABLE 6.8: TIME DIFFERENCE BETWEEN THE FIRST ALERT AND THE FIRST BLOOD CULTURE ORDER

PATIENT GROUPS	SIRS ALERT		SEVERE SEPSIS ALERT		ANY ALERT	
	N (%^)	Median time difference# (IQR), hours	N (%^)	Median time difference# (IQR), hours	N (%^)	Median time difference# (IQR), hours
An alert before BC* ordered	599 (17.9)	26.6 (7.9 - 116.9)	456 (16.1)	17.2 (2.5 - 75.5)	679 (13.3)	15.3 (2.8 - 70.8)
An alert after BC* ordered	565 (16.9)	-23.3 (-71.6 - -5.4)	604 (21.4)	-16.8 (-57.4 - -4.8)	1,004 (19.7)	-18.9 (-57.4 -4.7)
An alert, no BC* ordered	2,174 (65.1)		1,769 (62.5)		3,413 (67.0)	
Total	3,338 (100.0)		2,829 (100.0)		5,096 (100.0)	

** BC: blood culture. ^ percentage was calculated out of all admissions with at least one alert.*
#time difference = (BC ordering time – alert trigger time)

TABLE 6.9: PATIENT OUTCOMES FOR THOSE ADMISSIONS WITH ANY SEPSIS ALERT BY PATIENT GROUP AND SEPSIS CODING

PATIENT GROUPS	SEPSIS CODING	N (WITHIN GROUP %)	MEDIAN LOS (IQR), DAYS	MORTALITY, % (95% CI)
An alert before BC* ordered	No	459 (67.6)	9.9 (5.1 - 16.7)	7.4 (5.0 - 9.8)
	Yes	220 (32.4)	14.9 (8.2 - 26.4)	13.2 (8.7 - 17.7)
An alert after BC* ordered	No	648 (64.5)	9.4 (5.3 - 17.3)	11.3 (8.8 - 13.7)
	Yes	356 (35.5)	12.6 (6.7 - 23.6)	20.2 (16.0 - 24.4)
An alert, no BC* ordered	No	3,156 (92.5)	5.2 (3.0 - 9.4)	4.7 (4.0 - 5.4)
	Yes	257 (7.5)	6.8 (4.3 - 12.8)	14.0 (9.7 - 18.3)

** BC: blood culture*

6.9 ASSESSMENT OF THE PERFORMANCE OF QSOFA AND THE ADULT SEPSIS PATHWAY

6.9.1 MEASUREMENT DATA USED

To assess the qSOFA score, 1,073,265 measurement records were used (Table 6.10). Of the three measurements used in qSOFA, 97.7% were SBP and RR. Based on the algorithm developed for qSOFA, 48,516 measurements (4.5% of total measurements) would have satisfied the clinical criteria as shown in Figure 4.1 and 2,437 measurements (0.2%) would have been used for triggering the qSOFA alerts had the tool been applied in real time (Table 6.11). A total 2,189 alerts would have been triggered according to the qSOFA score.

To assess the Adult sepsis pathway, 2,719,779 measurement records were used (Table 6.10). Five of the eight measurements used in this tool were commonly available, including SpO_2, HR, RR, SBP, and temperature. A total of 86,666 measurements (3.2% of total measurements) would have satisfied the clinical criteria as shown in Figure 4.2 (Table 6.12). A total 20,048 alerts would have been triggered according to Adult Sepsis Pathway (ASP): 13,915 SIRS alerts (69.4%) and 6,133 severe sepsis alerts (30.6%), had the tool been applied in real time.

TABLE 6.10: NUMBER OF MEASUREMENTS AVAILABLE FOR ASSESSING THE PERFORMANCE OF QSOFA AND THE ADULT SEPSIS PATHWAY

MEASUREMENT	QSOFA	%	ADULT SEPSIS PATHWAY (ASP)	%
Base Excess			32,697	1.2
Lactate			32,640	1.2
SBP	525,101	48.9	525,101	19.3
SpO_2			556,911	20.5
GCS	24,327	2.3	24,327	0.9
HR			533,468	19.6
RR	523,837	48.8	523,837	19.3
Temperature			490,798	18.1
Total	**1,073,265**	**100.0**	**2,719,779**	**100.0**

TABLE 6.11: SEPSIS ALERTS BASED ON QSOFA BY NUMBER OF CLINICAL CRITERIA SATISFIED, N = 1,073,265 MEASUREMENTS.

	NUMBER OF CLINICAL CRITERIA SATISFIED			
	0	1	2	3
NO. OF MEASUREMENTS	1,024,749	46,079	2,401	36
			2,437 (0.2%) measurements would be involved for producing qSOFA alerts	

TABLE 6.12: SEPSIS ALERTS BASED ON THE ADULT SEPSIS PATHWAY BY NUMBER CLINICAL CRITERIA SATISFIED, N = 2,719,779 MEASUREMENTS

SEPSIS ALERT STATUS	NUMBER OF CLINICAL CRITERIA SATISFIED								TOTAL MEASUREMENTS (%)
	0	1	2	3	4	5	6	7	
No ASP Alert	2,633,113	60,284	--	--	--	--	--	--	**2,693,397 (99.0%)**
ASP SIRS Alert	--	--	16,736	1,956	429	53	6	0	**19,180 (0.7%)**
ASP Severe Sepsis	--	7,202	--	--	--	--	--	--	**7,202 (0.3%)**

6.9.2 ASSESSING THE PERFORMANCE OF THE SEPSIS RISK IDENTIFICATION TOOLS

Table 6.13 shows the performance of qSOFA and the Adult Sepsis Pathway compared against any ICD-10-AM coded sepsis cases. Note the performance results for the Modified St. John Rule (eMR) from section 6.6.2 are presented for comparison in this table and two other tables: Table 6.14 and Table D.1 in Appendix D.

Out of 1,279 admissions with a coded sepsis case, 173 (sensitivity 13.5%) would have been detected based on qSOFA, 694 (54.3%) based on the Adult Sepsis Pathway, and 833 (65.1%) based on the Modified St. John Rule (eMR) (Table 6.13). For 34,786 admissions without sepsis coded, the ability to detect these admissions was similar for qSOFA and the Adult Sepsis Pathway (specificity 98.0% and 96.9%, respectively), while it was lower for the Modified St. John Rule (eMR) (87.8%). The qSOFA score provided better PPV (20.1%) than the other two tools because it identified more true positives relative to false positives. The NPVs of these three tools were similarly high due to the low prevalence rate of sepsis (3.5%). The Modified St. John Rule (eMR) had the highest AUROC among three tools (0.76 versus 0.56 for qSOFA and 0.73 for the Adult Sepsis Pathway).

We assessed the severe sepsis alerts and SIRS alerts separately and results are presented in Table 6.14 and Table D.1 in Appendix D, respectively. The comparison was made between the Adult Sepsis Pathway and the Modified St. John Rule (eMR) as qSOFA does not differentiate between severe sepsis and SIRS. The sensitivity and AUROC of the Adult Sepsis Pathway for detecting severe sepsis cases dropped (from 31.1% and 0.64 respectively) while specificity and PPV increased (to 96.9% and 27.2%, respectively) (Table 6.14). Similarly, the sensitivity of the Modified St. John Rule (eMR) dropped from 65.1% to 45.5%, and the AUROC dropped from 0.76 to 0.70 while its specificity and PPV increased.

TABLE 6.13: ASSESSING ANY SEPSIS ALERT BASED ON THREE RISK IDENTIFICATION TOOLS COMPARED TO ICD-10-AM CODED SEPSIS (CHADX)

RISK IDENTIFICATION TOOL	ANY ICD-10-AM CODED SEPSIS	ANY ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		No	Yes	Total					
qSOFA	No	34,098	688	34,786	13.5	98.0	20.1	96.9	0.56 (0.55 - 0.57)
	Yes	1,106	173	1,279					
	Total	35,204	861	36,065					
Adult sepsis pathway	No	31,795	2,991	34,786	54.3	91.4	18.8	98.2	0.73 (0.72 - 0.74)
	Yes	585	694	1,279					
	Total	32,380	3,685	36,065					
Modified St. John Rule (eMR)	No	30,523	4,263	34,786	65.1	87.8	16.4	98.6	0.76 (0.75 - 0.78)
	Yes	446	833	1,279					
	Total	30,969	5,096	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

TABLE 6.14: ASSESSING ANY SEVERE SEPSIS ALERT BASED ON TWO RELEVANT RISK IDENTIFICATION TOOLS COMPARED TO ICD-10-AM CODED SEPSIS (CHADX)

RISK IDENTIFICATION TOOL	ANY ICD-10-AM CODED SEPSIS	ANY SEVERE SEPSIS ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		No	Yes	Total					
Adult sepsis pathway	No	33,721	1,065	34,786	31.1	96.9	27.2	97.5	0.64 (0.63 - 0.65)
	Yes	881	398	1,279					
	Total	34,602	1,463	36,065					
Modified St. John Rule (eMR)	No	32,539	2,247	34,786	45.5	93.5	20.6	97.9	0.70 (0.68 - 0.71)
	Yes	697	582	1,279					
	Total	33,236	2,829	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

6.10 EXAMINING THE ALGORITHM FOR THE MODIFIED ST. JOHN RULE

In this section, we applied the algorithm for the Modified St. John Rule to the Blacktown Hospital measurement data. We compared and explained the differences between the alerts from the algorithm versus the eMR system.

6.10.1 MEASUREMENT DATA USED

A total of 2,409,348 measurement records were used to assess this tool for the study population (Table 6.15). Four of the 10 measurements used in this tool were commonly available, including HR, RR, SBP, and temperature. A total of 220,524 measurements (9.2% of total measurements) would have satisfied the clinical criteria as shown in Figure 4.3 (Table 6.16).

A total of 15,730 alerts would have been triggered according to the modified St. John Rule (algorithm) had it been applied in real time: 39.7% of these were SIRS alerts (n=6,249) and 60.3% severe sepsis alerts (n=9,481).

TABLE 6.15: NUMBER OF MEASUREMENTS AVAILABLE FOR ASSESSING THE PERFORMANCE OF THE MODIFIED ST. JOHN RULE

MEASUREMENT	MODIFIED ST. JOHN RULE (ALGORITHM)	%
Bilirubin	31,921	1.3
Blood Glucose	114,735	4.8
Creatinine	78,081	3.2
Lactate	32,640	1.4
SBP	525,101	21.8
HR	533,468	22.1
MAP	1,913	0.1
RR	523,837	21.7
Temperature	490,798	20.4
WBC	76,854	3.2
Total	**2,409,348**	**100.0**

6.10.2 ASSESSING THE PERFORMANCE OF THE MODIFIED ST. JOHN RULE (ALGORITHM)

The performance of the Modified St. John Rule using the algorithm is presented in the following three tables: 1) Table 6.17 for any sepsis alert, 2) Table 6.18 for any severe sepsis alert and 3) Table D.2 in Appendix D for any SIRS alert. In these tables, results from the Modified St. John Rule (eMR) are shown for comparison. Overall, we identified fewer true positives, and hence lower sensitivity, using the algorithm than those from the Cerner eMR system. The possible explanations for these differences are explored in the next section.

TABLE 6.16: SEPSIS ALERTS BASED ON THE MODIFIED ST. JOHN RULE (ALGORITHM) BY NUMBER OF CLINICAL CRITERIA SATISFIED^, N = 2,409,348 MEASUREMENTS

SEPSIS ALERT STATUS		NUMBER OF CLINICAL CRITERIA SATISFIED						TOTAL MEASUREMENTS (%)
		0	1	2	3	4	5	
No Alert		2,188,824	158,549	43,006	--	--	--	**2,390,379 (99.2%)**
SIRS Alert		--	--	--	6,639	750	46	**7,435 (0.3%)**
Severe Sepsis	CEC*	--	3,161	--	--	--	--	**3,161 (0.1%)**
	SIRS + Organ dysfunction*	--	7,137	1,100	136	--	--	**8,373 (0.3%)**

^ *After adjusting for the patients coded with diabetes and the end-stage renal disease (see Figure 4.3)* * *As shown in Figure 4.3*

TABLE 6.17: ASSESSING ANY SEPSIS ALERT BASED ON THE MODIFIED ST. JOHN RULE USING ALERTS FROM THE ALGORITHM AND EMR

RISK IDENTIFICATION TOOL	ANY ICD-10-AM CODED SEPSIS	ANY ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		No	Yes	**Total**					
Modified St. John Rule (algorithm)	No	32,294	2,492	34,786	47.8	92.8	19.7	98.0	0.70 (0.69 - 0.72)
	Yes	668	611	1,279					
	Total	32,966	3,105	36,065					
Modified St. John Rule (eMR)	No	30,523	4,263	34,786	65.1	87.8	16.4	98.6	0.76 (0.75 - 0.78)
	Yes	446	833	1,279					
	Total	30,969	5,096	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

TABLE 6.18: ASSESSING ANY SEVERE SEPSIS ALERT BASED ON THE MODIFIED ST. JOHN RULE USING ALERTS FROM THE ALGORITHM AND EMR

RISK IDENTIFICATION TOOL	ANY ICD-10-AM CODED SEPSIS	ANY SEVERE SEPSIS ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		No	Yes	Total					
Modified St. John Rule (algorithm)	No	33,484	1,302	34,786	32.4	96.3	24.1	97.5	0.64 (0.63 - 0.66)
	Yes	865	414	1,279					
	Total	34,348	1,717	36,065					
Modified St. John Rule (eMR)	No	32,539	2,247	34,786	45.5	93.5	20.6	97.9	0.70 (0.68 - 0.71)
	Yes	697	582	1,279					
	Total	33,236	2,829	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

6.10.3 EXPLAINING THE DIFFERENCE BETWEEN THE ALERTS FROM THE ALGORITHM VERSUS THE EMR

Part 1: Testing algorithm using the measurement dataset in the sepsis alert data (eMR)

Measurements used to trigger alerts in the eMR system were recorded in the sepsis alert data. To test our algorithm against these system-generated alerts, we applied the algorithm to the same measurements and compared the results from the algorithm to those from the eMR system. To do this, we took the following steps:

1) Extracted the measurements, including numerical readings and time that each measurement was recorded in the system. There were 12,131 alerts in the sepsis alert data (eMR) and 34,322 corresponding measurements were also recorded in this data;
2) Applied the Modified St. John Rule (algorithm) to this measurement data. This identified 11,708 alerts, including 5,805 SIRS alerts and 5,903 severe sepsis alerts;
3) Compared the alerts from the algorithm with those from the eMR system. For 11,042 (91.0%) of the 12,131 eMR alerts, the alert trigger times were different from the last measurement time (see section 6.3). Thus, we used the last measurement time of each alert when comparing with alerts from the algorithm. A total of 9,924 alerts were correctly matched, which were 81.8% of all eMR alerts;
4) Explored the reasons for 2,207 (18.2%) alerts from the eMR system that did not match the alerts generated by the algorithm. We grouped these alerts according to alert type as shown in Table 6.19. Most of these mismatches occurred in group A, and B, where a sepsis alert was triggered in the eMR system, but did not appear when using algorithm.

TABLE 6.19: ALERT SUMMARY FOR THE NUMBER OF MISMATCHES

GROUP	ALERT TYPE FROM EMR	ALERT TYPE BASED ON THE ALGORITHM	MISMATCHED ALERTS, N
A	SIRS	-	1,181
B	Severe sepsis	-	860
C	Severe sepsis	SIRS	3
D	SIRS	Severe sepsis	163

We identified that the main reason for these mismatched cases was the difference in the lookback periods used in the eMR system compared to the algorithm. In the development of the Modified St. John Rule (algorithm), we used lookback periods provided by CEC as shown in Figure 4.3 (see section 4.2.3). For the alert data (eMR), we retrospectively calculated the lookback period for each measurement based on the difference between measurement time and last measurement time within each alert. For example, three measurements were taken on the same day and triggered a SIRS alert. WBC was taken at 8.00am, temperature was taken at 10.00am, HR at 11.00am. The last measurement time 11.00am was used a reference time for calculating the lookback period for WBC and temperature, i.e. 180 minutes and 60 minutes. Table 6.20 presents the summary of these lookback periods by measurement.

Mismatches under groups A, B, and C in Table 6.19 could be explained by the different lookback periods for temperature, HR and RR. Longer lookback periods were used in the eMR system compared with those in the algorithm. We observed that five of these measurements (WBC, blood glucose, MAP, bilirubin and creatinine) used the same lookback period as we used in the algorithm because 99% of these measurements had a lookback period within or close to those as shown in Figure 4.3. However, for temperature, HR and RR, about 25% of these measurements had the similar lookback period, i.e. 60 minutes as shown in Figure 4.3, while about 75% of the alerts in the eMR system applied a lookback period greater than 60 minutes. For instance, three measurements, temperature, RR and HR, were used to trigger a eMR SIRS alert. The time difference between the last measurement (i.e. HR) and temperature was 40 minutes and it was 2 hours for RR. It would not produce an alert using the algorithm since the lookback period for RR was outside the specified 60 minutes.

TABLE 6.20: THE LOOKBACK PERIODS REPRODUCED FROM THE ALERT DATA FROM THE EMR SYSTEM (IN MINUTES) BY MEASUREMENTS INVOLVED IN THE MODIFIED ST. JOHN RULE

MEASUREMENT	25TH PERCENTILE	95TH PERCENTILE	99TH PERCENTILE	MAXIMUM (MINUTES)	LOOKBACK PERIOD IN FIGURE 4.3 (MINUTES)
Temperature	74	1,395	1,708	1,794	60
HR	70	1,495	1,727	1,791	60
RR	66	1,593	1,744	1,786	60
WBC	325	1,574	1,753	522,322 (363 days)	1,800
Blood Glucose	231	1,608	1,781	418,461 (291 days)	1,800
Lactate	186	668	1,431	404,174 (281 days)	720
MAP	63	1,620	1,752	1,792	1,800
Bilirubin	377	1,591	1,750	2,198	1,800
Creatinine	329	1,773	2,967	4,236	4,320

Mismatches under group D in Table 6.19 could be explained by the different lookback periods for blood lactate measurements. Shorter lookback periods were used for some lactate measurements in the eMR system compared with those in the algorithm. Thus, more lactate measurements would be used in the algorithm to trigger more severe sepsis alerts, relative to those in eMR. For example, three measurements (temperature, RR and HR) could be used to trigger a SIRS alert for a patient. A lactate reading of the same patient was used in the previous alert. This lactate reading was within the 12-hour lookback period from the last measurement time of the three measurements. In this case, lactate reading together with three other measurement would be used to trigger a severe sepsis alert, instead of a SIRS alert. We identified that some of the eMR alerts did not consider lactate measurements which were within lookback period as explained in this example. Thus, some of SIRS alerts from eMR would be generated as severe sepsis alerts using the algorithm.

Part 2: Comparing sepsis alerts from eMR and the algorithm

To further examine the difference between the alerts from the algorithm and the eMR System, we compared the measurements used to generate alerts for each approach. The alerts from the algorithm were generated using the measurement data from the Blacktown Hospital (see section 6.10.1). The algorithm generated 15,730 alerts (Table 6.21). A total of 3,599 more alerts were generated from the algorithm compared to those from the eMR system. This could be partly due to 10,519 more measurements used in the algorithm than those in the eMR system. We explored this difference further by alert type (Table 6.21) and measurements involved (Table 6.22):

1) The algorithm generated 4,024 more severe sepsis alerts than the eMR system. Severe sepsis alerts were divided into two groups:
   a. 1,367 more were from two CEC clinical criteria (Figure 4.3), i.e. SBP<90 mmHg and lactate ≥ 4.0 mmol/L. This difference can be explained by 1,431 more measurements used in the algorithm compare to those in the eMR system, including 1,001 more lactate measurements and 430 more SBP measurements (Table 6.22); and

b. 2,657 more were from the combination of SIRS and organ dysfunction clinical criteria as shown in Figure 4.3. To produce these alerts, a total 8,227 more measurements were used in the algorithm than those in the eMR system. Among four organ dysfunction measurements, the algorithm used 1,711 more lactate measurements, 669 more bilirubin measurements and 1,422 more creatinine measurements, but 958 less MAP measurements.

