# Mortality Changes Associated with Mandated Public Reporting for Sepsis: The Results of the New York State Initiative

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All aspects of the New York State Sepsis Initiative were paid for by the New York State Department of Health. Investigator support was provided by grants (R35GM119519, to Dr. Seymour; and K08 GM115859, to Dr.Prescott) from the National Institutes of Health, by a grant (11-109 13-079, to Dr. Iwashyna) from the Veterans Affairs Health Services Research and Development Investigator-Initiated Research program (VA HSR&D IIR 13-079), and by IPRO (to Mr. Phillips). The views expressed in this article are those of the authors and do not necessarily represent the view of the U.S. government or the Department of Veterans Affairs.



**Impact of this Research:** Mandated public reporting of compliance with performance measures and outcomes are now common on a state-wide and national basis. This study demonstrates the association between state-wide mandated public reporting of compliance with sepsis performance measures and outcomes, improving care and decreasing mortality.

Subject Category: 4.12

Word Count: 3237

At a Glance Commentary: The New York State initiative was the first mandated public reporting initiative for sepsis, and it has been followed by similar initiatives by the U.S. Centers for Medicare and Medicaid Services (CMS) and other states. However, there remains limited and mixed data on the impact of mandated public reporting programs generally, and in particular, for sepsis. This study reports on the protocol initiation, 3-hour and 6-hour sepsis bundle completion, and risk-adjusted hospital mortality among adult patients with severe sepsis and septic shock over a two year period after implementation of the New York State initiative. The study adds important insights into the role mandated reporting may play in driving clinician behavior.

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

Abstract:

**Rationale**: In 2013, the New York State Department of Health (NYSDOH) began a mandatory, state-wide initiative to improve early recognition and treatment of severe sepsis and septic shock.

**Objectives:** This study examines protocol initiation, 3-hour and 6-hour sepsis bundle completion, and risk-adjusted hospital mortality among adult patients with severe sepsis and septic shock.

**Methods:** Cohort analysis of all patients from all 185 hospitals in New York State, reported to the NYSDOH from April 1, 2014 to June 30, 2016

**Participants:** 113,380 cases were submitted to NYSDOH of which 91,357 hospitalizations from 183 hospitals met study inclusion criteria. .

**Interventions:** NYSDOH required all hospitals to submit and follow evidenced-informed protocols (including elements of 3- and 6-hour sepsis bundles—lactate measurement, early blood cultures and antibiotic administration, fluids and vasopressors) for early identification and treatment of severe sepsis or septic shock (5).

**Measurements and main results:** Compliance with elements of the sepsis bundles and risk-adjusted mortality. Of 91,357 patients, 74,293 (81.3%) had the sepsis protocol intitiated. Among these individuals, 3-hour bundle compliance increased from 53.4% to 64.7% during the study period ($p < 0.001$)), while among those eligible for the 6-hour bundle ($n = 35,307$) compliance increased from 23.9% to 30.8% ($p < 0.001$). Risk-adjusted mortality decreased from 28.8% to 24.4% ($p < 0.001$) in patients among whom a sepsis protocol was initiated. Greater hospital compliance with 3-hour and 6-hour bundles was associated with shorter length of stay and lower risk and reliability-adjusted mortality.

**Conclusions:** New York's statewide initiative increased compliance with sepsis-performance measures. Risk-adjusted sepsis mortality decreased during the initiative and was associated with increased hospital-level compliance.

Abstract Word Count: 266

Key Words: Sepsis, Performance Improvement, Quality, Implementation science

Introduction

Sepsis is a common, lethal, and costly illness (1-4). In 2013, New York State Department of Health (NYSDOH) began a state-wide initiative to improve the early recognition and treatment of patients with severe sepsis and septic shock (5). It was motivated in part by the tragic case in 2012 of Rory Staunton, a previously healthy adolescent, who died of septic shock. The regulations required all hospitals in the state to develop, and submit for review and approval by the department, 'evidence informed' protocols to recognize and treat patients with severe sepsis and septic shock. Reporting of patient specific data to NYSDOH to evaluate sepsis process and mortality outcomes began April 1, 2014. Neither financial penalties nor incentives were associated with the program.

Over the past 30 years, there has been substantial growth in performance measurement and public reporting programs in healthcare. These approaches are intended to improve in healthcare quality and cost-effectiveness (6,7). However, there is substantial uncertainty regarding the effectiveness of these approaches and—for sepsis care—it was explicitly decried as premature by some (8). The efficacy of many of the common components of early sepsis therapy remained disputed (8-10). Concerns centered around medical effectiveness of bundle elements, potential unintended consequences, and uncertainty if hospital policies would translate into sustained meaningful outcome improvements (5-7). Unintended negative consequences for patients of such state interventions have been documented, including the unnecessary administration of antibiotics to patients who are not infected, the development of

antibiotic resistence, distraction of care from other disease states and important bedside activities, and ultimately protocol and metric fatigue (10-12).

Therefore, we sought to evaluate the initial 2 years of Rory's Regulations, as these NYSDOH initiatives came to be called in the popular press. As part of the evaluation we asked: to what extent and when were the newly instituted sepsis protocols activated? How did this change over the early life of the program and between hospitals? Were the changes in protocolized behavior associated with changes in risk-adjusted inpatient mortality among sepsis patients included in the protocol and, in comparison, among patients not included in the protocol?

Some of the results of these studies have been previously reported in the form of an abstract (16).

## Methods

*New York Sepsis Regulation*

The New York State (NYS) sepsis initiative originated with the New York State Executive Office in collaboration with the NYS Department of Health (NYSDOH). NYSDOH sought input from expert clinicians, hospital association representatives, the state's Quality Improvement Organization (IPRO) (17), and peer-reviewed literature to inform the new sepsis regulations. In early 2013, NYSDOH issued amendments to existing public health regulations requiring hospitals to submit and follow evidenced-informed protocols for early identification and treatment of severe sepsis or septic shock

(5). While protocols could be tailored to specific hospitals, they were required to include both of the following:

- 3-hour bundle: administration of antibiotics within 3 hours of patient identification, drawing blood cultures before administering those antibiotics, and measuring of blood lactate levels within 3 hours;
- 6-hour bundle: for patients with hypotension (systolic blood pressure < 90 mm Hg) or lactate ≥ 4 mmol/l the administration of a 30 cc/Kg bolus, vasopressors for refractory hypotension and remeasurement of lactate within 6 hours of bundle initiation.

Hospitals varied in their sepsis identification strategies; institutional triggers for sepsis protocol initiation included: i.) sepsis screening by clinical assessment only, ii.) clinical screening and abnormal labs (i.e., serum lactate, white blood cell count), iii.) clinical screening and a "code sepsis or rapid response" iv) Assessement for SIRS criteria indicators (**Appendix Table 2**). Regardless of identification strategy, all cases identified had severe sepsis or septic shock. The regulations permitted hospitals to have flexibility in case identification in order to facilitate broader adoption.

***Reporting of sepsis cases***

Because the initiative was introduced in 2013, the recommended criteria for prospectively identifying severe sepsis and septic shock were based on the 2003 consensus sepsis definitions ("Sepsis 2") (18), not the Third International Consensus definitions ("Sepsis 3") (19). Hospitals submitted the data on sepsis cases quarterly through a secure, online portal. To promote accurate data collection and reporting, a

*Data Dictionary for Severe Sepsis and Septic Shock* was provided to hospitals (20). Hospital Chief Executive Officers and Chief Medical Officers were also required by the state to confirm compliance and institutional support for the hospital protocol and regulatory requirements.

### *Patients*

Patients were reported from 185 hospitals in New York State between April 1, 2014 and June 30, 2016 (**Appendix Figure 1**). Patients excluded *a priori* were those with advanced directives that limited treatment with sepsis care interventions in hospital protocols, all inter-hospital transfers, and those who declined interventions. For patients with multiple eligible sepsis hospitalizations, each hospitalization was included.

While there was no required method for identifying severe sepsis and septic shock cases, NYSDOH strongly encouraged hospitals to use both clinical and administrative data, as well as prospective and retrospective approaches, to ensure complete reporting. Moreover, NYSDOH took several additional approaches to encourage complete reporting. First, NYSDOH screened the state-wide discharge database to assess under-reporting. Hospitals were notified of potential missed cases identified in the discharge database, and were provided the opportunity to review and submit these cases as appropriate. Secondly, IPRO nurse reviewers audited a 10% random sample of all submitted cases each quarter to assess the accuracy of reported variables. Hospitals received quarterly feedback on each relevant measure compared to statewide averages, as well as their performance trends over time. Percent protocol

initiation and raw mortality percents were also tracked and presented to hospitals quarterly.

***Statistical Analysis***

Hospital and patient characteristics are presented as frequencies and percentages for categorical variables while median and the interquartile range (IQR) for continuous variables. To assess variability across hospitals during the initiative, multi-level logistic regression models with patients nested within hospitals were used to estimate the probability and reliability-adjusted percent of protocol initiation. Based on these percents, hospitals were then categorized by quartiles. Multi-level models were also used to rank hospital's compliance with 3-hour and 6-hour sepsis treatment bundles. We compared the temporal trends in protocol initiation, bundle compliance among patients with a sepsis protocol initiated, and risk-adjusted in-hospital mortality over the study period using maximum likelihood logistic regression with a robust standard error clustering on patient. Fractional polynomials were used to determine whether changes over time were linear in the logit. Mortality was adjusted for illness severity using a multivariable logistic regression model incorporating patient data from the first full year of the NYSDOH initiative. This model was developed, elsewhere, to evaluate New York State hospital performance. The model is described in **Appendix Table 3**, as well as in a separate paper describing the model development and validation (21). The final risk adjustment model had an area under the receiver operater characteristic (ROC) curve (C statistic) of 0.77 in internal validation data.

We used separate multivariable logistic regression models to examine the association between (1) protocol initiation, (2) 3-hour bundle compliance, (3) 6-hour bundle compliance, and (4) individual bundle elements (first serum lactate reported within 3 hours, blood cultures obtained prior to antibiotics, broad spectrum antibiotics within 3 hours, completion of intravenous fluids for patients with hypotension or elevated serum lactate within 6 hours, vasopressors given for refractory hypotension within 6 hours, and serum lactate re-ordered if missing or elevated lactate within 6 hours) with in-hospital mortality. We calculated adjusted odds ratios for in-hospital mortality by study month, by protocol initiation, by bundle compliance, and by individual bundle elements. Because hospitals were required to report bundle compliance for only those patients with a sepsis protocol initiated, analyses of bundle compliance are restricted to patients with a sepsis protocol initiated.

Institutional Review Board approval (exemption) was obtained by NYSDOH. All analyses were run using Stata 14.2 (StataCorp, College Station, TX). *P*-values less than or equal to 0.05 were considered statistically significant. Analyses were conducted by independent statisticians at The Ohio State University in order to minimize risks of bias by interests of NYSDOH. This manuscript was prepared for publication utilizing the SQUIRE 2.0 guidelines for reporting quality improvement (22).



## Results

### *Patient characteristics*

Of 113,380 severe sepsis and septic shock cases submitted to NYSDOH from all 185 non-federal hospitals in NYS during the study period, 91,357 hospitalizations from

183 hospitals met study inclusion criteria (**Appendix Figure 1**). Of these, 47,778 (52.3%) had severe sepsis, and 43,579 (47.7%) had septic shock (**Table 1**). Median age was 71 years, and the most common sites of infection were respiratory, urinary, and gastrointestinal. 22.8%, 26.6%, and 30.3% received mechanical ventilation within 6, 12, and 24 hours of protocol initiation. In-hospital mortality was 26.7%. In bivariate analyses, patients who died were older (median age 75 vs. 70 years, $p < 0.001$) had more co-morbid disease and were less likely to have a sepsis protocol initiated in the ED (57.0% vs. 66.6%, $p < 0.001$). Patient characteristics by sepsis identification strategy are presented in **Appendix Table 2.** The proportion of patients with septic shock and mechanical ventilation prior to protocol initiation were stable across the study period (**Appendix Figures 5 and 7**), as were mean initial lactate and co-morbidity burden (**Appendix Figures 6 and 7**).

***Sepsis Protocol Initiation***

During the study period, 74,293 (81.3%) sepsis cases had a sepsis protocol initiated. (Patient characteristics by protocol initaiton status are reported in **Appendix Table 4**.) The percent of cases with a protocol initiated increased from 74% to 86% over the course of the study (**Appendix Figure 2**). Sepsis protocol initiation varied from less than 20% to nearly 100% across hospitals (Appendix **Figure 3**), and was 90.4% at the median hospital. Among cases with a protocol initiated, about 80% were initiated in the emergency department (ED), 10% were initiated in a hospital ward and 10% were inititated in an intensive care unit (ICU) (**Appendix Figure 4**). Hospitals with a higher percentage of protocol initiation were more likely to be non-profit, teaching facilities,

located in metropolitan areas, with a higher number of certified beds (**Appendix Table 5**). An analysis of patient-level data revealed that there were similarities amongst patient characteriistics across the 4 quartiles of protocol initiation. (Appendix Table 6).

***Sepsis Bundle Compliance***

Among 74,293 cases with a sepsis protocol initiated, overall compliance (all elegible elements completed) with the 3-hour and 6-hour sepsis bundles increased over the study period by 0.43%/month (95% confidence interval (CI) 0.37 – 0.49, p < 0.001) and 0.54%/month (95% CI 0.49 – 0.58, p < 0.001), respectively (**Figure 1**). 3-hour bundle compliance increased from 53.4% to 64.7% (p < 0.001), while among 35,307 hypotensive (and therefore eligible) patients, 6-hour bundle compliance increased from 23.9% to 30.8% (p < 0.001). These are standardized difference of the means equal to 7.98 and 3.69 for the 3-hour and the 6-hour bundle, respectively. Compliance with individual elements in the 3-hour and 6-hour bundles also improved over time (**Appendix Figure 8**).

***In-hospital mortality***

Among cases with a sepsis protocol initiated, risk-adjusted absolute mortality declined from 28.8% to 24.4% (p < 0.001), and decreased by 0.168%/month (95% CI 0.167 – 0.169, p < 0.001) over the course of the study. This is a standardized difference of the risk adjusted means equal to -8.67. Odds of in-hospital mortality declined by 1.1% each month in patients with a sepsis protocol initiated (N=74,293, odds ratio (OR) = 0.989 per additional month, p < 0.001, 95% CI 0.987 – 0.992), while odds of in-

hospital mortality were stable in patients without a sepsis protocol initiated (N =17,064, OR = 1.00 per additional month, p = 0.25, 95% CI 1.00 – 1.01) (**Figure 3**, **Appendix Figure 9**, **Appendix Figure 10, Appendix Table 7**). Overall risk adjusted hospital mortality in the entire population (both with and without a protocol initiated) also decreased over time, by 1% per month (OR = 0.991, 95% CI: 0.989 – 0.994, p < 0.001) (**Appendix Figure 11**).

