Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Seymour CW, Gesten F, Prescott HC, et al. Time to treatment and mortality during mandated emergency care for sepsis. N Engl J Med. DOI: 10.1056/NEJMoa1703058

Supplementary Appendix

Time to treatment and mortality during statewide mandated sepsis care in the emergency department

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Supplementary Methods

A. Sepsis identification strategies across New York State hospitals

New York hospitals were instructed to identify severe sepsis and septic shock cases using protocols with criteria suggested in Sepsis-2.0.[1] In the case report form, four categories were used to categorize how cases were identified at each facility.

i. Positive sepsis screening from clinical assessment, N=35,514 patients (72%)

- This category indicates that the facility used some form of screening of 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, serum 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

ii. Positive sepsis screen from clinical assessment AND abnormal laboratory values, N=5,920 patients (12%)

- This category includes the components of the previous category **plus** laboratory values
- In some facilities when the initial screening of a patient comes back as positive for possible sepsis, immediate laboratory tests are ordered. The clinician then used the laboratory values in deciding whether or not to initiate their protocol
- For this category, any laboratory value can be used that supports the sepsis assessment qualifies (WBC counts, % of band cells, platelet counts, serum lactate, blood glucose, creatinine, bilirubin, C-reactive protein, procalcitonin, coagulation abnormalities-INR/aPTT, blood gases)

iii. Positive sepsis screen from clinical assessment AND code sepsis, N=7,897 patients (16%)

- This category includes a positive sepsis screen by clinical assessment
- However, it identifies patients in whom a code sepsis or rapid response team call initiates the case identification

Figure S1. Patient accrual.

