Supplementary Material*

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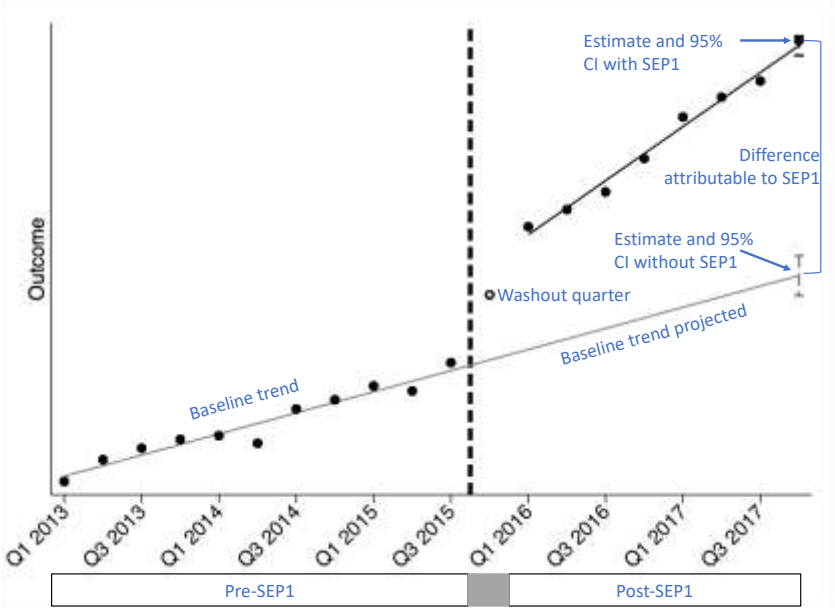
* This supplementary material was provided by the authors to give readers further details on their article. The material was reviewed but not copyedited.

I. Overview of analytic approach

In order to evaluate the impact of the SEP-1 measure program on sepsis treatment processes and clinical outcomes, we compared patients admitted with suspected infection and organ dysfunction prior to the October 2015 implementation of SEP-1 to those admitted after the program's implementation. The study timeframe ran from January 2013 to December 2017, excluding a washout period from October 2015 to December 2015. We used granular clinical data from the electronic health records of 11 hospitals in the UPMC Health System. Our analysis accounted for pre-existing temporal trends in treatment processes and outcomes, and the effect of SEP-1 on both the level and trend of these process and outcome variables. We did not include a control group, because the federal measure applied to all hospitals. Thus, our approach takes the form of a longitudinal study of hospitals using repeated cross-sectional patient cohorts.



Supplement Figure 1. Overview of analytic model. Solid black circles are the point estimates for the outcome across the population. Hollow black circle is Quarter 4 2015, excluded from the models as a washout quarter. Vertical dashed line demarcates SEP-1 implementation.

Our model estimates the baseline trend in the outcome of interest prior to SEP-1 implementation, which we can then project forward into the post-SEP-1 implementation period (solid gray line). Our model also estimates the change in level and slope associated with SEP-1 (solid black line). To illustrate the clinical impact of SEP-1 on a given process or clinical outcome variable, we used postestimation margins to estimate the difference between the outcome expected with SEP-1 and the outcome projected in the absence of SEP-1 in Quarter 4 2017 (blue bracket). This approach assumes that the linear trend in the pre-SEP-1 period extends unchanged in the post-SEP-1 period, which cannot be tested in the absence of a control group.

II. Analytic model

For each dependent variable of interest, we fitted a regression model at the patient level. We accounted for a change in level and trend of the dependent variable in association with SEP-1 implementation, using a model with the following general form for patient i admitted to hospital h in quarter q:

$$f(E(y_{ihq}|x)) = \beta_0 + \beta_1 time_q + \beta_2 post_i + \beta_3 time_q * post_i + \beta_4 winter_q + \sum_{j=5}^{34} \beta_j x_{ji} + \sum_{h=1}^{H-1} \eta_h I(Hospital = h)$$

We used Stata's `glm` generalized linear models command with robust standard errors. For binary outcomes we used a logit link function. For the continuous process measures we used a log gamma function. Because each patient was included only once, nesting of patients within hospitals was captured by the hospital indicator fixed effects.

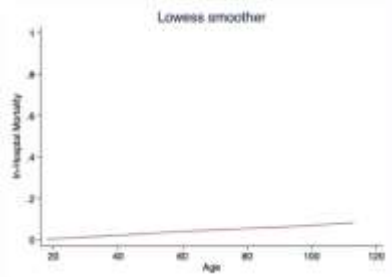
<u>The variables included in all models are</u>:

time: a quarterly time variable; the coefficient represents the baseline slope
post: an indicator for SEP-1 implementation, set to 0 in the pre-SEP1 period and 1 in the post-SEP1 period; the coefficient represents the shift in level associated with SEP1
time*post: the interaction of time and SEP1 implementation; the coefficient represents the change in slope associated with SEP1
Hospital: hospital indicators modeled as a hospital-specific fixed effect

<u>The adjustment covariates in the models for clinical outcomes are as follows</u>. These adjustment variables are NOT included in the models of process measures (antibiotics, lactate measurement, etc):

winter: an indicator for winter months to account for seasonality in sepsis outcomes, set to 1 for January, February, and March, and 0 in all others
x_5-x_{35}: patient-level variables as follows:

- Age: modeled as linear splines with knots at 50, 60, 70, 80 (see lowess plot below)



Supplement Figure 2. Lowess graph for age and mortality

- Indicators for Elixhauser comorbidities (combined hypertension with/without complication into single indicator; combined diabetes with/without complication into single indicator; excluded ulcer due to low prevalence; and excluded CHF due to significant increase in frequency following ICD-9 to ICD-10 transition).
- Source of infection categorical variable
- SOFA score within 6 hours of ED arrival, included as a continuous variable

To illustrate the clinical impact of SEP-1, we used Stata's `margins` command to estimate the expected values and confidence intervals of each dependent variable in Quarter 4 of 2017 in the presence of (post=1) and in the absence of (post=0) SEP1. This command estimates the expected value averaged across all observed patient covariate values and hospitals. We then used Stata's `margins, contrast(effects)` command to estimate the difference between these expected values, and confidence intervals for these estimates—representing the effect of SEP1 on the dependent variable of interest in Quarter 4 of 2017, two years after SEP-1 implementation.

