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**Implementing a quick Sequential [Sepsis-Related] Organ Failure Assessment  
sepsis screening tool: an interrupted times series study**

**Running title: Implementing qSOFA sepsis screening**

Laura Alberto<sup>1,2</sup>, Leanne M. Aitken<sup>1,3</sup>, Rachel Walker<sup>1,2,4</sup>, Fernando Pálizas<sup>5</sup>, Andrea P.  
Marshall<sup>1,2,6</sup>

<sup>1</sup> School of Nursing and Midwifery, Griffith University, Gold Coast, Queensland, Australia

<sup>2</sup> Menzies Health Institute Queensland, Griffith University, Gold Coast, Queensland,  
Australia

<sup>3</sup> School of Health Sciences, City, University of London, London, UK

<sup>4</sup> Division of Surgery, Princess Alexandra Hospital, Brisbane, Queensland, Australia

<sup>5</sup> Clínicas Bazterrica and Santa Isabel, Ciudad de Buenos Aires, Argentina

<sup>6</sup> Gold Coast University Hospital, Gold Coast Hospital and Health Service, Gold Coast,  
Queensland, Australia

Corresponding author

Laura Alberto, School of Nursing & Midwifery, Griffith University, Gold Coast Campus,  
Southport QLD 4222, Australia. Telephone: +54911 4915 8403

Email: [lauramaria.alberto@gmail.com](mailto:lauramaria.alberto@gmail.com)

## ABSTRACT

**Objective:** The aim of this study was to evaluate the outcomes of implementing a sepsis screening (SS) tool based on the quick Sequential [Sepsis-Related] Organ Failure Assessment (qSOFA) and the presence of confirmed/suspected infection. The implementation of the 6-hour (6-h) bundle was also evaluated.

**Design:** Interrupted times series with prospective data collection.

**Setting:** Five hospital wards in a developing nation, Argentina.

**Participants:** 1151 patients ( $\geq 18$  years) recruited within 24-48 hours of hospital admission.

**Intervention:** The qSOFA-based SS tool and the 6-h bundle.

**Main outcome measures:** The primary outcome was the timing of implementation of the first 6-h bundle element. Secondary outcomes were related to the adherence to the screening procedures.

**Results:** Of 1151 patients, 145 (12.6%) met the qSOFA-based SS tool criteria, among them intervention (39/64) patients received the first 6-h bundle element earlier (median 8 hours; 95% CI: 0.1-16) than baseline (48/81) patients (median 22 hours; 95% CI: 3-41); these times, however, did not differ significantly ( $p=0.525$ ). Overall, 47 (4.1%) patients had sepsis; intervention patients (18/25) received the first 6-h bundle element sooner (median 5 hours; 95% CI: 4-6) than baseline patients (15/22) did (median 12 hours; 95% CI: 0-33), however times were not significantly different ( $p=0.470$ ). While intervention patients were screened regularly, only one-third of patients that required sepsis alerts had them activated.

**Conclusion:** The implementation of the qSOFA-based SS tool resulted in early, but not significantly improved, provision of 6-h bundle care. Screening procedures were regularly conducted, but sepsis alerts rarely activated. Further research is needed to better understand implementation of sepsis care in developing settings.

Key words: implementation, qSOFA, sepsis screening, 6-h bundle, hospital ward, developing nation

## INTRODUCTION

Sepsis is a global health challenge affecting 30 million people resulting in 6-9 million deaths every year [1]. Reported mortality varies across developed and developing nations with lower rates found in Australia (18%) compared to Brazil (55%) [2, 3]. While most evidence is generated in the developed world, results are variable and with experts suggesting mortality rates are likely higher than reported [4]. However, in the last two decades, the implementation of guidelines has decreased mortality where timely treatment was provided [5, 6]. For example, studies in Brazil and Rwanda demonstrated that adherence to guidelines decreased mortality [7-9] and improved the use of evidenced based interventions [10]. Conversely, the implementation of an early resuscitation protocol for sepsis was associated with increased mortality in Zambia [11], suggesting implementation of sepsis guidelines in the developing world requires greater scrutiny.

Prompt recognition of sepsis has been acknowledged as a research priority [12, 13] and is necessary to facilitate timely implementation of treatment; however, the implementation of tools to recognise sepsis in the developing world remains under reported [14]. Therefore, the aim of this study was to evaluate the outcomes of implementing a sepsis screening (SS) tool based on the quick Sequential [Sepsis-Related] Organ Failure Assessment (qSOFA) [15], and the Surviving Sepsis Campaign (SSC) 6-hour (6-h) bundle [16] in a developing nation.

## METHODS

An interrupted times series study was conducted over a 24-week period in 2017 to evaluate the implementation of a qSOFA-based SS tool and the 6-h bundle in medical-surgical wards in a 169-bed tertiary referral hospital in Argentina, a developing nation. The study protocol was approved by Griffith University Human Research Ethics Committee and

relevant Institutional Review Boards. Individual consent was waived as the information collected was consistent with local regulation and aligned with that already collected in usual care.

## **Outcomes**

The primary outcome was the time to implement the first 6-h bundle element (any of cultures or lactate obtained, fluids, vasopressors, or antibiotics administered) after time zero. Time zero was the moment the patient met qSOFA-based SS tool criteria, which is consistent with the SSC which describes time zero as the time of presentation/triage, or the time the chart documentation indicated evidence of sepsis [17]. The primary outcome was measured in two groups of patients: those who met the qSOFA-based SS tool criteria, and those diagnosed with sepsis at discharge.

Secondary outcomes were: frequency and percentage of screenings (three times a day) completed by nurses using the qSOFA-based SS tool during patients' hospitalisation, and time to sepsis alert activation (time zero to the moment nurses requested a medical review for investigation of sepsis). Improvements in the documentation of qSOFA variables were evaluated at baseline and intervention periods.

## **Setting**

The hospital provided complex medical-surgical care, critical care and diagnostic services 24/7. Study wards comprised 55% (n=94) of hospital beds distributed over five floors. The nurse-to-patient ratio ranged from 1:3 in a 6-bed ward, to 1:6 in the larger 31-bed ward. Wards were staffed by one internal medicine specialist physician and residents. After-hours four residents were on duty supported by on-call specialist consultants. Staff had limited administrative support. The patient medical record comprised electronic health records for documenting routine reviews, treatment, and pathology, and paper-based

documents to record vital signs, medication and fluid orders. Access to computers (with slow internet connection) varied; wards had 3-5 computers shared by all professionals.

### **Sample**

Participants were adults ( $\geq 18$  years) admitted to the study wards. Exclusion criteria were: patients admitted to specialty areas, under palliation and do not resuscitate (DNR) status or existing sepsis diagnosis. Eight consecutive patients admitted to hospital in the previous 24-48 hours were recruited each day for 24 weeks. Prior to recruitment, wards were randomly ordered from first to fifth to allow for sample variation across larger and small wards. Recruitment was interrupted between weeks 12 and 13 when the intervention was introduced.