2) The algorithm generated 425 less alerts overall than the eMR system. However, 861 more measurements were used in the algorithm (Table 6.21). This reverse pattern can be partly explained by longer lookback period used in the eMR system (~30 hours) for three measurements (temperature, HR, and RR) compared to one-hour in the algorithm (as explained in the last part of this section).

In addition, we found that 27 patients only appeared in the eMR alert data, but not in the measurement data for the algorithm. There were 550 measurements for these 27 patients. This discrepancy resulted in 169 more alerts in the eMR system (97 SIRS, 7 CEC severe sepsis alerts and 65 severe sepsis alerts related organ dysfunctions), relative to alerts from the algorithm.

TABLE 6.21: COMPARISON OF THE EMR SEPSIS ALERT AND ALERTS FROM THE ALGORITHM

ALERT TYPE		ALERTS FROM EMR	ALERTS FROM THE ALGORITHM	NO OF MEASUREMENTS USED- IN THE EMR ALERT DATA	NO OF MEASUREMENTS USED-FOR THE ALGORITHM
SIRS alerts		6,674	6,249	19,030	19,891
Severe sepsis alerts	CEC*	1,752	3,119	1,688	3,119
	SIRS + Organ dysfunction*	3,705	6,362	13,604	21,831
Total		**12,131**	**15,730**	**34,322**	**44,841**

** As shown in Figure 4.3*

TABLE 6.22: SUMMARY OF NUMBER OF MEASUREMENTS USED IN THE MEASUREMENT DATA AND ALERT DATA

MEASUREMENT		ALERT DATA (EMR)	MEASUREMENT DATA USED FOR THE ALGORITHM
Temperature		5,502	5,188
HR		7,053	7,378
RR		3,784	4,687
WBC		6,766	10,171
Blood Glucose		5,036	6,961
Lactate	CEC*	719	1,720
	SIRS + Organ dysfunction*	1,624	3,335
MAP		1,006	48
Bilirubin		1,022	1,691
Creatinine		841	2,263
SBP (CEC)		969	1,399
Total		**34,322**	**44,841**

** As shown in Figure 4.3*

7. AIM 2: ASSESSING THREE SEPSIS RISK IDENTIFICATION TOOLS ACROSS FOUR RURAL AND REGIONAL NSW LOCAL HEALTH DISTRICTS

KEY FINDINGS:

- Out of all 100,087 patient admissions in the study period, 1,163 (1.2%) had a coded sepsis case. Among these sepsis patients, there were only 17 admissions with a coded SIRS case.
- Patients coded with sepsis were more likely to be admitted to ICUs and stay longer than patient without sepsis.
- The qSOFA score had the lowest sensitivity but the highest specificity and PPV of the three risk identification tools.
- Sensitivity for the Modified St. John Rule was higher than the other two tools but with the lowest specificity.
- Sensitivity estimates varied considerably between LHDs when assessing any sepsis alert: from 11.3% to 42.9% qSOFA; from 23.3% to 53.7% for the Adult Sepsis Pathway and from 26.7% to 57.1% for the Modified St. John Rule.
- Blood cultures ordered within two hours of the first ASP sepsis alert occurred in around 2% of admissions with alerts.

7.1 STUDY POPULATION AND DATA

The data from rural and regional NSW LHD facilities used in this study were extracted from select health facilities in four LHDs - Far West, Murrumbidgee, Southern NSW and Western NSW. These LHDs form part of seven rural and regional LHDs out of a total of 15 LHDs in NSW. Data from facilities in these four LHDs were included if they had implemented the eMR system by 31st March 2016. The data came from three sources:

1) **Hospital admissions data** from the Health Information Exchange, which comprised all patient admissions during the study period (see Table E.1 in the Appendix E for facility specific dates). Admission records were also restricted to patients aged 18 or over admitted where the primary diagnosis was unrelated to pregnancy or child birth;
2) **Measurement data** from the eMR system containing measurements on vital signs and pathology results (admission date range: 01/09/2014 – 30/10/2016; measurement date: 02/09/2014-20/01/2017); and
3) **Blood culture data** containing blood culture orders and similarly corresponds (Admission date: 01/09/2014-30/09/2016; Blood culture ordering date/time: 08/09/2014-15/11/2016).

7.2 DATA CLEANING AND LINKAGE

Data sets were supplied separately for each LHD and each data source, resulting in 12 data sources to be checked (supplied as 55 individual files), then cleaned and combined for analysis. Initially, each of the 12 data sources was checked for missing or invalid values in each variable, implausible values of continuous variables (e.g. age<0, date of birth>2016), and logical impossibilities (e.g. separation date preceding admission date). The concordance between patient admission records and both measurement and blood culture data were then checked. This involved merging patient admissions data with measurement data, and patient admissions with blood culture order data to determine if admissions were correctly represented in the other two data sets. Once the checking was complete, data from each LHD was formatted in a uniform way and then combined to form three final data sets for analysis: patient admissions, measurement data and blood culture order data.

7.2.1 HOSPITAL ADMISSIONS DATA

Cleaning of the hospital admissions data required a number of steps to create the final data set for analysis. The raw data contained records for facilities that had not implemented the eMR system by the required date for study inclusion, and these records had to be identified and removed. The result of this was that the data represents a subset of facilities for Murrumbidgee, Southern NSW and Western NSW LHDs. Far West LHD has only two facilities and both were included in the analysis. For each facility, the separation date had to occur before or on 30th September 2016 and admissions had to occur on or after the date that was one week (7 days) after the implementation date of the eMR system. The implementation date varied between facilities, and the facility-specific dates are shown in Table E.1 in the appendix.

In addition to reformatting and renaming most variables, several key variables required specific manipulation to allow combining of data from all four LHDs. For example, data from some LHDs contained an episode-level identifier (separate from patient ID), while others had an admission-level identifier. Both types of identifiers had to be created in a consistent way across all data sets.

To identify admissions in which at least some of the stay had been spent in ICU, a variable was constructed from multiple data sources. If the ward type appeared as ICU in either the admissions data or the measurement data, this was flagged as 'any ICU'. This approach was necessary since the variable indicating the ward in the admissions data represented the admitting ward for some LHDs and the current episode ward for other LHDs. Also, the ward variable in the measurement data sometimes disagreed with the ward variable in the admissions data despite the records referring to the same admission. The 'any ICU' approach was a way to accommodate these issues, but means that the ICU variable for NSW data does not represent the same thing as in the Blacktown Hospital data.

The raw hospital admissions data had over two million records, however approximately half of these were excluded due to having dates outside the study range, patient age less than 18 or principal diagnosis related to pregnancy or childbirth. The final admissions data set comprised 101,146 episodes corresponding to 100,087 admissions for 53,235 unique patients. The largest proportion of admissions was for Western NSW LHD (49.9%), followed by Southern NSW LHD (26.8%), Murrumbidgee LHD (19.5%) and Far West LHD (3.8%) (see Table 7.1).

TABLE 7.1: SUMMARY OF EPISODES, ADMISSIONS AND UNIQUE PATIENT IDS IN HOSPITAL ADMISSIONS DATA BY FOUR RURAL AND REGIONAL NSW LHDS

RURAL AND REGIONAL NSW LHD	EPISODES IN RAW DATA	FINAL DATA		
		EPISODES	ADMISSIONS	UNIQUE PATIENT IDS
All LHDs	**206,598**	**101,146**	**100,087**	**53,235**
Far West	4,838	3,909	3,774	2,055
Murrumbidgee	27,899	19,947	19,524	8,861
Southern NSW	36,974	26,873	26,870	13,964
Western NSW	136,887	50,417	49,919	28,357

7.2.2 MEASUREMENT DATA

The measurement data also required reformatting and renaming of many variables. Two patient identifiers were provided: MRN and AUID. These were the same for almost all records, however, as MRN was occasionally missing AUID was used when merging with hospital admissions data. Because some patient IDs were not unique across LHDs and admission date and time did not always agree for the same admission, measurement and admissions data could not be merged by simply matching on certain variables. Instead, the admission and separation date and time from the admissions data were matched with the measurement data on LHD and patient ID, then any measurement records where the date and time of the result fell between the admission and separation date and time was considered a match.

A total of 7,083,689 records in the measurement data matched with the admissions data, 62.4% of the measurement records for Western NSW LHD, 22.0% for Southern NSW LHD, 10.9% for Murrumbidgee LHD and 4.8% for Far West LHD. Of all admission records, some had no corresponding measurement data (4.6%), while others had measurement records that contained no valid results (24.2%) (Table 7.2). The remaining 71.2% of admissions had at least one valid measurement record. At LHD level, the proportion of admissions with at least one valid measurement record varied from 42.5% for Murrumbidgee LHD up to 89.2% for Western NSW LHD.

TABLE 7.2: NUMBER AND PROPORTION (%) OF ADMISSIONS MATCHING WITH MEASUREMENT DATA

RURAL AND REGIONAL NSW LHD	NO MEASUREMENT RECORD (%)	ONLY BLANK MEASUREMENT RECORDS (%)	ANY VALID MEASUREMENT RECORD (%)
All LHDs	**4,656 (4.6)**	**24,189 (24.2)**	**71,242 (71.2)**
Far West	15 (0.4)	1,382 (36.6)	2,377 (63.0)
Murrumbidgee	4,048 (20.7)	7,188 (36.8)	8,288 (42.5)
Southern NSW	384 (1.4)	10,465 (39.0)	16,021 (59.6)
Western NSW	209 (0.4)	5,154 (10.3)	44,556 (89.3)

In the measurement data, there was an apparent issue with results for creatinine and bilirubin. There were no bilirubin results for Far West, Murrumbidgee or Southern NSW LHDs, but there were almost four thousand for Western NSW LHD. For creatinine, there were very few records in total, and none for Murrumbidgee or Southern NSW LHDs. Both of these measurements were used in the Modified St. John Rule (algorithm).

7.2.3 BLOOD CULTURE DATA

There were 4,280 blood culture orders during the study period, and the majority of these were for Western NSW LHD with 3,072 (63.7%), followed by Southern NSW LHD with 781 (16.2%), Murrumbidgee LHD with 727 (15.1%) and Far West LHD with 240 (5.0%). These orders occurred during 2,738 admissions.

7.3 PRELIMINARY SUMMARY STATISTICS

Overall 1,163 (1.2%) admissions had a coded sepsis case, and this proportion varied between LHDs from 0.7% to 1.3% (Table 7.3). There were very few coded SIRS cases, with only 11 for admissions in Southern NSW LHD and six in Western NSW LHD during the study period. Patients with sepsis tended to be older, more likely to be in ICU at some point during their admission, and had longer median lengths of stay (Table 7.4) than patients without sepsis.

TABLE 7.3: PATIENT ADMISSIONS AND SEPSIS CASES BY RURAL AND REGIONAL NSW LHD AND FACILITY

RURAL AND REGIONAL NSW LHD FACILITY NAME	ADMISSIONS - N	PATIENT IDS - N	SEPSIS – CHADX - N (%)
ALL LHDS	**100,087**	**53,235**	**1,163 (1.2)**
FAR WEST	**3,774**	**2,055**	**49 (1.3)**
Broken Hill Base Hospital	3,731	2,019	49 (1.3)
Wilcannia Multi-Purpose Service	43	36	<5
MURRUMBIDGEE	**19,524**	**8,861**	**150 (0.8)**
Coolamon Multi-Purpose Service	478	333	<5
Culcairn Multi-Purpose Service	92	70	<5
Griffith Base Hospital	14,602	5,729	95 (0.7)
Gundagai Multi-Purpose Service	1,453	813	27 (1.9)
Temora Health Service	1,219	770	17 (1.4)
Tumut Health Service	1,680	1,146	8 (0.5)
SOUTHERN NSW	**26,870**	**13,964**	**293 (1.1)**
Bateman's Bay District Hospital	7,797	5,273	78 (1.0)
Goulburn Base Hospital	7,843	4,193	109 (1.4)
Moruya District Hospital	11,230	4,496	106 (0.9)
WESTERN NSW	**49,919**	**28,357**	**671 (1.3)**
Baradine Multi-Purpose Service	177	113	<5
Bathurst Base Hospital	10,029	5,193	78 (0.8)
Blayney Multi-Purpose Service	102	84	<5
Bourke Multi-Purpose Service	654	430	7 (1.1)
Brewarrina Multi-Purpose Service	245	155	<5
Cobar District Hospital	1,596	883	18 (1.1)
Collarenebri Multi-Purpose Service	59	45	<5
Coolah Multi-Purpose Service	79	61	<5
Coonabarabran District Hospital	757	579	<5
Coonamble Multi-Purpose Service	610	365	8 (1.3)

TABLE 7.3: PATIENT ADMISSIONS AND SEPSIS CASES BY RURAL AND REGIONAL NSW LHD AND FACILITY

RURAL AND REGIONAL NSW LHD FACILITY NAME	ADMISSIONS - N	PATIENT IDS - N	SEPSIS – CHADX - N (%)
Dubbo Base Hospital	17,732	9,491	269 (1.5)
Dunedoo War Memorial MPS	65	49	<5
Gilgandra Multi-Purpose Service	634	421	8 (1.3)
Lightning Ridge MPS	254	187	<5
Narromine District Hospital	792	549	6 (0.8)
Nyngan Multi-Purpose Service	471	344	14 (3.0)
Oberon Multi-Purpose Service	290	218	<5
Orange Health Service	11,515	7,170	179 (1.6)
Rylstone Multi-Purpose Service	238	168	<5
Walgett Multi-Purpose Service	1,560	659	14 (0.9)
Warren Multi-Purpose Service	380	210	14 (3.7)
Wellington Hospital	1,680	983	39 (2.3)

Note: Counts less than 5 are displayed as "<5".

TABLE 7.4: PATIENT CHARACTERISTICS BY SEPSIS CODING

PARAMETERS	NON-SEPSIS CODED ADMISSIONS	SEPSIS CODED ADMISSIONS
Age, median years (IQR)	65 (49-76)	72 (61-81)
Male, *n (%)*	51,789 (52.4%)	645 (55.5%)
Female, *n (%)*	47,135 (47.6%)	518 (44.5%)
ICU admissions, *n (%)**	763 (0.8%)	56 (4.8%)
LOS, median days (IQR)	0.3 (0.2-2.2)	5.1 (2.1-9.5)
Admissions, *n*	98,924 (98.8%)	1,163 (1.2%)

**Admissions with at least one ICU episode appearing in either the Hospital Admission data or the measurement data.*

7.4 ASSESSMENT OF THREE RISK IDENTIFICATION TOOLS

Most qSOFA alerts involved the clinical criteria for SBP and RR being satisfied, due to these being more commonly recorded measurements (Table 7.5). Of all 1,957,634 measurements used for the qSOFA algorithm, 7.3% satisfied the clinical criteria as show in Figure 4.1 (Table 7.6). In total, there were 9,982 qSOFA alerts which occurred during 3,119 admissions (3.1%).

Of all 4,696,393 measurements used for the Adult Sepsis Pathway, 3.6% satisfied the clinical criteria as show in Figure 4.2 (Table 7.7). For the Adult Sepsis Pathway, there were more alerts in total with 51,355. The majority of these were SIRS alerts (38,842), with 12,513 severe sepsis alerts. At admission level, this translated to 8,832 (8.8%) admissions with a SIRS alert, 4,641 (4.6%) with a severe sepsis alert, and 10,965 (11.0%) with any alert.

Of all 4,802,940 measurements used for the Modified St. John Rule (algorithm), 7.3% satisfied the clinical criteria as shown in Figure 4.1 (Table 7.8). In contrast, the Modified St. John Rule triggered fewer SIRS alerts (13,310 [1.2%]), but a greater number of severe sepsis alerts (22,688 [2.0%]) This corresponded to 3,991 (4.0%) admissions with a SIRS alert, 5,741 (5.7%) with a severe sepsis alert, and 8,793 (8.8%) with any alert.

TABLE 7.5: NUMBER OF MEASUREMENTS AVAILABLE FOR ASSESSING THE PERFORMANCE OF QSOFA, THE ADULT SEPSIS PATHWAY AND THE MODIFIED ST. JOHN RULE (ALGORITHM)

MEASUREMENT	QSOFA	%	ADULT SEPSIS PATHWAY	%	MODIFIED ST. JOHN RULE	%
Base Excess			9,543	0.2		
Bilirubin					3,788	0.1
Blood Glucose					117,364	2.4
Creatinine					21	0.0
Lactate			8,371	0.2	8,371	0.2
SBP	994,196	50.8	994,196	21.2	994,196	20.7
SpO_2			977,489	20.8		
GCS	20,129	1.0	20,129	0.4		
HR			990,961	21.1	990,961	20.6
MAP					931,182	19.4
RR	943,355	48.2	943,355	20.1	943,355	19.6
Temperature			752,349	16.0	752,349	15.7
WBC					61,353	1.3
Total	**1,957,680**	**100.0**	**4,696,393**	**100.0**	**4,802,940**	**100.0**

Table 7.9 shows the performance of the tools when both severe sepsis and SIRS alerts are used to identify ICD-10-AM coded sepsis admissions. As we would expect, the sensitivity is higher due to the more frequent alerts, but the number of false positives is also higher resulting in reduced specificity and PPV. This table also includes the results for qSOFA as the alerts for this tool identify any sepsis and do not distinguish between SIRS and severe sepsis. The sensitivity is lower compared to the other two tools with 23.3% overall, but both specificity and PPV are higher due to there being fewer false positives.

There were many more ICD-10-AM coded sepsis cases (1,163) and this larger sample enabled a clearer assessment of the performance of these two tools as shown in Table 7.10. The Adult Sepsis Pathway identified 306 of the 1,163 sepsis admissions (sensitivity 26.3%), while the Modified St. John Rule (algorithm) detected somewhat more with 361 (31.0%). Far West LHD and Western NSW LHD data showed the highest sensitivity for both tools. For every sepsis admission correctly detected there were over 14 false positives in the combined data, with the positive predictive value (PPV) less than 7% for both tools.

Due to the relatively low numbers of ICU related episodes, performance metrics for those records are more volatile (see Appendix F). In general, however, the sensitivity is markedly higher than for the data overall, with specificity correspondingly lower.

7.5 FOLLOWING UP SEPSIS ALERTS – ADULT SEPSIS PATHWAY (ASP)

The results in Tables 7.11 and 7.12 refer to the first observed alert and the first blood culture order during an admission. Out of admissions with an alert of any kind, the vast majority (>80%) did not have a blood culture ordered. Overall, the proportion of admissions with alerts that had a blood culture ordered within two hours of the first alert was low (2.0% for any alert) and this varied from 1.4% to 4.0% across LHDs. In some cases, blood culture may have been ordered before the first ASP alert for a non-sepsis related reason, then another order made within two hours of the first ASP alert. Including all such potential cases increases the above proportion to 6.1%, still a small proportion of alerts followed up with blood culture.