***Association between sepsis bundle compliance and mortality***

Hospitals with greater 3-hour and 6-hour compliance had lower risk-adjusted mortality and median hospital length of stay (LOS), p < 0.001 for each comparision (**Table 2**). For example, hospitals in the lowest quartile of 3-hour bundle compliance had a risk-adjusted mortality of 29.8%, compared to 23.5% risk-adjusted mortality in hospitals in the highest quartile of 3-hour bundle compliance.

Completion of individual bundle elements (including administration of fluids) were each associated with reduced odds of in-hospital mortality, with the exception of vasopressors for refractory hypotension (**Appendix Table 8**). Risk-adjusted mortality decreased by 5% (OR = 0.95, p < 0.001, 95% CI: 0.94 – 0.96) and 6% (OR = 0.94, p < 0.001, 95% CI: 0.93 – 0.95) for each 10% increase in hospital compliance with the 3-hour and 6-hour sepsis bundles, respectively (**Appendix Table 9**).



**Discussion**

New York State introduced regulations (“Rory’s Regulations”) in 2013 to improve state-wide sepsis care. The regulations mandated the development and implementation

of sepsis protocols in each hospital, as well as the reporting of patient-level treatment and outcomes. In this study, we examined New York's experience during the first 2 years of the ongoing initiative. Results of the initiative have also been reported on the NYSDOH website. However, the public report—designed for hospital administrators and public at large—provides just unadjusted aggregate results and each hospital's quintile ranking for protocol initiation, 3-hour bundle compliance, and 6-hour bundle compliance. By contrast, we examined aggregate trends in risk-adjusted hospital mortality over the first 27 months of the initiative, and the relationship between bundle compliance and outcomes. A study focused on patients in this database admitted thorugh the emergency department who had completion of the 3-hour bundle was also recently published (23).

During the first 27 months of Rory's Regulations, there was substantial—but not universal—implementation of sepsis protocols, with increasing compliance across the first two years of the program. Patients treated under the protocol experienced a risk-adjusted 4.4% absolute (15% relative) reduction in risk-adjusted mortality over the study period, which correlated with the improved bundle compliance at the hospital-level. All comers (patients with and without a sepsis protocol initiated) experienced a 3.6% absolute (12.2% relative) reduction in risk-adjusted mortality over the study period.

While we cannot prove that the improvement in risk-adjusted mortality among sepsis patient was a direct result of the regulations, there is reason to believe that this may be the case. First, there were aggregate increases in protocol initiation, 3- and 6-hour bundle completion, and individual bundle element completion over the study period, all of which were correlated with improved outcomes at the patient and hospital

level (except vasopressors for refractory hypotension, which we suspect is more strongly confounded by indication). Second, there was a drop in *risk-adjusted* mortality, suggesting that the improvements were not merely the result of stage migration or changes in coding that may confound sepsis trends measured in administrative data. Rather—in addition to finding a decline in risk-adjusted mortality—we found no evidence that less severely ill patients were increasingly identified over the study period, as median lactate, proportion with septic shock, and proportion with mechanical ventilation prior to protocol initiation remained stable (**Appendix Figures 5-7**).

It is important to consider the context of New York's sepsis regulations when assessing their implementation and outcomes. On the one hand, there were no formal financial incentives associated with New York's regulations. However, the regulations garnered substantial public attention, including commentary from the governor and coverage in the *New York Times (24)*. They also came at the same time that multiple advocacy groups and the U.S. Centers for Medicare and Medicaid Services (CMS) were particularly active in their efforts to increase public awareness of sepsis care (25-27). Public calls to professionalism and the attention of state leaders may be powerful drivers of quality improvement in sepsis care, perhaps complementing public reporting and financial incentive approaches, and a model that could potentially serve as a blueprint to implement similar strategies in other states.

While protocol initiation, bundle completion, and risk adjusted mortality all improved over the first 27 months of the initiative, implementation was not perfect. While all hospitals had a state-approved sepsis protocol in place with a structure for audit and

feedback, many did not achieve 100% initiation of the protocol and, even after 2 years, fully one-third of patients were not receiving the minimum package of blood cultures, antibiotics, and serum lactate measurement as quickly as desired. This emphasizes the important implementation gaps that remain to achieve standardization of care (28).

Strengths of our study include the evaluation of a first-in-the-nation, focused effort to improve sepsis care via an innovative state-wide mechanism, where we can measure both implementation and patient-related outcomes. Furthermore, NYSDOH's detailed audits provide quality control on both case ascertainment and individual data elements. Further strengths include our ability to conduct detailed physiologic risk-adjustment as a result of the detailed patient-level data collection, limiting bias from stage migration.

The study has several limitations. First, as with the evaluation of most quality improvement iniatives, it is difficult to prove a casual relationship between the intervention and reduced mortality from sepsis. As this was a broad, state-wide, mandated initiative, randomized assignment of interventions at a hospital-level did not occur. Second, the methods used by individual hospitals to identify sepsis patients varied, and there was no mechanism for centralized case finding nor adjudication. As such, the effects here represent the effects on sepsis-as-recognized across the state in an array of hospitals, not sepsis according to the standard of select efficacy trials. This is an extension of the widely understood efficacy / effectiveness trade-off in planning clinical trials. At the outset of the state-wide initiative, hospitals were given flexibility to develop their own protocols for guiding the interventions included in the 3- and 6-hour bundle; attempting to disentangle which triggers work best for which hospitals was

beyond the scope of this project given confounding by other unmeasured hospital processes. Third, a potential limitation of this design is that we cannot distinguish the general effects of knowing that a hospital will be monitored for public reporting with specific effects of the hospital protocols. This might seem to leave the study vulnerable to the so-called "Hawthorne" effect. However, in contrast, we believe the increased attention to sepsis patients caused by public reporting is a desired part of the mechanism of Rory's Regulations, not an unintended side-effect to be minimized; an analysis that removed such an effect would inappropriately underestimate the public health effect of the Regulations. Fourth, there were limits in the data accuracy for chart documentation of timing. This is consistent with the clinical reality of the gap between identifying a sepsis patient, intitiating treatment, and timing of documentation in the clinical record. In particular, we could not evaluate the impact of care on patients who did not have sepsis or, if they had sepsis, it was never recognized. Fifth, because complete data collection was not required for patients in whom a protocol was not initiated, compliance with the 3 and 6 hour bundle could not be determined in these patients. Lastly, we could not evaluate whether there were spill-over effects, either positive (because of streamlining care for a common condition) or negative (in that the care of sepsis patients might have distracted from the care of other patients).

In conclusion, this study reports the results of the New York State initiative for sepsis, which demonstrates improved care for patients with sepsis as evidenced by increased compliance with performance metrics and decreased risk-adjusted mortality over the first 2 years of the ongoing initiative. A state-wide initiative using regulations and non-financial incentives appears to have substantially changed care.

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**Table 1: Patient demographics and clinical characteristics by in-hospital mortality**

| Characteristic | Alive [N = 66,941] | | Died [N = 24,416] | | Total [N = 91,357] | | *p*-value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Median age, (IQR) | 70 | (58-81) | 75 | (63-85) | 71 | (59-82) | < 0.001 |
| Gender | | | | | | | |
| Male | 34,396 | 51.4 | 12,628 | 51.7 | 47,024 | 51.5 | 0.357 |
| Race | | | | | | | |
| White | 42,792 | 63.9 | 15,487 | 63.4 | 58,279 | 63.8 | |
| Black | 12,188 | 18.2 | 4,648 | 19.0 | 16,836 | 18.4 | |
| Native American | 121 | 0.2 | 36 | 0.1 | 157 | 0.2 | |
| Asian | 2,499 | 3.7 | 936 | 3.8 | 3,435 | 3.8 | 0.004 |
| Pacific Islander | 94 | 0.1 | 29 | 0.1 | 123 | 0.1 | |
| Multi-racial | 1,351 | 2.0 | 546 | 2.2 | 1,897 | 2.1 | |
| Other | 7,896 | 11.8 | 2,734 | 11.2 | 10,630 | 11.6 | |
| Ethnicity | | | | | | | |
| Spanich/Hispanic origin | 7,395 | 11.0 | 2,353 | 9.6 | 9,748 | 10.7 | |
| Not Spanich/Hispanic | 52,570 | 78.5 | 19,239 | 78.8 | 71,809 | 78.6 | < 0.001 |
| Unknown | 6,955 | 10.4 | 2,815 | 11.5 | 9,770 | 10.7 | |
| Multi-ethnic | 21 | 0.0 | 9 | 0.0 | 30 | 0.0 | |
| Protocol initiated | 54,658 | 81.7 | 19,635 | 80.4 | 74,293 | 81.3 | < 0.001 |
| Place of protocol initiation | | | | | | | |
| No | 12,283 | 18.3 | 4,781 | 19.6 | 17,064 | 18.7 | |
| ER | 44,566 | 66.6 | 13,908 | 57.0 | 58,474 | 64.0 | < 0.001 |
| Floor | 5,960 | 8.9 | 2,730 | 11.2 | 8,690 | 9.5 | |
| ICU | 4,132 | 6.2 | 2,997 | 12.3 | 7,129 | 7.8 | |
| Type of sepsis | | | | | | | |
| Severe sepsis | 40,461 | 60.4 | 7,317 | 30.0 | 47,778 | 52.3 | < 0.001 |
| Septic shock | 26,480 | 39.6 | 17,099 | 70.0 | 43,579 | 47.7 | |
| Site of infection | | | | | | | |
| Urinary | 18,643 | 27.8 | 3,603 | 14.8 | 22,246 | 24.4 | |
| Respiratiratory | 24,307 | 36.3 | 10,979 | 45.0 | 35,286 | 38.6 | |
| Gastrointestinal | 7,547 | 11.3 | 3,323 | 13.6 | 10,870 | 11.9 | |
| Skin | 4,952 | 7.4 | 1,171 | 4.8 | 6,123 | 6.7 | < 0.001 |
| Central Nervous System | 363 | 0.5 | 91 | 0.4 | 454 | 0.5 | |
| Other | 5,608 | 8.4 | 2,157 | 8.8 | 7,765 | 8.5 | |
| Unknown | 5,521 | 8.2 | 3,092 | 12.7 | 8,613 | 9.4 | |
| Mechancial ventilation prior to protocol initiation | 5,299 | 7.9 | 4,165 | 17.1 | 9,464 | 10.4 | < 0.001 |
| Thrombocytopenia | 13,659 | 20.4 | 7,013 | 28.7 | 20,672 | 22.6 | < 0.001 |
| Bandemia | 16,661 | 24.9 | 7,080 | 29.0 | 23,741 | 26.0 | < 0.001 |
| Lower respiratory infection | 29,863 | 44.6 | 13,846 | 56.7 | 43,709 | 47.8 | < 0.001 |
| Altered mental status | 26,579 | 39.7 | 13,822 | 56.6 | 40,401 | 44.2 | < 0.001 |

| Characteristic | Alive [N = 66,941] | | Died [N = 24,416] | | Total [N = 91,357] | | *p*-value |
|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | |
| Admitted to ICU | 37,695 | 56.3 | 19,038 | 78.0 | 56,733 | 62.1 | < 0.001 |
| Chronic respiratory failure | 7,000 | 10.5 | 4,272 | 17.5 | 11,272 | 12.3 | < 0.001 |
| AIDS/HIV diesease | 1,698 | 2.5 | 541 | 2.2 | 2,239 | 2.5 | 0.006 |
| Metastatic cancer | 6,001 | 9.0 | 4,023 | 16.5 | 10,024 | 11.0 | < 0.001 |
| Lymphoma/leukemia/Multipe Myeloma | 2,950 | 4.4 | 1,785 | 7.3 | 4,735 | 5.2 | < 0.001 |
| Immune modifying medications | 11,154 | 16.7 | 5,051 | 20.7 | 16,205 | 17.7 | < 0.001 |
| Congestive heart failure | 13,684 | 20.4 | 6,809 | 27.9 | 20,493 | 22.4 | < 0.001 |
| Chronic renal failure | 6,866 | 10.3 | 3,818 | 15.6 | 10,684 | 11.7 | < 0.001 |
| Chronic liver disease | 3,534 | 5.3 | 2,607 | 10.7 | 6,141 | 6.7 | < 0.001 |
| Diabetes | 24,670 | 36.9 | 8,647 | 35.4 | 33,317 | 36.5 | < 0.001 |
| Organ transplant | 1,387 | 2.1 | 586 | 2.4 | 1,973 | 2.2 | 0.003 |
| Median number of comorbidities, (IQR) | 2 | (1-3) | 3 | (2-4) | 2 | (1-4) | < 0.001 |

**Table 2: Patient outcomes by hospital quartile of compliance with the 3-hour and the 6-hour bundles**

| **Quartiles of 3-hour bundle compliance**** | **1st Lowest** | **2nd** | **3rd** | **4th Highest** | ***p*-value†** |
|---|---|---|---|---|---|
| Patients, N | 18,915 | 19,634 | 17,232 | 18,512 | |
| Risk adjusted hospital mortality, % (95% CI) | 29.8 (29.2 – 30.4) | 26.2 (25.6 – 26.8) | 25.9 (25.3 – 26.5) | 23.5 (22.9 – 24.1) | < 0.001 |
| Median hospital LOS in days for those that survived (IQR) | 11.0 (6.6 – 19.3) | 10.7 (6.2 – 18.9) | 9.7 (5.9 – 16.7) | 8.3 (5.2 – 14.0) | < 0.001 |
| **Quartiles of 6-hour bundle compliance **** | | | | | |
| Patients, N | 19,038 | 18,377 | 18,441 | 18,437 | |
| Risk adjusted hospital mortality, % (95% CI) | 28.4 (27.8 – 29.0) | 27.7 (27.1 – 28.3) | 25.9 (25.3 – 26.4) | 23.4 (22.9 – 24.0) | < 0.001 |
| Median hospital LOS in days for those that survived (IQR) | 10.3 (6.2 – 18.0) | 10.8 (6.3 – 19.0) | 9.2 (5.7 – 16.0) | 9.0 (5.4 – 15.7) | < 0.001 |

**The quartiles of probability of bundle compliance are based on two individual unadjusted random-effects logistic regression models where hospital is the random term. Only patients with a sepsis protocol initiated were included in the model (N=72,293)

†Risk adjusted hospital mortality is based on chi-square test of trend and hospital LOS is based on the nonparametric equality-of-medians test.