### **Intervention**

The intervention tested consisted of the qSOFA-based SS tool (Supplementary Figure 1) and the application of the 6-h bundle when a patient met the qSOFA-based SS tool criteria (Supplementary Figure 2). The screening tool, developed specifically for testing in this study, included vital signs and the source of suspected or confirmed infection or antibiotics administered. The vital signs, respiratory rate (RR), systolic blood pressure (SBP), and altered mentation (AM) were reported as per the qSOFA [18], as were common sepsis screening variables identified in a recent systematic review [14]. Listed sources of infection were based on the instrument tested by Gyang et al., and was consistent with the SSC [19, 20]. The qSOFA was selected because it demonstrated good predictive validity for in-hospital mortality in non-intensive care patients with infection [18].

Prior to implementation, the qSOFA-based SS tool and the SSC 6-h bundle were reviewed by management and bedside clinicians. The qSOFA-based SS tool was incorporated into nursing documentation workflows in a paper format. Evidence-based information about



sepsis and the intervention (Supplementary Figure 1 and 2) underpinned the education, was available for staff; all materials were in Spanish. Nurses were asked to screen for sepsis at admission, during routine observations or when they identified a change in a patient's clinical condition. If a patient scored  $\geq 2$  qSOFA points, with the presence of confirmed/suspected infection, or the patient had antibiotics administered, the nurse was directed to immediately activate a sepsis alert by calling the physician-in-charge, requesting a medical review, and documenting the alert in the screening form. Physicians were instructed to review these patients and, if required, to provide 6-h bundle care (Supplementary Figure 2) [16].

### **Data collection**

Data prospectively collected included demographics, comorbidities, use of operating room, admission to intensive care, hospital length of stay, and diagnosis at discharge. Diagnosis was informed by the Sepsis-3 criteria [15], and determined by an intensivist who reviewed the electronic health records and was blinded to the qSOFA-based SS tool assessments. Where a patient did not meet the Sepsis-3 criteria, they were classified as having an infection or other diagnosis.

Information collected to assess the primary outcome included the date and time cultures and lactate were obtained, fluids, vasopressors and antibiotics were administered, and the source of suspected/confirmed infection. If no source of infection was documented but the patient was receiving antibiotics, it was assumed clinicians suspected an infection. qSOFA variables collected during the patient's admission were recorded from the paper vital sign (RR, SBP), and electronic forms (AM). Times for these assessments were not always available owing to documentation omissions. Where the documented time was not available, the mean time of assessment was calculated from a random sample of screening forms for each of the morning, afternoon and night shifts and the relevant estimated time was used

(Supplementary Methods). The date and time the earliest qSOFA score of  $\geq 2$  documented became the time zero in patients with confirmed/suspected infection, or where antibiotics were administered. In the remaining patients the date and time of the first qSOFA score of  $\leq 1$  was considered.

To assess secondary outcomes, screening information including the number of screening procedures expected and completed, and the date and time the sepsis alerts were activated were collected from the screening forms. To evaluate improvements in documentation of the qSOFA variables, absence of documented variables was noted. Data were entered into a password protected Microsoft® Excel (version 2016) file or REDCap database.

### **Data analysis**

Following data cleaning, data accuracy was verified via review of 10% of randomly selected participant data (error rate 0.01). Median and interquartile ranges (IQR) were used to analyse continuous, non-normally distributed data, and frequencies to analyse categorical data. Patient characteristics were compared by diagnostic group using Chi-Square and Kruskal-Wallis techniques according to the type of data. The discharge diagnoses of sepsis and septic shock were grouped into one sepsis cohort.

Timing of implementation of the first 6-h bundle element was examined by Kaplan-Meier analysis for patients who met the qSOFA-based SS tool criteria and patients with sepsis diagnosis at discharge. The Log Rank test determined the statistical significance ( $p < 0.05$ ). The period considered from time zero to the first 6-h bundle element implemented was 48 hours. This time frame was a balance between what was desired and realistic given involvement of various practitioners, barriers to accessing patient information and limited administrative support. A subgroup analysis was conducted including the times of patients

who met the qSOFA-based SS tool criteria and received the first 6-h bundle element; times were examined between baseline and intervention groups using Mann-Whitney U and effect size. Patients who did not receive a 6-h bundle element during this 48-hour time-frame, were discharged or became DNR during this time, were censored.

Percentages, descriptive statistics and Statistical Process Control (SPC) were used to assess secondary outcomes. The percentage of screenings completed by nurses, was the ratio of screening assessments conducted in relation to the total number of expected procedures during admission. Time (from time zero to the alert time documented in the screening form) was presented as categories and its frequencies described. The improvement in documentation of qSOFA variables was evaluated using SPC R-Chart [21]. The number of patients with  $\geq 1$  non-documented qSOFA variables varied among subgroups and was not normally distributed. To address this limitation, 15 patients were randomly sampled per subgroup. Upper and lower control limits were then calculated using the average of subgroup ranges and the predetermined constants ( $D3=0.347$ ;  $D4=1.653$ ) [22]. This procedure provided a robust subgroup sample, greater than the minimum recommended, and contributed to the homogeneity of data points. The R-Chart was preferred because it is considered a usual SPC practice to assess variation and illustrated the spread of non-documentation practice [21]. IBM SPSS Statistics for Windows® Version 25 (IBM Corp: Armonk, NY) was used for all analyses.

## RESULTS

Among 1151 patients, 47 (4.1%) had sepsis, 413 (35.9%) had infection and 691 (60.0%) had other diagnoses at discharge (Table 1). Overall, 145 of 1151 patients met the qSOFA-based SS tool criteria; 28 of 145 were diagnosed with sepsis at discharge (Table 2); 19 of 47 with sepsis at discharge did not met the qSOFA-based SS tool criteria (Figure 1).

### **Primary outcomes**

Among patients who met the qSOFA-based SS tool criteria, 48/81 (59.3%) of baseline patients, and 39/64 (60.9%) of intervention patients received the first 6-h bundle element within 48 hours after time zero (Supplementary Table 1). Intervention patients received the first 6-h bundle element earlier (median 8 hours; 95% CI: 0.1-16) than baseline patients (median 22 hours; 95% CI: 3-41], yet the times did not differ significantly ( $p=0.525$ ) (Figure 2A). A smaller proportion (14.1%) of censored patients did not receive any element of the 6-h bundle during the intervention period when compared to baseline (25.9%) (Supplementary Table 1). The subgroup analysis of times in patients who met the qSOFA-based SS tool criteria and received the first 6-h bundle element within 48 hours of time zero (excluding censored patients), in baseline and intervention was consistent with the overall results. Times were not different (median 6 hours versus 4 hours) and represented a very low effect size ( $U=736$ ,  $z=-1.716$ ,  $p=0.086$ ,  $r=0.03$ ).

Among patients with sepsis at discharge (15 [68.2%] baseline; 18 [72.0%] intervention; Supplementary Table 2), there was a trend towards the first 6-h bundle element being applied sooner in intervention patients (median 5 hour; 95% CI: 4-6) than baseline (median 12 hours; 95% CI: 0-33), ( $p=0.470$ ) (Figure 2B). Patients with sepsis at discharge received the first 6-h bundle element sooner than those who met the qSOFA-based SS tool criteria when compared in the same periods, baseline (median 12 hours versus 22 hours) and intervention (median 5 hours versus 8 hours).