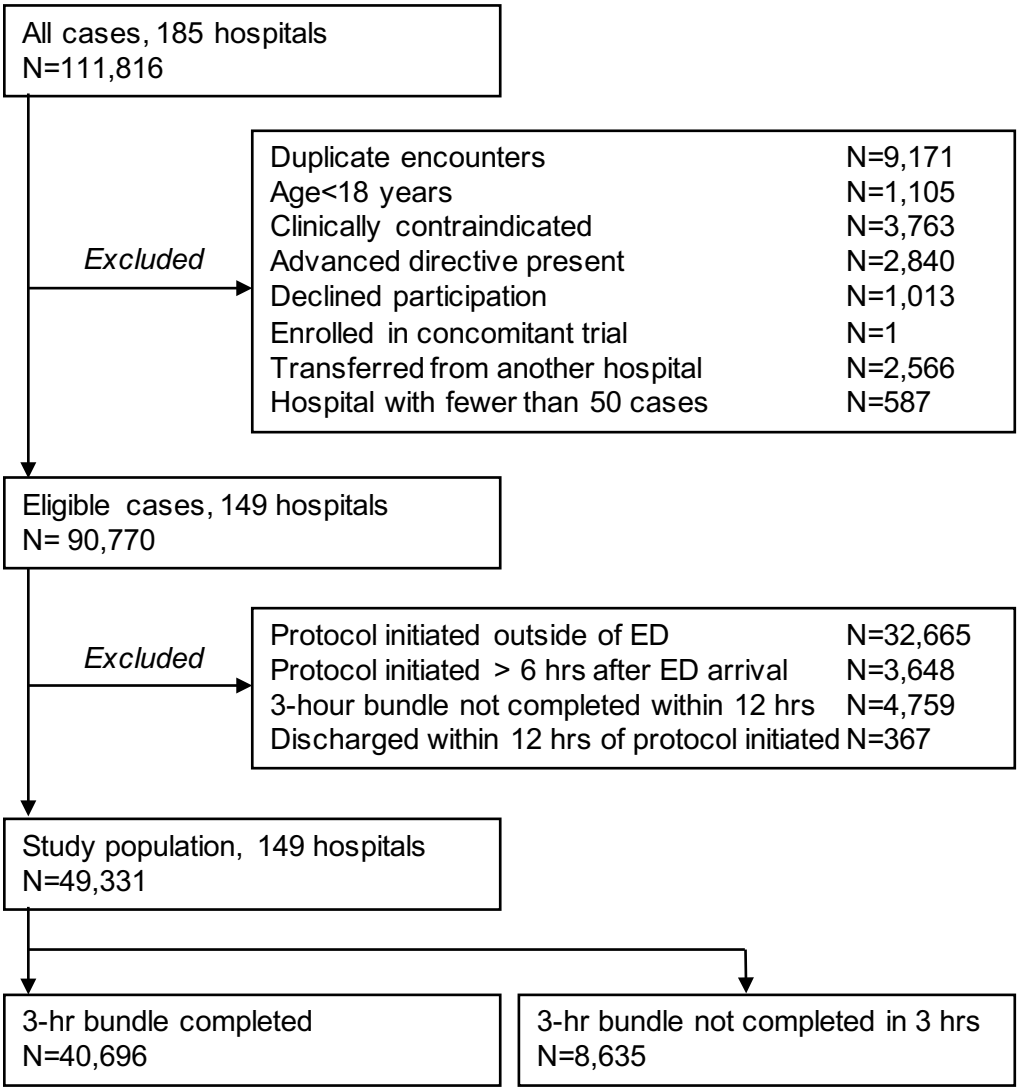


Figure S2. Calibration plot of the observed in-hospital mortality (x axis) vs. the expected in-hospital mortality (y axis) by decile of predicted risk. Derived from multivariable logistic regression model in internal validation cohort (N=4,319) using only risk-adjustment variables.

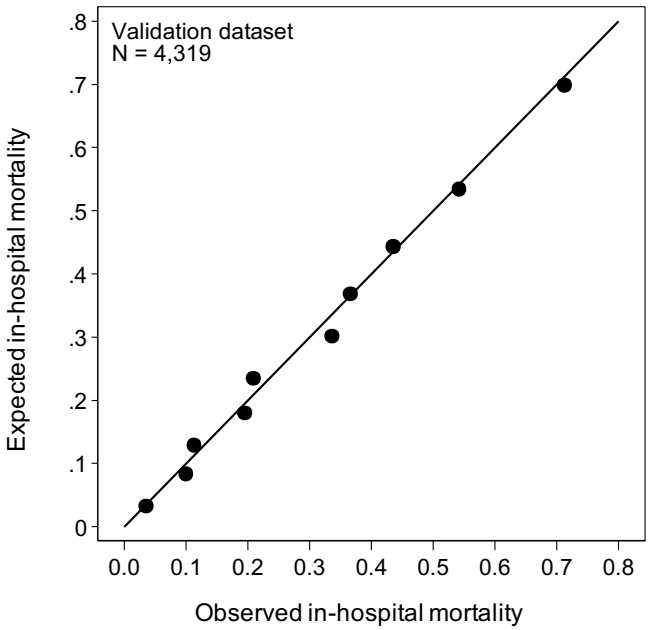


Figure S3. Risk-adjusted odd ratios of in-hospital mortality with 95% confidence interval for each hour until administration of broad spectrum antibiotics from primary model and multiple *a priori* subgroups