## Figure legends

**Figure 1: Compliance with the 3-hour bundle and the 6-hour bundle over time**

The regression lines for bundle compliance are based on individual unadjusted logistic regression models with time entered as a square root expression (3-hour model) and a quadratic expression (6-hour model). Using the 27 monthly observations, 3-hour bundle compliance and 6-hour bundle compliance increase 0.43%/month (95% CI: 0.37% – 0.49%, p-value < 0.001) and 0.54%/month (95% CI: 0.49% – 0.58%, p-value < 0.001), respectively.

**Figure 2: Change in risk adjusted mortality over time.**

Time is entered into the risk adjusted hospital mortality model as a linear expression. Using the 27 monthly observations, risk adjusted mortality decreases 0.17%/month (95% CI: 0.167 – 0.169), p-values < 0.001).

**Figure 3: Risk adjusted hospital mortality over time by protocol initiation status.**

Risk-adjusted mortality improved in patients with a sepsis protocol initiated throughout the study period, but was stable for patients without a protocol initiated. The difference in mortality between patients treated with and without a sepsis protocol first became significant (p = 0.019) during the 3rd month of the study

Figure 1: **Compliance with the 3-hour bundle and the 6-hour bundle over time**

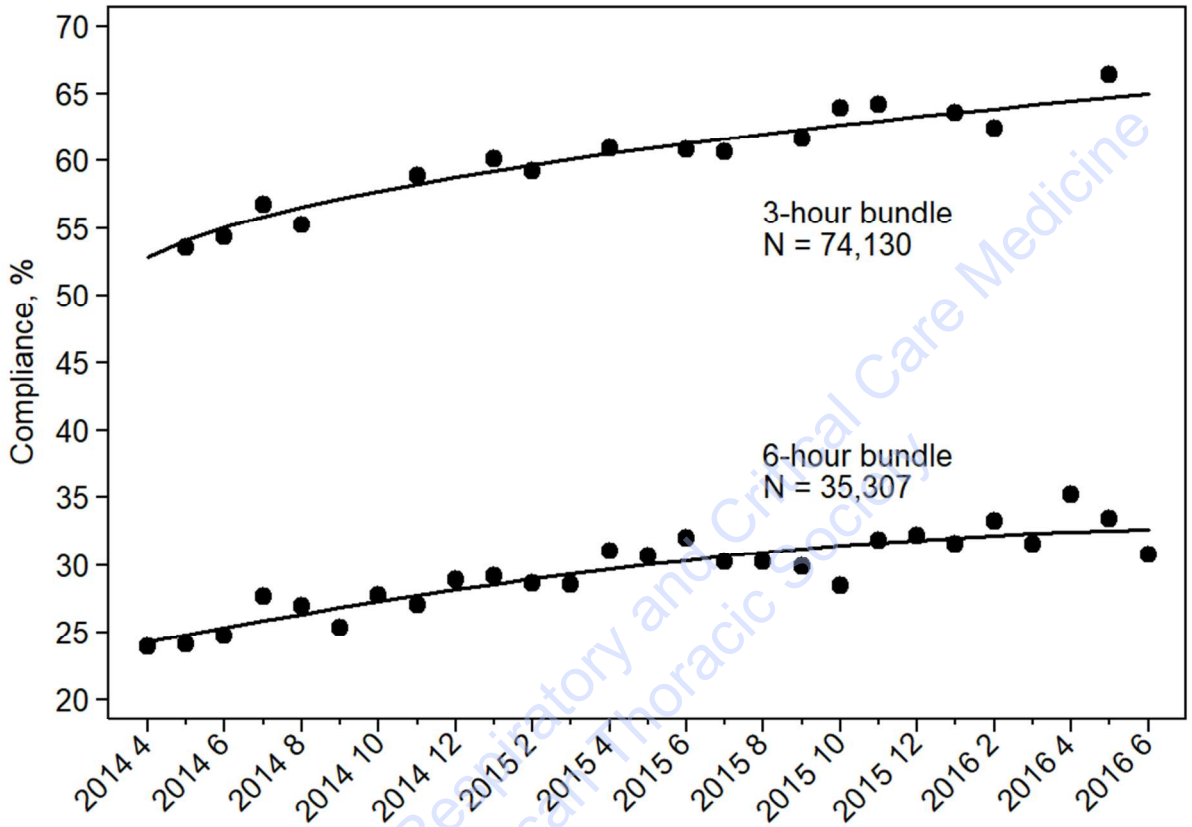


Figure 2: **Change in risk adjusted mortality over time.**

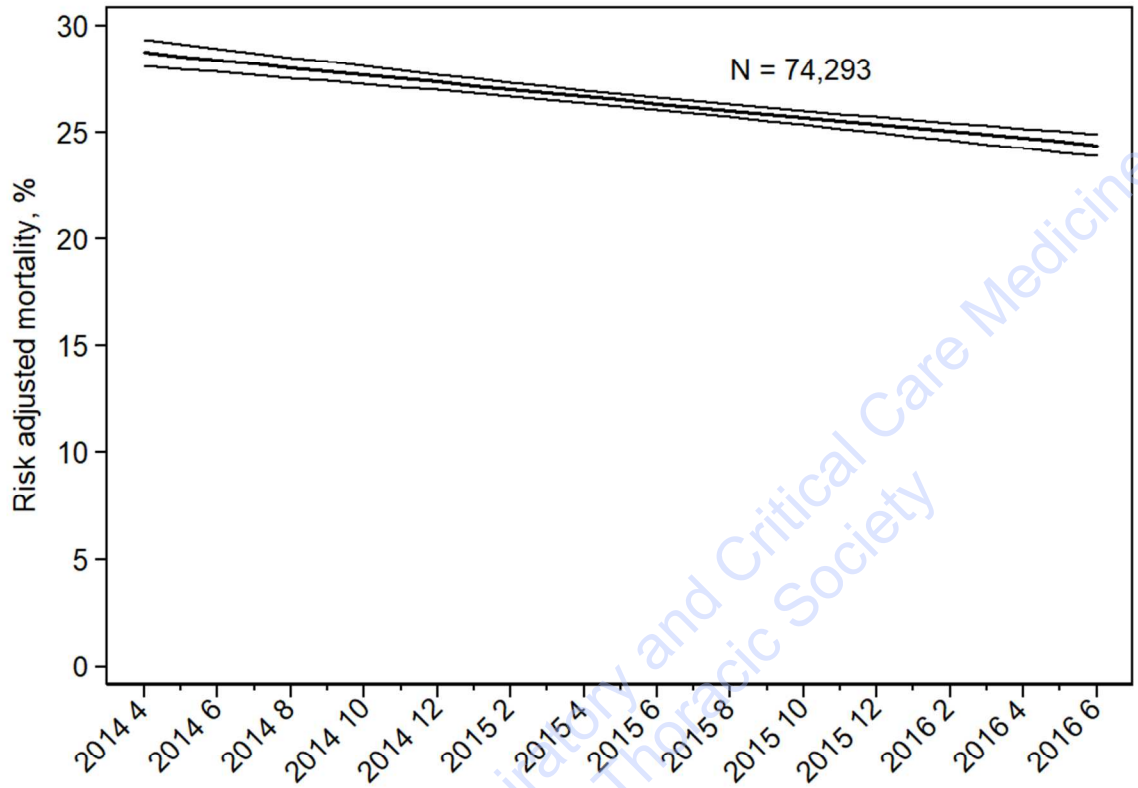
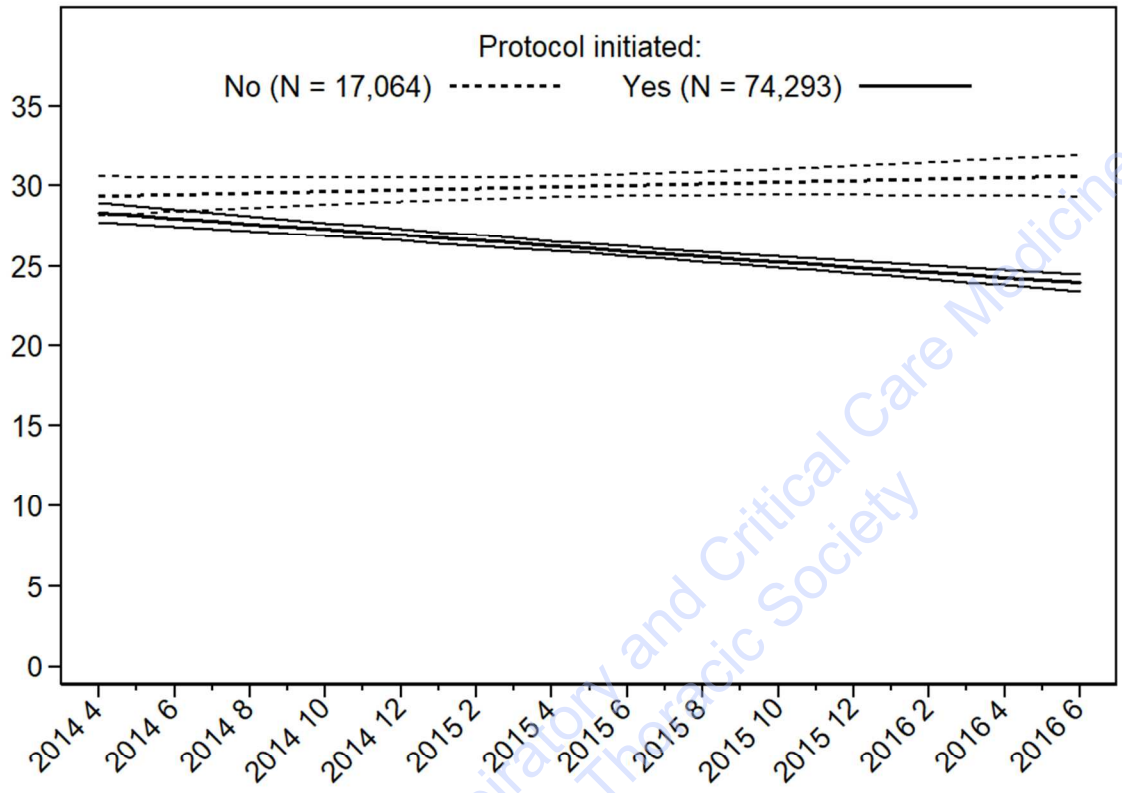
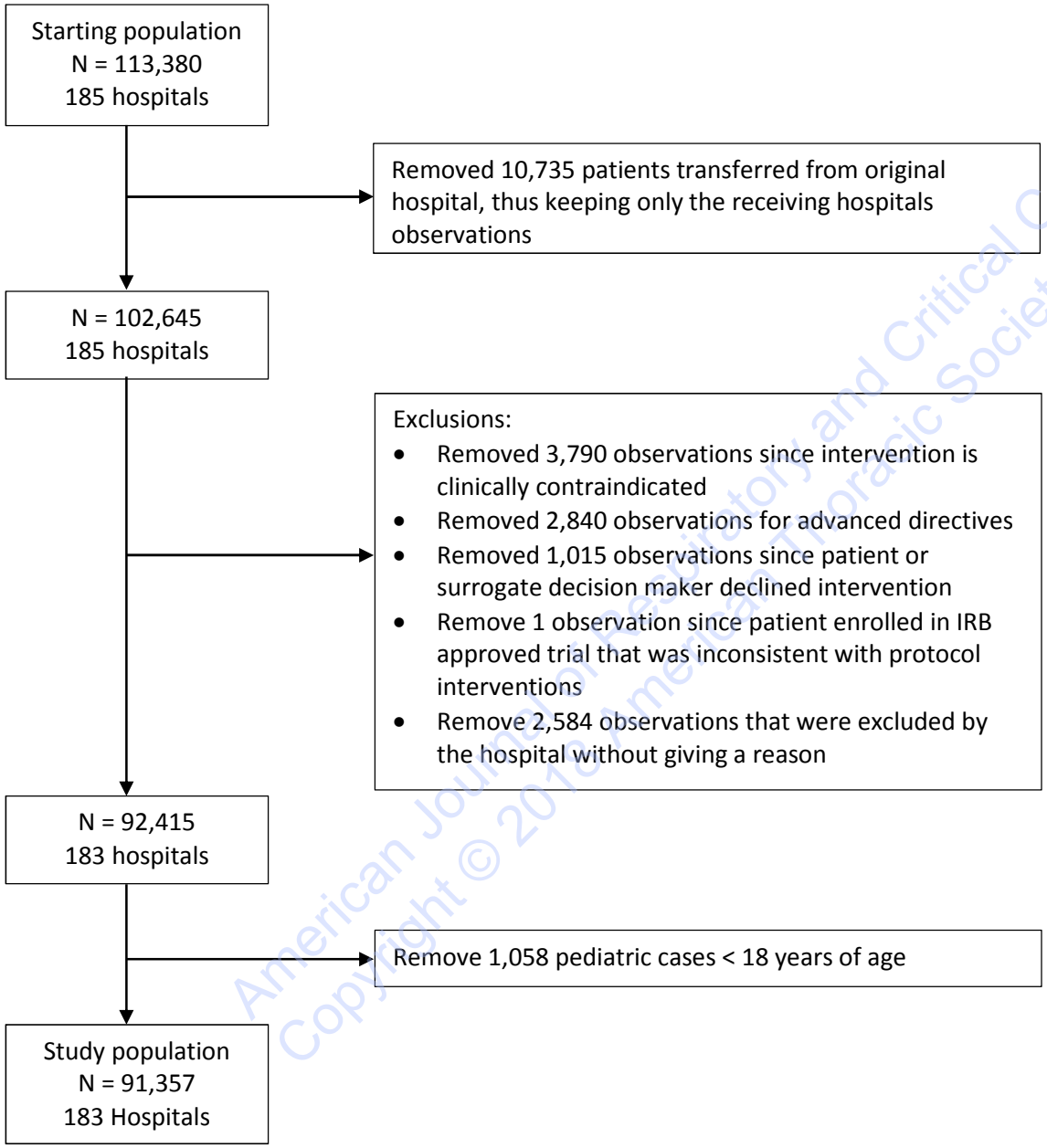