### **Secondary outcomes**

During the intervention period 506 (92.5%) patients were screened a total of 6519 times representing a median (IQR) of 70.9 (27%) of the possible times. There was variation in frequency across intervention weeks, with the first (week 13) being a median (IQR) of 64.3

(36), the highest 80.0 (30.0) in week 16, and the last of 70.7 (35.0) in week 24 (Supplementary Figure 3). Nurses activated sepsis alerts in 21/64 (32.8%) patients who met the qSOFA-based SS tool criteria, delays of  $\geq 7$  hours were observed for most patients with only five alerts communicated immediately (Supplementary Table 3).

In documentation of qSOFA variables, 722 (62.7%) patients had  $\geq 1$  non-documented qSOFA variable (Supplementary Table 4), most commonly AM (n=669; 58.1%), RR (n=171; 14.9%) and SBP (n=163; 14.2%). Analysis of non-documented qSOFA variables occurred generally within the control limits as examined via SPC R-Chart analyses (Figure 3); however, the process was not stable. Signals of instability were data points that raised above the control limits in weeks 2 and 6 (or above +3 sigma), and in weeks 14, 15, and 19 to 21 where points were below -2 sigma (equivalent to below -2 standard deviations) [23]. This cyclic pattern with erratic shifts above and below the central line suggests absence of statistical control, it is not possible to differentiate changes attributable to the intervention [24].

## DISCUSSION

Although there was a trend towards earlier implementation of the first 6-h bundle element, this did not reach statistical significance. The former 6-h bundle has recently been revised, and became the 1-h bundle [17]. The trend achieved is far behind the new standard. The low prevalence of sepsis found in the present study prevented the evaluation of effect on death.

Patients with sepsis at discharge were treated sooner than patients who met the qSOFA-based SS tool criteria. A limitation of this comparison is the overlap of patients in the sepsis group who also met the qSOFA-based SS tool criteria (Figure 1). There were also patients who did not meet the qSOFA-based SS tool criteria and yet received an element of

the 6-h bundle. This finding suggests clinical judgment was different for patients who later developed sepsis. Clinical judgment has shown to be reliable in distinguishing ward patients at risk of clinical deterioration and poor outcomes [25]. More understanding of clinical judgment in sepsis could help inform future screening strategies.

There were, however, patients who received no element of the 6-h bundle, or they did with significant delays. A quarter of patients in the baseline period and almost 15% in the intervention period met the qSOFA-based SS tool criteria but received no element of the 6-h bundle (Supplementary Table 1). These patients may have required a different treatment than that specified in the 6-h bundle, as only 28/145 patients who met the qSOFA-based SS tool criteria were diagnosed with sepsis. For a few patients diagnosed with sepsis at discharge, there was an absence or delay in treatment. It is likely, this sub-group of patients could have presented other unrecognised symptoms not explored in this study. The complexity of the cellular changes underlying sepsis make early recognition [26] of sepsis in this population challenging.

Implementation of the 6-h bundle was physician driven, yet nurses, pharmacist and pathology practitioners were also involved. Delays in its delivery may have been related to very busy staff particularly after hours. Poor implementation of the 6-h bundle was reported in low income country settings in Asia and South America [27, 28] suggesting context is an important consideration for effective implementation. Given the study wards in the Argentinean site had limited administrative support, reduced connectivity to the electronic health records and varied skill mix after-hours, it is likely physicians might have experienced competing priorities and challenges accessing patient information, which may have resulted in treatment delays. In addition, the small number of sepsis alerts activated and delays in alert activation by nurses could have influenced the implementation of the first 6-h bundle element. Similar to physicians, competing priorities may have resulted in delayed alert

activation. Further research may help to understand setting characteristics for effective implementation of sepsis screening and care.

Findings related to the improvement in the documentation of qSOFA variables are inconclusive. An important limitation in the R-Chart analysis is the lack of stability in the process during the baseline period, followed by a cyclic pattern during intervention [23]. Out of control points in baseline are explained by hospital demands. In week 2 an electronic procedure for requesting/dispensing medication was introduced, and in week 6 the annual resident physician's intake occurred. In the manufacturing industry, cyclic patterns are signals associated with changes in the environment [29]. However, having an out of control baseline process, interpretation of this signal would be speculative.

Of all the qSOFA variables, AM was most often missing. Documentation of mental status assessment is challenging [30] however, lack of documentation does not mean the patient was not assessed. It is unclear the extent to which non-documented AM can be attributed to difficulties with assessment or documentation.

Despite this study being prospective, with a large sample size, and the first of its kind in a developing nation health setting there are limitations to acknowledge. First, data collection was challenging owing to some information being unavailable in the paper and electronic patients' health records therefore some screening information may have been missed. In particular, identifying accurate times for assessment could have affected evaluation of the primary outcome. Second, hospital length of stay could not be reliably evaluated because some patients remained in hospital for non-medical reasons. Third, only the first 6-h bundle element after meeting the qSOFA-based SS tool criteria was evaluated as not all patients received all elements. Finally, it is also possible that using proven screening

tool and a different criterion to diagnose sepsis would have yielded a different outcome. The low frequency of sepsis prevented the evaluation of mortality.

Contextual details including nurse/physician-to-patient ratios, staff qualifications, non-professional and administrative support and the type of health records must be considered when planning practice change and associated research. Factors that prevent nurses from activating sepsis alerts and strategies that assist physicians provide timely treatment should also be considered. Finally, strategies that result in a sustained improvement in sepsis care in developing nation health settings and the outcomes of its use are required too.

In conclusion, in a developing nation health setting, while there was a trend towards early provision of the first 6-h bundle element in intervention patients, this change was not statistically significant. A higher percentage of screening procedures was achieved and sustained during the intervention period. Regardless, only one-third of patients who met the qSOFA-based SS tool criteria had the sepsis alert activated. Challenges to improve sepsis care in a developing nation health setting persist and require ongoing development.



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**Table 1 Patients clinical characteristics**

Clinical characteristics	Whole cohort	Sepsis	Infection	Other	p value
	n=1151	n=47	n=413	n=691	
Age, median (IQR)	69.9 (29.0)	76.4 (21.3)	72.0 (28.8)	68.4 (29.6)	0.004
Gender, n (%)					
Male	532 (46.2)	27 (57.4)	204 (49.4)	301 (43.6)	0.049
Female	619 (53.8)	20 (42.6)	209 (50.6)	(390 (56.4)	
Condition at discharge, n (%)					
Alive	1117 (97)	36 (76.6)	407 (98.5)	674 (97.5)	<0.001
Deaths excluding DNR	7 (0.6)	3 (7.9)	2 (0.5)	2 (0.3)	
DNR status					
Yes, n (%)	29 (2.5)	9 (19.1)	5 (1.2)	15 (2.2)	
Days from admission to DNR decision, median (IQR)	5.0 (7.0)	7.0 (11.0)	9.0 (11.5)	3.0 (5.0)	0.187
CCI, median (IQR)	2.0 (3.0)	3.0 (3.0)	3.0 (3.0)	2.0 (4.0)	<0.001
HLOS, median (IQR)	4.0 (4.0)	9.0 (11.0)	5.0 (4.0)	4.0 (3.0)	<0.001
Use of ICU or CCU, n (%)					
Yes,	114 (9.9)	13 (27.7)	18 (4.4)	83 (12.0)	<0.001
No	2037(90.1)	34 (72.3)	395 (95.6)	608 (88.0)	
ICU or CCU length of stay, median (IQR)	1.4 (2.0)	7.8 (7.8)	2.5 (2.2)	1.1 (1.1)	<0 .001
Use of OR, n (%)					

No use of OR	656 (57.0)	31 (66.0)	274 (66.3)	351 (50.8)	<0.001
≥1 procedure in OR	495 (43.0)	16 (34.0)	139 (33.7)	340 (49.2)	

Abbreviations: IQR, interquartile range; DNR, do not resuscitate; CCI, Charlson Comorbidity Index; HLOS, hospital length of stay; ICU, intensive care unit; CCU, coronary care unit; OR, operating room; qSOFA, quick Sequential [Sepsis-Related] Organ Failure Assessment; mmol/L, millimoles per litre; ml, millilitre.