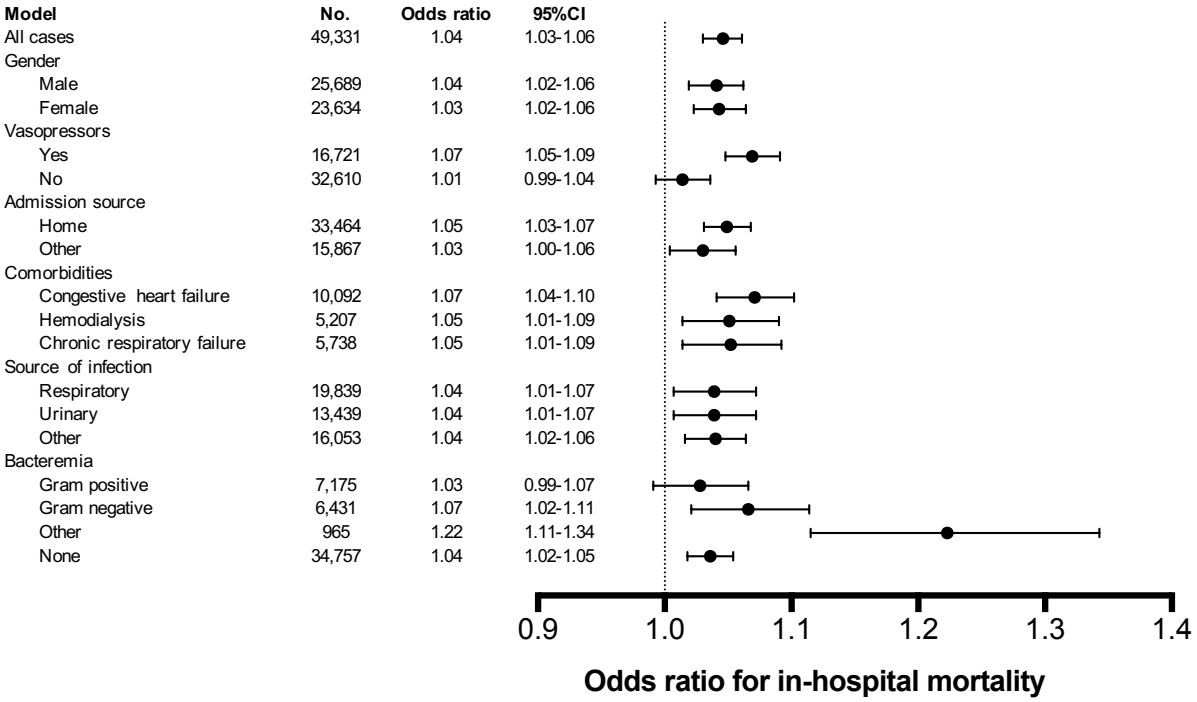


Figure S4. Risk-adjusted odd ratios of in-hospital mortality with 95% confidence interval for each hour in time to completion of the initial IV fluid bolus from primary model and multiple *a priori* subgroups

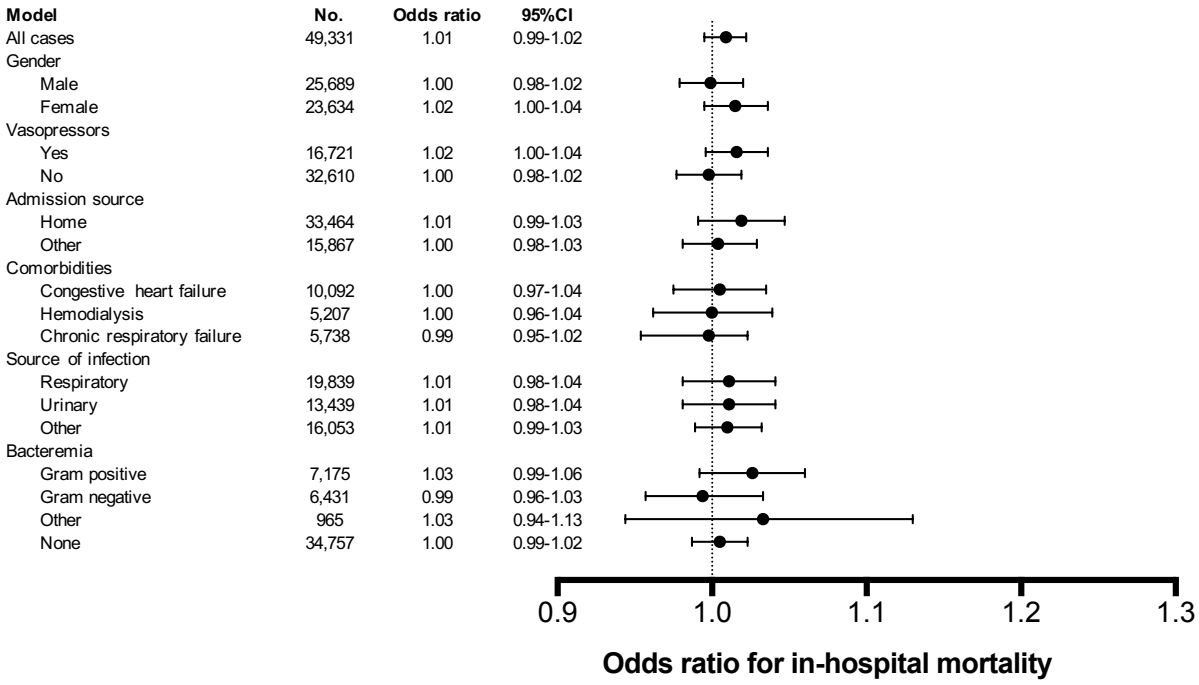


Figure S5. Risk-adjusted odd ratios of in-hospital mortality with 95% confidence interval for each hour in time to measurement of serum lactate from primary model and multiple *a priori* subgroups