TABLE 7.6: SEPSIS ALERTS BASED ON QSOFA BY NUMBER OF CLINICAL CRITERIA SATISFIED, N=1,957,680 MEASUREMENTS

	NUMBER OF CLINICAL CRITERIA SATISFIED			
	0	1	2	3
No. of measurements	1,814,135	131,822	11,383	340
			11,723 (0.4%) measurements would be involved for producing qSOFA alerts	

TABLE 7.7: SEPSIS ALERTS BASED ON THE ADULT SEPSIS PATHWAY BY NUMBER OF CLINICAL CRITERIA SATISFIED, N=4,696,393 MEASUREMENTS

SEPSIS ALERT STATUS	NUMBER OF CLINICAL CRITERIA SATISFIED								TOTAL MEASUREMENTS (%)
	0	1	2	3	4	5	6	7	
No ASP Alert	4,525,591	105,512	--	--	--	--	--	--	**4,631,103 (98.40%)**
ASP SIRS Alert	--	--	41,446	8,865	1,712	260	4	0	**52,287 (1.11%)**
ASP Severe Sepsis	--	13,003	--	--	--	--	--	--	**13,003 (0.02%)**

TABLE 7.8: SEPSIS ALERTS BASED ON THE MODIFIED ST. JOHN RULE (ALGORITHM) BY NUMBER OF CLINICAL CRITERIA SATISFIED^, N=4,802,940 MEASUREMENTS

SEPSIS ALERT STATUS		NUMBER OF CLINICAL CRITERIA SATISFIED						TOTAL MEASUREMENTS (%)
		0	1	2	3	4	5	
No Alert		4,389,901	286,485	77,749	--	--	--	4,754,136 (98.98%)
SIRS Alert		--	--	--	15,591	2,150	142	17,883 (0.37%)
Severe Sepsis	CEC*	--	11,104	--	--	--		11,104 (0.23%)
	SIRS + Organ dysfunction*	--	18,372	1,346	99	--		19,817 (0.41%)

^ *After adjusting for the patients coded with diabetes and the end-stage renal disease (see Figure 4.3)* * *As shown in Figure 4.3*

TABLE 7.9: ALERTS FOR ANY SEPSIS DURING ADMISSIONS COMPARED TO ANY CODED SEPSIS, BY RURAL AND REGIONAL NSW LHD

TOOL	RURAL AND REGIONAL LHD	NO SEPSIS		ANY ICD-10 CODED SEPSIS		SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
		NO ALERT	ANY ALERT	NO ALERT	ANY ALERT					
qSOFA	**All LHDs**	**96,076**	**2,848**	**892**	**271**	**23.3**	**97.1**	**8.7**	**99.1**	**0.60 (0.59, 0.61)**
	Far West	3,574	151	28	21	42.9	96.0	12.2	99.2	0.69 (0.62, 0.76)
	Murrumbidgee	18,984	390	133	17	11.3	98.0	4.2	99.3	0.55 (0.52, 0.57)
	Southern NSW	25,825	752	220	73	24.9	97.2	8.9	99.2	0.61 (0.59, 0.64)
	Western NSW	47,693	1,555	511	160	23.9	96.8	9.3	98.9	0.60 (0.59, 0.62)
Adult Sepsis Pathway	**All LHDs**	**88,509**	**10,415**	**613**	**550**	**47.3**	**89.5**	**5.0**	**99.3**	**0.68 (0.67, 0.70)**
	Far West	3,391	334	25	24	49.0	91.0	6.7	99.3	0.70 (0.63, 0.77)
	Murrumbidgee	18,454	920	115	35	23.3	95.3	3.7	99.4	0.59 (0.56, 0.63)
	Southern NSW	23,827	2,750	162	131	44.7	89.7	4.6	99.3	0.67 (0.64, 0.70)
	Western NSW	42,837	6,411	311	360	53.7	87.0	5.3	99.3	0.70 (0.68, 0.72)
Modified St. John Rule (algorithm)	**All LHDs**	**90,630**	**8,294**	**664**	**499**	**42.9**	**91.6**	**5.7**	**99.3**	**0.67 (0.66, 0.69)**
	Far West	3,385	340	21	28	57.1	90.9	7.6	99.4	0.74 (0.67, 0.81)
	Murrumbidgee	18,371	1,003	110	40	26.7	94.8	3.8	99.4	0.61 (0.57, 0.64)
	Southern NSW	24,607	1,970	167	126	43.0	92.6	6.0	99.3	0.68 (0.65, 0.71)
	Western NSW	44,267	4,981	366	305	45.5	89.9	5.8	99.2	0.68 (0.66, 0.70)

**PPV=positive predictive value; NPV=negative predictive value*

TABLE 7.10: ALERTS FOR SEVERE SEPSIS DURING ADMISSIONS COMPARED TO ANY ICD-10-AM CODED SEPSIS, BY RURAL AND REGIONAL NSW LHD

TOOL	RURAL AND REGIONAL LHD	NO SEPSIS		ANY ICD-10 CODED SEPSIS		SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
		NO ALERT	ANY ALERT	NO ALERT	ANY ALERT					
Adult Sepsis Pathway	**All LHDs**	**94,589**	**4,335**	**857**	**306**	**26.3**	**95.6**	**6.6**	**99.1**	**0.61 (0.60, 0.62)**
	Far West	3,605	120	35	14	28.6	96.8	10.5	99.0	0.63 (0.56, 0.69)
	Murrumbidgee	19,098	276	131	19	12.7	98.6	6.4	99.3	0.56 (0.53, 0.58)
	Southern NSW	25,495	1,082	235	58	19.8	95.9	5.1	99.1	0.58 (0.56, 0.60)
	Western NSW	46,391	2,857	456	215	32.0	94.2	7.0	99.0	0.63 (0.61, 0.65)
Modified St. John Rule (algorithm)	**All LHDs**	**93,544**	**5,380**	**802**	**361**	**31.0**	**94.6**	**6.3**	**99.2**	**0.63 (0.61, 0.64)**
	Far West	3,561	164	28	21	42.9	95.6	11.4	99.2	0.69 (0.62, 0.76)
	Murrumbidgee	18,900	474	125	25	16.7	97.6	5.0	99.3	0.57 (0.54, 0.60)
	Southern NSW	25,248	1,329	214	79	27.0	95.0	5.6	99.2	0.61 (0.58, 0.64)
	Western NSW	45,835	3,413	435	236	35.2	93.1	6.5	99.1	0.64 (0.62, 0.66)

**PPV=positive predictive value; NPV=negative predictive value*

TABLE 7.11: THE TIMING OF BLOOD CULTURE ORDERS RELATIVE TO ASP SEPSIS ALERTS, BY RURAL AND REGIONAL NSW LHD AND ALERT TYPE

RURAL AND REGIONAL LHD	PATIENT GROUPS	SIRS ALERT		SEVERE SEPSIS ALERT		ANY ALERT	
		N (%^)	MEDIAN TIME DIFFERENCE# (IQR), HOURS	N (%^)	MEDIAN TIME DIFFERENCE# (IQR), HOURS	N (%^)	MEDIAN TIME DIFFERENCE# (IQR), HOURS
All LHDs	An alert before BC*	708 (8.3)	12.4 (1.4 – 51.4)	350 (8.1)	6.6 (0.3 – 57.2)	771 (7.4)	14.8 (1.8 – 60.2)
	An alert after BC*	395 (4.6)	-21.7 (-76.6 – -3.7)	150 (3.5)	-28.2 (-115.6 – -4.7)	431 (4.2)	-20.2 (-73.9 – -2.9)
	An alert, no BC*	7403 (87.0)		3812 (88.4)		9151 (88.4)	
	Total	**3338 (100.0)**		**2829 (100.0)**		**5096 (100%)**	
Far West	An alert before BC*	49 (16.0)	12.9 (1.6 – 36.8)	31 (23.3)	1.5 (0.3 – 26.5)	53 (15.2)	11.3 (1.5 – 38.5)
	An alert after BC*	9 (2.9)	-31.6 (-53.8 – -8.0)	5 (3.8)	-21.6 (-24.0 – -5.7)	10 (2.9)	-22.8 (-31.6 – -1.1)
	An alert, no BC*	248 (81.0)		97 (72.9)		285 (81.9)	
	Total	**306 (100.0)**		**133 (100.0)**		**348 (100.0)**	
Murrumbidgee	An alert before BC*	58 (7.1)	9.6 (0.6 – 32.7)	16 (5.5)	6.6 (0.6 – 37.8)	61 (6.7)	12.4 (1.3 – 43.6)
	An alert after BC*	58 (7.1)	-25.2 (-94.9 – -7.0)	15 (5.9)	-55.1 (-112.5 – -7.0)	60 (6.6)	-23.5 (-96.0 – -6.7)
	An alert, no BC*	699 (85.8)		242 (88.6)		785 (86.6)	
	Total	**815 (100.0)**		**273 (100.0)**		**906 (100.0)**	
Southern NSW	An alert before BC*	170 (07.5)	18.2 (1.9 – 59.9)	64 (5.9)	18.4 (0.2 – 62.9)	183 (6.6)	19.2 (2.0 – 62.7)
	An alert after BC*	65 (02.9)	-20.2 (-44.1 – -5.1)	26 (2.4)	-38.0 (-156.1 – -5.5)	73 (2.6)	-18.5 (-44.1 – -3.5)
	An alert, no BC*	2038 (89.7)		999 (91.7)		2509 (90.7)	
	Total	**2273 (100.0)**		**1089 (100.0)**		**2765 (100.0)**	

TABLE 7.11: THE TIMING OF BLOOD CULTURE ORDERS RELATIVE TO ASP SEPSIS ALERTS, BY RURAL AND REGIONAL NSW LHD AND ALERT TYPE

RURAL AND REGIONAL LHD	PATIENT GROUPS	SIRS ALERT		SEVERE SEPSIS ALERT		ANY ALERT	
		N (%^)	MEDIAN TIME DIFFERENCE# (IQR), HOURS	N (%^)	MEDIAN TIME DIFFERENCE# (IQR), HOURS	N (%^)	MEDIAN TIME DIFFERENCE# (IQR), HOURS
Western NSW	An alert before BC*	431 (8.4)	11.0 (1.3 – 51.4)	239 (8.5)	6.6 (0.3 – 62.1)	474 (7.5)	14.0 (1.8 – 62.0)
	An alert after BC*	263 (5.1)	-21.1 (-78.4 – -3.0)	104 (3.7)	-26.1 (-115.4 – -3.6)	288 (4.5)	-18.5 (-77.6 – -2.5)
	An alert, no BC*	4418 (86.4)		2474 (87.8)		5572 (88.0)	
	Total	**5112 (100.0)**		**2817 (100.0)**		**6334 (100.0)**	

** BC: blood culture ordered. ^ percentage was calculated out of all admissions with at least one alert.*
 # time difference = (BC ordering time – alert trigger time)

TABLE 7.12: BLOOD CULTURES ORDERED WITHIN TWO HOURS AFTER THE FIRST ALERT BY ALERT TYPE

Rural and regional LHD	Any SIRS alert, N (%^)	Any severe sepsis alert, N (%^)	Any alert, N (%^)
All LHDs	**185 (2.2)**	**66 (1.5)**	**202 (2.0)**
Far West	11 (3.1)	10 (5.6)	15 (4.0)
Murrumbidgee	17 (1.6)	2 (0.4)	16 (1.4)
Southern NSW	42 (1.9)	6 (0.5)	45 (1.7)
Western NSW	115 (2.1)	48 (1.5)	126 (2.0)

^ *Denominator is the number of admissions with at least one alert of that type (SIRS, severe or any)*

8. AIM 3: OPTIMISING THE ACCURACY OF THE SEPSIS RISK IDENTIFICATION TOOLS

KEY FINDINGS:

Revised Modified St. John Rule (algorithm):

- For detecting coded sepsis cases, results for Blacktown Hospital data and Western NSW LHD data followed similar patterns across the seven revised versions of the Modified St. John Rule (algorithm).
- Option 2 had the highest specificity for detecting coded sepsis cases and deteriorating patients among all seven options.
- Options 6 and 7 had similar results with the highest sensitivity and AUROC for detecting coded sepsis cases and deteriorating patients among all seven options.

Optimisation of risk identification tool applicable at the bedside:

- Options with blood lactate generally resulted in a higher sensitivity compared to those without blood lactate.
- All top five options (including blood lactate) with the highest sensitivity and minimum specificity of 98.0% had better sensitivity than qSOFA (13.5%) based on the Blacktown Hospital data.
- All the best performing options developed had higher AUROC values than qSOFA (0.56) based on the Blacktown Hospital data.
- Sensitivities of options (including blood lactate) with minimum specificity of 95% or 98% based on the Western NSW LHD data were higher than those using the Blacktown Hospital data.

8.1 REVISED MODIFIED ST. JOHN RULE (ALGORITHM)

Each of the revised options of the St. John Rule described in Section 5.5.1 (as shown in Figure 8.1) were applied to data from both Blacktown Hospital and Western NSW LHD for detection of ICD-10-AM coded sepsis cases. In addition, Blacktown data were used to assess the performance of these revised options for detecting patients' deterioration.

8.1.1 DETECTION OF ICD-10-AM CODED SEPSIS CASES

At the level of admissions, sepsis alerts from the revised options were compared with ICD-10-AM coded sepsis to obtain performance metrics. Results for Blacktown Hospital data and Western NSW LHD data followed similar patterns across the seven options (Table 8.1). Options 1, 5, 6 and 7 identified more sepsis case, i.e. true positives (TPs) than the original Modified St. John Rule (algorithm), as shown by the increased sensitivity. However, these options also generated more false positives (FPs) resulting in lower specificity and PPV than the original tool. Options 6 and 7 had similar results with the highest sensitivity and AUROC.

Three other options with increased specificity and PPV were options 2, 3 and 4. Option 2 had the highest specificity (96.3% for Blacktown data and 93.1% for Western NSW LHD data) among all options. Options 3 and 4 had similar results and option 3 had the highest PPV. For each correctly identified sepsis admission from Blacktown Hospital data, option 3 flagged 3.0 false positives for every true positive (i.e. 1529/502), compared to 4.1 for the original tool (i.e. 2492/611). About 3 out of 10 admissions with alerts would be correctly identified as sepsis admissions (PPV: 24.7% for the option 3, and 19.7% for the original tool).

In contrast, options 6 and 7 identified 8.5-8.7 false positives for each correctly identified sepsis admission, despite having the highest AUROC. Similarly, for each correctly identified sepsis admission in the Western NSW LHD data, option 3 flagged 13.3 false positives for each correctly identified sepsis admission, compared to 8.0 for the original tool. In contrast, options 6 and 7 identified 22.4-23.2 false positives per true positive despite having the highest AUROC.

8.1.2 DETECTION OF DETERIORATING PATIENTS (DEATH/ICU ADMISSION)

Two outcomes were used to assess the performance of these revised options for detecting patients' deterioration in Blacktown Hospital: 1) mortality for 34,663 non-ICU admissions and 2) mortality and/or ICU admission for all 36,065 admissions. Results are displayed in Table 8.2. Similar to results for detecting sepsis cases, options 5, 6 and 7 had the highest sensitivity and AUROC for both outcome measures, but the lowest sensitivity and PPV. For each correctly identify death, these options indicated ~32 false positives per true positive compared to 11.0 for the original tool. However, options 6 and 7 had a PPV of 15.5%-15.7% for detecting deaths and/or ICU admissions. For each correctly identify death/ICU admission, these two options flagged 5.4 false positives per true positive compared to 2.5 for the original tool.

Option 2 had the highest specificity for both outcome measurements. It also had the highest PPV (12.1%) for detecting deaths. Option 3 had the highest PPV (43.6%) for detecting deaths/ICU admissions.

8.2 OPTIMISATION OF RISK IDENTIFICATION CRITERIA APPLICABLE AT THE BEDSIDE

Results of alternative risk identification tools applicable at the bedside are shown in Tables 8.3 to 8.6. The Blacktown Hospital data were used to derive these results based on 4,704 different combinations as described in section 5.5.2. The results were selected and presented by either specificity or sensitivity as explained in sections 8.2.1 and 8.2.2 respectively.

8.2.1 CRITERIA WITH HIGH SPECIFICITY

We separated results into two tables: without lactate (Table 8.3) and with lactate (Table 8.4). The highest specificity was 100%. The high performing options with specificity above 90% were selected and then divided into three groups by specificity: 1) ≥90% - < 95%, 2) ≥95% - < 98%, and 3) ≥98%. The top 5 options with the highest sensitivity in each group are presented in two tables, i.e. 15 options in each table.

For options considering only SBP, RR, GCS, temperature and HR, the most consistent measurements with thresholds appearing in Table 8.3 was temperature <35.5 or >38.5. For qSOFA, the sensitivity was 13.5% and specificity was 98.0% when applied to the Blacktown Hospital data. In comparison, for the options with at least 98% specificity, all five had higher sensitivity than qSOFA with the highest at 18.8%. Furthermore, all 30 options had higher AUROC values compared to the AUROC of 0.56 for qSOFA based on the Blacktown Hospital data. Sensitivity for Western NSW LHD data were generally higher than Blacktown Hospital data, while specificity was generally lower. This is consistent with the qSOFA results applied to the two data sets.

Including the blood lactate measurement provided slightly higher sensitivity and AUROC within the same specificity groups described above. The highest AUROC for bedside tools without blood lactate was 0.69 (Table 8.3), while for tools with lactate it was higher again at 0.74 (Table 8.4). The highest AUROC results appeared for the groups with specificity ≥90% among three specificity groups. The inclusion of a clinical criterion based on blood lactate made the options in Table 8.4 more comparable to the Adult Sepsis Pathway than to qSOFA. Of the options with a similar specificity to the Adult Sepsis Pathway applied to Blacktown Hospital data (≥90%), two had higher specificity when applied to both Blacktown and Western NSW LHD data.

Of the 30 options listed in two tables 8.3 and 8.4, the number of measurements involved varied from one to six. For bedside tools without the blood lactate measurement, one option had temperature as the only measurement, which produced sensitivity of 28.7% and specificity of 95.3% (Table 8.3). For bedside tools with the blood lactate measurement, one option had lactate as the only measurement, which produced sensitivity of 32.4% and specificity of 96.5% (Table 8.4). Both options had better sensitivity and AUROC than the qSOFA score.