**Table 2 Screening criteria and 6-h bundle implemented**

Screening criteria and 6-h bundle	Whole cohort	Sepsis	Infection	Other	p value
	n=1151	n=47	n=413	n=691	
Confirmed or suspected source of infection, n (%)					
No source of infection	635 (55.2)	1 (2.1)€	11 (2.7)	623 (90.2)	<0.001
1 source of infection	393 (34.1)	31 (66.0)	301 (72.9)	61 (8.8)	
≥2 sources of infection	123 (10.7)	15 (31.9)	101 (24.5)	7 (1.0)	
qSOFA, n (%)					
≥2 points	213 (18.5)	28 (59.6)	94 (22.8)	91 (13.2)	<0.001
≤1 point	938 (81.5)	19 (40.4)	319 (77.2)	600 (86.8)	
qSOFA-based sepsis screening tool criteria met, n (%)					
yes	145 (12.6)	28 (59.6)	92 (22.3)	25 (3.6)	<0.001
no	1006 (87.4)	19 (40.4)	321 (77.7)	666 (96.4)	

6-h bundle					
Antibiotics administered, n (%)					
yes	559 (48.6)	46 (97.9)	392 (94.9)	121 (17.5)	<0.001
no	592 (51.4)	1 (2.1)	21 (5.1)	570 (82.5)	
Patients with lactate obtained, n (%)					
yes	264 (22.9)	34 (72.3)	125 (30.3)	105 (15.2)	<0.001
no		13 (27.7)	288 (69.7)	586 (84.8)	
Lactate mmol/L, median (IQR)	1.8 (1.0)	1.9 (1.6)	1.7 (1.0)	1.8 (1.0)	0.153
Patients with higher lactate obtained n (%)	26 (2.3)	9 (19.1)	9 (2.2)	8 (1.2)	
Higher lactate mmol/L, median (IQR)	2.2 (3.1)	3.4 (3.3)	2.1 (1.3)	1.9 (1.5)	0.091
Patients with fluids administered, n (%)					
yes	38 (3.3)	11 (23.4)	13 (3.1)	14 (2.0)	<0.001
no	1113 (96.7)	36 (76.6)	400 (96.9)	677 (98.0)	
Amount of fluids, ml crystalloids, median (IQR)	500 (500)	500 (1000)	500 (500)	1000 (500)	0.477

Vasopressor initiated, n (%)					
yes	10 (0.9)	8 (17.0)	0 (0)	2 (0.3)	<0.001*
no	1141 (99.1)	39 (83.0)	413 (100)	689 (99.7)	
Cultures obtained, n (%)					
no cultures	626 (54.4)	2 (4.3)	56 (13.6)	568 (82.2)	<0.001
≥1 culture	525 (45.6)	45 (95.7)	357 (86.4)	123 (17.8)	
Type of Culture, n (%)					
Blood cultures ≥1	364 (31.6)	43 (91.5)	259 (62.7)	62 (9.0)	<0.001†
Urine culture ≥1	256 (22.2)	31 (66.0)	163 (39.5)	62 (9.0)	<0.001†
Other cultures ≥1	231 (20.1)	20 (42.6)	167 (40.4)	44 (6.4)	<0.001†
Culture reports, n (%)					
≥1 negative culture	428 (37.2)	39 (83.0)	281 (68.0)	108 (15.6)	<0.001*
≥1 positive culture	268 (23.3)	33 (70.2)	206 (49.9)	29 (4.2)	<0.001*
≥1 gram-negative bacteria	145 (12.6)	17 (36.2)	110 (26.6)	10 (1.4)	<0.001‡

≥1 gram-positive bacteria	75 (6.5)	11 (23.4)	46 (11.1)	5 (0.7)	<0.001‡
≥1 fungi	20 (1.7)	2 (12.8)	12 (2.9)	2 (0.3)	<0.001‡
All multiresistant bacteria ≥1 (MRSA, ESBL, KPC)	35 (3.0)	2 (4.3)	29 (7.0)	4 (0.6)	<0.001¶

Abbreviations: qSOFA, quick Sequential [Sepsis-Related] Organ Failure Assessment; IQR, interquartile range; mmol/L, millimoles per litre; ml, millilitre; MRSA, Methicillin-resistant *Staphylococcus Aureus*; ESBL, Extended-spectrum  $\beta$ -lactamases; KPC, *Klebsiella Pneumoniae* Carbapenemase.

Notes:

€ This patient did not have information related to infection or antibiotics, in the blind diagnosis was found with sepsis.

\*2 cells (33.3%) had expected count less than 5; the minimum expected count is .41.

† Chi-square calculated based on dichotomised variable ≥1 blood, urine and other culture and no culture; no culture is not reported.

\* Chi-square calculated based on dichotomised variable ≥1 positive, negative and no culture; no culture is not reported.

‡ Chi-square calculated based on dichotomised variable ≥1 microbe and no microbe; no microbe is not reported.

¶ Chi-square calculated based on dichotomised variable ≥1 multiresistant bacteria and no multiresistant bacteria; no multiresistant bacteria is not reported.