III: Hospital characteristics

The data for our analyses came from electronic health records of patients admitted to any of 11 hospitals in the UPMC Health System. To characterize these hospitals' characteristics (for assessment of generalizability), we used 2016 data from Medicare's Healthcare Cost Reporting Information System. The median number of hospital beds was 194, with a range of 47 to 1160. The hospitals had a median of 14 intensive care unit beds, with a range of 4 to 212. Four of the hospitals were non-teaching, and in the remaining seven teaching hospitals there was a median of 62 resident full-time-equivalents, with a range of 14 to 700.

We also obtained data from the Hospital Compare release of fiscal year 2017 SEP-1 performance information. The median SEP-1 compliance rate in fiscal year 2017 was 38%, with a range of 19 to 54%; the median number of cases reported for the SEP-1 measure was 148, with a range of 71 to 241.

Thus, we analyzed data from a broad group of hospitals with varying size, teaching status, SEP-1 performance, and SEP-1 reported case volume, increasing the generalizability of our findings to other settings.

IV: Definition of process variables

We defined process variables with the goal of aligning how the SEP-1 measure gives "credit" for compliant treatment, within the limits of available data (as abstraction for the measure itself often requires manual chart review). In the primary analysis, these variables are all defined in reference to the "time zero" of suspected infection, based on the time stamp for the initial body fluid culture.

1. SEP-1 compliant antibiotics

Treatment for a patient was considered compliant with SEP-1's antibiotic requirement if the patient received either monotherapy with an antibiotic that provides broad coverage, or combination gram-positive and gram-negative therapy (see Supplement Table 1 below).

Supplement Table 1. SEP-1 compliant monotherapy or combination therapy antibiotics

	Combination therapy; requires A + B	
Monotherapy	Combination A Gram-negative	Combination B Gram-positive
• Ampicillin-sulbactam	• Amikacin	• Ampicillin
• Cefepime	• Aztreonam	• Cefazolin
• Cefotaxime	• Ciprofloxacin	• Cefotetan
• Ceftaroline	• Gentamicin	• Cefoxitin
• Ceftazidime	• Tigecycline	• Dalbavancin
• Ceftazidime-avibactam	• Tobramycin	• Daptomycin
• Ceftolazone-tazobactam		• Linezolid
• Ceftriaxone		• Nafcillin
• Doripenem		• Oxacillin
• Ertapenem		• Penicillin
• Imipenem-cilastatin		• Tedizolid
• Levofloxacin		• Teleavancin
• Meropenem		• Vancomycin
• Moxifloxacin		• Clindamycin
• Piperacillin-tazobactam		
• Ticarcillin-clavulanate		

2. SEP-1 compliant lactate measurement

Treatment for a patient was considered compliant with SEP-1's lactate requirement if the lactate was measured within 6 hours prior to sepsis onset, and up to 3 hours after sepsis onset, which is consistent with the time window allowed within the SEP-1 measure.

3. SEP-1 compliant fluid administration

Treatment for a patient was considered compliant with SEP-1's IV fluid 30cc/kg requirement if the volume recorded as administered to the patient was greater than or

equal to 27cc/kg, as the SEP-1 measure information form allows credit given when the volume administered is within 10% of 30cc/kg. The time window for administration ran from up to 6 hours prior to sepsis onset and up to 3 hours after sepsis onset, again consistent with the measure specifications.

4. SEP-1 compliant repeat lactate measurement

Treatment for a patient was considered compliant with the repeat lactate requirement if there was an initial lactate checked within 3 hours of sepsis onset, that initial lactate value was >=2mmol/L, and there was any repeat lactate checked within 6 hours of sepsis onset.

5. Vasopressors within 6 hours of hypotension

The SEP-1 measure requires the administration of vasopressors in the setting of persistent hypotension despite fluid resuscitation. This is contingent on the density of vital sign recordings surrounding sepsis onset and fluid administration. For simplicity, we defined vasopressor administration as compliant if it occurred within 6 hours of the first blood pressure recording that included a mean arterial pressure of <65 mm Hg.