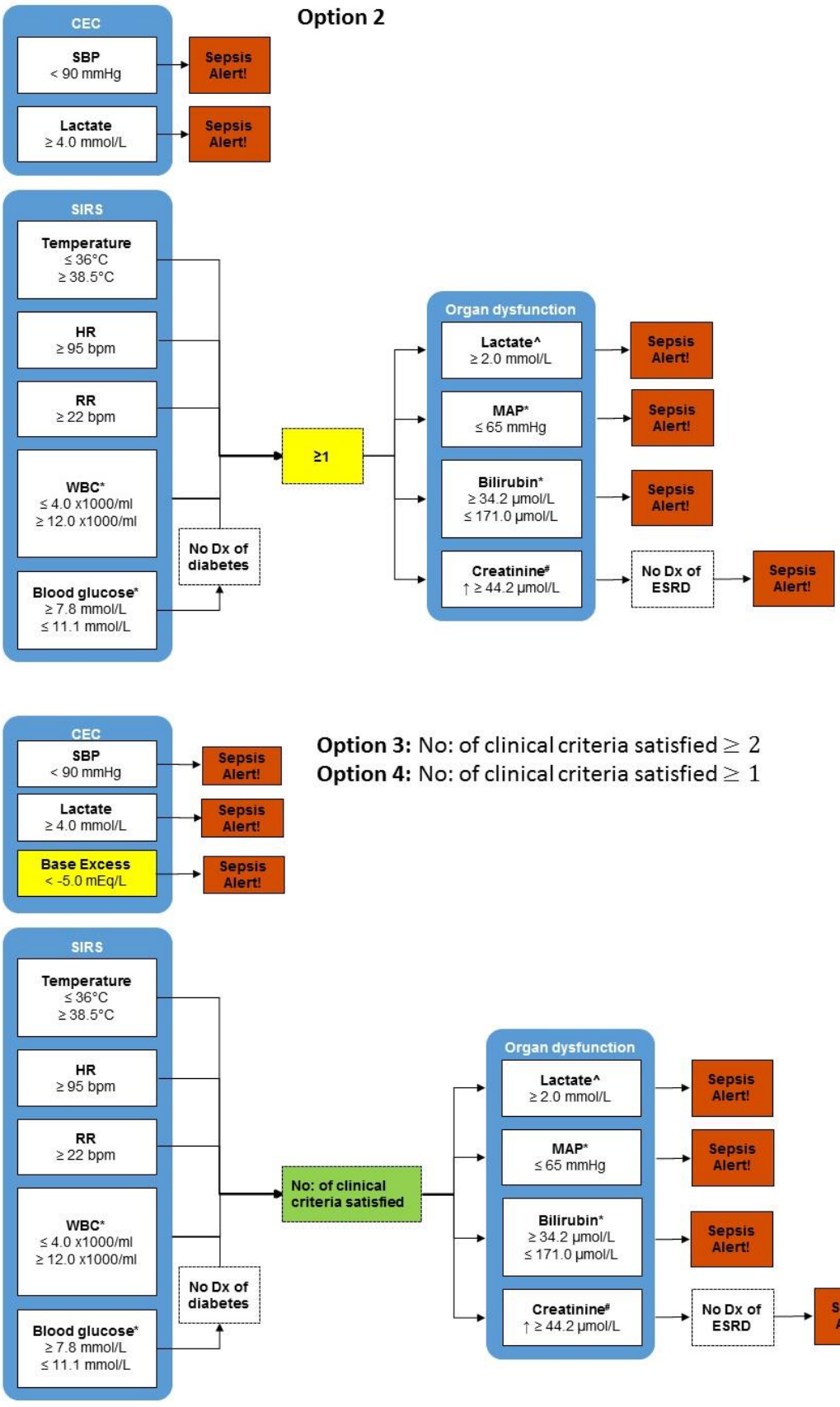
8.2.2 CRITERIA WITH HIGH SENSITIVITY

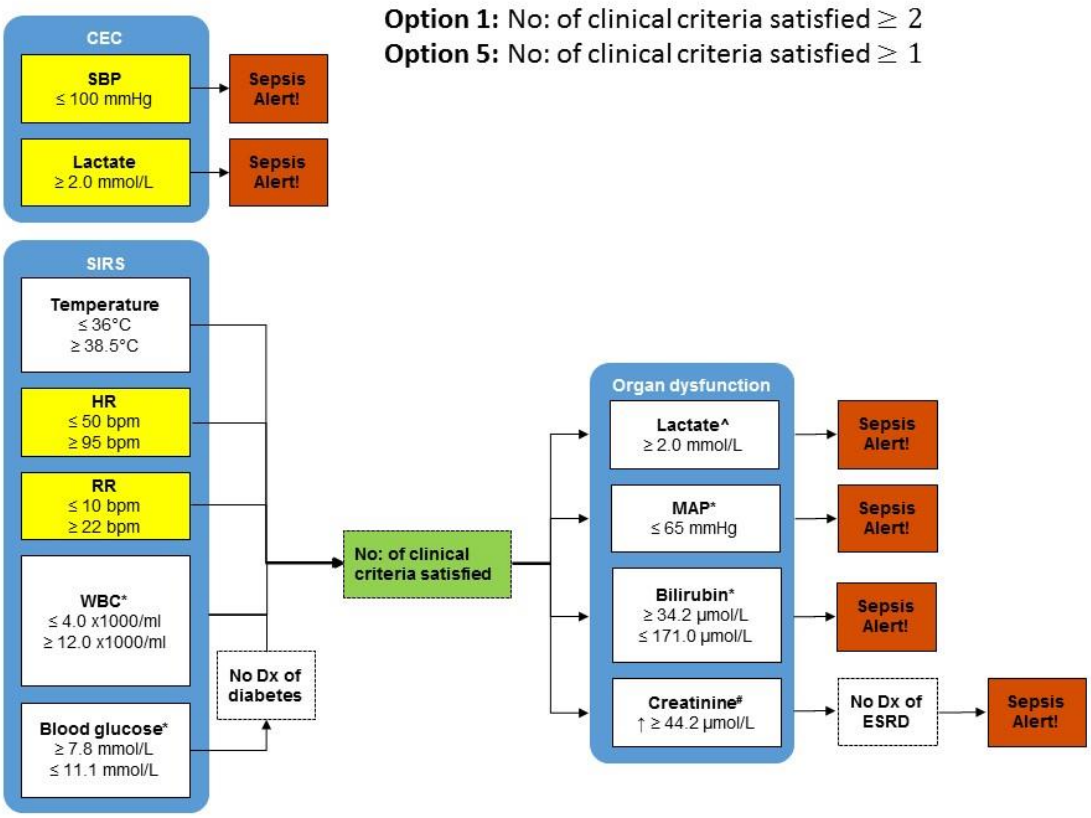
The second set of results were selected as per the first set but with sensitivity and specificity used the opposite way around. Results were chosen based on a minimum sensitivity level and were separated into two groups: without lactate and with lactate. The highest sensitivity was 91.2% for results without lactate. The high performing options were chosen from those with sensitivity above 80% and then divided into three categories by sensitivity: 1) ≥ 80% - < 85%, 2) ≥ 85% - < 90%, and 3) ≥ 90%. The highest sensitivity was 95.5% for results with lactate. Similarly, the high performing options with sensitivity above 85% were selected and then divided into three categories by sensitivity as follows: 1) ≥ 85% - < 90%, 2) ≥ 90% - < 95%, and 3) ≥ 95%. The top five options with the highest specificity in each group are presented in two tables: Table 8.5 (without lactate) and Table 8.6 (with lactate).

The options listed under tables 8.5 and 8.6 can be compared against the results of the qSOFA. Based on Blacktown Hospital data, sensitivity results from these 30 bedside tools were higher than sensitivity for qSOFA, i.e. 13.5% while specificity values were lower than specificity for qSOFA, i.e. 98.0%. However, the AUROC results for all 30 bedside tools in two tables were higher compared to the AUROC of 0.56 for qSOFA. The exactly same pattern was observed based on the Western NSW LHD data.

Blood lactate measurement along with the other five possible measurements produced higher sensitivity and AUROC (Table 8.6) compared to those results without blood lactate in Table 8.5 for both Blacktown Hospital data and Western NSW LHD data. The highest AUROC was 0.77 based on the Blacktown data in Table 8.6, which was higher than that for Adult Sepsis Pathway (0.73). Sensitivity results from the 15 bedside tools in Table 8.6 were higher than that for Adult Sepsis Pathway (54.3%) while the specificities were lower than that for Adult Sepsis Pathway (91.4%).

FIGURE 8.1: FLOW DIAGRAMS OF THE SEVEN REVISED OPTIONS FOR MODIFIED ST. JOHN RULE (AS DISCUSSED IN SECTION 5.5.1)




Option 1: No: of clinical criteria satisfied ≥ 2
Option 5: No: of clinical criteria satisfied ≥ 1
CEC
SBP
≤ 100 mmHg
Sepsis Alert!
Lactate
≥ 2.0 mmol/L
Sepsis Alert!
SIRS
Temperature
≤ 36°C
≥ 38.5°C
HR
≤ 50 bpm
≥ 95 bpm
RR
≤ 10 bpm
≥ 22 bpm
WBC*
≤ 4.0 x1000/ml
≥ 12.0 x1000/ml
Blood glucose*
≥ 7.8 mmol/L
≤ 11.1 mmol/L
No Dx of diabetes
No: of clinical criteria satisfied
Organ dysfunction
Lactate^
≥ 2.0 mmol/L
Sepsis Alert!
MAP*
≤ 65 mmHg
Sepsis Alert!
Bilirubin*
≥ 34.2 µmol/L
≤ 171.0 µmol/L
Sepsis Alert!
Creatinine#
↑ ≥ 44.2 µmol/L
No Dx of ESRD
Sepsis Alert!

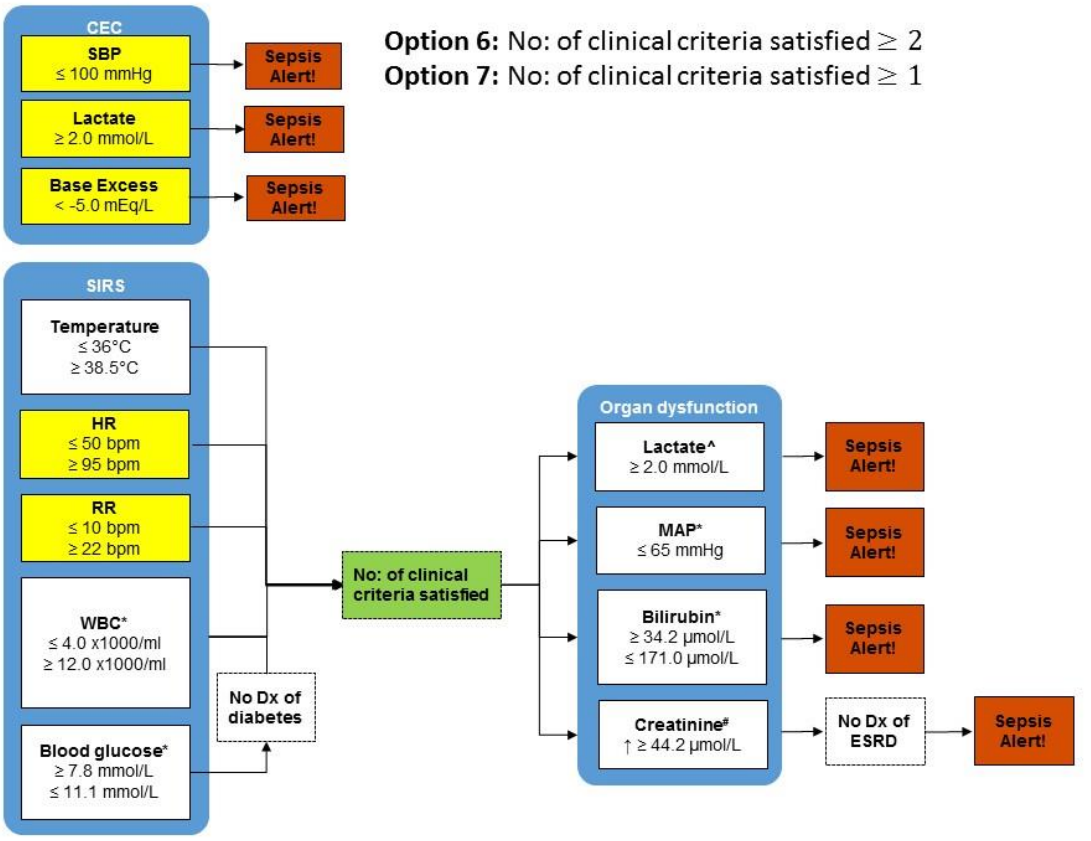

Option 6: No: of clinical criteria satisfied ≥ 2
Option 7: No: of clinical criteria satisfied ≥ 1
CEC
SBP
≤ 100 mmHg
Sepsis Alert!
Lactate
≥ 2.0 mmol/L
Sepsis Alert!
Base Excess
< -5.0 mEq/L
Sepsis Alert!
SIRS
Temperature
≤ 36°C
≥ 38.5°C
HR
≤ 50 bpm
≥ 95 bpm
RR
≤ 10 bpm
≥ 22 bpm
WBC*
≤ 4.0 x1000/ml
≥ 12.0 x1000/ml
Blood glucose*
≥ 7.8 mmol/L
≤ 11.1 mmol/L
No Dx of diabetes
No: of clinical criteria satisfied
Organ dysfunction
Lactate^
≥ 2.0 mmol/L
Sepsis Alert!
MAP*
≤ 65 mmHg
Sepsis Alert!
Bilirubin*
≥ 34.2 µmol/L
≤ 171.0 µmol/L
Sepsis Alert!
Creatinine#
↑ ≥ 44.2 µmol/L
No Dx of ESRD
Sepsis Alert!

TABLE 8.1: REVISED MODIFIED ST. JOHN RULE OPTIONS FOR DETECTING ICD-10-AM CODED SEPSIS (CHADX)

	BLACKTOWN HOSPITAL DATA								
	TN	FP	FN	TP	SENSITIVITY	SPECIFICITY	PPV	NPV	AUROC
OPTION 1	27,853	6,933	484	795	62.2	80.1	10.3	98.3	0.71
OPTION 2	33,484	1,302	865	414	32.4	96.3	24.1	97.5	0.64
OPTION 3	33,257	1,529	777	502	39.2	95.6	24.7	97.7	0.67
OPTION 4	32,760	2,026	730	549	42.9	94.2	21.3	97.8	0.69
OPTION 5	27,686	7,100	475	804	62.9	79.6	10.2	98.3	0.71
OPTION 6	27,747	7,039	455	824	64.4	79.8	10.5	98.4	0.72
OPTION 7	27,588	7,198	448	831	65.0	79.3	10.4	98.4	0.72
ORIGINAL^	32,294	2,492	668	611	47.8	92.8	19.7	98.0	0.70
	WESTERN NSW LHD DATA								
	TN	FP	FN	TP	SENSITIVITY	SPECIFICITY	PPV	NPV	AUROC
OPTION 1	41,581	7,667	344	327	48.7	84.4	4.1	99.2	0.67
OPTION 2	45,835	3,413	435	236	35.2	93.1	6.5	99.1	0.64
OPTION 3	45,669	3,579	401	270	40.2	92.7	7.0	99.1	0.66
OPTION 4	44,406	4,842	363	308	45.9	90.2	6.0	99.2	0.68
OPTION 5	41,090	8,158	334	337	50.2	83.4	4.0	99.2	0.67
OPTION 6	41,465	7,783	324	347	51.7	84.2	4.3	99.2	0.68
OPTION 7	40,979	8,269	314	357	53.2	83.2	4.1	99.2	0.68
ORIGINAL^	44,267	4,981	366	305	45.5	89.9	5.8	99.2	0.68

^: From the assessment for any alerts using the Modified St. John Rule (algorithm) in section 6 and 7

TABLE 8.2: REVISED MODIFIED ST. JOHN RULE FOR DETECTING DETERIORATING PATIENTS BASED ON THE BLACKTOWN HOSPITAL DATA

	MORTALITY FOR 34,663 NON-ICU ADMISSIONS								
	TN	FP	FN	TP	SENSITIVITY	SPECIFICITY	PPV	NPV	AUROC
OPTION 1	27,776	6,569	110	208	65.4	80.9	3.1	99.6	0.73
OPTION 2	33,318	1,027	177	141	44.3	97.0	12.1	99.5	0.71
OPTION 3	33,199	1,146	166	152	47.8	96.7	11.7	99.5	0.72
OPTION 4	32,790	1,555	156	162	50.9	95.5	9.4	99.5	0.73
OPTION 5	27,621	6,724	106	212	66.7	80.4	3.1	99.6	0.74
OPTION 6	27,716	6,629	107	211	66.4	80.7	3.1	99.6	0.74
OPTION 7	27,564	6,781	103	215	67.6	80.3	3.1	99.6	0.74
ORIGINAL^	32,119	2,226	116	202	63.5	93.5	8.3	99.6	0.79
	MORTALITY AND/OR ICU ADMISSION FOR ALL 36,065 ADMISSIONS								
	TN	FP	FN	TP	SENSITIVITY	SPECIFICITY	PPV	NPV	AUROC
OPTION 1	27,776	6,569	561	1,159	67.4	80.9	15.0	98.0	0.74
OPTION 2	33,318	1,027	1,031	689	40.1	97.0	40.2	97.0	0.69
OPTION 3	33,199	1,146	835	885	51.5	96.7	43.6	97.5	0.74
OPTION 4	32,790	1,555	700	1,020	59.3	95.5	39.6	97.9	0.77
OPTION 5	27,621	6,724	540	1,180	68.6	80.4	14.9	98.1	0.75
OPTION 6	27,716	6,629	486	1,234	71.7	80.7	15.7	98.3	0.76
OPTION 7	27,564	6,781	472	1,248	72.6	80.3	15.5	98.3	0.76
ORIGINAL^	32,119	2,226	843	877	51.0	93.5	28.3	97.4	0.72

^: From the assessment for any alerts using the Modified St. John Rule (algorithm) for all patients

TABLE 8.3: BEDSIDE TOOLS (WITHOUT BLOOD LACTATE) WITH THE HIGHEST SENSITIVITY FOR AT LEAST 90%, 95% AND 98% SPECIFICITY

SPEC. GROUP[1].	SBP	RR	GCS	TEMPERATURE	HR	N^c	BLACKTOWN HOSPITAL (TRAINING DATA)					WESTERN NSW LHD (TEST DATA)				
							SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC
90%[2]	≤100	≥22	<15	<35.5 or >38.5	≤50 or ≥95	≥2	48.9	90.0	15.3	98.0	0.69	51.4	85.6	4.6	99.2	0.68
	≤100	≤10 or ≥22	<15	<35.5 or >38.5	≥95	≥2	48.4	90.6	16.0	97.9	0.70	51.4	86.5	4.9	99.2	0.69
	≤100	≥22	<15	<35.5 or >38.5	≥95	≥2	48.3	90.7	16.0	97.9	0.69	50.8	87.1	5.1	99.2	0.69
	≤100	≤10 or ≥22		<35.5 or >38.5	≤50 or ≥95	≥2	47.5	90.5	15.5	97.9	0.69	51.6	85.1	4.5	99.2	0.68
	≤100	≥22		<35.5 or >38.5	≤50 or ≥95	≥2	47.5	90.6	15.6	97.9	0.69	51.0	85.7	4.6	99.2	0.68
95%[3]	<100	≤10 or ≥25	<15	<35.5 or >38.5	≥95	≥2	33.0	95.3	20.5	97.5	0.64	38.3	92.8	6.7	99.1	0.66
	<100	≤10 or ≥25		<35.5 or >38.5	≤50 or ≥95	≥2	31.4	95.4	20.2	97.4	0.63	37.9	91.7	5.8	99.1	0.65
	<100	≤10 or ≥25		<35.5 or >38.5	≥95	≥2	30.6	95.9	21.5	97.4	0.63	37.1	93.0	6.7	99.1	0.65
	≤100			<35.5 or >38.5	≥95	≥2	29.4	95.4	18.9	97.4	0.62	31.9	93.9	6.6	99.0	0.63
				<35.5 or >38.5		1	28.7	95.3	18.3	97.3	0.62	24.4	93.8	5.1	98.9	0.59
98%[4]	<90			<35.5 or >38.5	≤50 or ≥95	≥2	18.8	98.1	26.5	97.0	0.58	21.2	96.3	7.2	98.9	0.59
	<90			<35.5 or >38.5	≥95	≥2	17.9	98.2	27.3	97.0	0.58	20.4	97.1	8.8	98.9	0.59
	<90	≥22		<35.5 or >38.5	≤50 or ≥120	≥2	17.0	98.0	23.9	97.0	0.57	28.0	95.7	8.1	99.0	0.62
	<100	≤10 or ≥25	<15	<35.5 or >38.5	≤50 or ≥120	≥2	15.8	98.0	22.5	96.9	0.57	25.0	95.5	7.1	98.9	0.60
				<35.5 or >38.5	≤50 or ≥95	2	15.6	98.5	28.2	96.9	0.57	13.1	98.1	8.5	98.8	0.56
qSOFA[#]	≤100	≥22	<15				13.5	98.0	20.1	96.9	0.56	23.9	96.8	9.3	98.9	0.60

***Spec. group[1]**: Specificity group: 1) **90%[2]:** ⩾90% - < 95%, 2) **95%[3]:** ⩾95% - < 98%, and 3) **98%[4]**: ⩾98%*
***N^c**: Number of clinical criteria satisfied for alert [#]From the qSOFA results from sections 6 and 7*

TABLE 8.4: BEDSIDE TOOLS (INCLUDING BLOOD LACTATE) WITH THE HIGHEST SENSITIVITY FOR AT LEAST 90%, 95% AND 98% SPECIFICITY