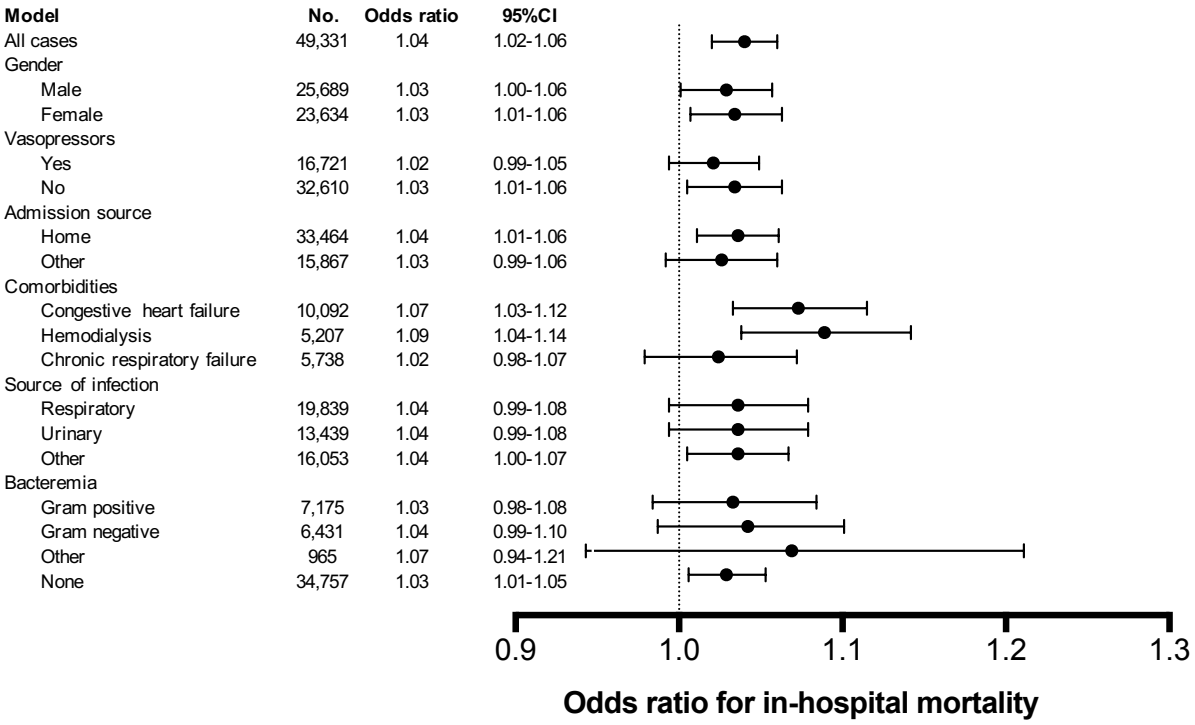


Figure S6. Risk-adjusted odd ratios of in-hospital mortality with 95% confidence interval for each hour in time to blood cultures obtained from primary model and multiple *a priori* subgroups