V. Definition of hierarchical infection source categorical variable

We used clinical microbiology results to identify positive cultures. We did not consider blood cultures positive for skin contaminants (coagulase negative staph, diphtheroids) to represent a true infection source. We did not consider Candida or yeast in the urine or lung to represent a true infection source. Below is information on the mortality and ICU admission rates according to source of positive cultures in a univariate manner:

Supplement Table 2. Clinical outcomes by source of positive microbiologic sample

Positive clinical microbiology source	In-hospital mortality rate	ICU admission rate
Lung	13.3%	53.4%
Bloodstream	9.2%	40.2%
Urine	4.9%	24.8%
Wound	4.2%	25.3%
Other	8.1%	43.0%

Based on these observations, we made a hierarchical infection source categorical variable, in which the hierarchical order was lung→bloodstream→urine→wound→other. The mortality and ICU admission rates for this hierarchical variable are outlined below:

Supplement Table 3. Clinical outcomes for hierarchical infectious source variable

Hierarchical source category	Frequency in cohort	In-hospital mortality rate	ICU admission rate
Lung	3.6%	12.8%	52.7%
Bloodstream	9.0%	8.4%	38.5%
Urine	17.7%	4.2%	20.4%
Wound	2.8%	2.1%	18.0%
Other	3.4%	7.1%	35.8%
None	63.4%	3.6%	20.3%

VI. Patient exclusion criteria

We excluded patients who were transferred between hospitals, because the process of interfacility transfer can disrupt time-sensitive care processes (1), and the SEP-1 measure does not apply to transfers. We excluded patients who were discharged from the hospital within 24 hours, because these patients were likely either too well or too ill to benefit from protocolized sepsis care. We also excluded patients with a hospital length of stay of greater than 30 days, because of the potential for discharge bias in mortality assessment (2). We excluded patients with an order for comfort measures within 24 hours of hospital admission, because their outcomes were likely modified by factors unrelated to the quality of sepsis resuscitation, and there is an exclusion in the SEP-1 measure for patients treated with early comfort measures. We excluded a small number of patients who had time stamps for process measures prior to the time of ED registration. In the event of multiple encounters per patient, we randomly selected a single encounter, in order to preserve independence of observations.

VII: Report of coefficients for slope and level change from primary analyses

Supplement Table 4. Coefficients for slope and level change for process measures from primary analysis

	Pre-SEP-1 quarterly trend				Post-SEP-1 level change				Post-SEP-1 quarterly trend change			
Variable	β	P	CI low	CI high	β	P	CI low	CI high	β	P	CI low	CI high
All patients												
Antibiotics within 3 hours	0.007	0.073	-0.001	0.014	0.019	0.62	-0.056	0.094	0.023	<0.001	0.011	0.038
Lactate within 3 hours	0.064	<0.001	0.055	0.072	0.523	<0.001	0.444	0.602	0.071	<0.001	0.056	0.085
30cc/kg IVF within 3 hours	0.019	0.007	0.005	0.033	0.288	<0.001	0.159	0.417	0.008	0.50	-0.015	0.030
Repeat Lactate within 6 hours*	0.002	0.86	-0.020	0.024	0.759	<0.001	0.575	0.943	0.073	<0.001	0.045	0.102
Vasopressors within 6 hours**	0.009	0.39	-0.011	0.029	-0.090	0.40	-0.300	0.121	<0.001	0.98	-0.038	0.040
Patients with MAP<65 in first 6hr												
Antibiotics within 3 hours	0.017	0.03	0.002	0.032	-0.095	0.23	-0.242	0.062	0.035	0.02	0.006	0.065
Lactate within 3 hours	0.068	<0.001	0.053	0.084	0.552	<0.001	0.384	0.719	0.074	<0.001	0.041	0.108
30cc/kg IVF within 3 hours	0.027	0.007	0.008	0.047	0.303	0.002	0.113	0.494	0.009	0.60	-0.025	0.043
Repeat Lactate within 6 hours*	0.015	0.34	-0.016	0.045	0.642	<0.001	0.380	0.904	0.075	<0.001	0.032	0.117
Vasopressors within 6 hours**	0.009	0.39	-0.011	0.029	-0.090	0.40	-0.300	0.121	<0.001	0.98	-0.038	0.040
Patients requiring vasopressors												
Antibiotics within 3 hours	0.037	0.04	0.002	0.073	-0.239	0.20	-0.606	0.127	0.022	0.54	-0.047	0.090
Lactate within 3 hours	0.074	<0.001	0.037	0.111	0.254	0.26	-0.189	0.697	0.058	0.23	-0.036	0.151
30cc/kg IVF within 3 hours	0.042	0.03	0.004	0.080	0.201	0.29	-0.172	0.574	-0.011	0.75	-0.078	0.056
Repeat Lactate within 6 hours*	0.045	0.041	0.002	0.088	0.415	0.045	0.010	0.819	0.063	0.089	-0.010	0.135

MAP: mean arterial pressure; IVF: intravenous fluid

*indicates a repeat lactate within 6 hours of suspected infection, when the initial lactate is over 2 mmol/L

**indicates vasopressor initiation within 6 hours of initial hypotension. The results are identical between the overall cohort and the hypotensive cohort, because patients without hypotension were by definition excluded in the regression.

Supplement Table 5. Coefficients for slope and level change for clinical outcome measures from primary analysis

	Pre-SEP-1 quarterly trend				Post-SEP-1 level change				Post-SEP-1 quarterly trend change			
Variable	β	P	CI low	CI high	β	P	CI low	CI high	β	P	CI low	CI high
All patients												
ICU admission	-0.022	<0.001	-0.032	-0.012	-0.050	0.33	-0.151	0.051	0.028	0.003	0.010	0.046
In-hospital mortality	-0.019	0.046	-0.037	0.000	0.012	0.90	-0.184	0.208	0.002	0.92	-0.033	0.037
Discharge home*	0.021	<0.001	0.012	0.030	0.089	0.065	-0.005	0.184	-0.028	0.001	-0.045	-0.011
Patients with MAP<65 in first 6hr												
ICU admission	-0.016	0.074	-0.033	0.002	0.051	0.58	-0.234	0.131	0.028	0.100	-0.005	0.060
In-hospital mortality	-0.012	0.28	-0.044	0.013	0.490	0.75	-0.255	0.350	0.012	0.66	-0.042	0.066
Discharge home*	0.034	<0.001	0.015	0.052	0.050	0.62	-0.148	0.248	-0.055	0.003	-0.091	-0.019
Patients requiring vasopressors												
ICU admission	-0.086	0.185	-0.213	0.041	0.001	0.99	-1.180	1.181	0.283	0.012	0.063	0.504
In-hospital mortality	-0.018	0.38	-0.059	0.022	-0.068	0.76	-0.495	0.360	0.029	0.46	-0.048	0.105
Discharge home*	-0.012	0.63	-0.061	0.037	0.370	0.156	-0.141	0.881	0.061	0.186	-0.152	0.030