SPEC. GROUP[1]	SBP	RR	GCS	TEMPERATURE	HR	LACTATE	N^c	BLACKTOWN HOSPITAL (TRAINING DATA)					WESTERN NSW LHD (TEST DATA)				
								SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC
90%[2]		≤10 or ≥25		<35.5 or >38.5		≥2.0	≥1	57.1	90.2	17.6	98.3	0.74	59.8	86.7	5.8	99.4	0.73
			<15	<35.5 or >38.5		≥2.0	≥1	55.8	90.3	17.5	98.2	0.73	52.2	90.5	7.0	99.3	0.71
	<90			<35.5 or >38.5		≥2.0	≥1	55.3	91.4	19.1	98.2	0.73	58.4	86.2	5.5	99.3	0.72
				<35.5 or >38.5		≥2.0	≥1	52.8	92.3	20.1	98.2	0.73	50.2	91.2	7.2	99.3	0.71
	≤100	≤10 or ≥22	<15	<35.5 or >38.5	≥95	≥2.0	≥2	50.1	90.1	15.7	98.0	0.70	53.9	86.0	5.0	99.3	0.70
95%[3]	<90					≥2.0	≥1	37.4	95.4	23.0	97.6	0.66	47.8	91.1	6.9	99.2	0.69
	<100	≤10 or ≥25		<35.5 or >38.5	≥95	≥2.0	≥2	34.2	95.2	20.7	97.5	0.65	41.1	92.2	6.7	99.1	0.67
	<100	≤10 or ≥25	<15	<35.5 or >38.5	≥95	≥4.0	≥2	33.5	95.1	20.2	97.5	0.64	43.4	91.8	6.8	99.2	0.68
	<100		<15	<35.5 or >38.5	≤50 or	≥2.0	≥2	32.6	95.0	19.4	97.5	0.64	37.3	92.8	6.6	99.1	0.65
						≥2.0	1	32.4	96.5	25.4	97.5	0.64	34.7	97.0	13.4	99.1	0.66
98%[4]	<90			<35.5 or >38.5	≥95	≥4.0	≥2	19.2	98.1	26.5	97.2	0.59	31.9	95.9	9.5	99.0	0.64
	<90	≤10 or ≥22	<15	<35.5 or >38.5		≥2.0	≥2	18.1	98.2	26.4	97.2	0.58	30.8	96.4	10.4	99.0	0.64
	<90	≥22	<15	<35.5 or >38.5		≥2.0	≥2	18.0	98.2	26.6	97.2	0.58	20.9	98.0	12.7	98.9	0.59
	<90	≥22		≤36 or ≥38.5	≥95	≥2.0	≥3	17.4	98.1	25.1	97.2	0.58	17.7	98.4	13.2	98.9	0.58
	<90	≤10 or ≥22		≤36 or ≥38.5	≥95	≥2.0	≥3	17.4	98.1	25.0	97.2	0.58	26.1	96.6	9.4	99.	0.61
qSOFA[#]	≤100	≥22	<15					13.5	98.0	20.1	96.9	0.56	23.9	96.8	9.3	98.9	0.60
Adult*								54.3	91.4	18.8	98.2	0.73	53.7	87.0	5.3	99.3	0.70

Spec. group[1]: *Specificity group: 1)* ***90%[2]:*** *⩾90% - < 95%, 2)* ***95%[3]:*** *⩾95% - < 98%, and 3)* ***98%[4]:*** *⩾98%*
N^c: *Number of clinical criteria satisfied for alert* *#From the qSOFA results from sections 6 and 7* ***Adult****: the Adult Sepsis Pathway results from section 6 and 7 for any sepsis alert.*

TABLE 8.5: BEDSIDE TOOLS (WITHOUT BLOOD LACTATE) WITH THE HIGHEST SPECIFICITY FOR AT LEAST 80%, 85% AND 90% SENSITIVITY

SENS. GROUP[1]	SBP	RR	GCS	TEMPERATURE	HR	N^c	BLACKTOWN HOSPITAL (TRAINING DATA)					WESTERN NSW LHD (TEST DATA)				
							SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC
80%[2]	<90	≤10 or ≥25	<15	<35.5 or >38.5	≥95	≥1	80.2	67.2	8.2	98.9	0.74	82.5	62.7	7.5	99.0	0.73
		≥22			≥95	≥1	81.5	66.3	8.2	99.0	0.74	82.1	62.6	7.5	99.0	0.72
	<90	≥22			≥95	≥1	81.6	66.0	8.1	99.0	0.74	85.6	62.6	7.5	99.0	0.73
		≤10 or ≥22			≥95	≥1	81.6	66.0	8.1	99.0	0.74	83.7	62.5	7.6	99.1	0.73
	<90	≤10 or ≥22			≥95	≥1	81.8	65.7	8.1	99.0	0.74	82.8	62.4	7.5	99.0	0.73
85%[3]	≤100	≤10 or ≥25	<15	<35.5 or >38.5	≥95	≥1	85.3	60.1	7.3	99.1	0.73	86.6	56.2	6.8	99.1	0.71
	<100	≥22		<35.5 or >38.5	≤50 or ≥95	≥1	85.1	59.6	7.2	99.1	0.72	87.1	56.2	6.8	99.2	0.72
	<100	≤10 or ≥22		<35.5 or >38.5	≤50 or ≥95	≥1	85.2	59.4	7.2	99.1	0.72	87.2	56.0	6.8	99.2	0.72
	≤100	≥22			≥95	≥1	85.8	59.2	7.2	99.1	0.73	87.3	55.8	6.8	99.2	0.72
	<100	≥22	<15	<35.5 or >38.5	≤50 or ≥95	≥1	85.4	59.1	7.1	99.1	0.72	87.3	55.6	6.7	99.2	0.71
90%[4]		≥22		≤36 or ≥38.5	≤50 or ≥95	≥1	90.2	39.2	5.2	99.1	0.65	90.9	37.5	5.1	99.1	0.64
	<90	≥22		≤36 or ≥38.5	≤50 or ≥95	≥1	90.2	39.1	5.2	99.1	0.65	91.1	37.1	5.1	99.1	0.64
		≥22	<15	≤36 or ≥38.5	≤50 or ≥95	≥1	90.2	39.1	5.2	99.1	0.65	91.1	37.0	5.1	99.1	0.64
		≤10 or ≥22		≤36 or ≥38.5	≤50 or ≥95	≥1	90.3	39.1	5.2	99.1	0.65	91.2	37.0	5.1	99.1	0.64
	<90	≥22	<15	≤36 or ≥38.5	≤50 or ≥95	≥1	90.2	39.0	5.2	99.1	0.65	91.2	37.0	5.0	99.1	0.64
qSOFA[#]	≤100	≥22	<15				13.5	98.0	20.1	96.9	0.56	23.9	96.8	9.3	98.9	0.60

Sens. group[1]: *Sensitivity group: 1)* ***80%[2]:*** *⩾80% - < 85%, 2)* ***85%[3]:*** *⩾85% - < 90%, and 3)* ***90%[4]:*** *⩾90%*
N^c: *Number of clinical criteria satisfied for alert* ***[#]:*** *From the qSOFA results from sections 6 and 7*

TABLE 8.6: BEDSIDE TOOLS (INCLUDING BLOOD LACTATE) WITH THE HIGHEST SPECIFICITY FOR AT LEAST 85%, 90% AND 95% SENSITIVITY

SENS. GROUP[1]	SBP	RR	GCS	TEMPERATURE	HR	LACTATE	N^c	BLACKTOWN HOSPITAL (TRAINING DATA)					WESTERN NSW LHD (TEST DATA)				
								SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC	SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC
85%[2]				<35.5 or >38.5	≥95	≥2.0	≥1	85.3	68.1	8.9	99.2	0.77	88.9	63.3	8.2	99.4	0.76
	<90			<35.5 or >38.5	≥95	≥2.0	≥1	85.7	67.7	8.9	99.2	0.77	87.1	63.2	8.0	99.3	0.75
			<15	<35.5 or >38.5	≥95	≥2.0	≥1	85.7	67.3	8.8	99.2	0.77	86.3	62.9	7.9	99.2	0.75
		≤10 or ≥25		<35.5 or >38.5	≥95	≥2.0	≥1	85.6	67.3	8.8	99.2	0.76	85.1	62.8	7.8	99.1	0.74
	<90	≤10 or ≥25		<35.5 or >38.5	≥95	≥2.0	≥2	86.0	67.0	8.7	99.2	0.76	85.1	62.7	7.7	99.1	0.74
90%[3]	<100	≤10 or ≥22	<15	<35.5 or >38.5	≥95	≥2.0	≥1	90.1	60.7	7.8	99.4	0.75	92.0	55.1	7.0	99.5	0.74
	≤100	≤10 or ≥25		<35.5 or >38.5	≥95	≥2.0	≥1	90.1	59.9	7.6	99.4	0.75	92.1	55.0	7.0	99.5	0.74
	≤100		<15	<35.5 or >38.5	≥95	≥2.0	≥1	90.1	59.8	7.6	99.4	0.75	90.5	44.9	5.7	99.2	0.68
	≤100	≤10 or ≥25	<15	<35.5 or >38.5	≥95	≥2.0	≥1	90.3	59.3	7.5	99.4	0.75	90.4	44.8	5.7	99.2	0.68
	<100	≥22		<35.5 or >38.5	≤50 or ≥95	≥2.0	≥1	90.3	58.9	7.5	99.4	0.75	90.7	44.7	5.7	99.2	0.68
95%[4]	<100	≥22		≤36 or ≥38.5	≤50 or ≥95	≥2.0	≥1	95.2	37.7	5.3	99.5	0.66	95.3	37.0	5.3	99.5	0.66
	<100	≥22	<15	≤36 or ≥38.5	≤50 or ≥95	≥2.0	≥1	95.2	37.6	5.3	99.5	0.66	95.5	36.7	5.3	99.5	0.66
	<100	≤10 or ≥22		≤36 or ≥38.5	≤50 or ≥95	≥2.0	≥1	95.2	37.6	5.3	99.5	0.66	95.5	36.6	5.2	99.5	0.66
	<100	≤10 or ≥22	<15	≤36 or ≥38.5	≤50 or ≥95	≥2.0	≥1	95.2	37.5	5.3	99.5	0.66	95.5	36.6	5.2	99.6	0.66
	≤100			≤36 or ≥38.5	≤50 or ≥95	≥2.0	≥1	95.1	37.4	5.3	99.5	0.66	95.5	36.5	5.2	99.6	0.66
qSOFA[#]	≤100	≥22	<15					13.5	98.0	20.1	96.9	0.56	23.9	96.8	9.3	98.9	0.60
Adult*								54.3	91.4	18.8	98.2	0.73	53.7	87.0	5.3	99.3	0.70

Sens. group[1]: *Sensitivity group: 1)* ***85%[2]:*** *≥85% - < 90%, 2)* ***90%[3]:*** *≥90% - < 95%, and 3)* ***95%[4]:*** *≥95%*
N^c: *Number of clinical criteria satisfied for alert* ***#:*** *From the qSOFA results from sections 6 and 7* ***Adult*:*** *the Adult Sepsis Pathway results from section 6 and 7 for any sepsis alert.*

9. DISCUSSION

9.1 PROFILE OF SEPSIS PATIENTS AT BLACKTOWN HOSPITAL AND FOUR RURAL AND REGIONAL NSW LHDS

We evaluated the performance of three sepsis risk identification tools for adult inpatients using Blacktown Hospital data and data from select facilities in four rural and regional NSW LHDs (referred to as *rural facilities*). The study populations from these two study arms had different demographics. The hospital population in the rural facilities tended to be slightly older than those at Blacktown Hospital (rural facilities median 65 years versus Blacktown Hospital 58 years). However, Blacktown Hospital had a higher proportion of admissions with coded sepsis cases than rural facilities (3.5% versus 1.2%, respectively). The age distribution for admissions with a coded sepsis case was similar, around 71-72 years. Patients with sepsis stayed longer at Blacktown Hospital (median 8.4 days) than at rural facilities (5.1 days). Fewer admissions in rural facilities involved a period in ICU compared to the Blacktown Hospital cohort. This was particularly true among sepsis admissions (rural facilities 4.8% of admissions, versus Blacktown Hospital 35.5%).

9.2 DETECTING SEPSIS CASES

9.2.1 BEDSIDE SEPSIS RISK IDENTIFICATION TOOLS

The qSOFA score

We assessed the performance of the qSOFA score using data from Blacktown Hospital versus rural facilities. We found that the sensitivity was higher for rural facilities (23.3%) compared to Blacktown (13.5%), specificity was similar (97.1% for rural versus 98.0% for Blacktown), but PPV was much higher for Blacktown Hospital (20.1% versus 8.7% for rural facilities). The distribution of the three measurements (systolic blood pressure, respiratory rate and Glasgow coma scale) used for calculating the qSOFA score were similar for the two data sets (see tables 6.10 and 7.5). Data from rural facilities had a much higher proportion of measurements satisfying the clinical thresholds for qSOFA than Blacktown Hospital data (7.3% versus 4.5%). This resulted in a higher proportion of admissions with alerts in the rural facility data, with 3.1% compared to 2.4% for Blacktown Hospital. The more frequent alerts in the rural facility data seemed to identify relatively more true positives, resulting in higher sensitivity, but there were also more false positives causing the markedly lower PPV (8.7% for rural versus 20.1% for Blacktown). The AUROC values were slightly higher in rural facilities (0.60 versus 0.56 for Blacktown Hospital).

The Adult Sepsis Pathway

We assessed the performance of the Adult Sepsis Pathway using data from two study arms (Blacktown Hospital versus rural facilities). For detecting admissions with a coded sepsis case, we found that the Adult Sepsis Pathway had a higher sensitivity for Blacktown Hospital data (54.3% versus 47.3% for rural facilities), higher PPV (18.8% versus 5.0% for rural facilities), higher specificity (91.4% versus 89.5%), and higher AUROC (0.73 versus 0.68). A similar pattern was observed for detecting admissions with a severe sepsis alert, indicating that overall the Adult Sepsis Pathway performed better when applied to the data from Blacktown Hospital. The number of measurements per patient admission was much higher in Blacktown Hospital (75.4) than that in rural facilities (46.9). The overall distribution of the eight measurements relevant to the Adult Sepsis Pathway was similar for two data sets. Blacktown Hospital data had a higher proportion of base excess, lactate, GCS and temperature. However, the proportions of measurements satisfying the clinical criteria for the Adult Sepsis Pathway were very similar (3.2% for Blacktown Hospital versus 3.5% for rural facilities).

9.2.2 AUTOMATED ELECTRONIC SEPSIS ALERT SYSTEM – THE MODIFIED ST. JOHN RULE

The Modified St. John Rule has been implemented in the electronic Medication Record system at Blacktown Hospital. We assessed the performance of the Modified St. John Rule using the Blacktown Hospital data extracted from eMR. Of 1,279 coded sepsis cases, 771 were correctly detected, resulting in sensitively of 65.1%.

To assess the performance of the Modified St. John Rule across two study arms, we developed the algorithm and generated the alerts based on the algorithm using data from Blacktown Hospital and the rural facilities. The overall performance of the Modified St. John Rule (algorithm) for detecting sepsis cases was better when applied to Blacktown Hospital data compared to rural LHD data (Table 6.17 and Table 7.9), with higher

sensitivity, specificity, PPV and AUROC. This may be partly explained by the low numbers of creatinine and bilirubin measurements available in the rural facility data compared to Blacktown Hospital data. A further reason may be that, the proportion of measurements satisfying the clinical thresholds was higher in the Blacktown Hospital data (9.2% versus 8.6% for rural facilities).

9.2.3 OPTIMISED ALTERNATIVES

We explored alternative versions of these tools to identify opportunities to optimise sensitivity, specificity, PPV and NPV compared to three existing tools. Two sets of optimised alternatives were developed. In the first set, we made several adjustments without changing the structure of the existing Modified St. John Rule. Seven options were developed as revised versions of the Modified St. John Rule. Six of all seven options produced improved sensitivity and AUROC at the cost of reduced specificity. In the second set, we made use of the five most common bedside measurements (systolic blood pressure, respiratory rate, heart rate, Glasgow coma scale and temperature) with their clinical thresholds taken from the three existing tools. All 15 of the best performing options had higher sensitivity and AUROC than the qSOFA score (Table 8.3). Among the options with at least 98% specificity, the one with the highest sensitivity also had higher specificity and PPV than qSOFA. Lactate was added as a clinical criterion to derive another 15 bedside alternatives as lactate reading may be easily obtained using the point of care testing devices if available. These options with blood lactate generally resulted in a higher sensitivity compared to those without blood lactate. The inclusion of a clinical criterion based on blood lactate made the options (Table 8.4) more comparable to the Adult Sepsis Pathway than to qSOFA. Of the options with a similar specificity to the Adult Sepsis Pathway applied to Blacktown Hospital data (≥90%), two had higher specificity when applied to data from both Blacktown and rural facilities.

9.3 DETECTION OF DETERIORATING PATIENTS

The performance of these alerts in terms of facilitating early diagnosis of sepsis and minimising time to intervention is crucial for reducing hospital mortality for sepsis patients (19). When used for predicting the in-hospital mortality rate for non-ICU admissions, the qSOFA score had the lowest sensitivity and AUROC among the three tools, but higher specificity and PPV than the other two tools. When used for predicting the in-hospital mortality rate for non-ICU patients who had blood cultures ordered, three tools had similar performance pattern. The AUROC for qSOFA was 0.71 (95% CI: 0.66-0.75). A 2017 study reported a similar AUROC (0.69, 95% CI: 0.67-0.70) based on the similar study population (patients with infections outside ICU) (20).

9.4 BLOOD CULTURES ORDERED FOLLOWING SEPSIS ALERTS

Blood cultures are considered to be the “gold standard” for the detection of microbial pathogens related to bacteraemia and sepsis despite newer molecular techniques (21). This method allows for microbial identification and susceptibility testing to be performed which is a critical component in managing sepsis (22). We found that a higher proportion of admissions had blood cultures ordered after a severe sepsis alert than after any SIRS alert. However, overall only a small proportion of admissions with alerts had a follow-up blood culture ordered. Patients coded with sepsis and experiencing a sepsis alert, but no blood cultures, had a high mortality rate (14.0%).

9.5 CAVEATS AND LIMITATIONS

Independent of data related issues, assessing the performance of sepsis risk identification tools against ICD-10-AM coded sepsis has several challenges. First, the fact that sepsis is difficult to define means there is no ideal choice of a gold standard against which to compare risk identification tools. Sepsis cases were recorded using ICD-10-AM codes. These coded cases represent the best available “gold standard” for this study, however, it is likely that not all cases are identified or documented during the admission or in the post separation clinical coding process. The result of this is that our gold standard likely underestimates the true prevalence of sepsis. Second, SIRS cases would be underreported because SIRS would have not been coded in addition to sepsis if patients progressed to sepsis or if SIRS was of an infectious origin (e.g. urinary tract infection, or pneumonia) according to Australian Coding Standard. Third, all three risk identification tools are aimed at early detection of sepsis. In this study, we did not have information on the time when patients became septic as the ICD-10-AM coded cases are determined after separation. Results indicate the ability of each tool to identify sepsis cases during the whole admission period and may overstate their effectiveness for early detection.

Tool performance was assessed with metrics from confusion matrices including sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and area under the receiver operating characteristic curve (AUROC). The multiple metrics for assessing the performance of the sepsis risk identification tools in this study do not provide a simple measure for determining the best tool. In general, improved sensitivity comes at the expense of decreased specificity, that is, there tends to be a trade-off between the two metrics. The AUROC statistic is a measure intended to identify an optimal balance between these competing factors. Typically, however, the AUROC values in this study are based one value each of sensitivity and specificity. In this case the area under the curve is triangular and is equivalent to the average of the two values. Due to the relative rarity of sepsis admissions, the AUROC results need to be interpreted with caution. Any small increase in the number of sepsis cases identified was generally accompanied by a large increase in false positives. This can cause a disproportionate increase in sensitivity relative to a more modest decrease in specificity, resulting in a higher AUROC but not necessarily better discrimination between sepsis cases and non-cases.

Considerable differences in the performance of the three tools were observed when applied to data from Blacktown Hospital versus rural facilities. There are likely many reasons for this, but two main factors stand out. First, there were fewer admissions in the rural hospitals data that had valid matching measurement data, less than half of admissions compared to three quarters for Blacktown Hospital. The rural facility measurement data also had some specific issues with bilirubin and creatinine measurements, where there were no bilirubin measurements for three of the four LHDs, and much lower than expected numbers of creatinine measurements for all LHDs (see section 7.2.2). This raises further questions about the reliability of the measurement data for other measurement types. Second, PPV is known to depend on prevalence, so although data issues were more pervasive for rural facilities, the consistently lower PPV (higher false positive rate) in rural facility data across most scenarios may largely be a function of the lower prevalence of ICD-10-AM coded sepsis (1.2% of admissions for rural facilities versus 3.5% for Blacktown Hospital).