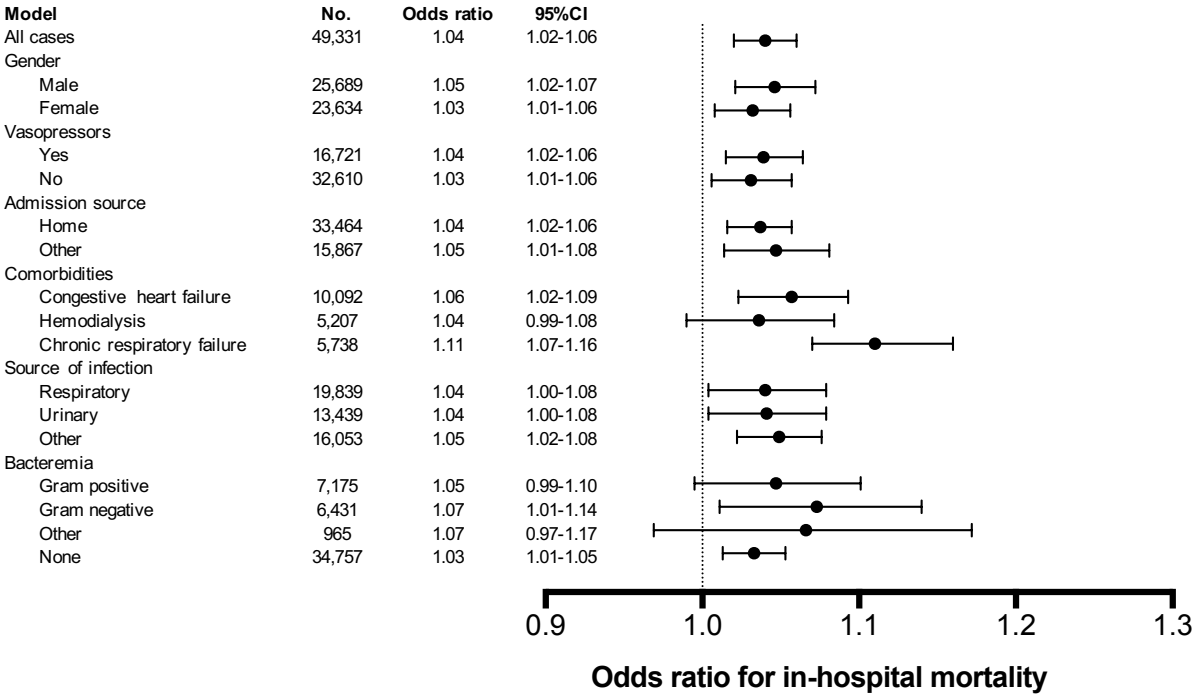
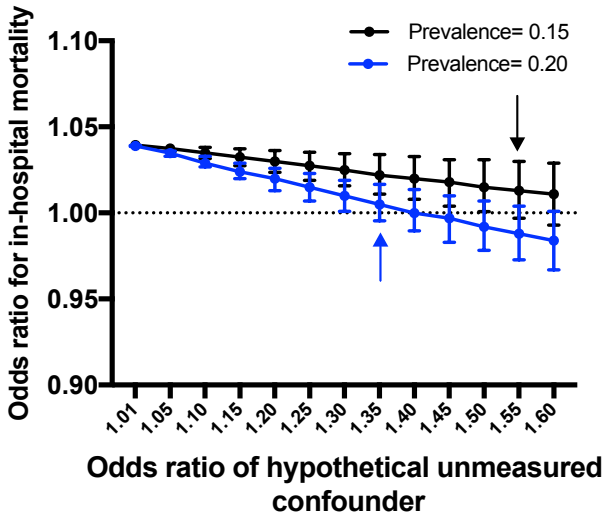


Figure S7. Quantitative bias analysis of a hypothetical unmeasured confounder.[2] This plot shows the strength of a hypothetical confounder (x axis, univariate odds ratios of confounder with in-hospital mortality) versus the odds ratio of in-hospital mortality from our adjusted model for completing the 3-hour bundle if the hypothetical confounder was included (y axis). Blue line corresponds to prevalence of hypothetical confounder (0.20) among (exposed) patients completing the 3-hour bundle one hour later than a comparable patient (unexposed), while the black line corresponds to a lower prevalence (0.15).



Model assumptions:

- Prevalence of unmeasured confounder among unexposed (completing 3-hour bundle one hour earlier) is 0.10.
- No modification of the effect of time to completing the 3-hour bundle by the unmeasured confounder
- Unmeasured confounder uncorrelated with other variables in the model

Interpretive example: To abrogate the odds ratio for the time to completing the 3-hour bundle from our primary model (OR=1.04, 95%CI: 1.02-1.06), the hypothetical unmeasured confounder must be twice as common among exposed vs. unexposed and have an odds ratio for in-hospital mortality that exceeds 1.35. Stronger confounders are required if the prevalence among exposed is lower.

Figure S8. Reliability adjusted rates across hospitals of receiving broad spectrum antibiotics within 3 hours (*Panel A*) and completing the initial IV fluid bolus within 6 hours (*Panel B*). Error bars are 95% confidence intervals.