ICU: intensive care unit
*discharge to home only evaluated among patients who survived to hospital discharge
All outcomes adjusted for age, Elixhauser comorbidities, admission SOFA score, source of infection, and seasonality

VIII: Hospital-level analyses

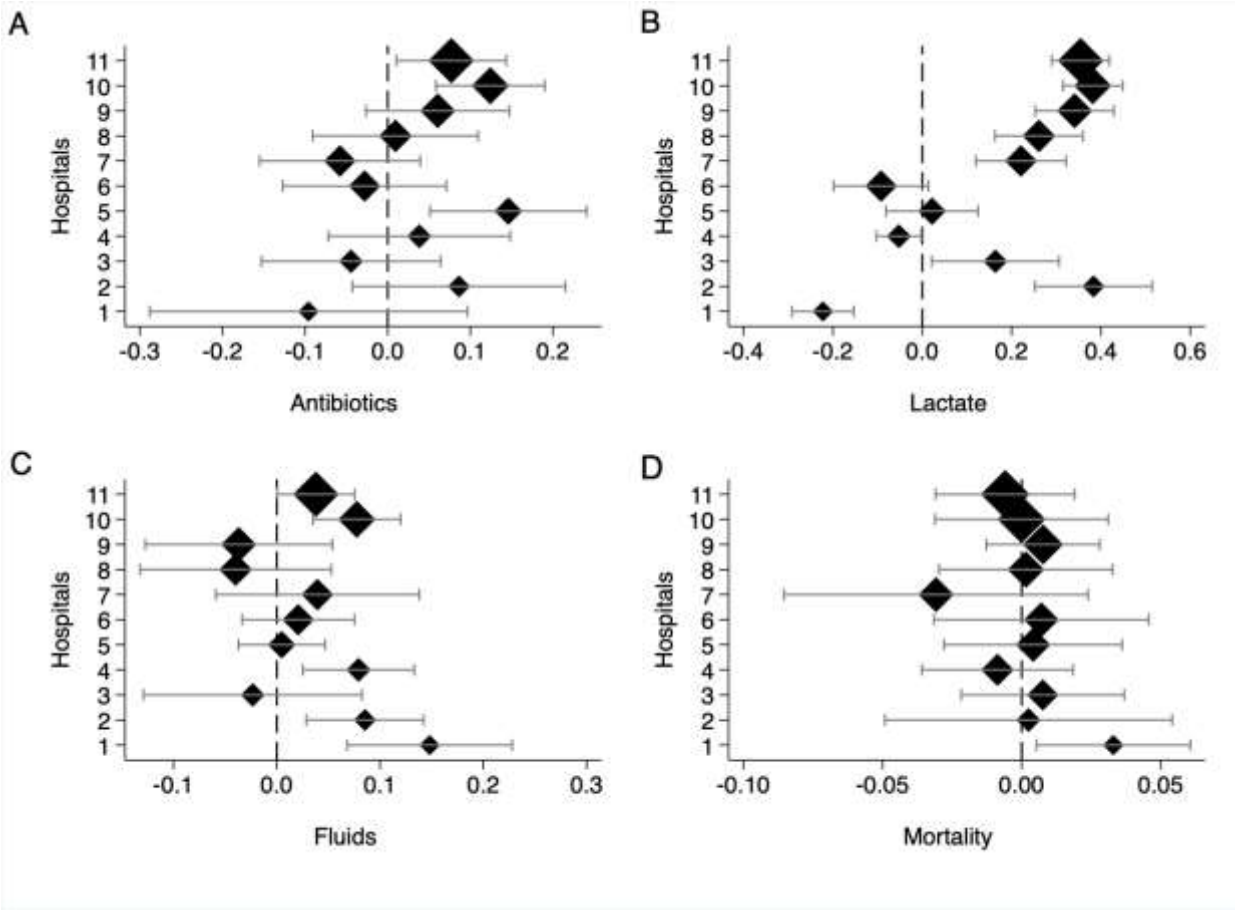
Our primary analysis reported results averaged across hospitals, leaving open the possibility that processes and outcomes changed in some hospitals but not others, and in particular that any null effects were due to the averaging out of significant changes in opposing directions. To assess variation in the effects of SEP-1 across hospitals, we performed a hospital-level analysis of changes in antibiotic compliance at 3 hours, lactate compliance at 3 hours, fluid compliance at 3 hours, and risk-adjusted in-hospital mortality. We repeated the models from the main analysis stratified by hospital (i.e. 11 separate models for each outcome), and estimated the difference in Quarter 4 of 2017 for each dependent variable in each hospital.

To visualize the results, we created a graph for each dependent variable (see figure below). On the X-axis of each panel is the absolute difference in expected values in Quarter 4 of 2017 (i.e. effect of SEP-1), on the same [0,1] probability scale as illustrated on the y-axis of the graphs in the main manuscript. On the y-axis of each panel are the hospitals, ordered by sample size in Quarter 4 of 2017. The diamonds are also sized according to the sample size in each hospital. The error bars represent 95% confidence intervals for the difference in Quarter 4 of 2017 for each hospital.