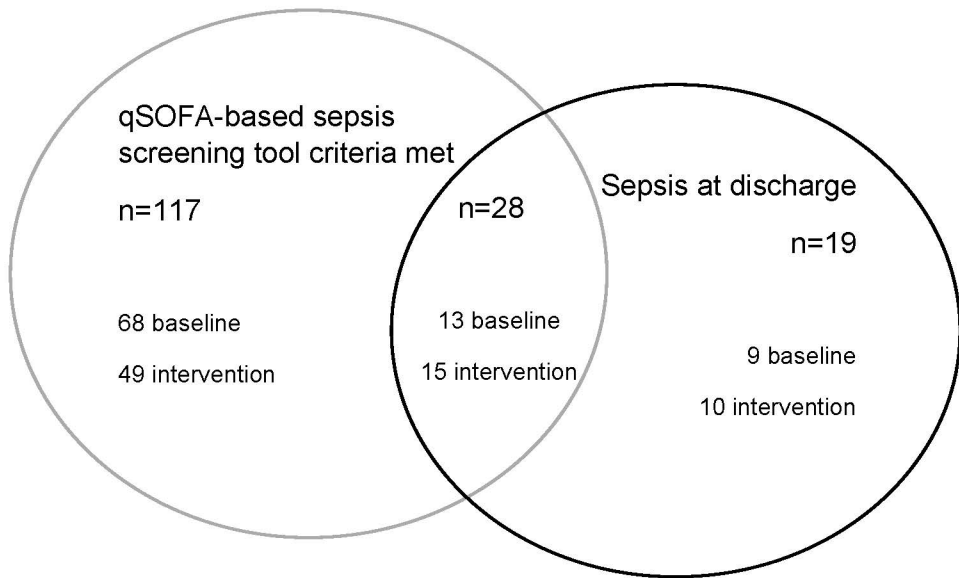


## Figure Legends

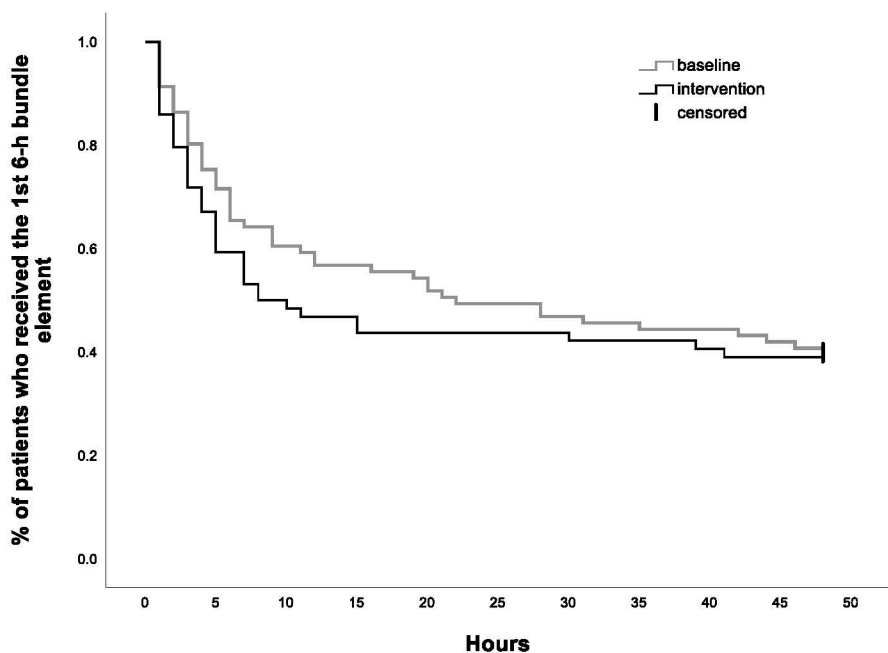
**Figure 1 Patients who met the quick Sequential [Sepsis-Related] Organ Failure Assessment based sepsis screening tool criteria and patients with sepsis diagnosis at discharge**

**Figure 2 Timing of implementation of the first 6h-bundle element in patients who met the quick Sequential [Sepsis-Related] Organ Failure Assessment sepsis screening tool criteria (A), and in patients with sepsis diagnosis at discharge (B).**

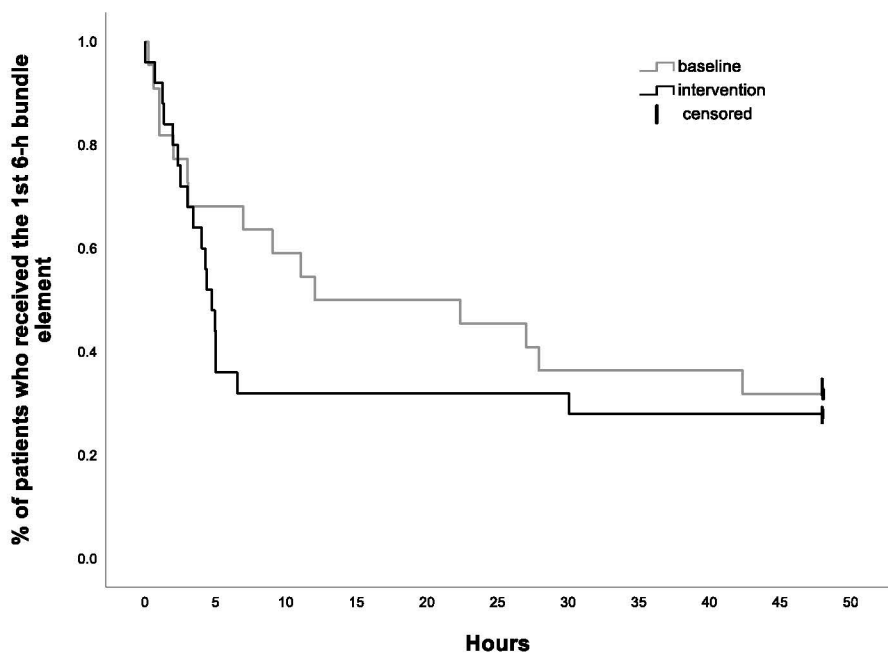
**Figure 3 Patients with  $\geq 1$  non-documented quick Sequential [Sepsis-Related] Organ Failure Assessment variable per study week**