9.6 COMPARISON AMONG THREE EXISTING TOOLS AND OPTIMISED ALTERNATIVES

The qSOFA score clearly identified the least number of ICD-10-AM coded sepsis cases. This was also the case for identifying patients at risk of dying in hospital. As the name implies, the score is quick to apply and can easily be done at the bedside. With an electronic risk identification tool in place, such as the Modified St. John Sepsis Rule, there may still be value in using a sepsis risk identification tool like qSOFA as additional cases may be detected with minimal investment of time or effort. However, as a stand-alone tool it may not be adequate. The investigation into improved versions of a bedside tool based on the same kind of logic as qSOFA revealed several possibilities that identified more ICD-10-AM coded sepsis cases for a comparable level of specificity (Table 8.3). Accepting a lower level of specificity allowed identification of tools with higher sensitivity values comparable to those of the Adult Sepsis Pathway and the Modified St. John Rule.

While the Adult Sepsis Pathway and the Modified St. John Rule (algorithm) both identified more sepsis cases than qSOFA, they performed similarly to each other. The sensitivity was higher for the Adult Sepsis Pathway when any sepsis alerts were used to identify sepsis admissions, but the Modified St. John Rule performed better when only severe sepsis alerts were used. The Adult Sepsis Pathway had higher sensitivity than qSOFA, but can also be applied at the bedside which may make it a preferable bedside tool. It does, however, rely on measurements from pathology tests and so may not be as timely as qSOFA in generating alerts.

In this report, we present the best possible scenarios for qSOFA and the Adult Sepsis Pathway as if they were applied to all available measurements for a given patient. However, it would be unlikely that a clinician would be able to check the risk of sepsis using all available measurements. In contrast, the Modified St. John Rule (eMR) was implemented in real time, and all the available measurements recorded for patients in eMR could be utilised. Electronic implementation of sepsis detection tools allows the use of more complex logic that is better able to discriminate between cases and non-cases.

9.7 CONCLUSION

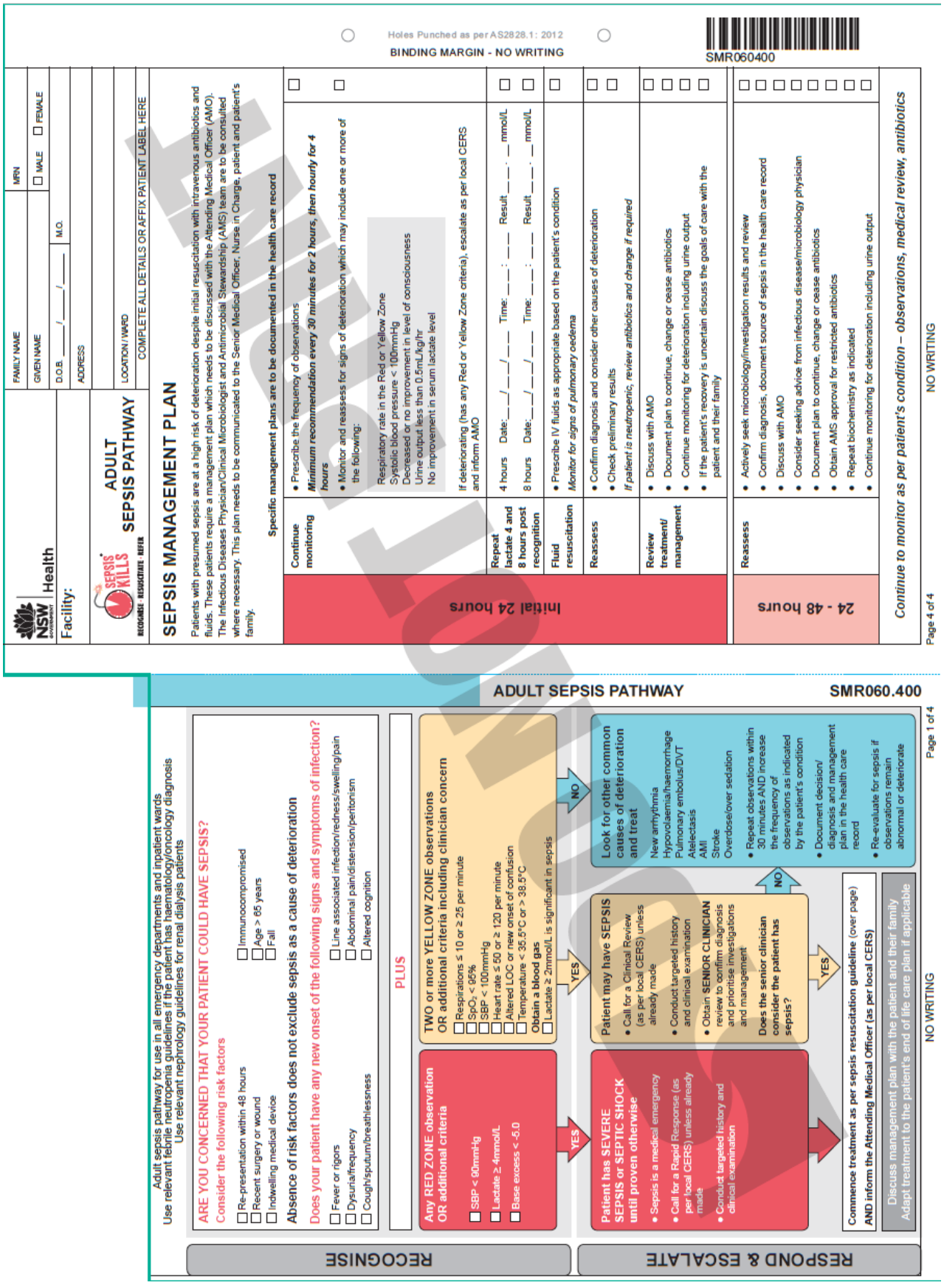
This project is the first to evaluate the Adult Sepsis Pathway and the Modified St. John Rule in New South Wales (NSW), and to compare the performance between these two tools and the qSOFA score. We used more than 130,000 patient admissions from 34 healthcare facilities across metropolitan, rural and regional localities to evaluate these tools and explore improved alternatives.

Sepsis is difficult to define and therefore challenging to detect and diagnose. This is reflected in the fact that the discrimination across all scenarios was not particularly high, with large numbers of false positive cases compared to true positives even for the best performing tools. Factors contributing to this may include the extent to which the ICD-10-AM coded sepsis cases capture all true cases, the extent to which logical combinations of clinical criteria can identify true cases, and issues of data quality.

In this report, we derived optimised alternative options using a data driven approach. We did not make a final recommendation about which alternative tool represents the optimal choice, since other clinical factors must be considered based on the performance metrics of the different options. Ultimately, an optimal tool will identify as many true sepsis cases as possible, that is, it will have high sensitivity. However, a certain rate of false positives must be tolerated. One approach to selecting an optimal tool is to decide upon an acceptable minimum sensitivity and/or PPV, and then select the most sensitive approach within those constraints.

APPENDIX

A. CEC ADULT SEPSIS PATHWAY



NSW Health
Facility:
SEPSIS KILLS RECOGNISE · RESUSCITATE · REFER
ADULT SEPSIS PATHWAY
FAMILY NAME | MRN
GIVEN NAME | ☐ MALE ☐ FEMALE
D.O.B. ___/___/___ | M.O.
ADDRESS
LOCATION / WARD
COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE

Holes Punched as per AS2828.1: 2012
BINDING MARGIN - NO WRITING
SMR060400

SEPSIS MANAGEMENT PLAN

Patients with presumed sepsis are at a high risk of deterioration despite initial resuscitation with intravenous antibiotics and fluids. These patients require a management plan which needs to be discussed with the Attending Medical Officer (AMO). The Infectious Diseases Physician/Clinical Microbiologist and Antimicrobial Stewardship (AMS) team are to be consulted where necessary. This plan needs to be communicated to the Senior Medical Officer, Nurse in Charge, patient and patient's family.

Specific management plans are to be documented in the health care record

Initial 24 hours

Continue monitoring
- ☐ Prescribe the frequency of observations
  Minimum recommendation every 30 minutes for 2 hours, then hourly for 4 hours
- ☐ Monitor and reassess for signs of deterioration which may include one or more of the following:
  Respiratory rate in the Red or Yellow Zone
  Systolic blood pressure < 100mmHg
  Decreased or no improvement in level of consciousness
  Urine output less than 0.5mL/kg/hr
  No improvement in serum lactate level

If deteriorating (has any Red or Yellow Zone criteria), escalate as per local CERS and inform AMO

Repeat lactate 4 and 8 hours post recognition
- ☐ 4 hours Date:__/__/__ Time:__ __ : __ __ Result__ __ . __ mmol/L
- ☐ 8 hours Date:__/__/__ Time:__ __ : __ __ Result__ __ . __ mmol/L

Fluid resuscitation
- ☐ Prescribe IV fluids as appropriate based on the patient's condition
  Monitor for signs of pulmonary oedema

Reassess
- ☐ Confirm diagnosis and consider other causes of deterioration
- ☐ Check preliminary results
  If patient is neutropenic, review antibiotics and change if required

Review treatment/ management
- ☐ Discuss with AMO
- ☐ Document plan to continue, change or cease antibiotics
- ☐ Continue monitoring for deterioration including urine output
- ☐ If the patient's recovery is uncertain discuss the goals of care with the patient and their family

24 - 48 hours

Reassess
- ☐ Actively seek microbiology/investigation results and review
- ☐ Confirm diagnosis, document source of sepsis in the health care record
- ☐ Discuss with AMO
- ☐ Consider seeking advice from infectious disease/microbiology physician
- ☐ Document plan to continue, change or cease antibiotics
- ☐ Obtain AMS approval for restricted antibiotics
- ☐ Repeat biochemistry as indicated
- ☐ Continue monitoring for deterioration including urine output

Continue to monitor as per patient's condition – observations, medical review, antibiotics

Page 4 of 4
NO WRITING

ADULT SEPSIS PATHWAY SMR060.400

Adult sepsis pathway for use in all emergency departments and inpatient wards
Use relevant febrile neutropenia guidelines if the patient has haematology/oncology diagnosis
Use relevant nephrology guidelines for renal dialysis patients

RECOGNISE

ARE YOU CONCERNED THAT YOUR PATIENT COULD HAVE SEPSIS?

Consider the following risk factors
- ☐ Re-presentation within 48 hours
- ☐ Recent surgery or wound
- ☐ Indwelling medical device
- ☐ Immunocompromised
- ☐ Age > 65 years
- ☐ Fall

Absence of risk factors does not exclude sepsis as a cause of deterioration

Does your patient have any new onset of the following signs and symptoms of infection?
- ☐ Fever or rigors
- ☐ Dysuria/frequency
- ☐ Cough/sputum/breathlessness
- ☐ Line associated infection/redness/swelling/pain
- ☐ Abdominal pain/distension/peritonism
- ☐ Altered cognition

PLUS

Any RED ZONE observation OR additional criteria
- ☐ SBP < 90mmHg
- ☐ Lactate ≥ 4mmol/L
- ☐ Base excess < -5.0

YES

TWO or more YELLOW ZONE observations OR additional criteria including clinician concern
- ☐ Respirations ≤ 10 or ≥ 25 per minute
- ☐ SpO_2 < 95%
- ☐ SBP < 100mmHg
- ☐ Heart rate ≤ 50 or ≥ 120 per minute
- ☐ Altered LOC or new onset of confusion
- ☐ Temperature < 35.5°C or > 38.5°C

Obtain a blood gas
- ☐ Lactate ≥ 2mmol/L is significant in sepsis

YES

Patient may have SEPSIS
- Call for a Clinical Review (as per local CERS) unless already made
- Conduct targeted history and clinical examination
- Obtain **SENIOR CLINICIAN** review to confirm diagnosis and prioritise investigations and management

Does the senior clinician consider the patient has sepsis?

NO

Look for other common causes of deterioration and treat

New arrhythmia
Hypovolaemia/haemorrhage
Pulmonary embolus/DVT
Atelectasis
AMI
Stroke
Overdose/over sedation

- Repeat observations within 30 minutes AND increase the frequency of observations as indicated by the patient's condition
- Document decision/ diagnosis and management plan in the health care record
- Re-evaluate for sepsis if observations remain abnormal or deteriorate

YES

Patient has SEVERE SEPSIS or SEPTIC SHOCK until proven otherwise
- Sepsis is a medical emergency
- Call for a Rapid Response (as per local CERS) unless already made
- Conduct targeted history and clinical examination

RESPOND & ESCALATE

Commence treatment as per sepsis resuscitation guideline (over page)
AND inform the Attending Medical Officer (as per local CERS)

Discuss management plan with the patient and their family
Adapt treatment to the patient's end of life care plan if applicable

NO WRITING

Page 1 of 4

NSW GOVERNMENT Health

Facility:

SEPSIS KILLS
RECOGNISE · RESUSCITATE · REFER

ADULT SEPSIS PATHWAY

FAMILY NAME	MRN
GIVEN NAME	☐ MALE ☐ FEMALE
D.O.B. ____/____/____	M.O.
ADDRESS	
LOCATION / WARD	
COMPLETE ALL DETAILS OR AFFIX PATIENT LABEL HERE	

SMR060400

Holes Punched as per AS2828.1: 2012
BINDING MARGIN - NO WRITING

Sepsis recognition

Date: __/__/__ Time: __:__

☐ Emergency Department Patient

Triage category 1 2 3 4 5

☐ Inpatient Ward: _____

☐ Clinical Review ☐ Rapid Response

RESUSCITATE

A **Airway** - Assess and maintain patent airway

B **Breathing** - Assess and administer oxygen if required; aim SpO_2 ≥ 95% (or 88-92% for COPD)

C **Circulation - Vascular access, blood/culture collection, fluid resuscitation and antibiotics**

Consider intraosseous access after two failed attempts at cannulation

Collect Blood Cultures Take two (2) sets from two (2) separate sites	☐ Yes ☐ Not obtained
For patients with a central venous access device (CVAD), take one set from the CVAD plus one set peripherally	
Collect Lactate Lactate ≥ 2mmol/L after adequate fluid resuscitation is significant	☐ Yes ☐ Not obtained Lactate:__ __.__mmol/L
Collect FBC, EUC, CRP/PCT, LFTs, coags and glucose BGL > 7.7mmol/L in the absence of diabetes may be significant	☐ Yes ☐ Not obtained BGL:__ __.__mmol/L
Order and collect other investigations and cultures prior to antibiotics (unless a **SENIOR CLINICIAN** assesses that this would result in an unacceptable delay in commencing antibiotic therapy) Eg. Urine, cerebrospinal fluid, wound swab, joint or organ space aspirate	Document investigations and cultures collected: _____ _____ _____ _____
Fluid Resuscitation (intravenous or intraosseous) • Use crystalloid • Aim Systolic Blood Pressure > 100mmHg • Monitor for signs of pulmonary oedema and review at risk patients more frequently	☐ **Emergency Department patient** Give initial 20mL/kg bolus STAT, if no response repeat 20mL/kg STAT ☐ **Inpatient** Initial 250-500mL bolus STAT, if no response repeat 250-500mL STAT **If no response in SBP after 1000mL call a Rapid Response**
Consider commencement of vasopressors	

H-7700/06 0508 36

NO WRITING

RESUSCITATE

C

Antibiotics First/new antibiotic administered Date:__ __/__ __/__ __ __ Time: __ __ : __ __

Blood cultures (at least two sets) and other relevant cultures should be collected **PRIOR** to antibiotic administration. However in patients with severe sepsis or septic shock, if difficult to obtain cultures do not delay administration of antibiotic(s). Refer to local Antimicrobial Stewardship policies/procedures regarding antibiotic instructions.
Consult Infectious Diseases Physician or Clinical Microbiologist if required.

☐ Severe sepsis or septic shock	Use CEC Adult Antibiotic Guideline for Severe Sepsis & Septic Shock or locally endorsed antibiotic prescribing guideline	Prescribe and administer antibiotics **within 60 MINUTES** of sepsis recognition
☐ Sepsis	Use locally endorsed antibiotic prescribing guideline	Prescribe and administer antibiotics promptly *in a timeframe directed by senior clinician (must be within 2 hours)*

D **Disability - Assess level of consciousness (LOC)** using Alert, Voice, Pain, Unresponsive (AVPU)

E **Exposure** - Re-examine the patient for other potential sources of infection to guide further investigations

F **Fluid** - Monitor/document strict fluid input/output and consider IDC (if not already inserted)

G **Check Blood Glucose Level** - Manage as per local guidelines

Monitor and Reassess

Continue monitoring, assess for signs of deterioration and escalate as per local CERS

- Respiratory rate in the Red or Yellow Zone
- SBP < 100mmHg
- Decreased or no improvement in level of consciousness
- Urine output < 0.5mL/kg/hour
- Serum lactate level of ≥ 2mmol/L (or increasing) or no improvement after adequate fluid resuscitation may be indicative of septic shock
- Consider other causes of deterioration

REFER

If no improvement Intensive Care may be required

Update the Attending Medical Officer on the patient's condition using ISBAR	☐
Discuss the management plan with the patient and their family/carers	☐
Sepsis management plan documented by a medical officer in the health care record as per page 4 (over)	☐

Name: _____ Designation: _____ Signature: _____

NO WRITING

B. R SCRIPTS FOR THREE ALGORITHMS

ALGORITHM FOR THE QSOFA SCORE

- Defining the measurements, clinical thresholds and lookback time periods for qSOFA

```
grouperlist=c("Base Excess","Bilirubin","Blood Glucose Level","Blood Creatinine","GCS",
"Heart Rate/Pulse Rate","Blood Lactate","Mean Blood Pressure","Resp Rate","Blood Pressu
re Systolic","O2 Saturation","Temperature","White Blood Cell Count")
varlist=c(10,9,5)
timegap=c(60,60,60)
threshold=c(100,22,15)
```

Grouper codes 1: Base excess, 2: Bilirubin, 3: Blood glucose, 4: Creatinine, 5: GCS, 6: HR, 7: Lactate, 8: MAP, 9: RR, 10: SBP, 11: SpO2, 12: Temperature, 13: WBC.