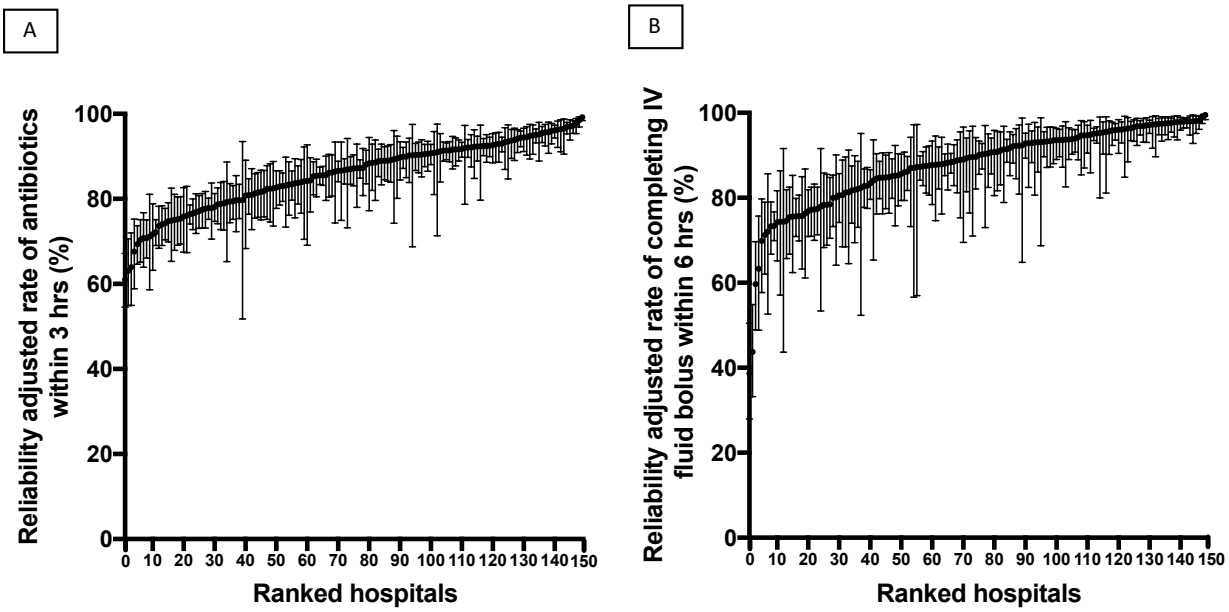


Table S1. Details of the 3- and 6- hour severe sepsis and septic shock bundles

Bundle	Eligible	Elements
3-hour	Severe sepsis or septic shock	Administration of antibiotics within 1 hour of protocol initiation *
		Drawing blood cultures prior to administration of antibiotics
		Measurement of blood lactate within 3 hours of protocol initiation
6-hour	Above plus hypotension (SBP<90) or serum lactate ≥4.0 mmol/L	Administration of a 30cc/kg intravenous fluid bolus
		Administration of vasopressors for refractory hypotension
		Re-measurement of serum lactate within 6 hours of protocol initiation

***** To be considered compliant with the 3-hour bundle within 3 hours in the primary statistical analysis, broad spectrum antibiotics were considered complete if within 3 hours after the protocol was initiated.

Table S2. Sample of New York State audit of database variables, including sepsis characteristics, comorbidities, laboratory values, and 3 and 6-hour bundle elements.

Variable	No. of charts audited	Proportion of cases with agreement (%)
Sepsis data		
Severe sepsis / shock present	7,492	98.4
Infection etiology	7,492	87.8
Site of infection	5,452	98.9
Comorbidities		
Chronic respiratory failure	2,039	89.9
Congestive heart failure	2,039	93.4
Chronic renal failure	2,039	92.7
Laboratory values and vital signs		
Platelet count	5,452	97.7
Lactate level	7,492	93.9
Hypotension	7,492	90.0
Bundle elements		
Blood cultures obtained	7,492	96.7
Lactate reported	7,492	99.0
Antibiotics given	7,492	92.5
30cc/kg IV fluid bolus completed	7,492	75.2
Vasopressors given	7,492	97.3
Outcome data		
ICU admission	7,492	99.3
Discharge status	7,492	99.2

Table S3. Characteristics of patients not completing the 3-hour bundle within 12 hours after protocol initiated (N=4,759) compared to primary cohort (N=49,331)