A



B



Range of non-documented qSOFA variables

Introduction of the qSOFA-based sepsis screening tool  
and the 6-h bundle

UCL = 15.09

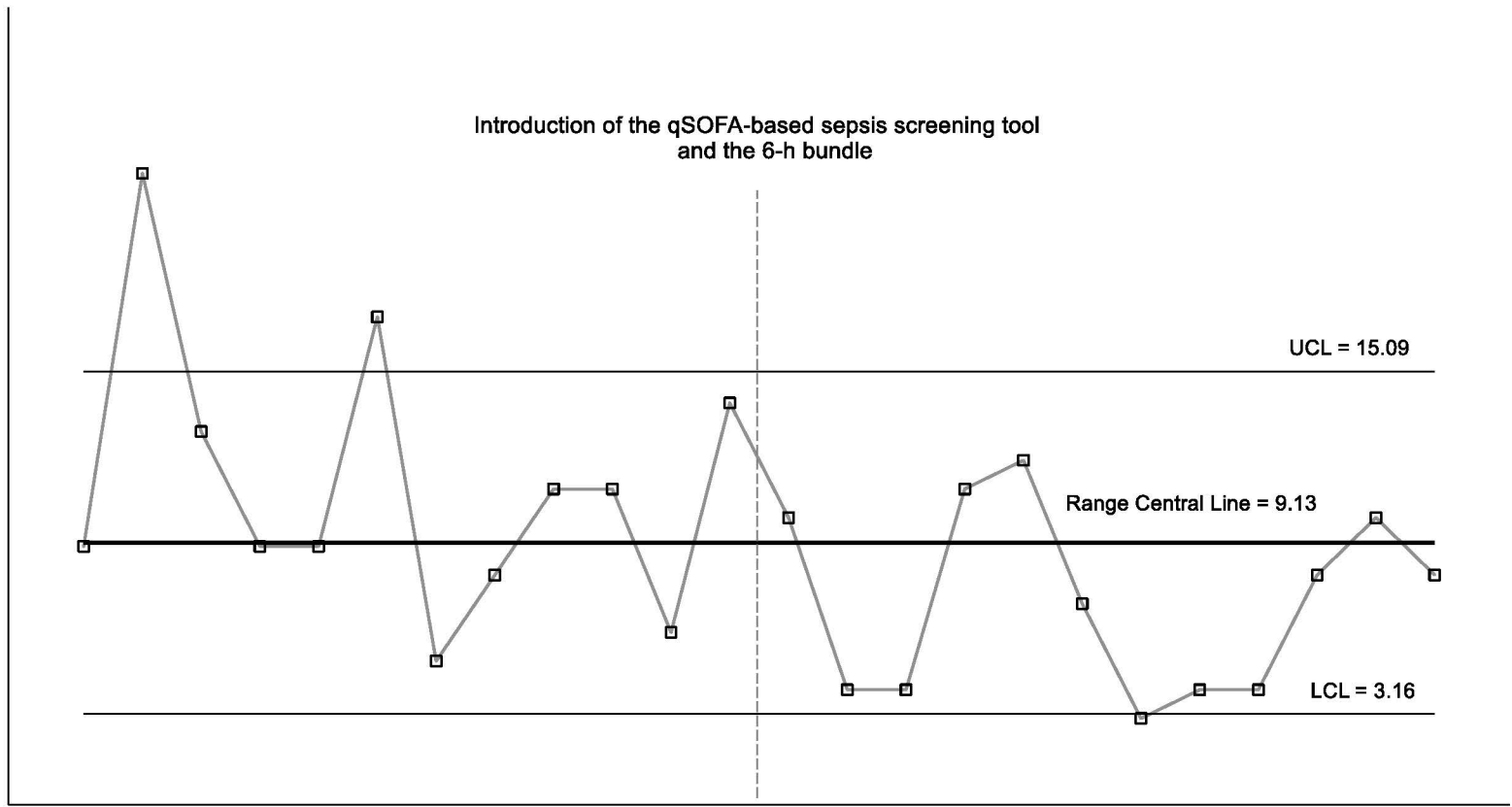
Range Central Line = 9.13

LCL = 3.16

Sigma level: 3

Week 1 Week 2 Week 3 Week 4 Week 5 Week 6 Week 7 Week 8 Week 9 Week 10 Week 11 Week 12 Week 13 Week 14 Week 15 Week 16 Week 17 Week 18 Week 19 Week 20 Week 21 Week 22 Week 23 Week 24

25  
20  
15  
10  
5  
0



## **Online-only supplementary Data**

### **Supplementary Methods**

**Supplementary Figure 1 Sepsis screening and assessment form**

**Supplementary Figure 2 Sepsis screening and care poster**

**Supplementary Table 1 First 6-h bundle element implemented up to 48 hours of time zero and reasons for censoring in patients that met the qSOFA-based sepsis screening tool criteria**

**Supplementary Table 2 First 6-h bundle element implemented up to 48 hours of time zero and reasons for censoring in patient with sepsis diagnosis at discharge**

**Supplementary Figure 3 Adoption of the quick Sequential [Sepsis-related] Organ Failure Assessment sepsis screening tool per study week during intervention**

**Supplementary Table 3 Time to sepsis alert activation in intervention patients**

**Supplementary Table 4 Patients with  $\geq 1$  non-documented quick Sequential [sepsis-Related] Organ Failure Assessment (qSOFA) variable per study week**

## Supplementary Methods

A respiratory rate (RR) of  $\geq 22$ /min and systolic blood pressure (SBP) of  $\leq 100$ mmHg were considered positive; altered mentation (AM) scored positively when the patient had a documented sudden change in consciousness with a 2-point decrease in their Glasgow Coma Scale score, demonstrated disorientation to person, space or time; somnolence, confusion or agitation. Because of omissions in paper-based documentation, the time of RR and SBP observations were not always available, and the electronic record did not provide the time of AM assessment. To address this inconsistency, times were defined using a random sample of screening forms that indicated times of RR, AM and SBP assessed during the intervention, and then applied to baseline and intervention quick Sequential [Sepsis-related] Organ Failure Assessment data. Among intervention patients with screening forms (n=506), 134 (26.5%) screening forms were randomly selected. The selected forms provided a total of 936 times of screening procedures documented by nurses, 251 from the morning shifts, 289 from the afternoon shifts and 396 from the night shifts. The average (Range) time the screening procedures were conducted in each nursing shift were: 8:06 (7:00 – 10:00) in the morning, 13:57 (13:00 – 16:00) in the afternoon, and 20:47 (20:00 – 23:00) in the nights. These times reflected routine observation times.

### Supplementary Figure 1 Sepsis Screening and assessment form

English



## Sepsis screening and assessment

Patient name:

Age:

Admission number:

Bed number:

Diagnosis:

Mental status at admission:

[illegible]

\* A sudden change in consciousness with a drop of 2 Glasgow Coma Scale points OR disorientation to person OR space OR time, OR somnolence OR confusion OR agitation. Consider the change in relation to the last time the patient was assessed.

\*\* If the patient presents  $\geq 2$  qSOFA points plus a confirmed or suspected infection or ATBs administered, the screening is positive, tick “yes”. Report to the physician in charge immediately.

Note: Routine observations were once per nursing shift after handover, there were three nursing shifts in 24hrs, three screening procedures were expected per day.



Spanish



## Registro de screening para sepsis

Nombre del paciente:

Edad: \_\_\_\_\_ Número Admisión: \_\_\_\_\_ Habitación/cama: \_\_\_\_\_

Diagnóstico:

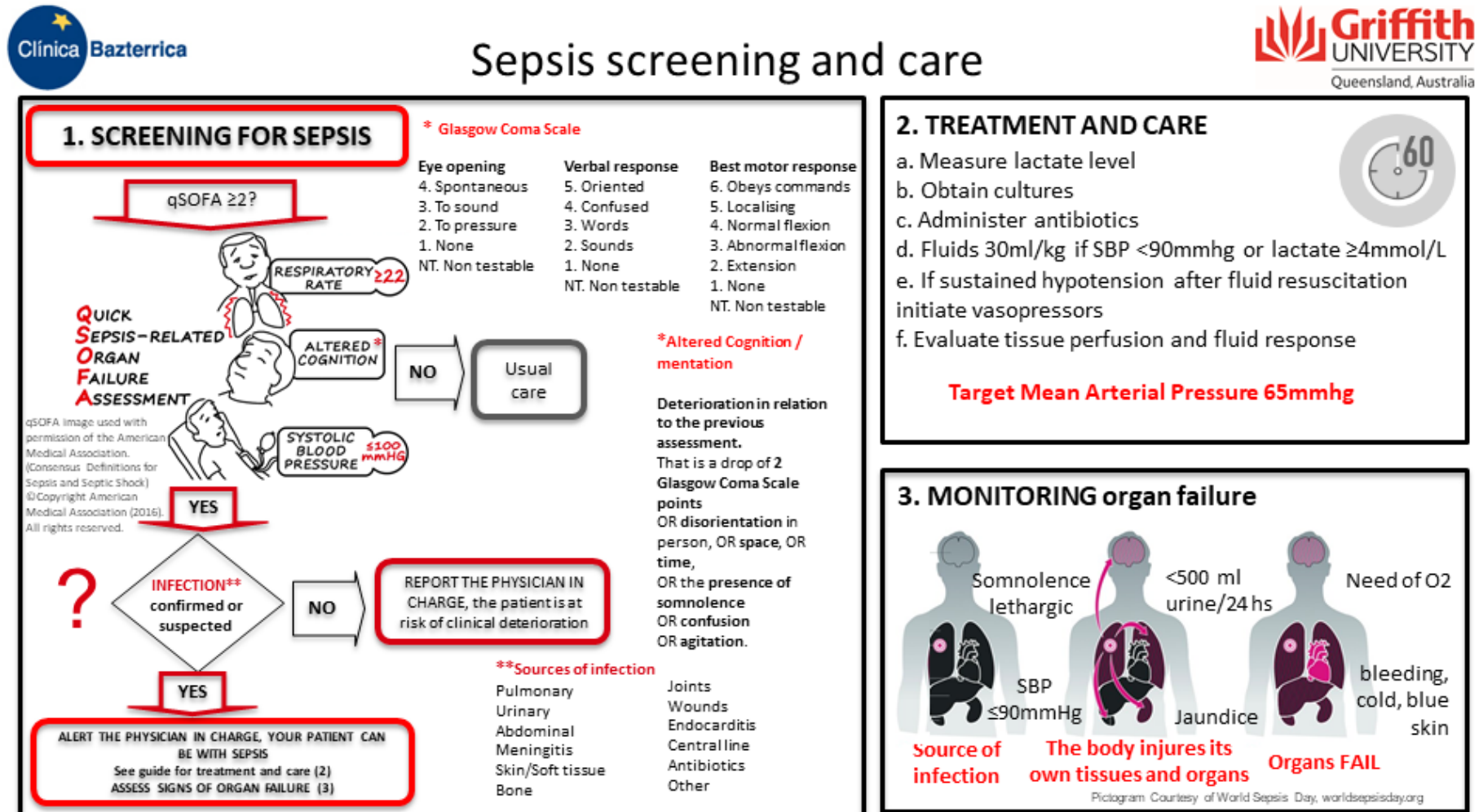
[illegible]