The figures illustrate that seven of 11 hospitals had an increase in antibiotic compliance, which was statistically significant in four of the hospitals. Eight of 11 hospitals had an increase in lactate compliance, which was statistically significant in seven of the hospitals. Eight of 11 hospitals had an increase in fluid compliance, which was statistically significant in four hospitals. Seven of 11 hospitals had an increase in mortality while four hospitals had a decrease, although the magnitude of the changes was generally small, with results clustering around zero and confidence intervals crossing zero. In only one hospital did the confidence interval for the difference in mortality not cross zero; this was for an increase in mortality in the hospital with the fewest cases

Overall, while these results show some variation in the effect across hospitals, the effects were generally consistent and in a similar direction in the largest hospitals (with the most reliable estimates). The results were also most consistent for risk-adjusted mortality, and so do not suggest that the overall null effect of SEP-1 on mortality in the main analysis was the result of significant positive and negative differences cancelling one another out. Nor is there a clear pattern to suggest that mortality improved in hospitals that demonstrated increases in compliance with process measures.

Supplement Figure 3. Hospital-specific differences in antibiotics (panel A), lactate (panel B), fluids (panel C), and risk-adjusted in-hospital mortality (panel D) in Quarter 4 of 2017. On the X-axis of each panel is the absolute difference in expected values in Quarter 4 of 2017 (i.e. effect of SEP-1), on the same [0,1] probability scale as illustrated on the y-axis of the graphs in the main manuscript. On the y-axis of each panel are the hospitals, ordered by sample size in Quarter 4 of 2017. The diamonds are also sized according to the sample size in each hospital. The error bars represent 95% confidence intervals for the difference in Quarter 4 of 2017 for each hospital. Vertical dashed lines are reference lines for a null effect.



IX: Sensitivity analyses

A. Process measures as dichotomized variables at 3 hours relative to ED registration

In our primary analysis, we used the time of suspected infection (based on orders placed for body fluid cultures) as "time zero" for sepsis onset. In this sensitivity analysis, we used the time of ED registration as time zero and examined compliance with antibiotics and lactate measurement within 3 hours of ED registration as dichotomized outcomes. We used a logit model without patient-level covariate adjustment.

Supplement Table 6. Changes in unadjusted process measures after SEP-1, defined relative to ED registration time. The table shows the effect of SEP-1 on processes of care, illustrated as rate differences in Quarter 4 of 2017, 2 years after SEP-1 implementation.

	Quarter 3, 2015 (pre-SEP-1)	**Quarter 4, 2017**		**Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)**	
		Expected (without SEP-1)	**Observed (with SEP-1)**		
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
All patients					
Antibiotics within 3 hours (%)	30.2 (29.2 – 31.2)	29.7 (27.3 – 32.0)	36.6 (35.5 – 37.8)	7.0 (4.4 – 9.6)	<0.001
Lactate within 3 hours (%)	31.1 (30.0 – 32.1)	44.0 (41.1 – 46.9)	67.1 (66.0 – 68.2)	32.1 (20.0 – 26.2)	<0.001
Patients with MAP<65 in first 6 hours					
Antibiotics within 3 hours (%)	35.3 (33.1 – 37.4)	34.3 (29.3 – 39.6)	46.5 (43.9 – 49.1)	12.1 (6.3 – 17.8)	<0.001
Lactate within 3 hours (%)	47.3 (45.0 – 49.6)	61.6 (56.4 – 66.8)	81.1 (79.1 – 83.0)	19.5 (14.0 – 25.0)	<0.001
Patients requiring vasopressors					
Antibiotics within 3 hours (%)	49.3 (44.3 – 54.4)	54.0 (41.8 – 66.1)	56.6 (50.9 – 62.2)	2.6 (-10.8 – 16.0)	0.70
Lactate within 3 hours (%)	70.3 (65.8 – 74.7)	80.8 (72.9 – 88.7)	86.7 (82.9 – 90.6)	5.9 (-2.8 – 14.7)	0.184

MAP: mean arterial pressure; IVF: intravenous fluid

Time zero is ED registration time, so all process measures are reported within 3 hours of ED registration.

B. Process measures as continuous variables relative to suspected infection

In our primary analysis, we evaluated changes in process measures as dichotomized performance at 3 hours from time zero (suspected infection). In a sensitivity analysis, we examined changes in time to completion of the processes of care (antibiotics and lactate), and the amount of fluid administered by 3 hours. For these models, we assumed a gamma distribution with log link, and we did not adjust for patient-level covariates. We performed this analysis in the overall cohort.

Supplement Table 7. Changes in unadjusted process measures after SEP-1, defined as continuous variables relative to time of suspected infection. The table shows the effect of SEP-1 on processes of care, illustrated as differences in Quarter 4 of 2017, 2 years after SEP-1 implementation.

	Quarter 3, 2015 (pre-SEP-1)	**Quarter 4, 2017**		**Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)**	
		Expected (without SEP-1)	**Observed (with SEP-1)**		
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
All patients					
Time to antibiotic, hours	4.1 (3.9 – 4.3)	3.8 (3.4 – 4.2)	3.7 (3.5 – 3.9)	-0.1 (-0.5 – 0.3)	0.73
Time to lactate, hours	0.8 (0.5 – 1.2)	0.7 (0.2 – 1.2)	0.3 (0.1 – 0.4)	-0.4 (-0.9 – 0.1)	0.102
Volume of IVF within 3 hours, cc/kg	13.9 (13.6 – 14.3)	15.0 (14.2 – 15.9)	16.4 (16.0 – 16.8)	1.4 (0.4 – 2.3)	0.004

IVF: intravenous fluid
Measures are defined relative to time of suspected infection

C. Process measures as continuous variables relative to ED registration

Similar to (B), we repeated the analysis of time to antibiotic and lactate measurement as continuous outcomes relative to the time of ED registration. We used a model with a gamma distribution and log link, without patient level covariate adjustment. The results are below and relatively similar to those in (B).