- Importing the measurement dataset

```
Sepsis_subdata=long_inhie
```

- Defining common variable names for critical variables & identifying column indices of those variables

```
colnames(Sepsis_subdata)[1]="Patient_Id"                                    col_inde
x_ID=which(colnames(Sepsis_subdata)=="Patient_Id")
colnames(Sepsis_subdata)[11]="Dt_Tm_triggered"                                  col
_index_DT=which(colnames(Sepsis_subdata)=="Dt_Tm_triggered")
colnames(Sepsis_subdata)[12]="Grouper"
col_index_Grouper=which(colnames(Sepsis_subdata)=="Grouper")
colnames(Sepsis_subdata)[16]="Result"
col_index_Results=which(colnames(Sepsis_subdata)=="Result")
```

- Defining common grouper names

```
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper]        =="Arteria
l Blood Gas Base Excess"]="Base Excess"
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper]        =="Venous
Blood Gas Base Excess"]="Base Excess"
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper]         =="Arteri
al Blood Gas O2 Saturation"]="O2 Saturation"
```

- Identifying missing records for critical variables and eliminating

```
Sepsis1=Sepsis_subdata[complete.cases(Sepsis_subdata[,c(col_index_ID,col_index_DT,col_i
ndex_Grouper,col_index_Results)]),]
```

- Extracting records interested in qSOFA

```
Sepsis1_1=Sepsis1[Sepsis1$Grouper %in% grouperlist[varlist],]
```

- Ordering the data by Patient Id and Date/time triggered

```
Sepsis1_2=Sepsis1_1[order(Sepsis1_1$Patient_Id,Sepsis1_1$Dt_Tm_triggered),]
```

- Extracting the relavent variables

```
Sepsis1_3=Sepsis1_2[,c(11:12,16,2,1,4:9)]
```

- Identifying the corresponding thresholds and lookback time periods for measurements

```
varlist_i=thresholdlist_i=timegap_i=rep(NA,dim(Sepsis1_3)[1])
success=rep(0,dim(Sepsis1_3)[1])
for(m in 1:dim(Sepsis1_3)[1]){
  varlist_i[m]=which(grouperlist==Sepsis1_3$Grouper[m])
  thresholdlist_i[m]=threshold[varlist==varlist_i[m]]
  timegap_i[m]=timegap[varlist==varlist_i[m]]
}

col_index_Res=which(colnames(Sepsis1_3)=="Result")
col_index_Group=which(colnames(Sepsis1_3)=="Grouper")
```

- Loop to compare measurement reading with corresponding threshold

```
for(jj in 1:dim(Sepsis1_3)[1]){
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[varlist][1]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<=threshold[1]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[varlist][2]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold[2]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[varlist][3]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold[3]) success[jj]=1
    else success[jj]=0
  }
}
```

- Extracting only the measurements which satisfy the thresholds

```
Sepsis1_4=cbind(Sepsis1_3,varlist_i,thresholdlist_i,timegap_i,success)
Sepsis2=Sepsis1_4[Sepsis1_4$success==1,]
```

- Generating indicator variables for the patients and measurements

```
Sepsis2_1= transform(Sepsis2, id_o2=match(Sepsis2$Patient_Id, unique(Sepsis2$Patient_Id
)))
Sepsis2_2=transform(Sepsis2_1, id_i3= ave(xtfrm(Sepsis2_1$Dt_Tm_triggered),Sepsis2_1$Pa
tient_Id, FUN=function(id_i3) order(id_i3,decreasing=F)))
```

- Defining sepsis status variables and flags for each measurement

```
ind_date_i=NULL; k=1
Status=Count=rep(NA,dim(Sepsis2_2)[1])
Flag_BP=Flag_GCS=Flag_RR=rep(0,dim(Sepsis2_2)[1])
```

- Sepsis alert generating procedure

```
for(i in 1:max(Sepsis2_2$id_o2)){ #OUTER Loop start
  #measurement trigger times for the ith patient
  ind_date=Sepsis2_2$Dt_Tm_triggered[Sepsis2_2$id_o2==i]
  for(j in 1:max(Sepsis2_2$id_i3[Sepsis2_2$id_o2==i])){ #INNER Loop start
    #measurement trigger times on or before the jth measurement
```

```
    ind_date_i=as.numeric((ind_date[j]-ind_date[1:j])/60)
    info_mat=Sepsis2_2[Sepsis2_2$id_o2==i,][1:j,]
    info_mat2=cbind(info_mat,ind_date_i)
    timeid=rep(0,j)
    for(kk in 1:j){ #Loop to check the lookback time periods
      if(info_mat2$ind_date_i[kk] <= info_mat2$timegap_i[kk]) timeid[kk]=1
      else timeid[kk]=0
    }
    info_mat3=cbind(info_mat2,timeid)

    #Extracting only the measurements within lookback time period
    info_mat4=info_mat3[info_mat3$timeid==1,]

    col_index_Group2=which(colnames(info_mat4)=="Grouper")

    #Identifying unique measurements satisfying clinical thresholds & within        lo
okback period
    sum1=sum2=sum3=0
      sum1=Flag_BP[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist[
1]],])[1]>=1)*1
    sum2=Flag_RR[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist[2]
],])[1]>=1)*1
    sum3=Flag_GCS[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist[3
]],])[1]>=1)*1

    Count[k]=sum(sum1,sum2,sum3) #Sepsis risk score
    if(Count[k]>=2){ #Loop to generate sepsis status
      Status[k]="Sepsis Alert"
    } else Status[k]="No Alert"
    k=k+1

    ind_date_i=NULL
  }
  ind_date=NULL
}
```

- Dataset 1: Final dataset with sepsis alerts for the measurements which satisfy the thresholds

```
Sepsis2_3=cbind(Sepsis2_2,Count,Status,Flag_BP,Flag_RR,Flag_GCS)
```

- Dataset 2: Assign "No alert" status for the measurements which does not satisfy the thresholds

```
Sepsis3=Sepsis1_4[success==0,];Count=rep(0,dim(Sepsis3)[1]);Status=rep("No Alert",dim(S
epsis3)[1])
id_o2=id_i3=rep(0,dim(Sepsis3)[1]);Flag_BP=Flag_RR=Flag_GCS=rep(0,dim(Sepsis3)[1])
Sepsis3_1=cbind(Sepsis3,id_o2,id_i3,Count,Status,Flag_BP,Flag_RR,Flag_GCS)
```

- Merging Dataset 1 with Dataset 2 and order them by Patient Id and Date/time triggered

```
Sepsis_results1=rbind(Sepsis2_3,Sepsis3_1)
Sepsis_results=Sepsis_results1[order(Sepsis_results1$Patient_Id,Sepsis_results1$Dt_Tm_t
riggered),]
```

ALGORITHM FOR THE ADULT SEPSIS PATHWAY

- Defining the measurements, clinical thresholds and lookback time periods for Adult Sep Pathway

```
grouperlist=c("Base Excess","Bilirubin","Blood Glucose Level","Blood Creatinine","GCS",
"Heart Rate/Pulse Rate","Blood Lactate","Mean Blood Pressure","Resp Rate","Blood Pressu
re Systolic","O2 Saturation","Temperature","White Blood Cell Count")
c_varlist=c(12,6,9,5,11,7,10,1)
varlist_red=c(10,7,1)
varlist_yellow_l=c(12,6,9,5,11,7,10,1)
varlist_yellow_u=c(12,6,9)
timegap=c(60,60,60,60,1800,720,60,0)
threshold_red=c(90,4,-5)
#Defining threshold lower limits and upper limits for some measurements
threshold_yellow_l=c(35.5,50,10,15,95,2,100,-5)
threshold_yellow_u=c(38.5,120,25)
```

Grouper codes 1: Base excess, 2: Bilirubin, 3: Blood glucose, 4: Creatinine, 5: GCS, 6: HR, 7: Lactate, 8: MAP, 9: RR, 10: SBP, 11: SpO2, 12: Temperature, 13: WBC.

- Importing the measurement dataset

```
Sepsis_subdata=long_inhie
```

- Defining common variable names for critical variables & identifying column indices of those variables

```
colnames(Sepsis_subdata)[1]="Patient_Id" col_index_ID=which(colnames(Sepsis_subdata)=="
Patient_Id")
colnames(Sepsis_subdata)[11]="Dt_Tm_triggered" col_index_DT=which(colnames(Sepsis_subda
ta)=="Dt_Tm_triggered")
colnames(Sepsis_subdata)[12]="Grouper" col_index_Grouper=which(colnames(Sepsis_subdata)
=="Grouper")
colnames(Sepsis_subdata)[16]="Result" col_index_Results=which(colnames(Sepsis_subdata)=
="Result")
```

- Defining common grouper names

```
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper] =="Arterial Blood
Gas Base Excess"]="Base Excess"
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper] =="Venous Blood G
as Base Excess"]="Base Excess"
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper] =="Arterial Blood
Gas O2 Saturation"]="O2 Saturation"
```

- Identifying missing records for critical variables and eliminating

```
Sepsis1=Sepsis_subdata[complete.cases(Sepsis_subdata[,c(col_index_ID,col_index_DT,col_i
ndex_Grouper,col_index_Results)]),]
```

- Extracting records interested in Adult Sep

```
Sepsis1_1=Sepsis1[Sepsis1$Grouper %in% grouperlist[c_varlist],]
```

- Ordering the data by Patient Id and Date/time triggered

```
Sepsis1_2=Sepsis1_1[order(Sepsis1_1$Patient_Id,Sepsis1_1$Dt_Tm_triggered),]
```

- Extracting the relavent variables

```
Sepsis1_3=Sepsis1_2[,c(11:12,16,2,1,4:9)]
```

- Identifying the corresponding thresholds and lookback time periods for measurements

```
varlist_i=thresholdlist_il=thresholdlist_iu=timegap_i=rep(NA,dim(Sepsis1_3)[1])
success=rep(0,dim(Sepsis1_3)[1])
for(m in 1:dim(Sepsis1_3)[1]){
  varlist_i[m]=which(grouperlist==Sepsis1_3$Grouper[m])
  thresholdlist_il[m]=threshold_yellow_l[varlist_yellow_l==varlist_i[m]]
  thresholdlist_iu[m]=max(0,threshold_yellow_u[varlist_yellow_u==varlist_i[m]])
  timegap_i[m]=timegap[c_varlist==varlist_i[m]]
}

col_index_Res=which(colnames(Sepsis1_3)=="Result")
col_index_Group=which(colnames(Sepsis1_3)=="Grouper")
```

- Loop to compare measurement reading with corresponding threshold

```
for(jj in 1:dim(Sepsis1_3)[1]){
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][1]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold_yellow_l[1] || as.numeric(Seps
is1_3[jj,col_index_Res])>threshold_yellow_u[1]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][2]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<=threshold_yellow_l[2] || as.numeric(Sep
sis1_3[jj,col_index_Res])>=threshold_yellow_u[2]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][3]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<=threshold_yellow_l[3] || as.numeric(Sep
sis1_3[jj,col_index_Res])>=threshold_yellow_u[3]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][4]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold_yellow_l[4]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][5]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold_yellow_l[5]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][6]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold_yellow_l[6]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][7]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold_yellow_l[7]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[varlist_red][3]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold_red[3]) success[jj]=1
    else success[jj]=0
```

```
  }
}
```

- Extracting only the measurements which satisfy the thresholds

```
Sepsis1_4=cbind(Sepsis1_3,varlist_i,thresholdlist_il,thresholdlist_iu,timegap_i,success
)
Sepsis2=Sepsis1_4[Sepsis1_4$success==1,]
```

- Generating indicator variables for the patients and measurements

```
Sepsis2_1= transform(Sepsis2, id_o2=match(Sepsis2$Patient_Id, unique(Sepsis2$Patient_Id
)))
Sepsis2_2=transform(Sepsis2_1, id_i3=ave(xtfrm(Sepsis2_1$Dt_Tm_triggered),Sepsis2_1$Pat
ient_Id, FUN=function(id_i3) order(id_i3,decreasing=F)))
```

- Defining sepsis status variables and flags for each measurement

```
ind_date_i=NULL; k=1
Status=Count=Count2=rep(0,dim(Sepsis2_2)[1])
Flag_Temp=Flag_HR=Flag_RR=Flag_GCS=Flag_SpO2=Flag_Lactate=Flag_SBP=rep(0,dim(Sepsis2_2)
[1])
```

- Sepsis alert generating procedure

```
for(i in 1:max(Sepsis2_2$id_o2)){ #OUTER Loop start
  #measurement trigger times for the ith patient
  ind_date=Sepsis2_2$Dt_Tm_triggered[Sepsis2_2$id_o2==i]
  for(j in 1:max(Sepsis2_2$id_i3[Sepsis2_2$id_o2==i])){ #INNER Loop start
    #measurement trigger times on or before the jth measurement
    ind_date_i=as.numeric((ind_date[j]-ind_date[1:j])/60)
    info_mat=Sepsis2_2[Sepsis2_2$id_o2==i,][1:j,]
    info_mat2=cbind(info_mat,ind_date_i)
    timeid=rep(0,j)
    for(kk in 1:j){ #Loop to check the lookback time periods
      if(info_mat2$ind_date_i[kk] <= info_mat2$timegap_i[kk]) timeid[kk]=1
      else timeid[kk]=0
    }
    info_mat3=cbind(info_mat2,timeid)

    #Extracting only the measurements within lookback time period
    info_mat4=info_mat3[info_mat3$timeid==1,]

    col_index_Group2=which(colnames(info_mat4)=="Grouper")
    col_index_Res2=which(colnames(info_mat4)=="Result")

    #Identifying unique measurements which satisfies the clinical thresholds & within l
ookback period
    sum1=sum2=sum3=sum4=sum5=sum6=sum7=0
    sum1=Flag_Temp[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_
yellow_l[1]],])[1]>=1)*1
    sum2=Flag_HR[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_ye
llow_l[2]],])[1]>=1)*1
    sum3=Flag_RR[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_ye
llow_l[3]],])[1]>=1)*1
    sum4=Flag_GCS[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_y
ellow_l[4]],])[1]>=1)*1
```

```
    sum5=Flag_SpO2[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_
yellow_l[5]],])[1]>=1)*1
    sum6=Flag_Lactate[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varli
st_yellow_l[6]],])[1]>=1)*1
    sum7=Flag_SBP[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_y
ellow_l[7]],])[1]>=1)*1


    #Sepsis risk score to trigger SIRS alerts
    Count[k]=sum(sum1,sum2,sum3,sum4,sum5,sum6,sum7)    if(Count[k]>=2){
      Status[k]="SIRS Alert"
    } else Status[k]="No Alert"

    #Checking the measurements under RED ZONE to trigger Severe Sepsis alerts
    if(info_mat$varlist_i[j] %in% varlist_red){
      if(info_mat[j,col_index_Group2]==grouperlist[varlist_red][1]){
        if(as.numeric(info_mat[j,col_index_Res2])<threshold_red[1]) {
          Status[k]="Severe Sepsis"
          Count2[k]=Count2[k]+1}
      }
      if(info_mat[j,col_index_Group2]==grouperlist[varlist_red][2]){
        if(as.numeric(info_mat[j,col_index_Res2])>=threshold_red[2]) {
          Status[k]="Severe Sepsis"
          Count2[k]=Count2[k]+1}
      }
      if(info_mat[j,col_index_Group2]==grouperlist[varlist_red][3]){
        if(as.numeric(info_mat[j,col_index_Res2])<threshold_red[3]) {
          Status[k]="Severe Sepsis"
          Count2[k]=Count2[k]+1}
      }
    }

    k=k+1
    ind_date_i=NULL
  }
  ind_date=NULL
}
```

- Dataset 1: Final dataset with sepsis alerts for the measurements which satisfy the thresholds

```
Sepsis2_3=cbind(Sepsis2_2,Count1=Count,Count2,Status,Flag_Temp,Flag_HR,Flag_RR,Flag_GCS
,Flag_SpO2,Flag_Lactate,Flag_SBP)
```

- Dataset 2: Assign "No alert" status for the measurements which does not satisfy the thresholds

```
Sepsis3=Sepsis1_4[Sepsis1_4$success==0,];Count1=Count2=rep(0,dim(Sepsis3)[1]);Status=re
p("No Alert",dim(Sepsis3)[1]);id_o2=id_i3=rep(0,dim(Sepsis3)[1])
Flag_Temp=Flag_HR=Flag_RR=Flag_GCS=Flag_SpO2=Flag_Lactate=Flag_SBP=rep(0,dim(Sepsis3)[1
])
Sepsis3_1=cbind(Sepsis3,id_o2,id_i3,Count1,Count2,Status,Flag_Temp,Flag_HR,Flag_RR,Flag
_GCS,Flag_SpO2,Flag_Lactate,Flag_SBP)
```

- Merging Dataset 1 with Dataset 2 and order them by Patient Id and Date/time triggered

```
Sepsis_results1=rbind(Sepsis2_3,Sepsis3_1)
Sepsis_results=Sepsis_results1[order(Sepsis_results1$Patient_Id,Sepsis_results1$Dt_Tm_triggered),]
```

ALGORITHM FOR THE MODIFIED ST. JOHN RULE

- Defining the measurements, clinical thresholds and lookback time periods for Modified St. John Rule

```
grouperlist=c("Base Excess","Bilirubin","Blood Glucose Level","Blood Creatinine","GCS","Heart Rate/Pulse Rate","Blood Lactate","Mean Blood Pressure","Resp Rate","Blood Pressure Systolic","O2 Saturation","Temperature","White Blood Cell Count")c_varlist=c(12,6,9,13,3,7,8,2,4,10)
varlist_red=c(10,7)
varlist_yellow_l=c(12,6,9,13,3,7,8,2,4,10)
varlist_yellow_u=c(12,13,3,2)
timegap=c(30,30,30,1800,1800,720,1800,1800,4320,0)
threshold_red=c(90,4)
#Defining threshold lower limits and upper limits for some measurements
threshold_yellow_l=c(36,95,22,4,7.8,2,65,34.2,44.2,90)
threshold_yellow_u=c(38.5,12,11.1,171)
```

Grouper codes 1: Base excess 2: Bilirubin 3: Blood glucose 4: Creatinine 5: GCS 6: HR 7: Lactate 8: MAP 9: RR 10: SBP 11: SpO2 12: Temperature 13: WBC

- Importing the measurement dataset

```
Sepsis_subdata=long_inhie
```

- Defining common variable names for critical variables & identifying column indices of those variables

```
colnames(Sepsis_subdata)[1]="Patient_Id" col_index_ID=which(colnames(Sepsis_subdata)=="Patient_Id")
colnames(Sepsis_subdata)[11]="Dt_Tm_triggered" col_index_DT=which(colnames(Sepsis_subdata)=="Dt_Tm_triggered")
colnames(Sepsis_subdata)[12]="Grouper" col_index_Grouper=which(colnames(Sepsis_subdata)=="Grouper")
colnames(Sepsis_subdata)[16]="Result" col_index_Results=which(colnames(Sepsis_subdata)=="Result")
```

- Defining common grouper names

```
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper] =="Arterial Blood Gas Base Excess"]="Base Excess"
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper] =="Venous Blood Gas Base Excess"]="Base Excess"
Sepsis_subdata[,col_index_Grouper][Sepsis_subdata[,col_index_Grouper] =="Arterial Blood Gas O2 Saturation"]="O2 Saturation"
```

- Identifying missing records for critical variables and eliminating

```
Sepsis1=Sepsis_subdata[complete.cases(Sepsis_subdata[,c(col_index_ID,col_index_DT,col_index_Grouper,col_index_Results)]),]
```

- Extracting records interested in St. John Rule

```
Sepsis1_1=Sepsis1[Sepsis1$Grouper %in% grouperlist[c_varlist],]
```

- Ordering the data by Patient Id and Date/time triggered

```
Sepsis1_2=Sepsis1_1[order(Sepsis1_1$Patient_Id,Sepsis1_1$Dt_Tm_triggered),]
```

- Extracting the relavent variables

```
Sepsis1_3=Sepsis1_2[,c(11:12,16,2,1,4:9)]
```

- Extracting only blood creatinine measurements

```
Sepsis_creat=Sepsis1_3[Sepsis1_3$Grouper=="Blood Creatinine",]
```

- Identifying the corresponding thresholds and lookback time periods for measurements

```
varlist_i=thresholdlist_il=thresholdlist_iu=timegap_i=rep(NA,dim(Sepsis1_3)[1])
success=rep(0,dim(Sepsis1_3)[1]); creat_count=0
for(m in 1:dim(Sepsis1_3)[1]){
  varlist_i[m]=which(grouperlist==Sepsis1_3$Grouper[m])
  thresholdlist_il[m]=threshold_yellow_l[varlist_yellow_l==varlist_i[m]]
  thresholdlist_iu[m]=max(0,threshold_yellow_u[varlist_yellow_u==varlist_i[m]])
  timegap_i[m]=timegap[c_varlist==varlist_i[m]]
}

col_index_Res=which(colnames(Sepsis1_3)=="Result")
col_index_Group=which(colnames(Sepsis1_3)=="Grouper")
```