Variable	Did not complete the bundle within 12 hours	Primary cohort (completed the 3-hr bundle within 12 hours)
No.	**4,759**	**49,331**
Age at admission, median (IQR)	72 (60 - 84)	73 (60 - 83)
Gender, no. (%)		
Female	2,421 (50.9)	23,634 (47.9)
Male	2,336 (40.1)	25,689 (52.1)
Race, no. (%)		
White	2,967 (62.3)	33,075 (67.0)
Black	929 (19.5)	8,269 (16.8)
Asian	198 (4.2)	2,167 (4.4)
Other	665 (14.0)	5,820 (11.8)
Ethnicity, no. (%)		
Spanish/Hispanic origin	459 (9.6)	4,851 (9.8)
Not of Spanish/Hispanic	3,698 (77.7)	39,588 (80.2)
Unknown	599 (12.6)	4,874 (9.9)
Multi-ethnic	3 (0.1)	18 (0.0)
Comorbidities, no. (%)		
Chronic respiratory failure	617 (13.0)	5,738 (11.6)
Congestive heart failure	1,047 (22.0)	10,092 (20.5)
End-stage renal disease	687 (14.4)	5,207 (10.6)
Admission source, no. (%)		
Home	3,414 (71.7)	33,464 (67.8)
Clinic	202 (4.2)	1,793 (3.6)
Skilled nursing facility	1,038 (21.8)	13,233 (26.8)
Other	105 (2.3)	841 (1.8)
Site of infection, no. (%)		
Urinary	1,164 (24.5)	13,439 (27.2)
Respiratory	1,682 (35.3)	19,839 (40.2)
Gastrointestinal	703 (14.8)	4,649 (9.4)
Skin	290 (6.1)	3,480 (7.1)
Central Nervous System	13 (0.3)	239 (0.5)
Other	450 (9.5)	3,770 (7.6)
Unknown	457 (9.6)	3,915 (7.9)
Sepsis severity, no. (%)		
Severe sepsis	2,696 (56.7)	26,995 (54.7)
Septic shock	2,063 (43.3)	22,336 (45.3)
First serum lactate > 4.0 mmol/L, no. (%)	1,363 (28.6)	14,143 (28.7)
Persistent hypotension, no. (%)	2,145 (45.1)	19,469 (39.5)
In-hospital mortality, no. (%)	1,359 (28.6)	11,251 (22.8)

Table S4. Additional patient characteristics

		3-hour bundle completed in 3 hours		
	All patients	**Yes**	**No**	**P value†**
No.	49,331 (100.0)	40,696 (82.5)	8,635 (17.5)	
Site of infection, no. (%) Urinary	13,439 (27.2)	10,963 (26.9)	2,476 (28.7)	<0.001
Respiratory	19,839 (40.2)	16,806 (41.3)	3,033 (35.1)	
Gastrointestinal	4,649 (9.4)	3,580 (8.8)	1,069 (12.4)	
Skin	3,480 (7.1)	2,921 (7.2)	559 (6.5)	
Central Nervous System	239 (0.5)	201 (0.5)	38 (0.4)	
Other	3,770 (7.6)	3,073 (7.6)	697 (8.1)	
Unknown	3,915 (7.9)	3,152 (7.8)	763 (8.8)	
Positive blood cultures, no. (%)				<0.001
Gram positive	7,178 (14.5)	6,078 (14.9)	1,100 (12.7)	
Gram negative	6,431 (13.0)	5,455 (13.4)	976 (11.3)	
Other ^	965 (2.0)	789 (1.9)	176 (2.0)	
None	34,757 (70.5)	28,374 (69.2)	6,383 (73.9)	
First serum lactate > 4.0 mmol/L, no. (%)	14,143 (28.7)	11,941 (29.3)	2,205 (25.5)	< 0.001
Persistent hypotension, no. (%)	19,469 (39.5)	15,915 (39.1)	3,554 (41.2)	< 0.001

† *p*-values based on Pearson chi-square for categorical variables and the Wilcoxon rank-sum test for continuous variables
^ Other includes anaerobic, mixed, viral, fungal, and yeast cultures

Table S5. Risk adjusted odds ratio of in-hospital mortality with 95% confidence interval for time to completing the 3-hour bundle and confounders

Variable	Odds ratio for in-hospital mortality	95% CI		*p*-value
Time to complete the 3-hour bundle, per hour	1.036	1.023	1.048	< 0.001
Month of study	0.992	0.988	0.995	< 0.001
Race/ethnicity				
White, non-Hispanic	ref			
Black, non-Hispanic	0.996	0.92	1.077	0.912
Hispanic	0.871	0.793	0.958	0.004
Multi-racial	1.171	0.943	1.454	0.154
Unknown, non-Hispanic	0.955	0.865	1.054	0.356
Unknown	0.995	0.908	1.091	0.918
Payer				
Medicare	ref			
Medicaid	0.983	0.904	1.068	0.684
Private, Health Maintenance Organization	1.038	0.965	1.116	0.316
Self-Pay	1.797	1.441	2.241	< 0.001
Other	1.043	0.908	1.199	0.55
Site of infection				
Urinary	ref			
Respiratory	1.773	1.65	1.907	< 0.001
Gastrointestinal	1.948	1.781	2.131	< 0.001
Skin	1.588	1.42	1.776	< 0.001
Central Nervous System	1.446	0.977	2.139	0.065
Other	1.666	1.504	1.845	< 0.001
Unknown	2.309	2.101	2.538	< 0.001
Admission source				
Non-health facility	ref			
Clinic	0.908	0.781	1.055	0.207
Skilled nursing facility / intermediate care facility	1.286	1.216	1.36	< 0.001
Another health care facility	1.068	0.84	1.357	0.593
Between unit transfer	1.311	0.758	2.266	0.333
Hospice	1.951	0.99	3.844	0.053
Other	0.893	0.609	1.31	0.562
Septic shock diagnosis				
Severe Sepsis	ref			
Septic Shock	2.199	2.075	2.331	< 0.001
Platelet count				
No	ref			
Yes	1.339	1.268	1.414	< 0.001
Metastatic cancer				
No	ref			