Supplement Table 8. Changes in unadjusted process measures after SEP-1, defined as continuous variables relative to time of ED registration. The table shows the effect of SEP-1 on processes of care, illustrated as differences in Quarter 4 of 2017, 2 years after SEP-1 implementation.

	Quarter 3, 2015 (pre-SEP-1)	**Quarter 4, 2017**		**Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)**	
		Expected (without SEP-1)	**Observed (with SEP-1)**		
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
All patients					
Time to antibiotic, hours	5.4 (5.2 – 5.6)	5.1 (4.7 – 5.5)	4.9 (4.8 – 5.1)	-0.2 (-0.6 – 0.3)	0.43
Time to lactate, hours	1.8 (1.7 – 1.9)	1.6 (1.4 – 1.7)	1.3 (1.2 – 1.3)	-0.3 (-0.5 – 0.1)	0.003

Measures are defined relative to time of ED registration

E. Including hospice in definition of mortality

Our primary analysis did not include discharge to hospice in the definition of in-hospital mortality. We repeated the analysis, including both inpatient mortality and hospice discharge in a single mortality indicator variable. We analyzed changes in this combined mortality and hospice variable using a logit model adjusted for comorbidities, source of infection, age, SOFA score, and seasonality, as in our primary analysis.

Supplement Table 9. Changes in risk-adjusted composite of mortality and hospice discharge after SEP-1. The table shows the effect of SEP-1, illustrated as rate differences in Quarter 4 of 2017, 2 years after SEP-1 implementation.

	Quarter 3, 2015 (pre-SEP-1)	**Quarter 4, 2017**		**Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)**	
		Expected (without SEP-1)	**Observed (with SEP-1)**		
Morality or hospice, %	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
All patients	8.3 (7.9 – 8.9)	8.2 (6.8 – 9.6)	6.8 (6.3 – 7.4)	-1.4 (-2.9 – 0.1)	0.064
Patients with MAP<65 within 6 hours	14.7 (13.2 – 16.3)	15.1 (11.3 – 18.9)	13.1 (11.4 – 14.8)	-2.0 (-6.0 – 2.1)	0.34
Patients requiring vasopressors	36.1 (31.4 – 40.7)	34.2 (23.1 – 45.3)	36.0 (30.7 – 41.3)	1.9 (-10.2 – 13.9)	0.76

MAP: mean arterial pressure

Adjusted for age, Elixhauser comorbidities, admission SOFA score, source of infection, and seasonality

G. Processes and outcomes in subgroup of patients based on SEP1 reporting

Rationale for sensitivity analysis

Our case definition for the primary analysis—the combination of suspected infection plus organ dysfunction—differs from the ICD-10-based definition used by CMS in the SEP-1 measure. We made this choice deliberately, as outlined in the methods and discussion. However, we also obtained information on which patients were captured as part of hospitals' SEP-1 reporting and noted that the patients in our cohort whose data were reported to CMS as part of the SEP-1 measure differed from those who were not captured as part of the reporting (**Supplement Table 10**). It is also important to note that SEP-1 requires reporting of only a sample of patients with sepsis—so by definition there are many patients potentially eligible for the measure who do not have data reported. We therefore sought to repeat the primary analysis in a population of patients who more closely shared the characteristics of patients reported as part of SEP-1.

Supplement Table 10: Characteristics of patients reported vs. not reported for SEP-1

Variable	**Not Reported** N=21,110	**Reported** N=1649
Age, med (IQR)	71 (59, 83)	71 (59, 81)
Female Sex	10929 (51.8%)	829 (50.3%)
White Race	17992 (85.2%)	1431 (86.8%)
Comorbidity Count, med (IQR)	4 (3, 6)	5 (3, 6)
SOFA within first 6 hours, med (IQR)	3 (2, 4)	4 (3, 5)
MAP<65 within first 6 hours	3970 (18.8%)	831 (50.4%)
Mechanical ventilation	1397 (6.6%)	276 (16.7%)
Vasopressors	656 (3.1%)	307 (18.6%)
SEP-1 antibiotics within 3 hours of infection	9520 (45.1%)	1199 (72.7%)
Lactate checked within 3 hours of infection	12094 (57.3%)	1457 (88.4%)
30cc/kg IVF within 3 hours of infection	2277 (10.8%)	530 (32.1%)
ICU admission	4099 (19.4%)	932 (56.5%)
In-hospital mortality	775 (3.7%)	172 (10.4%)

Approach

We used a logistic regression model to generate a patient-level probability of being reported as part of the SEP-1 measure. In this model, the dependent variable was an indicator for SEP-1 reporting, and the independent variables were age (as splines), sex, comorbidities, SOFA score at 6 hours from ED presentation, presence of bandemia (>=10% band forms on WBC count in first 6 hours), presence of leukocytosis (WBC count >=10.4k/uL in first 6 hours), presence of fever (maximum temperature >38 degrees Celsius in first 6 hours), and a hospital fixed effect. Because only patients in the post-SEP-1 period were eligible for reporting, we ran the model on just the post-SEP-1 cohort. We then used the coefficients from this logistic model to generate a patient-level predicted probability of SEP-1 reporting for each patient across the whole cohort (both pre- and post-SEP-1). We divided patients into quartiles based on this predicted probability of SEP-1 reporting and identified patients in the top quartile as the

"SEP-1 reporting subgroup". We then ran the analysis of process and outcome measures on this subgroup.