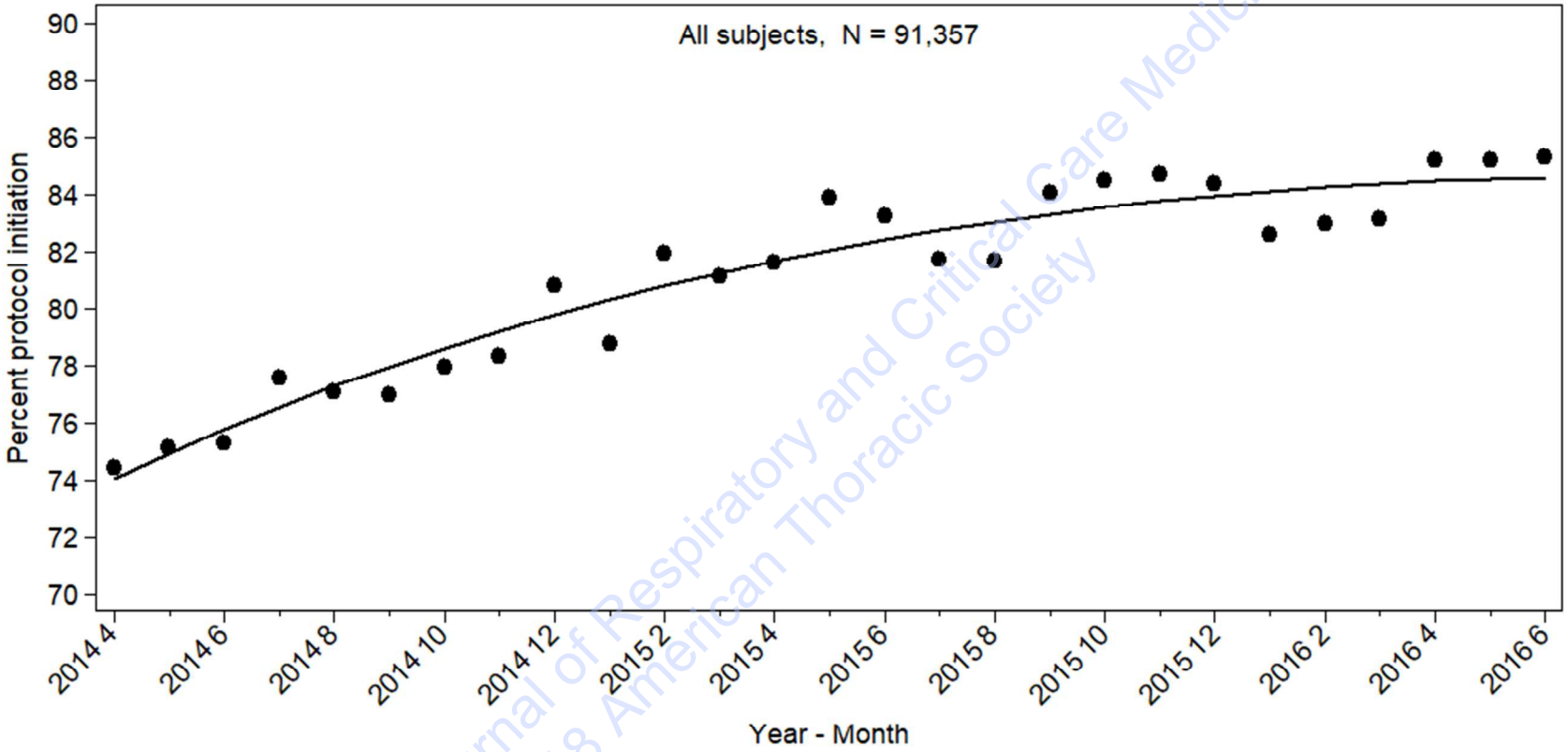
Figure 3: **Risk adjusted hospital mortality over time by protocol initiation status.**



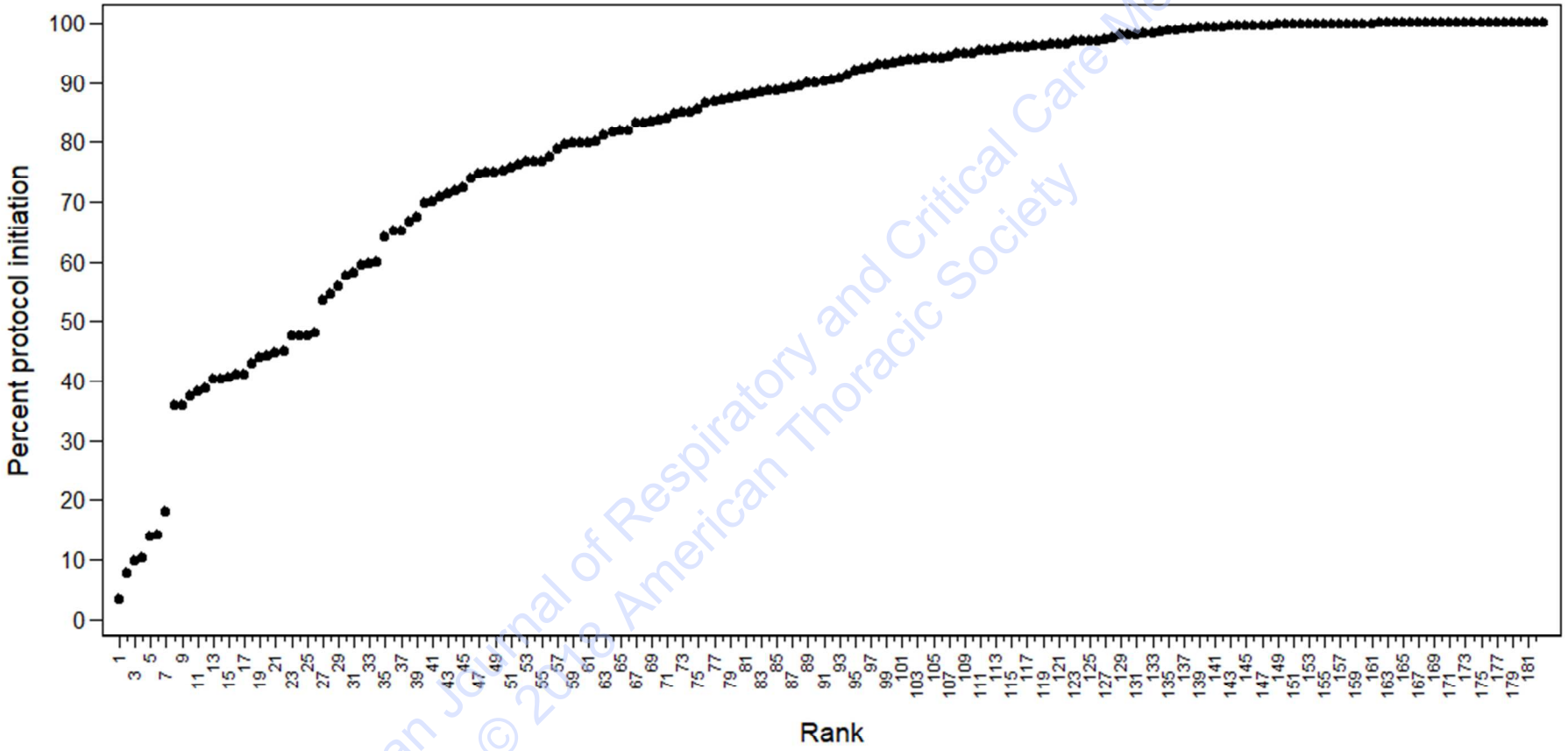
**Appendix Figure 1: Consort Diagram**



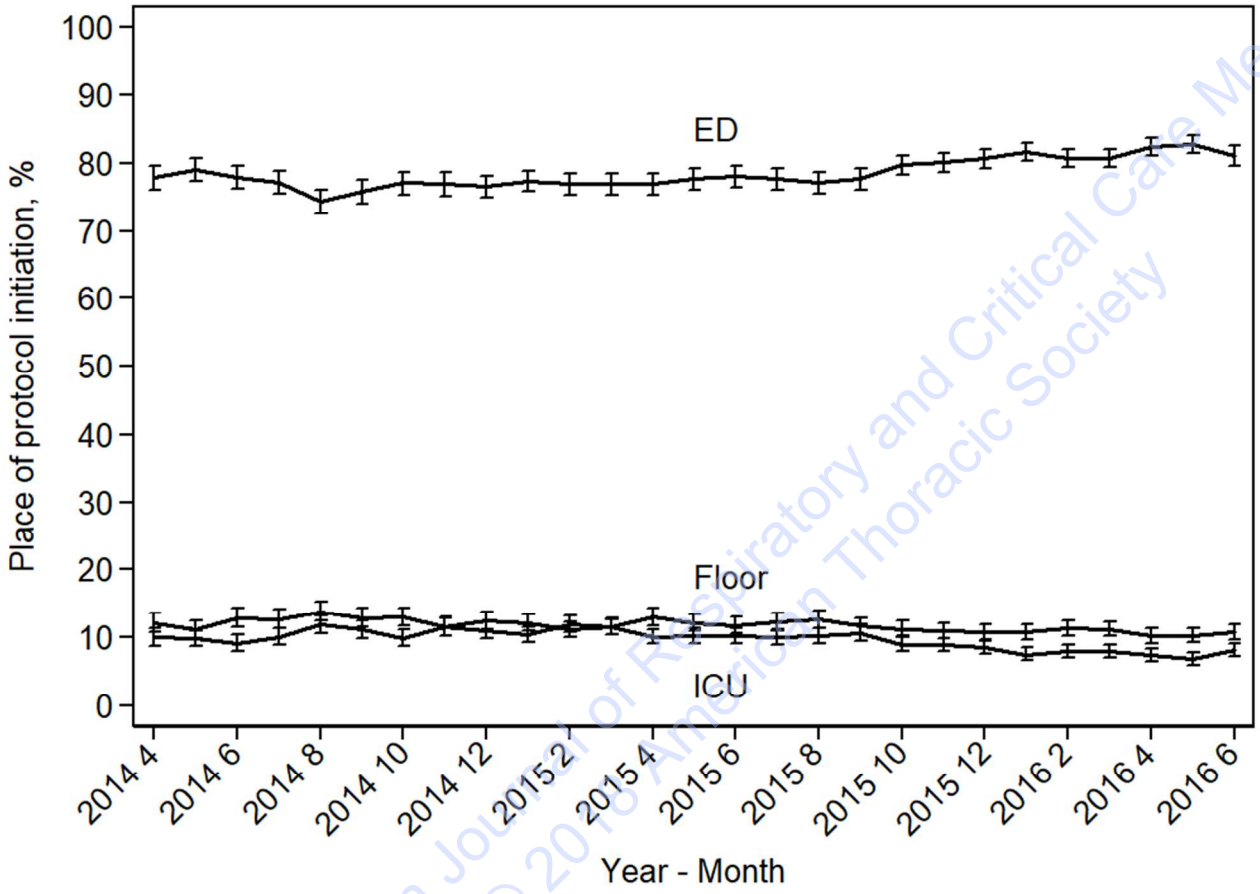
**Appendix Figure 2: Percent protocol initiation during the study period where the circles are the actual values. The line is based on an unadjusted logistic regression model where month is entered into the model as a quadratic expression**



**Appendix Figure 3: This figure depicts the wide variation in the percent of protocol initiation (April 2014 through June 2016) for 183 hospitals, based on a reliability-adjusted random-effects logistic regression model. The median ranked hospital had a 90.4% percent of protocol initiation.**