\* Caída de 2 puntos de Escala de Coma Glasgow O desorientación en espacio O tiempo O persona, O presenta somnolencia O confusión O excitación. Considere el deterioro respecto de la última vez que el paciente fue valorado.

\*\* Si el paciente presenta  $\geq 2$  puntos qSOFA + fuente confirmada O sospechada de infección O recibe ATB, el screening es positivo, marcar "si". Llamar inmediatamente al médico.

Supplementary Figure 2 Sepsis screening and care poster

English

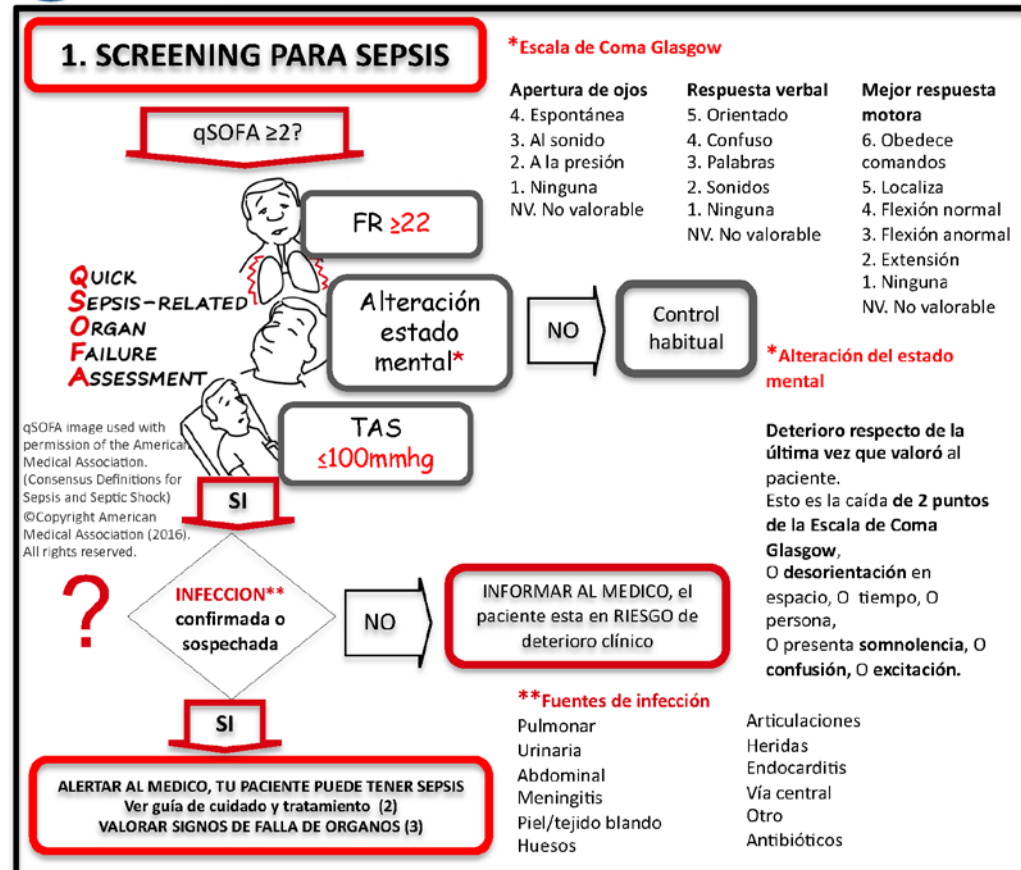


Note: Senior nurses, physicians and the researchers delivered education in the form of face to face sessions / lectures and ward rounding to all staff including bedside nurses, head nurses and all physicians. Several education activities were conducted for a period of 2-weeks to reach all staff, but additional support was provided throughout the duration of the study. All new staff was exposed to the intervention content upon their arrival.

Spanish



## Screening y cuidado de la sepsis



**2. CUIDADO Y TRATAMIENTO**

a. Medir ácido láctico

b. Obtener cultivos

c. Administrar ATB

d. Fluidos 30 ml/kg si TAS  $< 90$ mmhg  
o ácido láctico  $\geq 4$ mmol/L **TAM Objetivo: 65mmhg**

e. Si persiste hipotensión después de reanimación con líquidos, iniciar vasopresores

f. Evaluar perfusión tisular y respuesta a fluidos

**3. MONITOREO de falla de organos**

Somnolencia letargia

$< 500$  ml orina/24 hs

necesidad O2

sangrado, piel fría, azulada

TAS  $\leq 90$ mmHg

Ictericia

**Foco de infección**

**El cuerpo ataca propios organos**

**Los órganos fallan**

**Supplementary Table 1** First 6-h bundle element implemented up to 48 hours of time zero and reasons for censoring in patients that met the qSOFA-based sepsis screening tool criteria

6-h bundle and reasons for censoring	qSOFA-based sepsis screening tool criteria met n=145	
	Baseline n (%)	Intervention n (%)
First 6-h bundle element implemented up to 48 hours of time zero	48 (59.3)	39 (60.9)
Cultures	20	17
Antibiotics	15	12
Lactate	11	7
Fluids	1	3
Vasopressor	1	0
No 6-h bundle element implemented*	21 (25.9)	9 (14.1)
First 6-h bundle implemented after 48 hours of time zero*	3 (3.7)	7 (10.9)
Discharge before 48 hours*	6 (7.4)	2 (3.1)
DNR before 48 hours*	3 (3.7)	7 (10.9)
Total	81 (100)	64 (100)

Abbreviation: qSOFA, quick Sequential [Sepsis-Related] Organ Failure Assessment; DNR, do not resuscitate