Results and Interpretation

The c-statistic for the prediction model was 0.82, indicating very good discrimination. We used the model to classify 13,556 patients in the SEP-1 reporting subgroup, including 7,208 in the pre-SEP-1 period and 5,753 in the post-SEP1 period, excluding 595 in the washout quarter. The patient characteristics are displayed in **Supplement Table 11**, which demonstrates they represent a sicker subgroup with higher mortality and illness severity than the overall cohort. However, the results of analyses of process and outcome measures (**Supplement Tables 12 and 13**) are similar to the results from the primary analyses in the overall cohort and the subgroups of patients with hypotension or a vasopressor requirement. There were variable changes in process measures, with the greatest increase in lactate measurement, and no statistically significant change in mortality or ICU admissions. These results further support the conclusions of the primary analyses.

Supplement Table 11: Characteristics of patients in the SEP-1 reporting subgroup

Variable	**Before SEP-1** N=7208	**After SEP-1** N=5753
Age, med (IQR)	72 (60, 82)	70 (59, 81)
Female Sex	3705 (51.4%)	2884 (50.1%)
White Race	6159 (85.4%)	4861 (84.5%)
Comorbidity Count, med (IQR)	4 (3, 6)	5 (3, 6)
SOFA within first 6 hours, med (IQR)	4 (3, 6)	4 (3, 6)
MAP<65 within first 6 hours	2752 (38.2%)	2088 (36.3%)
Mechanical ventilation	1253 (17.4%)	825 (14.3%)
Vasopressors	930 (12.9%)	660 (11.5%)
SEP-1 antibiotics within 3 hours of infection	4018 (55.7%)	3554 (61.8%)
Lactate checked within 3 hours of infection	2941 (40.8%)	4476 (77.8%)
30cc/kg IVF within 3 hours of infection	1028 (14.3%)	1261 (21.9%)
ICU admission	3097 (43.0%)	2252 (39.1%)
In-hospital mortality	692 (9.6%)	480 (8.3%)

Supplement Table 12. Changes in unadjusted process measures after SEP-1, in the SEP-1 reporting subgroup. The table shows the effect of SEP-1 on processes of care, illustrated as rate differences in Quarter 4 of 2017, 2 years after SEP-1 implementation.

	Quarter 3, 2015 (pre-SEP-1)	**Quarter 4, 2017**		**Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)**	
		Expected (without SEP-1)	**Observed (with SEP-1)**		
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
Reporting subgroup					
Antibiotics within 3 hours (%)	57.8 (55.6 – 60.0)	61.3 (56.3 – 66.3)	65.7 (63.5 – 67.90	4.4 (-1.1 – 9.8)	0.12
Lactate within 3 hours (%)	48.0 (45.8 – 50.2)	60.5 (55.4 – 65.5)	85.7 (84.2 – 87.2)	25.2 (20.0 – 30.5)	<0.001
30cc/kg IVF within 3 hours (%)	15.7 (14.1 – 17.3)	18.3 (13.9 – 22.7)	23.3 (21.3 – 25.3)	5.0 (0.2 – 9.8)	0.040
Repeat Lactate within 6 hours* (%)	14.7 (12.6 – 16.9)	14.8 (9.6 – 20.0)	39.6 (37.1 – 42.1)	24.8 (19.1 – 30.6)	<0.001
Vasopressors within 6 hours** (%)	30.9 (27.6 – 34.2)	35.6 (27.1 – 44.0)	26.3 (22.9 – 29.8)	-9.2 (-18.3 – 0)	0.048

IVF: intravenous fluid
*indicates a repeat lactate within 6 hours of suspected infection, when the initial lactate is over 2 mmol/L
**indicates vasopressor initiation within 6 hours of initial hypotension

Supplement Table 13. Changes in risk-adjusted outcomes after SEP-1, in the reporting subgroup. The table shows the effect of SEP-1, illustrated as rate differences in Quarter 4 of 2017, 2 years after SEP-1 implementation.

	Quarter 3, 2015 (pre-SEP-1)	**Quarter 4, 2017**		**Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)**	
		Expected (without SEP-1)	**Observed (with SEP-1)**		
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
Reporting subgroup					
ICU admission, %	40.6 (38.6 – 42.5)	36.9 (32.4 – 41.4)	38.6 (36.5 – 40.6)	1.7 (-3.2 – 6.6)	0.49
In-hospital mortality, %	8.7 (7.5 – 9.9)	7.6 (5.1 – 10.1)	8.1 (6.9 – 9.4)	0.5 (-2.2 – 3.3)	0.71

Adjusted for age, Elixhauser comorbidities, admission SOFA score, source of infection, and seasonality

H. Evaluation for ascertainment bias

Ascertainment bias is a key consideration in longitudinal studies of sepsis. A major strength of our study is that we used an EHR-based definition, which overcomes the inherent limitations of an ICD-based case definition in the setting of the ICD-9 to ICD-10 transition and known coding trends over time (3). However, we cannot completely overcome the concern that SEP-1 induced an increase in the index of suspicion for infection in hospitalized patients, changing our denominator. Identifying a case definition for sepsis that is not affected by changes in diagnostic coding or clinicians' suspicion for infection is an enduring challenge in the field (4).