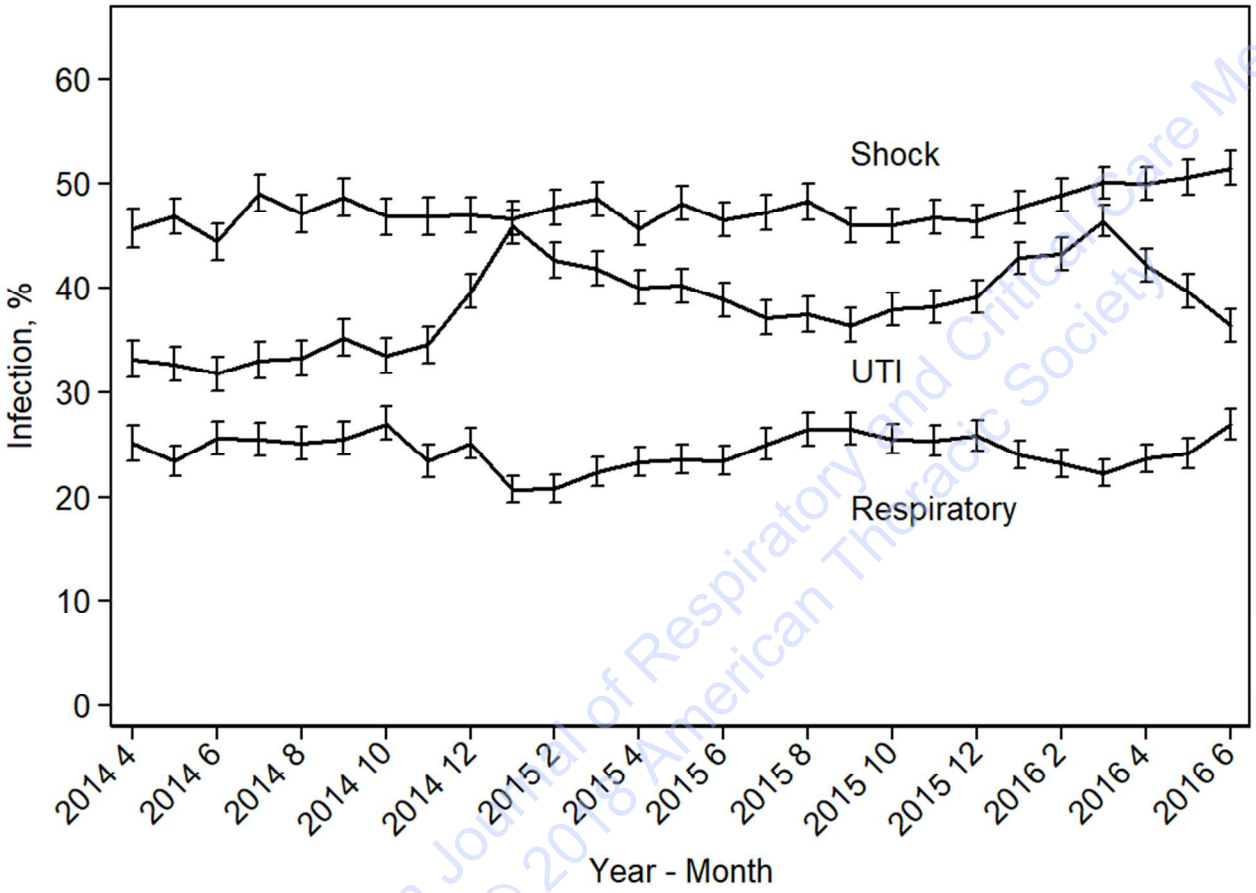


**Appendix Figure 4: Percentage of protocol initiation by location over time**



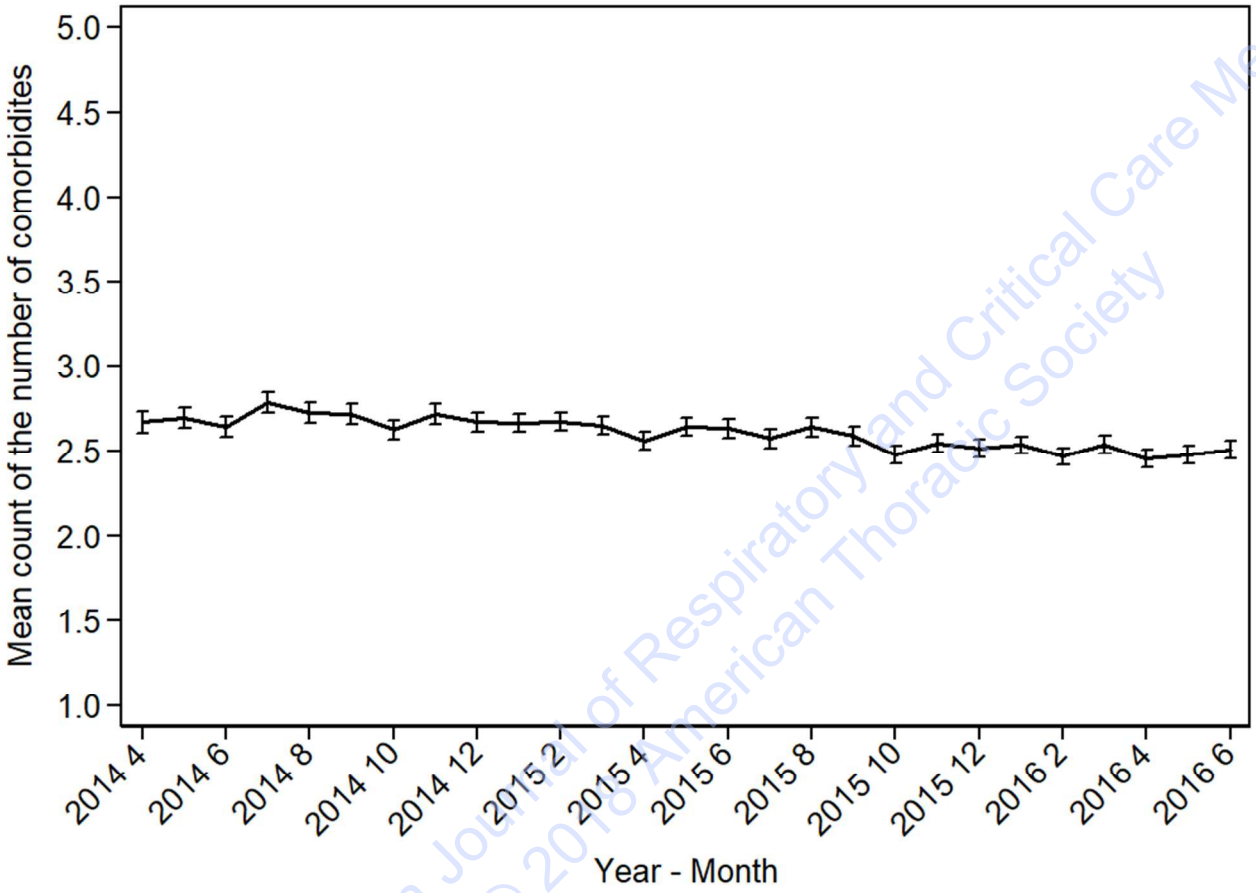

**Abbreviation: ED – Emergency department and ICU – Intensive care unit**

**Appendix Figure 5: Patient percentage with infection during the study period**

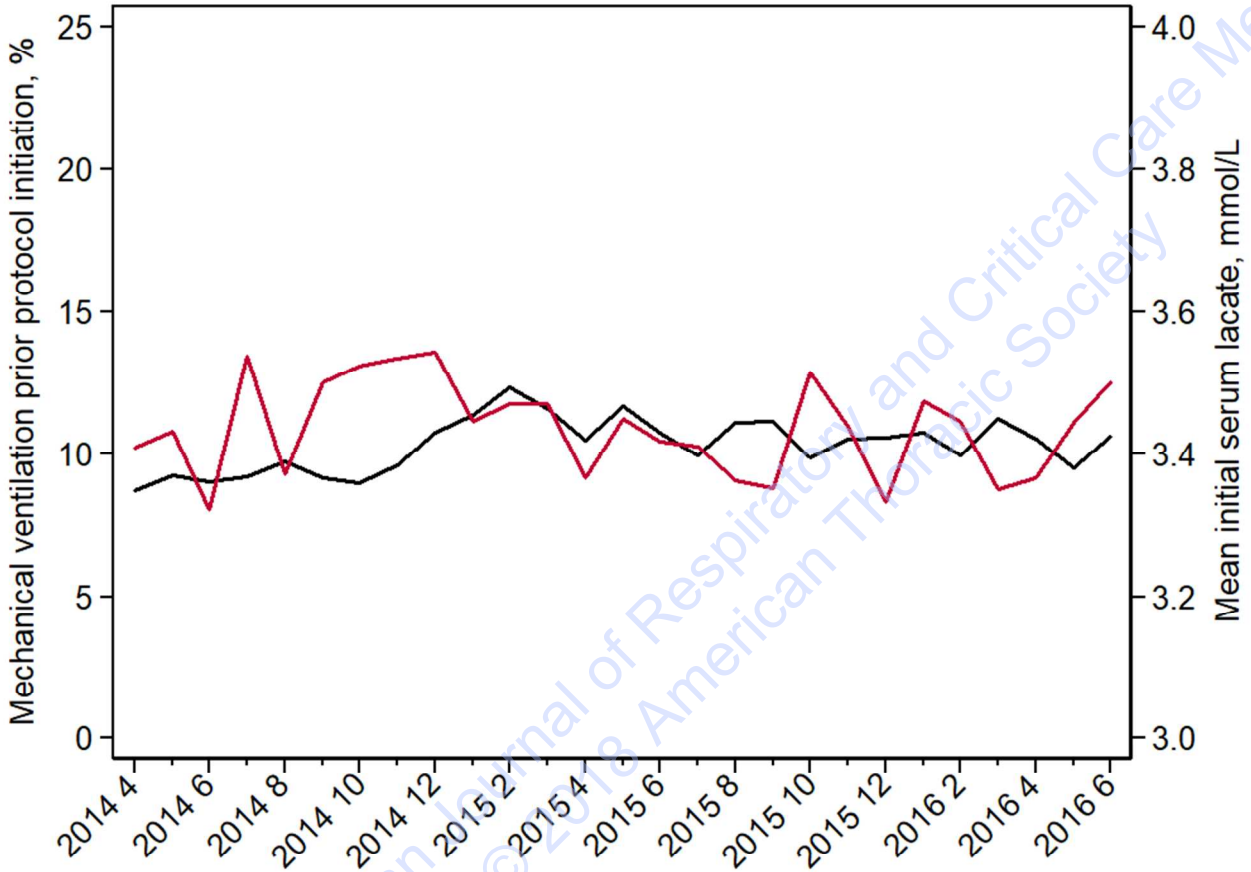



**Abbreviation: UTI – Urinary tract infection**

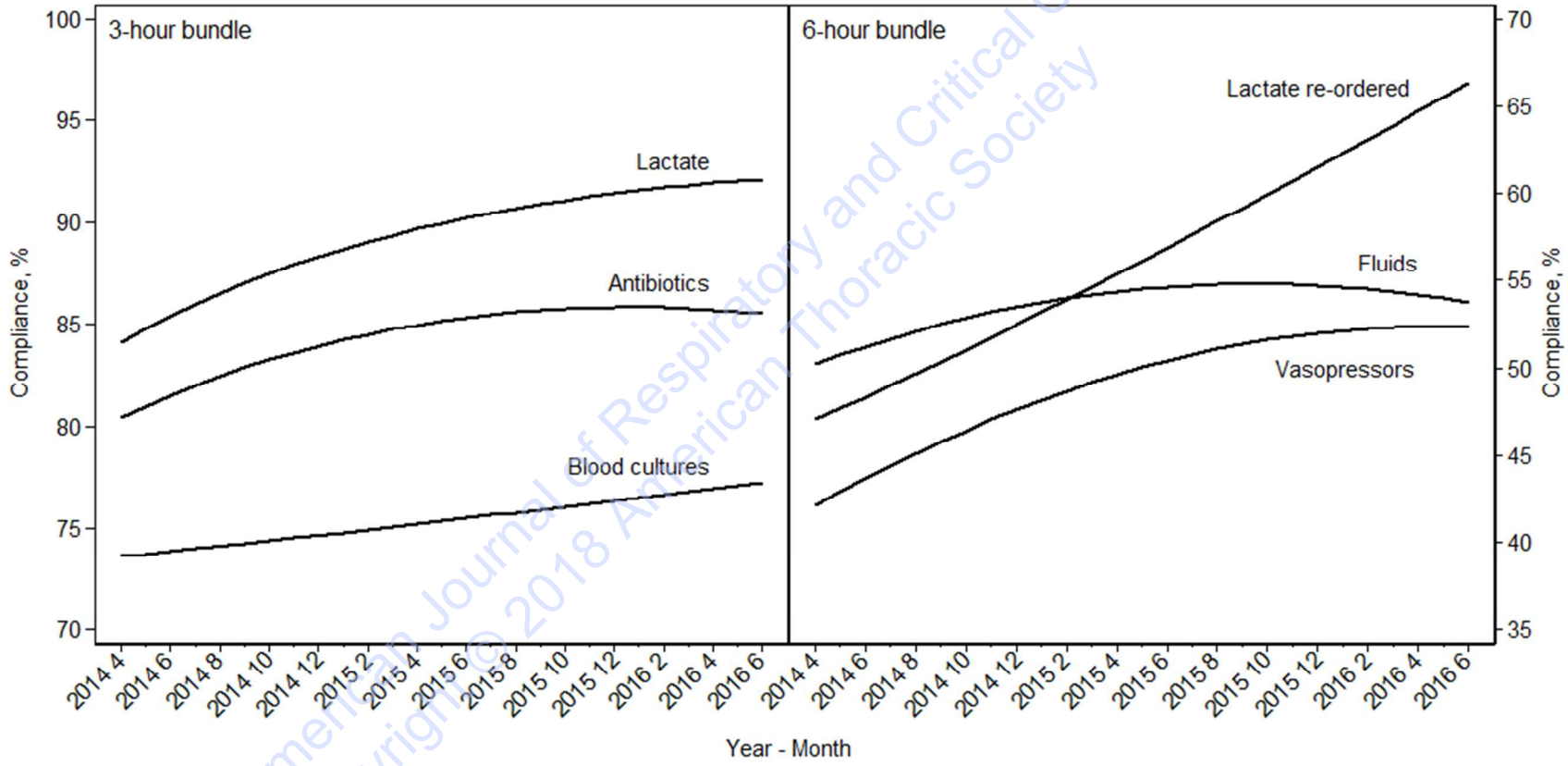
**Appendix Figure 6: Mean of the count of the number of all comorbidities during the study period**



**Appendix Figure 7: The black line represents the percent of patients with mechanical ventilation prior to protocol initiation over the study period and the red line represents the mean initial serum lactate in mmol/L over the study period**



**Appendix Figure 8: Compliance with each bundle element over time. The regression lines are based on individual unadjusted logistic regression models where month is entered into the 3- and the 6-hour model as a quadratic expression. Using the 27 monthly observations compliance with serum lactate measured within 3 hours starts at 84.3% and ends at 92.0% (*p*-value < 0.001). Compliance with blood cultures obtained prior to antibiotics starts at 73.6% and ends at 77.1% (*p*-value < 0.001). Compliance with antibiotics given within 3 hours starts at 80.6% and ends at 85.4% (*p*-value < 0.001). Compliance with fluids for hypotension or elevated serum lactate within 6 hours starts at 50.2% and ends at 53.7% (*p*-value = 0.012). Compliance with vasopressor for refractory hypotension within 6 hours starts at 42.3% and ends at 52.3% (*p*-value < 0.001). Compliance with serum lactate re-order for missing lactate or elevated lactate within 6 hours starts at 46.6% and ends at 66.6% (*p*-value < 0.001).**



## Appendix Table 1: Categories for the Start of Sepsis Protocol

For each facility, the start of their sepsis protocol is initiated by a particular event. These events are classified into 1 of 4 categories, and they are listed below:

a) **Positive sepsis screening from clinical assessment**

b) **Clinical assessment & indicative, abnormal labs**

c) **Code Sepsis after positive sepsis screening/assessment**

d) **Assessment for** Systemic Inflammatory Response Syndrome (**SIRS) Criteria indicators ONLY**

**Category Descriptions:**

**A. Positive sepsis screening from clinical assessment**

- This category indicates that the facility used some form of screening of emergency department (ED) patients or inpatients, and the result was positive for sepsis/severe sepsis/septic shock
- For many facilities, the sepsis screen tool will utilize an assessment for at least 2 of the 4 SIRS criteria (temp, heart rate, respiratory rate, WBC's) **and** a suspected/confirmed infection
- This screening process can also incorporate clinical assessments for blood pressure/hypotension, altered

mental status, etc.