Notes: \*Censored

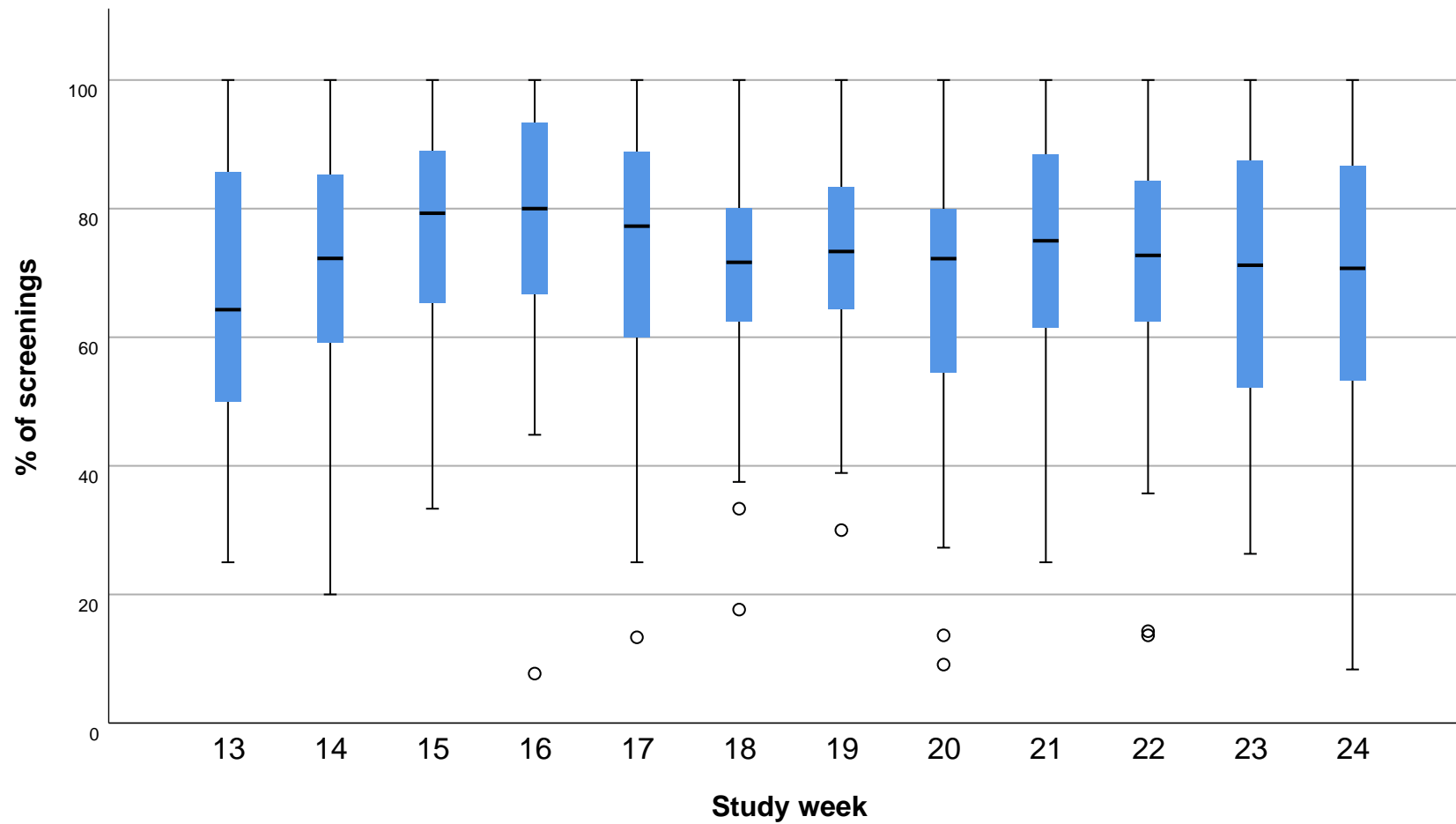
**Supplementary Table 2** First 6-h bundle element implemented up to 48 hours of time zero and reasons for censoring in patient with sepsis diagnosis at discharge

6-h bundle and reasons for censoring	Patients with sepsis diagnosis at discharge n=47	
	Baseline n (%)	Intervention n (%)
First 6-h bundle element implemented up to 48 hours of time zero	15 (68.2)	18 (72.0)
Cultures	6	8
Antibiotics	6	4
Lactate	2	3
Fluids	0	3
Vasopressor	1	0
No 6-h bundle element implemented*	2 (9.1)	2 (8.0)
First 6-h bundle implemented after 48 hours of time zero*	2 (9.1)	2 (8.0)
Discharge before 48 hours*	-	-
DNR before 48 hours*	3 (13.6)	3 (12.0)
Total	22 (100)	25 (100)

Abbreviation: qSOFA, quick Sequential [Sepsis-Related] Organ Failure Assessment; DNR, do not resuscitate

Notes: \*Censored

**Supplementary Figure 3** Adoption of the quick Sequential [Sepsis-related] Organ Failure Assessment sepsis screening tool per study week during intervention



Box plots represent median (IQR).

**Supplementary Table 3** Time to sepsis alert activation in intervention patients

Number of screenings and time	Cohort n=506	Sepsis n=25	Infection n=195	Others n=286	p value
Number of screenings conducted per patient, median (IQR)	10 (9)	14 (17)	10 (10)	9 (9)	0.001
Sepsis alerts, n	21	11	6	4	
Time zero to sepsis alert, n					
Immediate	5	2	2	1	
1 hour	1			1	
2 hours	4	3	1		
4 hours	1	1			
5 hours	2	2			
6 hours	1		1		
≥7 hours	7	3	2	5	

Note: Only screenings from 506 of 547 are presented, no data about screening procedures was collected from 41 patients; most of them were recruited in week 13, the first week after the introduction of the intervention.



**Supplementary Table 4** Patients with  $\geq 1$  non-documented quick Sequential [sepsis-Related] Organ Failure Assessment (qSOFA) variable per study week

Study week	Whole cohort n=1151 n	Patients with $\geq 1$ non-documented qSOFA variable n=722 n (%)	non-documented qSOFA variable Median (IQR)
Week 1	56	31 (55)	2 (3)
Week 2	50	19 (38)	2 (5)
Week 3	54	34 (63)	3 (3)
Week 4	54	38 (70)	3 (3)
Week 5	49	31 (63)	2 (3)
Week 6	35	24 (69)	3 (5)
Week 7	43	33 (77)	2 (3)
Week 8	65	35 (54)	2 (3)
Week 9	49	33 (67)	3 (5)
Week 10	56	41 (73)	2 (3)
Week 11	48	33 (69)	2 (3)
Week 12	45	35 (78)	2 (2)
Week 13	49	31 (63)	2 (3)
Week 14	49	31 (63)	1 (1)
Week 15	41	27 (66)	1 (1)
Week 16	41	18 (44)	2 (1)
Week 17	41	25 (61)	2 (2)
Week 18	46	27 (59)	2 (2)
Week 19	46	28 (61)	2 (2)
Week 20	59	37 (63)	2 (2)
Week 21	41	28 (68)	2 (2)
Week 22	44	28 (64)	3 (2)
Week 23	36	26 (72)	2 (3)
Week 24	54	29 (54)	1 (2)

Note: qSOFA variable is count information either documented or non-documented