Yes	1.871	1.734	2.018	< 0.001
Lymphoma/leukemia/multiple myeloma				
No	ref			
Yes	1.077	0.967	1.201	0.178
Interaction terms included (not shown, all p<0.001): i.) Lower respiratory tract infection x mechanical ventilation, ii.) age x square root of comorbidities x age, iii.) first serum lactate x square root of comorbidities				

Table S6. Sensitivity analyses

Model	No. of encounters in the model	OR (95%CI) for one hour change in completing the 3-hr bundle	OR (95%CI) for hour change in administration of antibiotics	OR (95%CI) for hour change in completing the initial IV fluid bolus
Primary cohort	49,331	1.036 (1.023 – 1.048) p < 0.001	1.046 (1.030 – 1.061) p < 0.001	1.009 (0.995 – 1.022) p = 0.215
Includes protocol initiated within 24 hours after ED arrival	51,573	1.035 (1.023 – 1.047) p < 0.001	1.044 (1.029 – 1.059) p < 0.001	1.001 (1.000 – 1.002) p = 0.029
All encounters with 3-hour bundle completed up to 24 hours after protocol initiated	49,921	1.023 (1.015 – 1.030) p < 0.001	1.034 (1.028 – 1.045) p < 0.001	1.001 (1.000 – 1.003) p = 0.012
Up to 24 hours for protocol initiated and up to 24 hours to complete the 3 hour bundle	52,902	1.025 (1.018 – 1.033) p < 0.001	1.037 (1.027 – 1.048) p < 0.001	1.001 (1.000 – 1.002) p = 0.019
ED arrival as “time zero”	49,331	1.032 (1.023 – 1.048) p < 0.001	1.037 (1.023 – 1.051) p < 0.001	1.009 (0.995 – 1.024) p = 0.198
Including hospice discharges as in-hospital deaths	49,331	1.034 (1.021 – 1.046) p < 0.001	1.044 (1.039 – 1.059) p < 0.001	1.009 (0.995 – 1.023) p = 0.226
Excluding bundle elements that occur prior to protocol initiation	30,782	1.036 (1.022 – 1.047) p < 0.001	1.043 (1.027 – 1.059) p < 0.001	1.012 (0.996 – 1.027) p = 0.139

Table S7. Hospital characteristics stratified by quartile of reliability-adjusted rate of completing the 3-hr bundle within 3 hours.

Characteristic	Quartiles of the probability of completing the 3-hour bundle in 3 hours			
	1st	2nd	3rd	4th
	Lowest	Below median	Above median	Highest
No. of hospitals	38	41	35	35
No. of patients	12,647	12,048	12,891	11,745
Serum lactate, median [IQR], mmol/L	2.8 [1.8 - 4.5]	2.7 [1.7 - 4.3]	2.7 [1.7 - 4.4]	2.7 [1.7 - 4.3]
Area, no. (%) *				
Metro	37 (97.4)	32 (78.1)	30 (85.7)	31 (88.6)
Rural	1 (2.65)	9 (21.9)	5 (14.3)	4 (11.4)
Teaching facility, no. (%) ~				
No	8 (21.0)	14 (34.1)	10 (28.6)	16 (45.7)
Yes	30 (79.0)	27 (65.9)	25 (71.4)	19 (54.3)
Number of hospital beds, median (IQR)	312 (223-464)	265 (130-362)	312 (192-514)	228 (171-375)

*Teaching hospital defined by NYSDOH using graduate medical education codes on Medicaid clams, verified by the Office of Primary Care and Health Systems Management and the Department of Education

~Hospital rurality is defined by rural-urban commuting codes, where rural corresponds to non-metropolitan / urban population

References

1. Levy MM, Fink MP, Marshall JC, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31(4):1250-1256.
2. Lash TL FM, Fink AK. Applying quantitative bias analysis to epidemiologic data. Springer; 2009.