- Laboratory values (e.g. WBCs, lactate levels, creatinine, bilirubin, etc.) may also contribute to a positive screening, but for this category, lab values are **not always** necessary to reach a positive screening result
- The location of this screening (ED triage, ED, ICU, patient room, etc.) and the clinician that officially initiated the protocol (MD, PA, NP, RN, etc.) may vary by facility
- Facilities may document some form of exact wording for sepsis:
    - "Patient screened positive for sepsis"
    - "Positive sepsis screening"
    - Or a similar variation of exact wording
- The auditor may use the exact wording **or** the clinical indications (assessment, sepsis diagnosis, and the initiation of treatment) to determine if the protocol was initiated

**B. Clinical assessment & indicative, abnormal labs**

- This category includes the components of the previous category **plus** laboratory values in order to initiate the sepsis protocol
- In some facilities when the initial screening of a patient comes back as positive for possible sepsis, stat labs are

ordered. The clinician will then use the lab values in deciding whether or not to officially initiate their protocol

- In other cases, the facility may have a separate Sepsis Protocol and Severe Sepsis Protocol, and lab values (such as lactate levels) may be what triggered the higher Severe Sepsis Protocol
- For this category, any lab value can be used (WBC counts, % of band cells, platelet counts, lactate, blood glucose, creatinine, bilirubin, C-reactive protein, procalcitonin, coagulation abnormalities-INR/aPTT, blood gases)
- The auditor will need to see documentation of sepsis assessment/screening **and** a lab value to determine if the protocol was initiated

**C. Code Sepsis after positive sepsis screening/assessment**

- This category also includes the components of category A
- Of note, an indication of "RRT" (Rapid Response Team) being called for an inpatient unit is equivalent to "Code Sepsis" in the ED
- The difference for category 3 is that some facilities utilize a "Code Sepsis" to announce the identification of a positive sepsis screening in their facility
- So documentation from these facilities **must** include either "Code Sepsis" or "RRT" for the auditor to determine that protocol was initiated

**D. Assessment for SIRS Criteria indicators ONLY**

- This category indicates that the facility used **only** the SIRS criteria to identify possible sepsis
- The SIRS (Systemic Inflammatory Response Syndrome) Criteria include the following:
  - Temperature of more than 100.4°F (38°C) or less than 96.8°F (36°C)
  - Heart rate of more than 90 beats per minute
  - Respiratory rate of more than 20 breaths per minute or an arterial carbon dioxide tension ($PaCO_2$) of less than 32 mmHg
  - Abnormal white blood cell count (> 12,000/µL or < 4,000/µL) or >10% immature/band white blood cells
- Having at least 2 of the above criteria indicates a positive for SIRS

**Appendix Table 2: Clinical characteristics of the patients based on how sepsis was identified**

| Variable | Assessment for SIRS Criteria indicators | Clinical assessment AND indicative, abnormal labs | Code Sepsis after positive sepsis screening/ assessment | Positive sepsis screening from clinical assessment |
|---|---|---|---|---|
| Sepsis admissions, N (%) | 14 (0.0%) | 10,626 (11.6%) | 13,120 (14.4%) | 67,597 (74.0%) |
| Hospitals, N (%) | 1 (0.5) | 26 (14.2) | 23 (12.6) | 133 (72.7) |
| Observed in-hospital mortality, N (%) | 3 (21.4) | 2,895 (27.2) | 3,700 (28.2) | 17,818 (26.4) |
| Risk adjusted in-hospital mortality, % | 22.3 | 25.9 | 29.5 | 26.3 |
| Median age, (IQR) | 76 (70 - 83) | 70 (57 - 82) | 74 (62 - 84) | 71 (59 - 82) |
| Protocol initiated, N (%) | 14 (100.0) | 9,270 (87.2) | 12,532 (95.5) | 52,477 (77.6) |
| Place where protocol was initiated, N (%)<br>ED<br>Floor<br>ICU | <br>13 (92.9)<br>1 (7.1)<br>0 (0.0) | <br>7,024 (75.98)<br>1,261 (13.6)<br>985 (10.6) | <br>9,484 (75.8)<br>1,736 (13.2)<br>1,312 (10.0) | <br>41,953 (79.9)<br>5,692 (10.9)<br>4,832 (9.2) |
| Septic shock, N (%) | 1 (7.1) | 5,063 (47.7) | 5,782 (44.1) | 32,733 (48.4) |
| Median number of comorbidities, (IQR) | 2 (1 - 3) | 3 (2 - 4) | 2 (1 - 3) | 3 (1 - 4) |

**Appendix Table 3: Risk-Adjusted Mortality Model Statistical Methods**

A logistic regression model was developed to estimate the probability of mortality for patients with severe sepsis or septic shock during their hospital stay. A random sample of 10% (N = 4,319) of the observations was set aside and the logistic regression model was developed on the remaining 90% (38,884) of the observations. The final model was validated on the 10% of observations that were set aside. A multivariable logistic regression model was built using the developmental dataset and starting with all possible covariates in the model. Using an iterative procedure, variables were removed from the model, one by one, if their *p*-values were not significant at 0.05 level until a parsimonious model was reached. Variables removed during the development procedure were added back into the reduced model if their *p*-values were significant at the 0.05 level and if model calibration (Hosmer-Lemeshow goodness of fit) was improved through their inclusion. We then assessed the scale of the 3 continuous variables (patient age, first serum lactate, and the count of the number of comorbidities) remaining in the model. Specifically, we were interested in determining whether these variables had a linear relationship with mortality (i.e., linear in the logit). Using the method of fractional polynomials patient age was included in the model as a linear term, number of comorbidities was transformed by taking the square root, and first serum lactate was entered into the model as a quadratic expression (linear and a squared term). Model calibration was further improved by adding the following interactions to the model: lower respiratory infection (LRI) by MV severity, patient age by the square root of the number of comorbidities, and first serum lactate by the square root of the number of comorbidities. Model calibration was assessed using the Hosmer-Lemeshow goodness of fit test on both the developmental and the validation datasets. Group sizes of 10, 100, 500, and 1,000 were chosen for the large, developmental dataset and the *p*-values for the tests were 0.57, 0.97, 0.74, and 0.74, respectively. All suggest good agreement between the observed and the estimated probabilities of mortality

Similarly, for the validation dataset, we used group sizes of 10, 50, 100, and 150 and the *p*-values for these tests were 0.65, 0.98, 0.99, and 0.97, respectively. Again, all indicate good fit. Area under the receiver operating characteristic (ROC) curve indicates how well the model discriminates between those patients who die in the hospital and those who do not die. The ROC area for the developmental and validation datasets are 0.770 and 0.773, respectively, indicating good discrimination. The model coefficients, standard errors, 95% confidence intervals of the coefficients, and the p-values are shown in the following Table 1.

**Logistic regression model base on developmental dataset (N = 38,884)**

| Term in the logistic regression model | β | β: 95% CI | | SE | *p*-value |
|---|---|---|---|---|---|
| Race/ethnicity | | | | | |
| White, non-Hispanic (Referent) | 0.000 | | | | |
| Black, non-Hispanic | 0.188 | 0.116 | 0.259 | 0.036 | < 0.001 |
| Hispanic | -0.073 | -0.163 | 0.017 | 0.046 | 0.11 |
| Multi-racial | 0.165 | -0.029 | 0.359 | 0.099 | 0.096 |
| Unknown, non-Hispanic | 0.043 | -0.053 | 0.139 | 0.049 | 0.38 |
| Unknown | 0.101 | 0.019 | 0.183 | 0.042 | 0.016 |
| Payer | | | | | |
| Medicare (Referent) | 0.000 | | | | |
| Medicaid | 0.099 | 0.023 | 0.176 | 0.039 | 0.011 |
| Private, HMO | 0.067 | -0.002 | 0.136 | 0.035 | 0.056 |
| Self-Pay | 0.646 | 0.422 | 0.870 | 0.114 | < 0.001 |
| Other | -0.023 | -0.167 | 0.120 | 0.073 | 0.75 |
| Site of infection | | | | | |
| Urinary (Referent) | 0.000 | | | | |
| Respiratory | 0.599 | 0.521 | 0.677 | 0.040 | < 0.001 |
| Gastrointestinal | 0.543 | 0.454 | 0.632 | 0.045 | < 0.001 |
| Skin | 0.484 | 0.367 | 0.600 | 0.059 | < 0.001 |
| Central Nervous System | 0.723 | 0.396 | 1.050 | 0.167 | < 0.001 |
| Other | 0.558 | 0.457 | 0.659 | 0.052 | < 0.001 |
| Unknown | 0.900 | 0.802 | 0.997 | 0.050 | < 0.001 |
| Admission source | | | | | |
| Non-health facility, POA (Referent) | 0.000 | | | | |
| Clinic | -0.033 | -0.157 | 0.091 | 0.063 | 0.61 |
| Different Hospital | 0.418 | 0.322 | 0.515 | 0.049 | < 0.001 |
| Skilled nursing facility/Intermediate care facility | 0.289 | 0.227 | 0.351 | 0.032 | < 0.001 |
| Another health care facility | 0.278 | 0.012 | 0.544 | 0.136 | 0.040 |
| Between unit transfer | 0.459 | 0.096 | 0.823 | 0.186 | 0.013 |
| Hospice | 0.727 | -0.073 | 1.528 | 0.408 | 0.075 |
| Other | -0.330 | -0.730 | 0.070 | 0.204 | 0.106 |
| Lower respiratory infection | | | | | |
| No (Referent) | 0.000 | | | | |

| Term in the logistic regression model | β | β: 95% CI | | SE | *p*-value |
|---|---|---|---|---|---|
| Yes | 0.281 | 0.217 | 0.345 | 0.033 | < 0.001 |
| MV severity | | | | | |
| No (Referent) | 0.000 | | | | |
| Yes | 0.519 | 0.402 | 0.636 | 0.060 | < 0.001 |
| Lower respiratory infection and MV severity | -0.398 | -0.538 | -0.258 | 0.072 | < 0.001 |
| Septic shock diagnosis | | | | | |
| Severe Sepsis | 0.000 | | | | |
| Septic Shock | 0.770 | 0.712 | 0.828 | 0.029 | < 0.001 |
| Thrombocytopenia | | | | | |
| No (Referent) | 0.000 | | | | |
| Yes | 0.285 | 0.229 | 0.341 | 0.029 | < 0.001 |
| Metastatic cancer | | | | | |
| No (Referent) | 0.000 | | | | |
| Yes | 0.460 | 0.385 | 0.535 | 0.038 | < 0.001 |
| Lymphoma/leukemia/multiple myeloma | | | | | |
| No (Referent) | 0.000 | | | | |
| Yes | 0.135 | 0.030 | 0.239 | 0.053 | 0.011 |
| Patient age | 0.060 | 0.054 | 0.065 | 0.003 | < 0.001 |
| Square root of comorbidity count | 2.410 | 2.153 | 2.667 | 0.131 | < 0.001 |
| Age and the square root of comorbidity count | -0.021 | -0.024 | -0.018 | 0.002 | < 0.001 |
| First serum lactate | 0.245 | 0.210 | 0.279 | 0.018 | < 0.001 |
| First serum lactate squared | -0.002 | -0.004 | -0.001 | 0.001 | 0.001 |
| Serum lactate and the square root of comorbidity count | -0.043 | -0.059 | -0.026 | 0.008 | < 0.001 |
| Constant term | -8.548 | -9.018 | -8.078 | 0.240 | < 0.001 |

**Appendix Table 4: Patient characteristics by protocol initiation status**

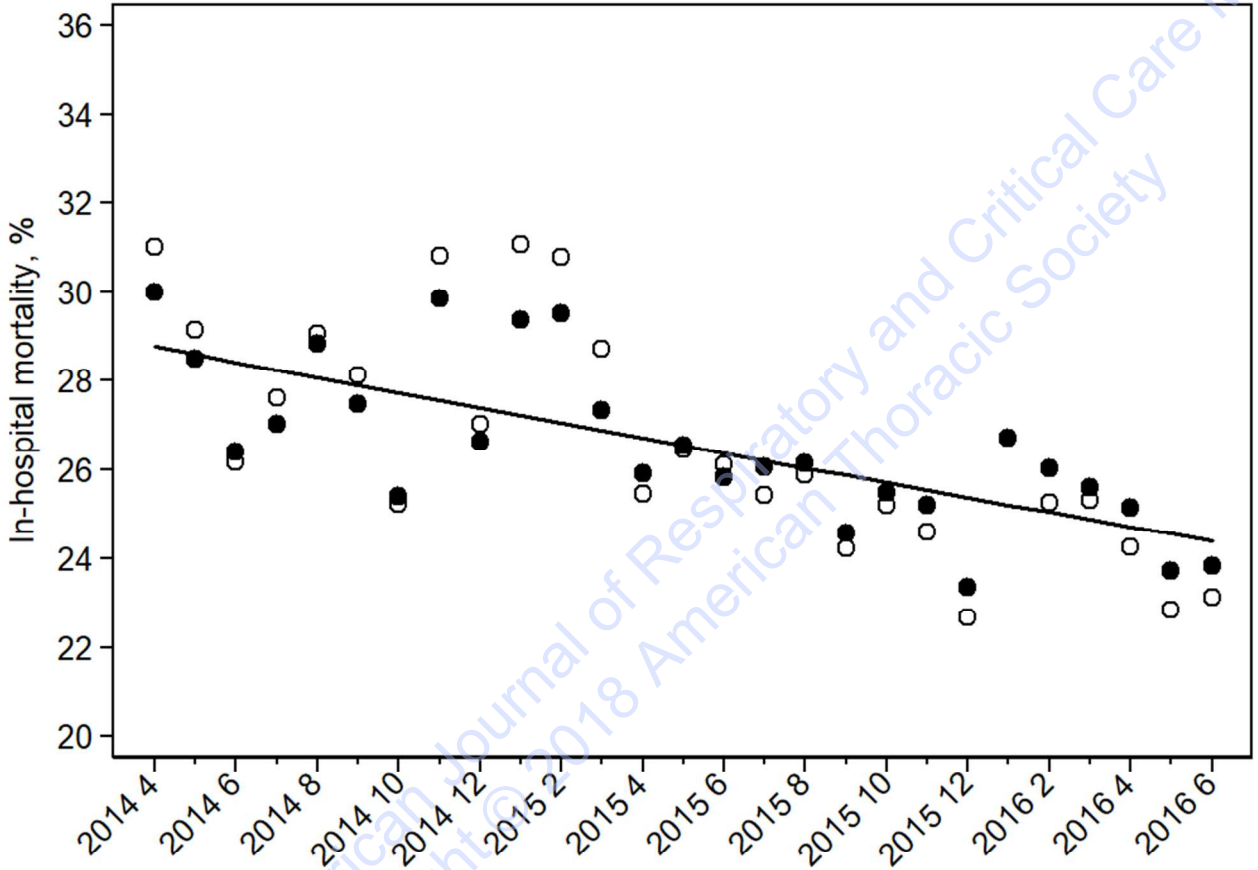
| Variable | Protocol Initiated | | *p*-value |
|---|---|---|---|
| | No | Yes | |
| Number of observations, N | 17,064 | 74,293 | |
| Age at admission, median (IQR) | 70 (59 - 81) | 72 (60 - 83) | < 0.001 |
| Gender, N (%) | | | < 0.001 |
| Female | 8,573 (50.2) | 35,746 (48.1) | |
| Male | 8,490 (49.8) | 38,534 (51.9) | |
| Race, N (%) | | | < 0.001 |
| White | 9,811 (57.5) | 48,468 (65.2) | |
| Black | 3,760 (22.0) | 13,076 (17.6) | |
| Asian | 214 (1.2) | 3,221 (4.3) | |
| Other | 3,279 (19.3) | 9,528 (12.9) | |
| Ethnicity, N (%) | | | < 0.001 |
| Spanish/Hispanic origin | 2,237 (13.1) | 7,511 (10.1) | |
| Not of Spanish/Hispanic | 13,007 (76.2) | 58,802 (79.2) | |
| Unknown | 1,818 (10.7) | 7,952 (10.7) | |
| Multi-ethnic | 2 (0.01) | 28 (0.04) | |
| Comorbidities, N (%) | | | |
| Chronic respiratory failure | 2,393 (14.0) | 8,879 (12.0) | < 0.001 |
| Congestive heart failure | 4,896 (28.7) | 15,597 (21.0) | < 0.001 |
| End-stage renal disease | 1,726 (10.1) | 8,958 (12.1) | < 0.001 |
| Admission source, N (%) | | | < 0.001 |
| Home | 13,569 (79.5) | 52,231 (70.3) | |
| Clinic | 401 (2.4) | 3,244 (4.4) | |