- Loop to compare measurement reading with corresponding threshold

```
for(jj in 1:dim(Sepsis1_3)[1]){
  creat_date_i=NULL
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][1]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<=threshold_yellow_l[1] || as.numeric(Sep
sis1_3[jj,col_index_Res])>=threshold_yellow_u[1]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][2]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold_yellow_l[2]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][3]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold_yellow_l[3]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][4]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<=threshold_yellow_l[4] || as.numeric(Sep
sis1_3[jj,col_index_Res])>=threshold_yellow_u[2]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][5]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold_yellow_l[5] & as.numeric(Seps
is1_3[jj,col_index_Res])<=threshold_yellow_u[3]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][6]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold_yellow_l[6]) success[jj]=1
    else success[jj]=0
  }
```

```
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][7]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<=threshold_yellow_l[7]) success[jj]=1
    else success[jj]=0
  }
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][8]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])>=threshold_yellow_l[8] & as.numeric(Seps
is1_3[jj,col_index_Res])<=threshold_yellow_u[4]) success[jj]=1
    else success[jj]=0
  }
  #Loop to identify the blood creatinine readings which satisfy the clinical threshold
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[c_varlist][9]){
    pt_id=Sepsis1_3$Patient_Id[jj]
    Sepsis_creat21=Sepsis_creat[Sepsis_creat$Patient_Id==pt_id,]
   row_id=which(Sepsis_creat21$Dt_Tm_triggered==Sepsis1_3$Dt_Tm_triggered[jj] & Sepsis_
creat21$Patient_Id==Sepsis1_3$Patient_Id[jj] )
    Sepsis_creat2=Sepsis_creat21[1:row_id,]
    creat_date=Sepsis_creat2$Dt_Tm_triggered
    creat_val=Sepsis_creat2$Result
    creat_count=dim(Sepsis_creat2)[1]
    {if(creat_count==1) {success[jj]=0}
     else{ creat_date_i=as.numeric((creat_date[creat_count]-creat_date[1:creat_count])/
60)
     creat_val_i=as.numeric(creat_val[creat_count])- as.numeric(creat_val[1:creat_count
])
        Sepsis_creat1=cbind(Sepsis_creat2[1:creat_count,],creat_date_i,creat_val_i)
        Sepsis_creat_sub=Sepsis_creat1[which(Sepsis_creat1$creat_date_i<=timegap[9]),]
    if(max(Sepsis_creat_sub$creat_val_i)>=threshold_yellow_l[9]) success[jj]=1
     else success[jj]=0
    }}}
  if(Sepsis1_3[jj,col_index_Group]==grouperlist[varlist_red][1]){
    if(as.numeric(Sepsis1_3[jj,col_index_Res])<threshold_red[1]) success[jj]=1
    else success[jj]=0
  }
}
```

- Extracting only the measurements which satisfy the thresholds

```
Sepsis1_4=cbind(Sepsis1_3,varlist_i,thresholdlist_il,thresholdlist_iu, timegap_i,succes
s)
Sepsis2=Sepsis1_4[Sepsis1_4$success==1,]
```

- Generating indicator variables for the patients and measurements

```
Sepsis2_1= transform(Sepsis2, id_o2=match(Sepsis2$Patient_Id, unique(Sepsis2$Patient_Id
)))
Sepsis2_2=transform(Sepsis2_1, id_i3= ave(xtfrm(Sepsis2_1$Dt_Tm_triggered),Sepsis2_1$Pa
tient_Id,FUN=function(id_i3) order(id_i3,decreasing=F)))
```

- Defining sepsis status variables and flags for each measurement

```
ind_date_i=NULL; k=1
Status=Count=Count2=Count3=rep(0,dim(Sepsis2_2)[1])
Flag_Temp=Flag_HR=Flag_RR=Flag_WBC=Flag_BG=Flag_Lactate=rep(0,dim(Sepsis2_2)[1])
Flag_MAP=Flag_Billi=Flag_Creat=Flag_SBP=rep(0,dim(Sepsis2_2)[1])
```

- Sepsis alert generating procedure

```
for(i in 1:max(Sepsis2_2$id_o2)){ #OUTER Loop start
  #measurement trigger times for the ith patient
  ind_date=Sepsis2_2$Dt_Tm_triggered[Sepsis2_2$id_o2==i]
  for(j in 1:max(Sepsis2_2$id_i3[Sepsis2_2$id_o2==i])){ #INNER Loop start
    #measurement trigger times on or before the jth measurement
    ind_date_i=as.numeric((ind_date[j]-ind_date[1:j])/60)
    info_mat=Sepsis2_2[Sepsis2_2$id_o2==i,][1:j,]
    info_mat2=cbind(info_mat,ind_date_i)
    timeid=rep(0,j)
    for(kk in 1:j){ #Loop to check the lookback time periods
      if(info_mat2$ind_date_i[kk] <= info_mat2$timegap_i[kk]) timeid[kk]=1
      else timeid[kk]=0
    }
    info_mat3=cbind(info_mat2,timeid)

    #Extracting only the measurements within lookback time period
    info_mat4=info_mat3[timeid==1,]

    col_index_Group2=which(colnames(info_mat4)=="Grouper")
    col_index_Res2=which(colnames(info_mat4)=="Result")

    #Identifying unique measurements which satisfies the clinical thresholds & within l
ookback period
    sum1=sum2=sum3=sum4=sum5=sum6=sum7=sum8=sum9=0   sum1=Flag_Temp[k]=(dim(info_mat4[i
nfo_mat4[,col_index_Group2]==grouperlist[varlist_yellow_l[1]],])[1]>=1)*1
    sum2=Flag_HR[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_ye
llow_l[2]],])[1]>=1)*1
    sum3=Flag_RR[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_ye
llow_l[3]],])[1]>=1)*1
    sum4=Flag_WBC[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_y
ellow_l[4]],])[1]>=1)*1
    sum5=Flag_BG[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_ye
llow_l[5]],])[1]>=1)*1
    sum6=Flag_Lactate[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varli
st_yellow_l[6]],])[1]>=1)*1
    sum7=Flag_MAP[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist_y
ellow_l[7]],])[1]>=1)*1
    sum8=Flag_Billi[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist
_yellow_l[8]],])[1]>=1)*1
    sum9=Flag_Creat[k]=(dim(info_mat4[info_mat4[,col_index_Group2]==grouperlist[varlist
_yellow_l[9]],])[1]>=1)*1

    Count[k]=sum(sum1,sum2,sum3,sum4,sum5) #Count for SIRS category
    Count2[k]=sum(sum6,sum7,sum8,sum9) #Count for the organ dys. category
    if(Count[k]>=2 & Count2[k]>=1) Status[k]="Severe Sepsis"
    if(Count[k]>=3 & Count2[k]==0) Status[k]="SIRS Alert"
    if(Count[k]<=2 & Count2[k]==0) Status[k]="No Alert"
    if(Count[k]<2 & Count2[k]>=1) Status[k]="No Alert"

    #Checking measurements in CEC category to trigger Severe Sepsis alerts
    if(info_mat$varlist_i[j] %in% varlist_red){
      if(info_mat[j,col_index_Group2]==grouperlist[varlist_red][1]){
        if(as.numeric(info_mat[j,col_index_Res2])<threshold_red[1]){
          Status[k]="Severe Sepsis"
```

```
          Count3[k]=Count3[k]+1
        }}
      if(info_mat[j,col_index_Group2]==grouperlist[varlist_red][2]){
        if(as.numeric(info_mat[j,col_index_Res2])>=threshold_red[2]) {
          Status[k]="Severe Sepsis"
          Count3[k]=Count3[k]+1
        }}
    }

    k=k+1
    ind_date_i=NULL
  }
  ind_date=NULL
}
```

- Dataset 1: Final dataset with sepsis alerts for the measurements which satisfy the thresholds

```
Sepsis2_3=cbind(Sepsis2_2,Count1=Count,Count2,Count3,Status,Flag_Temp,Flag_HR,Flag_RR,F
lag_WBC,Flag_BG,Flag_Lactate,Flag_MAP,Flag_Billi,Flag_Creat,Flag_SBP)
```

- Dataset 2: Assign "No alert" status for the measurements which does not satisfy the thresholds

```
Sepsis3=Sepsis1_4[success==0,];Count1=Count2=Count3=rep(0,dim(Sepsis3)[1]);Status=rep("
No Alert",dim(Sepsis3)[1]);id_o2=id_i3=id_lhd=rep(0,dim(Sepsis3)[1])
Flag_Temp=Flag_HR=Flag_RR=Flag_WBC=Flag_BG=Flag_Lactate=Flag_MAP=Flag_Billi=Flag_Creat=
Flag_SBP=rep(0,dim(Sepsis3)[1])
Sepsis3_1=cbind(Sepsis3,id_o2,id_i3,Count1,Count2,Count3,Status,Flag_Temp,Flag_HR,Flag_
RR,Flag_WBC,Flag_BG,Flag_Lactate,Flag_MAP,Flag_Billi,Flag_Creat,Flag_SBP)
```

- Merging Dataset 1 with Dataset 2 and order them by Patient Id and Date/time triggered

```
Sepsis_results1=rbind(Sepsis2_3,Sepsis3_1)
Sepsis_results=Sepsis_results1[order(Sepsis_results1$Patient_Id,Sepsis_results1$Dt_Tm_t
riggered),]
```

C. BLOOD CULTURE

TABLE C.1. BLOOD CULTURES ORDERED WITHIN SIX HOURS AFTER THE FIRST ALERT BY ALERT TYPE

WITHIN	SIRS, N (%, OUT OF 3,338 PATIENT ADMISSIONS WITH AT LEAST ONE SIRS ALERT)	SEVERE SEPSIS ALERT, N (%, OUT OF 2,829 PATIENT ADMISSIONS WITH AT LEAST ONE SEVERE SEPSIS ALERT)	ANY ALERT, N (%, OUT OF 5,096 PATIENT ADMISSIONS WITH ANY ALERT)
1 hour	49(1.5%)	64(2.3%)	93(1.8%)
2 hours	76(2.3%)	103(3.6%)	149(2.9%)
3 hours	88(2.6%)	120(4.2%)	173(3.4%)
4 hours	104(3.1%)	142(5.0%)	202(4.0%)
5 hours	116(3.5%)	155(5.5%)	221(4.3%)
6 hours	129(3.9%)	162(5.7%)	235(4.6%)

D. CODED SIRS CASES

TABLE D.1: ASSESSING ANY SIRS ALERT BASED ON TWO RELEVANT RISK IDENTIFICATION TOOLS COMPARED TO ICD-10-AM CODED SIRS (CHADX)

RISK IDENTIFICATION TOOL	ANY ICD-10-AM CODED SIRS	ANY SIRS ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		NO	YES	TOTAL					
Adult Sepsis Pathway	No	33,799	2,230	36,029	13.9	93.8	0.2	99.9	0.54 (0.48 - 0.60)
	Yes	31	5	36					
	Total	33,737	2,328	36,065					
Modified St. John Rule (eMR)	No	32,714	3,315	36,029	63.9	90.8	0.7	100.0	0.77 (0.69 - 0.85)
	Yes	13	23	36					
	Total	32,727	3,338	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

TABLE D.2: ASSESSING ANY SIRS ALERT BASED ON THE MODIFIED ST. JOHN RULE USING ALERTS FROM THE ALGORITHM AND EMR

RISK IDENTIFICATION TOOL	ANY ICD-10-AM CODED SIRS	ANY SIRS ALERT			SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC (95% CI)
		NO	YES	TOTAL					
Modified St. John Rule (algorithm)	No	34,084	1,945	36,029	30.6	94.6	0.6	99.9	0.63 (0.55 - 0.70)
	Yes	25	11	36					
	Total	34,115	1,961	36,065					
Modified St. John Rule (eMR)	No	32,714	3,315	36,029	63.9	90.8	0.7	100.0	0.77 (0.69 - 0.85)
	Yes	13	23	36					
	Total	32,727	3,338	36,065					

**PPV=positive predictive value; NPV=negative predictive value*

TABLE D.3: ALERTS FOR SIRS DURING ADMISSIONS COMPARED TO ICD-10-AM CODED SIRS, BY RURAL AND REGIONAL NSW LHD

TOOL	RURAL LHD	NO SEPSIS		ANY ICD-10 CODED SEPSIS		SENSITIVITY (%)	SPECIFICITY (%)	PPV (%)	NPV (%)	AUROC (95% CI)
		No alert	Any alert	No alert	Any alert					
Adult Sepsis Pathway	**All LHDs**	**91,248**	**8,822**	**7**	**10**	**58.8**	**91.2**	**0.1**	**100.0**	**0.75 (0.63, 0.87)**
	Far West	3,460	314	0	0	.	91.7	0.0	100.0	.
	Murrumbidgee	18,682	842	0	0	.	95.7	0.0	100.0	.
	Southern NSW	24,525	2,334	*	*	63.6	91.3	0.3	100.0	0.77 (0.63, 0.92)
	Western NSW	44,581	5,332	*	*	50.0	89.3	0.1	100.0	0.70 (0.48, 0.92)
Modified St. John Rule (algorithm)	**All LHDs**	**96,086**	**3,984**	**10**	**7**	**41.2**	**96.0**	**0.2**	**100.0**	**0.69 (0.57, 0.81)**
	Far West	3,534	240	0	0	.	93.6	0.0	100.0	.
	Murrumbidgee	18,889	635	0	0	.	96.8	0.0	100.0	.
	Southern NSW	25,984	875	*	*	45.5	96.7	0.6	100.0	0.71 (0.56, 0.87)
	Western NSW	47,679	2,234	*	*	33.3	95.5	0.1	100.0	0.64 (0.44, 0.85)

**PPV=positive predictive value; NPV=negative predictive value*

Due to the rarity of admissions with a coded SIRS case (without sepsis), it is difficult to assess the performance of the Adult Sepsis Pathway and the Modified St. John Rule (algorithm) in detecting SIRS. In Table D.3, the Adult Sepsis Pathway and Modified St. John Rule (algorithm) detected 10 out of 17 and 7 out of 17 SIRS cases, respectively, for all rural LHDs combined. This corresponds to relatively high sensitivity (58.8% and 41.2%, respectively), but comes at the expense of a very high numbers of admissions with false positive SIRS alerts.

E. FACILITY SPECIFIC DATES ACROSS FOUR RURAL AND REGIONAL NSW LHDS

TABLE E.1. STUDY DATE RANGES FOR INCLUSION OF HOSPITAL ADMISSION RECORDS BY HEALTH FACILITY

RURAL AND REGIONAL LHD	FACILITY NAME	EMR DATE	ADMISSION DATE ≥	SEPARATION DATE ≤
Far West	Broken Hill Base Hospital	1/03/2016	8/03/2016	30/09/2016
	Wilcannia Multi-Purpose Service	1/03/2016	8/03/2016	30/09/2016
Murrumbidgee	Coolamon Multi-Purpose Service	1/06/2015	8/06/2015	30/09/2016
	Culcairn Multi-Purpose Service	1/02/2016	8/02/2016	30/09/2016
	Griffith Base Hospital	1/12/2015	8/12/2015	30/09/2016
	Gundagai Multi-Purpose Service	1/05/2015	8/05/2015	30/09/2016
	Temora Health Service	1/09/2015	8/09/2015	30/09/2016
	Tumut Health Service	1/09/2015	8/09/2015	30/09/2016
Southern NSW	Bateman's Bay District Hospital	1/04/2015	8/04/2015	30/09/2016
	Goulburn Base Hospital	1/11/2015	8/11/2015	30/09/2016
	Moruya District Hospital	1/04/2015	8/04/2015	30/09/2016
Western NSW	Baradine Multi-Purpose Service	1/09/2015	8/09/2015	30/09/2016
	Bathurst Base Hospital	1/11/2015	8/11/2015	30/09/2016
	Blayney Multi-Purpose Service	1/11/2015	8/11/2015	30/09/2016
	Bourke Multi-Purpose Service	1/09/2015	8/09/2015	30/09/2016
	Brewarrina Multi-Purpose Service	1/09/2015	8/09/2015	30/09/2016
	Cobar District Hospital	1/11/2014	8/11/2014	30/09/2016
	Collarenebri Multi-Purpose Service	1/10/2015	8/10/2015	30/09/2016
	Coolah Multi-Purpose Service	1/03/2016	8/03/2016	30/09/2016
	Coonabarabran District Hospital	1/10/2015	8/10/2015	30/09/2016
	Coonamble Multi-Purpose Service	1/10/2015	8/10/2015	30/09/2016
	Dubbo Base Hospital	1/09/2015	8/09/2015	30/09/2016
	Dunedoo War Memorial MPS	1/03/2016	8/03/2016	30/09/2016
	Gilgandra Multi-Purpose Service	1/08/2015	8/08/2015	30/09/2016
	Lightning Ridge Multi-Purpose Service	1/10/2015	8/10/2015	30/09/2016
	Narromine District Hospital	1/08/2015	8/08/2015	30/09/2016
	Nyngan Multi-Purpose Service	1/07/2015	8/07/2015	30/09/2016
	Oberon Multi-Purpose Service	1/02/2016	8/02/2016	30/09/2016
	Orange Health Service	1/02/2016	8/02/2016	30/09/2016
	Rylstone Multi-Purpose Service	1/11/2015	8/11/2015	30/09/2016
	Walgett Multi-Purpose Service	1/10/2014	8/10/2014	30/09/2016
	Warren Multi-Purpose Service	1/08/2015	8/08/2015	30/09/2016
	Wellington Hospital	1/09/2014	8/09/2014	30/09/2016

F. EPISODE LEVEL ANALYSIS OF ICU-RELATED EPISODES FOR RURAL AND REGIONAL NSW LHDS

TABLE F.1: ALERTS FOR SIRS DURING EPISODES WITH ANY ICU INDICATION, COMPARED TO CODED SIRS BY RURAL AND REGIONAL NSW LHD

TOOL	RURAL LHD^	NO SEPSIS		ANY ICD-10 CODED SEPSIS		SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC
		NO ALERT	ANY ALERT	NO ALERT	ANY ALERT					
Adult Sepsis Pathway	**All LHDs**	**538**	**287**	**1**	**1**	**50.0**	**65.2**	**0.4**	**99.8**	**0.58 (0.09, 1.00)**
	Far West	93	40	0	0	.	69.9	0.0	100.0	.
	Southern	104	143	0	1	100.0	42.1	0.7	100.0	0.71 (0.64, 0.74)
	Western	341	104	1	0	0.0	76.6	0.0	99.7	.
Modified St. John Rule (algorithm)	**All LHDs**	**697**	**128**	**1**	**1**	**50.0**	**84.5**	**0.8**	**99.9**	**0.67 (0.18, 1.00)**
	Far West	112	21	0	0	.	84.2	0.0	100.0	.
	Southern	195	52	0	1	100.0	79.0	1.9	100.0	0.89 (0.87, 0.92)
	Western	390	55	1	0	0.0	87.6	0.0	99.7	.

**PPV=positive predictive value; NPV=negative predictive value; ^Rural & regional LHD*

TABLE F.2: ALERTS FOR SEVERE SEPSIS EPISODES WITH ANY ICU INDICATION, COMPARED TO ANY CODED SEPSIS BY RURAL AND REGIONAL NSW LHD

TOOL	RURAL LHD^	NO SEPSIS		ANY ICD-10 CODED SEPSIS		SENSITIVITY (%)	SPECIFICITY (%)	PPV* (%)	NPV* (%)	AUROC
		NO ALERT	ANY ALERT	NO ALERT	ANY ALERT					
Adult Sepsis Pathway	**All LHDs**	**643**	**128**	**24**	**32**	**57.1**	**83.4**	**20.0**	**96.4**	**0.70 (0.64, 0.77)**
	Far West	115	17	0	1	100.0	87.1	5.6	100.0	0.94 (0.91, 0.96)
	Southern	192	44	5	7	58.3	81.4	13.7	97.5	0.70 (0.55, 0.85)
	Western	336	67	19	24	55.8	83.4	26.4	94.7	0.70 (0.62, 0.77)
Modified St. John Rule (algorithm)	**All LHDs**	**632**	**139**	**26**	**30**	**53.6**	**82.0**	**17.8**	**96.1**	**0.68 (0.61, 0.75)**
	Far West	111	21	0	1	100.0	84.1	4.6	100.0	0.92 (0.89, 0.95)
	Southern	172	64	3	9	75.0	72.9	12.3	98.3	0.74 (0.61, 0.87)
	Western	349	54	23	20	46.5	86.6	27.0	93.8	0.67 (0.59, 0.74)

**PPV=positive predictive value; NPV=negative predictive value; ^Rural & regional LHD*

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