| Variable | Protocol Initiated | | *p*-value |
|---|---|---|---|
| | No | Yes | |
| Skilled nursing facility/Intermediate care facility | 2,263 (13.3) | 17,134 (23.1) | |
| Other | 831 (4.8) | 1,684 (2.2) | |
| Site of infection, N (%) | | | < 0.001 |
| Urinary | 3,666 (21.5) | 18,580 (25.0) | |
| Respiratory | 6,387 (37.4) | 28,899 (38.9) | |
| Gastrointestinal | 2,162 (12.7) | 8,708 (11.7) | |
| Skin | 1,158 (6.8) | 4,965 (6.7) | |
| Central Nervous System | 88 (0.5) | 366 (0.5) | |
| Other | 1,355 (7.9) | 6,410 (8.6) | |
| Unknown | 22,487 (13.2) | 6,365 (8.6) | |
| Positive blood cultures, N (%) | | | < 0.001 |
| Gram positive | 1,273 (7.4) | 9,751 (13.1) | |
| Gram negative | 891 (5.2) | 8,852 (11.9) | |
| Other | 778 (4.6) | 1,374 (1.9) | |
| None/Missing | 14,122 (82.8) | 54,316 (73.1) | |
| Sepsis severity, N (%) | | | 0.025 |
| Severe sepsis | 8,792 (51.5) | 38,986 (52.5) | |
| Septic shock | 8,272 (48.8) | 35,307 (47.5) | |
| Protocol screening type, N (%) | | | < 0.001 |
| Clinical assessment | 15,120 (88.6) | 52,477 (70.6) | |
| Clinical assessment with abnormal labs | 1,356 (8.0) | 9,270 (12.5) | |
| Code sepsis | 588 (3.4) | 12,538 (16.9) | |
| First serum lactate, mmol/L, median (IQR) | 2.2 (1.4 – 3.8) | 2.6 (1.6 – 4.3) | < 0.001 |

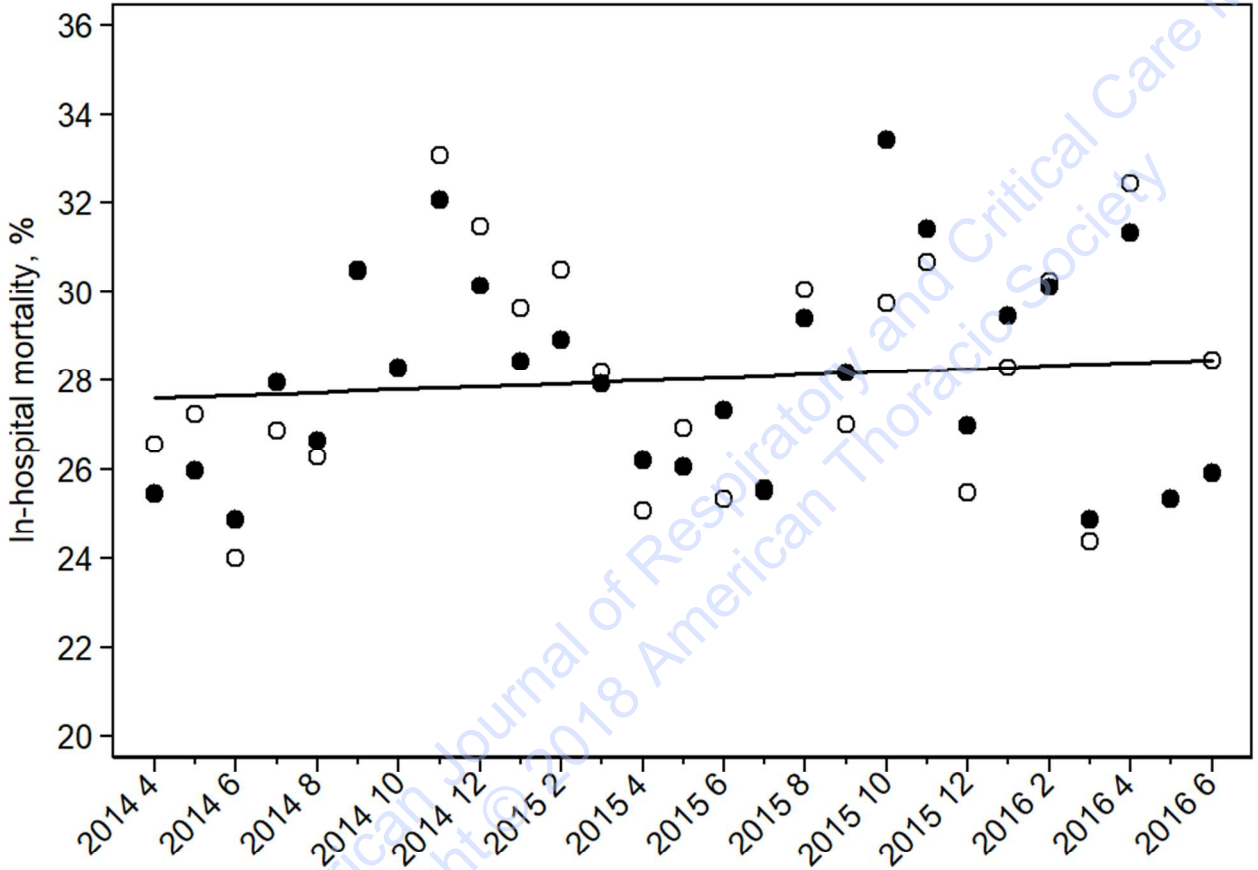
| Variable | Protocol Initiated | | *p*-value |
|---|---|---|---|
| | No | Yes | |
| First serum lactate > 4.0 mmol/L, N (%) | 3,887 (22.8) | 20,759 (27.9) | < 0.001 |
| Persistent hypotension, N (%) | 8,455 (49.6) | 31,663 (42.6) | < 0.001 |
| Total certified hospital beds, median (IQR) | 409 (286 - 457) | 431 (282 - 591) | < 0.001 |
| Teaching facility, N (%) | | | < 0.001 |
| No | 3,369 (19.8) | 11,552 (15.6) | |
| Yes | 13,689 (80.2) | 62,734 (84.4) | |
| In-hospital mortality, N (%) | | | < 0.001 |
| No | 12,283 (72.0) | 54,658 (73.6) | |
| Yes | 4,781 (28.0) | 19,635 (26.4) | |

**Abbreviation: IQR – Interquartile range**

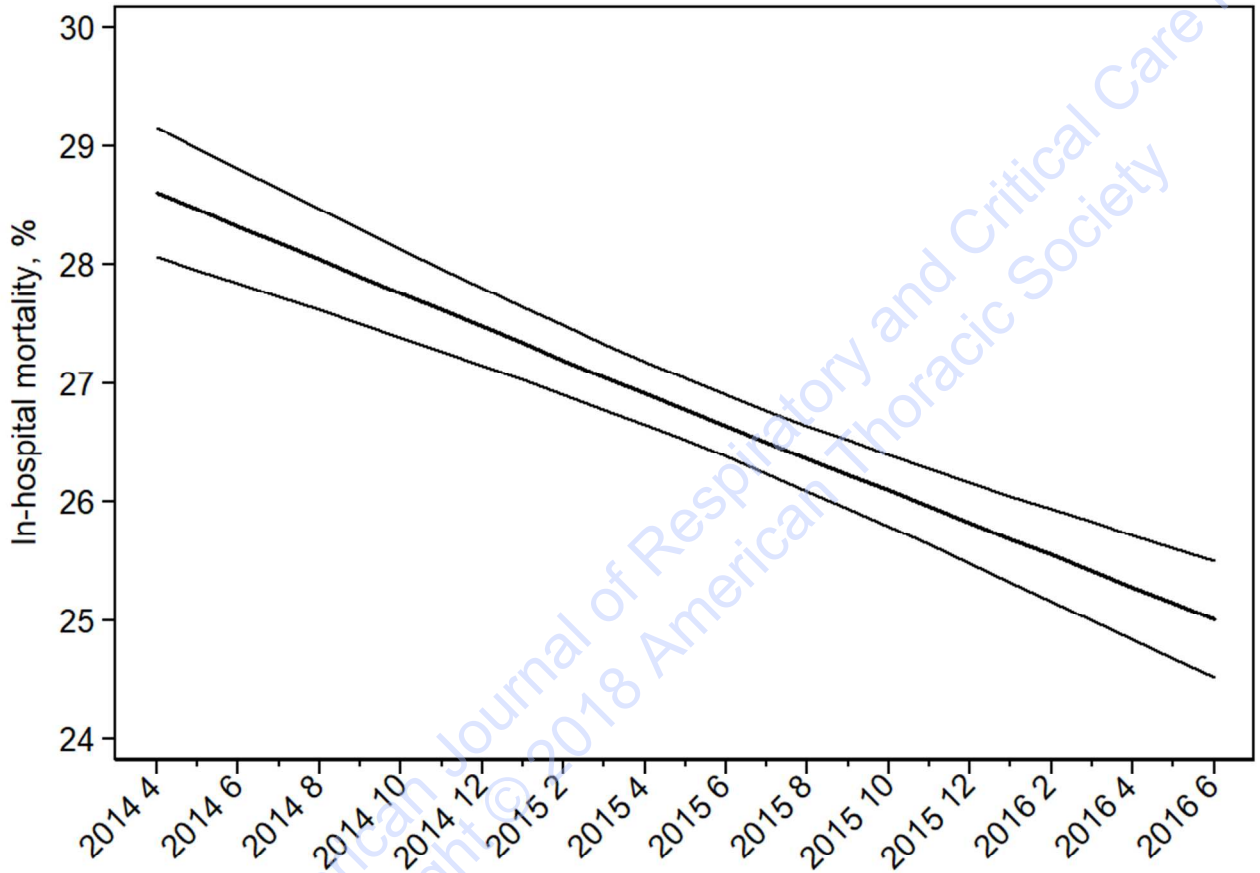
**Appendix Figure 9: Risk adjusted in-hospital mortality during the study period in patients *with* protocol initiated. The hollow circles are the observed mortality, the solid circles are the risk adjusted in-hospital mortality where time is entered into the model as a categorical variable, and the line is the risk adjusted in-hospital mortality where time is entered into the model as a linear continuous variable.**



**Appendix Figure 10: Risk adjusted in-hospital mortality during the study period in patients with protocol *not* initiated. The hollow circles are the observed mortality, the solid circles are the risk adjusted in-hospital mortality where time is entered into the model as a categorical variable, and the line is the risk adjusted in-hospital mortality where time is entered into the model as a linear continuous variable.**



**Appendix Figure 11: Risk adjusted hospital mortality over time without regard to protocol initiation status (intent to treat analysis). The odds of in-hospital mortality decrease 1% (OR = 0.991, 95% CI: 0.989 – 0.994, *p*-value < 0.001) for a one month increase between any two months during the study period. [N = 91,357]**



**Appendix Table 5: Hospital characteristics by protocol initiation status**

| Characteristic, N (%) | Quartiles of the probability of protocol initiation | | | | Total |
|---|---|---|---|---|---|
| | 1st Lowest | 2nd | 3rd | 4th Highest | |
| Number of hospitals† | 48 | 49 | 51 | 31 | 179 |
| Facility type | | | | | |
| Hospital | 45 (93.8) | 46 (93.9) | 45 (88.2) | 31 (100) | 167 (93.3) |
| Primary care hospital – critical access hospital | 3 (6.3) | 3 (6.1) | 6 (11.8) | 0 (0) | 12 (6.7) |
| Facility legal description | | | | | |
| Not for profit corporation | 44 (91.7) | 44 (89.8) | 42 (82.4) | 26 (83.9) | 156 (87.2) |
| Proprietary – public benefit corporation | | | | | |
| Public – county | 3 (6.3) | 1 (2) | 1 (2) | 0 (0) | 5 (2.8) |
| Public – municipality | 1 (2.1) | 2 (4.1) | 5 (9.8) | 4 (12.9) | 12 (6.7) |
| Public- state | 0 (0) | 2 (4.1) | 2 (3.9) | 0 (0) | 4 (2.2) |
| RUCA – 2013 description | | | | | |
| Metro – Counties in metro areas ≥ 1,000,000 | 27 (56.3) | 27 (55.1) | 36 (70.6) | 29 (93.6) | 119 (66.5) |
| Metro – Counties in metro areas 250,000 to 1,000,000 | 4 (8.3) | 10 (20.4) | 7 (13.7) | 1 (3.2) | 22 (12.3) |
| Metro – Counties in metro areas < 250,000 | 4 (8.3) | 3 (6.1) | 1 (2) | 0 (0) | 8 (4.5) |
| Non-metro – Urban population of 2,500 to 19,999 adjacent to metro area | 2 (4.2) | 4 (8.2) | 2 (3.9) | 0 (0) | 8 (4.5) |
| Non-metro – Urban population of 2,500 to 19,999 not adjacent to metro area | 2 (4.2) | 1 (2) | 2 (3.9) | 0 (0) | 5 (2.8) |
| Non-metro – Urban population of ≥ 20,000 adjacent to metro area | 8 (16.7) | 4 (8.2) | 3 (5.9) | 1 (3.2) | 16 (8.9) |
| Non-metro – Urban population of ≥ 20,000 not adjacent to metro area | 1 (2.1) | 0 (0) | 0 (0) | 0 (0) | 1 (0.6) |
| Area | | | | | |
| Metro | 35 (72.9) | 40 (81.6) | 44 (86.3) | 30 (96.8) | 149 (83.2) |
| Rural | 13 (27.1) | 9 (18.4) | 7 (13.7) | 1 (3.2) | 30 (16.8) |
| Teaching facility | | | | | |
| No | 30 (62.5) | 21 (42.9) | 20 (39.2) | 2 (6.5) | 73 (40.8) |
| Yes | 18 (37.5) | 28 (57.1) | 31 (60.8) | 29 (93.6) | 106 (59.2) |
| Number of beds, Median (IQR) | 163 (71 - 303) | 243 (162 - 370) | 245 (113 – 450) | 321 (204 - 632) | 242 (128 - 408) |

†Note that 4 of the 183 New York State hospitals did not provide this information

**Appendix Table 6: Patient characteristics by protocol initiation status**

| Characteristic, N (%) | Quartiles of the probability of protocol initiation | | | | Total |
|---|---|---|---|---|---|
| | 1st Lowest | 2nd | 3rd | 4th Highest | |
| Number of patients | 23,051 | 22,822 | 23,497 | 21,987 | 91,357 |
| Protocol initiated | 9,886 (42.9) | 19,579 (85.8) | 22,848 (97.2) | 21,980 (100.0) | 74,293 (81.3) |
| Median age, (IQR) | 70 (59-81) | 71 (59-82) | 72 (60-83) | 72 (60-83) | 71 (59-82) |
| Gender | | | | | |
| Male | 11,673 (50.6) | 11,879 (52.1) | 12,175 (51.8) | 11,297 (51.4) | 47,024 (51.5) |
| Race | | | | | |
| White | 14,096 (61.2) | 16,606 (72.8) | 15,030 (64.0) | 12,547 (57.1) | 58,279 (63.8) |
| Black | 4,708 (20.4) | 3,105 (13.6) | 4,534 (19.3) | 4,489 (20.4) | 16,836 (18.4) |
| Other | 4,247 (18.4) | 3,111 (13.3) | 3,933 (16.7) | 4,951 (22.5) | 16,242 (17.8) |
| Ethnicity | | | | | |
| Spanish/Hispanic origin | 2,884 (12.5) | 1,814 (8.0) | 2,530 (10.8) | 2,520 (11.5) | 9,748 (10.7) |
| Place of protocol initiation | | | | | |
| No | 13,165 (57.1) | 3,243 (14.2) | 649 (2.8) | 7 (0.03) | 17,064 (18.7) |
| ER | 8,157 (35.4) | 16,275 (71.3) | 18,237 (77.6) | 15,805 (71.9) | 58,474 (64.0) |
| Floor | 610 (2.6) | 1,718 (7.5) | 2,563 (10.9) | 3,799 (17.3) | 8,690 (9.5) |
| ICU | 1,119 (4.9) | 1,586 (7.0) | 2,048 (8.7) | 2,376 (10.8) | 7,129 (7.8) |
| Septic shock | 11,853 (51.4) | 11,774 (51.6) | 10,678 (45.4) | 9,274 (42.2) | 43,579 (47.7) |
| Site of infection | | | | | |
| Urinary | 5,366 | 5,707 | 6,015 | 5,158 | 22,246 |

| | | | | | |
|---|---|---|---|---|---|
| | (23.3) | (25.0) | (25.6) | (23.5) | (24.3) |
| Respiratory | 9,217 (40.0) | 8,778 (38.5) | 8,913 (37.9) | 8,378 (38.1) | 35,286 (38.6) |
| Gastrointestinal | 2,215 (9.6) | 3,058 (13.4) | 2,855 (12.1) | 2,742 (12.5) | 10,870 (11.9) |
| Skin | 1,597 (6.9) | 1,626 (7.1) | 1,546 (6.6) | 1,354 (6.2) | 6,123 (6.7) |
| Central Nervous System | 102 (0.4) | 122 (0.5) | 115 (0.5) | 115 (0.5) | 454 (0.5) |
| Other | 1,728 (7.5) | 1,539 (6.7) | 2,347 (10.0) | 2,151 (9.8) | 7,765 (8.5) |
| Unknown | 2,826 (12.3) | 1,992 (8.7) | 1,706 (7.3) | 2,089 (9.5) | 8,613 (9.4) |
| Mechanical ventilation prior to protocol initiation | 1,392 (6.0) | 2,279 (10.0) | 2,967 (12.6) | 2,826 (12.9) | 9,464 (10.4) |
| Admitted to ICU | 14,610 (68.4) | 14,735 (64.6) | 14,176 (60.3) | 13,212 (60.1) | 56,733 (62.1) |
| Chronic respiratory failure | 2,715 (11.8) | 3,719 (16.3) | 2,773 (11.8) | 2,065 (9.4) | 11,272 (12.3) |
| Congestive heart failure | 5,835 (25.3) | 4,899 (21.5) | 5,511 (23.5) | 4,248 (19.3) | 20,493 (22.4) |
| Chronic renal failure | 2,164 (9.4) | 2,752 (12.1) | 2,814 (12.0) | 2,954 (13.4) | 10,684 (11.7) |
| Chronic liver disease | 1,324 (5.7) | 1,699 (7.4) | 1,886 (8.0) | 1,232 (5.6) | 6,141 (6.7) |
| Diabetes | 9,135 (39.6) | 8,116 (35.6) | 8,630 (36.7) | 7,436 (33.8) | 33,317 (36.5) |
| Serum lactate > 4 mmol/L | 5,903 (25.6) | 5,745 (25.2) | 6,881 (29.3) | 6,117 (27.8) | 24,646 (27.0) |
| Median number of comorbidities, (IQR) | 2 (1-4) | 3 (2-4) | 2 (1-4) | 2 (1-3) | 2 (1-4) |

**Appendix Table 7: Risk adjusted in-hospital mortality over time by protocol initiation status**

| Year | Month | Protocol not initiated (N = 17,064) | | | Protocol initiated (N = 74,293) | | | Difference in mortality across protocol initiated and not initiated | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Percent | 95% CI | | Percent | 95% CI | | Percent | 95% CI | | *p*-value |
| 2014 | 4 | 29.4 | 28.2 | 30.6 | 28.3 | 27.7 | 29.0 | 1.0 | -0.3 | 2.4 | 0.138 |
| 2014 | 5 | 29.4 | 28.3 | 30.6 | 28.2 | 27.6 | 28.7 | 1.2 | 0.0 | 2.5 | 0.056 |
| 2014 | 6 | 29.5 | 28.4 | 30.5 | 28.0 | 27.4 | 28.5 | 1.5 | 0.3 | 2.7 | 0.017 |
| 2014 | 7 | 29.5 | 28.5 | 30.5 | 27.8 | 27.3 | 28.3 | 1.7 | 0.6 | 2.8 | 0.004 |
| 2014 | 8 | 29.6 | 28.6 | 30.5 | 27.6 | 27.2 | 28.1 | 1.9 | 0.8 | 3.0 | 0.001 |
| 2014 | 9 | 29.6 | 28.7 | 30.5 | 27.5 | 27.0 | 27.9 | 2.1 | 1.1 | 3.1 | < 0.001 |
| 2014 | 10 | 29.7 | 28.8 | 30.5 | 27.3 | 26.9 | 27.7 | 2.4 | 1.4 | 3.3 | < 0.001 |
| 2014 | 11 | 29.7 | 28.9 | 30.5 | 27.1 | 26.7 | 27.5 | 2.6 | 1.7 | 3.5 | < 0.001 |
| 2014 | 12 | 29.7 | 29.0 | 30.5 | 27.0 | 26.6 | 27.3 | 2.8 | 1.9 | 3.6 | < 0.001 |
| 2015 | 1 | 29.8 | 29.1 | 30.5 | 26.8 | 26.4 | 27.1 | 3.0 | 2.2 | 3.8 | < 0.001 |
| 2015 | 2 | 29.8 | 29.2 | 30.5 | 26.6 | 26.3 | 26.9 | 3.2 | 2.5 | 4.0 | < 0.001 |
| 2015 | 3 | 29.9 | 29.2 | 30.6 | 26.4 | 26.1 | 26.8 | 3.4 | 2.7 | 4.2 | < 0.001 |
| 2015 | 4 | 29.9 | 29.3 | 30.6 | 26.3 | 26.0 | 26.6 | 3.7 | 2.9 | 4.4 | < 0.001 |
| 2015 | 5 | 30.0 | 29.3 | 30.6 | 26.1 | 25.8 | 26.4 | 3.9 | 3.2 | 4.6 | < 0.001 |
| 2015 | 6 | 30.0 | 29.4 | 30.7 | 25.9 | 25.7 | 26.2 | 4.1 | 3.4 | 4.8 | < 0.001 |
| 2015 | 7 | 30.1 | 29.4 | 30.8 | 25.8 | 25.5 | 26.1 | 4.3 | 3.6 | 5.1 | < 0.001 |
| 2015 | 8 | 30.1 | 29.4 | 30.8 | 25.6 | 25.3 | 25.9 | 4.5 | 3.7 | 5.3 | < 0.001 |
| 2015 | 9 | 30.2 | 29.4 | 30.9 | 25.4 | 25.1 | 25.8 | 4.7 | 3.9 | 5.6 | < 0.001 |
| 2015 | 10 | 30.2 | 29.4 | 31.0 | 25.3 | 25.0 | 25.6 | 4.9 | 4.1 | 5.8 | < 0.001 |
| 2015 | 11 | 30.3 | 29.4 | 31.1 | 25.1 | 24.8 | 25.5 | 5.2 | 4.2 | 6.1 | < 0.001 |
| 2015 | 12 | 30.3 | 29.4 | 31.2 | 25.0 | 24.6 | 25.3 | 5.4 | 4.4 | 6.3 | < 0.001 |
| 2016 | 1 | 30.4 | 29.4 | 31.3 | 24.8 | 24.4 | 25.2 | 5.6 | 4.5 | 6.6 | < 0.001 |
| 2016 | 2 | 30.4 | 29.4 | 31.4 | 24.6 | 24.2 | 25.0 | 5.8 | 4.7 | 6.9 | < 0.001 |
| 2016 | 3 | 30.5 | 29.4 | 31.6 | 24.5 | 24.0 | 24.9 | 6.0 | 4.8 | 7.2 | < 0.001 |
| 2016 | 4 | 30.5 | 29.4 | 31.7 | 24.3 | 23.8 | 24.8 | 6.2 | 5.0 | 7.5 | < 0.001 |
| 2016 | 5 | 30.6 | 29.3 | 31.8 | 24.1 | 23.6 | 24.6 | 6.4 | 5.1 | 7.7 | < 0.001 |
| 2016 | 6 | 30.6 | 29.3 | 31.9 | 24.0 | 23.5 | 24.5 | 6.6 | 5.2 | 8.0 | < 0.001 |

**Appendix Table 8: Probabilities and odds ratios of in-hospital mortality based on separate logistic regression models containing the compliance risk factor along with each of the variables in the risk adjusted model for hospital mortality developed through collaboration with the State of New York.**

| Compliance risk factor | N | Probability of in-hospital mortality % | 95% CI | OR for In-hospital mortality | 95% CI | *p*-value |
|---|---|---|---|---|---|---|
| 3-hour bundle | | | | | | |
| No | 29,134 | 29.3 | 28.8 – 29.8 | 0.73 | 0.70 – 0.76 | < 0.001 |
| Yes | 44,996 | 24.2 | 23.9 – 24.6 | | | |
| 6-hour bundle | | | | | | |
| No | 46,390 | 27.4 | 27.1 – 27.8 | 0.74 | 0.71 – 0.77 | < 0.001 |
| Yes | 27,361 | 22.8 | 22.3 – 23.3 | | | |
| Lactate reported in 3 hours | | | | | | |
| No | 7,721 | 30.2 | 29.3 – 31.1 | 0.76 | 0.72 – 0.81 | < 0.001 |
| Yes | 66,409 | 25.8 | 25.5 – 26.1 | | | |
| Blood cultures obtained prior to antibiotics | | | | | | |
| No | 18,179 | 30.2 | 29.6 – 30.8 | 0.72 | 0.69 – 0.75 | < 0.001 |
| Yes | 55,951 | 24.9 | 24.6 – 25.3 | | | |
| Antibiotics started in 3 hours | | | | | | |
| No | 11,448 | 29.7 | 28.9 – 30.4 | 0.78 | 0.74 – 0.82 | < 0.001 |
| Yes | 62,682 | 25.7 | 25.3 – 26.0 | | | |
| Adequate fluids in hypotensive or elevated lactate | | | | | | |
| No | 24,052 | 32.1 | 31.6 – 32.7 | 0.79 | 0.76 – 0.83 | < 0.001 |
| Yes | 27,855 | 28.1 | 27.6 – 28.6 | | | |
| Vasopressors if refractory hypotension | | | | | | |
| No | 12,449 | 38.2 | 37.4 – 39.0 | 1.03 | 0.97 – 1.10 | 0.32 |
| Yes | 12,145 | 38.8 | 38.0 – 39.6 | | | |
| Lactate re-ordered if | | | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| missing or elevated | | | | | | |
| No | 9,893 | 40.0 | 39.1 – 40.9 | 0.77 | 0.72 – 0.82 | < 0.001 |
| Yes | 12,979 | 35.0 | 34.3 – 35.8 | | | |

**Appendix Table 9: Risk adjusted in-hospital mortality odds ratios by continuous compliance for those who had the sepsis protocol initiated. Continuous compliance was estimated for each hospital using the hospital's last two quarters during the study period. Odds ratios are based on two individual logistic regression models.**

| Risk factors | OR | 95% CI | *p*-value |
|---|---|---|---|
| 10% increase in 3-hour bundle compliance | 0.95 | 0.94 – 0.96 | < 0.001 |
| 10% increase in 6-hour bundle compliance | 0.94 | 0.93 – 0.95 | < 0.001 |