To address this concern, we performed three analyses designed to understand the potential role of ascertainment bias in our study. All three analyses index the number of cases to the number of ED visits per quarter. In the first, we examined the number of sepsis cases (i.e. suspected infection and organ dysfunction within 6 hours) per 1000 ED visits. In the second, we examined the number of ED encounters in which a blood culture was ordered within 6 hours regardless of organ dysfunction, per 1000 ED visits. In the third, we examined the number of cases with suspected infection, organ dysfunction, and hypotension (MAP<65) within 6 hours per 1000 ED visits.

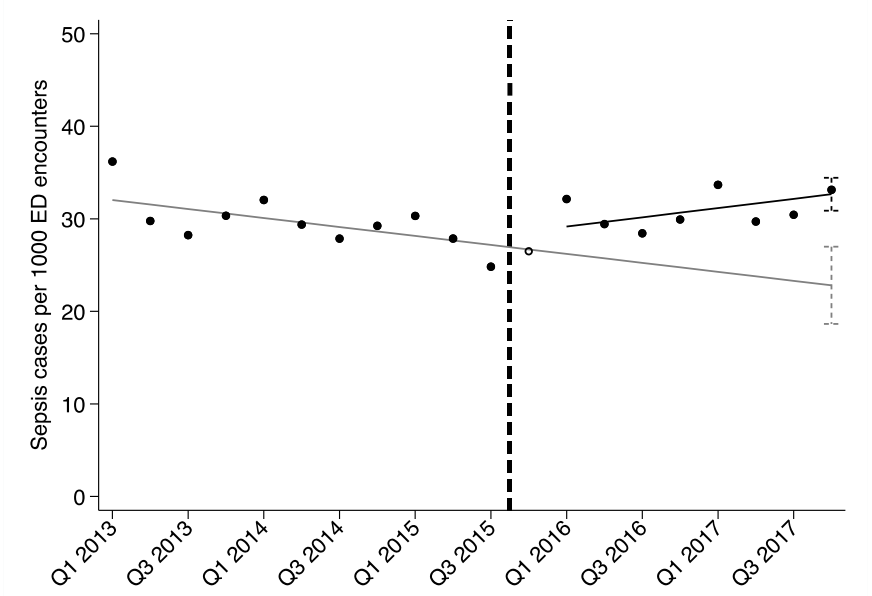
The results of these analyses were mixed (see the table and figures below). There was a potentially clinically meaningful increase in case incidence by Quarter 4 of 2017 when examining just suspected infection and organ dysfunction, consistent with observed increasing ordering of any blood cultures. However, this potential ascertainment bias was less notable in the cases with presenting hypotension.

If anything, the increase in blood cultures would tend to include people with relatively low likelihood of death, which would in turn bias our results toward seeing a mortality reduction with SEP-1. The fact that we saw no effect makes this an unlikely source of bias. This lack of mortality improvement was also observed in the cohort of hypotensive patients, in which there was less evidence for ascertainment bias.

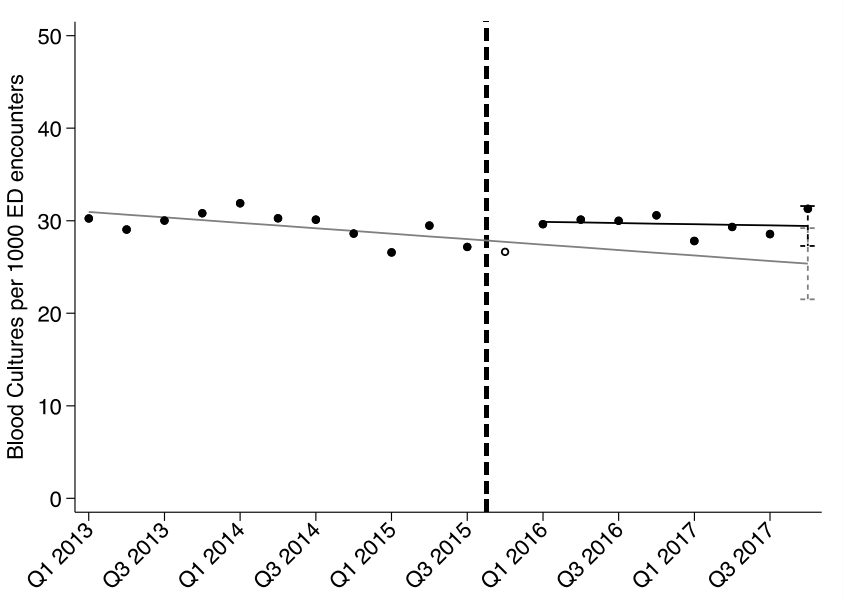
Supplement Table 14. Changes in sepsis case incidence and blood culture ordering in ED encounters.

	Quarter 4, 2017		Estimated difference between expected and observed in Quarter 4, 2017 (effect of SEP-1)	
	Expected (without SEP-1)	**Observed (with SEP-1)**		
	Estimate (95% CI)	Estimate (95% CI)	Estimate (95% CI)	p-value
Reporting subgroup				
Sepsis cases per 1000 ED visits	22.8 (18.6 – 27.0)	32.7 (30.9 – 34.4)	9.8 (5.2 – 14.4)	<0.001
Blood cultures per 1000 ED visits	25.3 (21.5 – 29.2)	29.4 (27.3 – 31.6)	4.1 (-0.1 – 8.3)	0.056
Sepsis cases with MAP<65 per 1000 ED visits	4.7 (3.4 – 6.0)	6.2 (5.6 – 6.7)	1.5 (0.05 – 2.9)	0.04

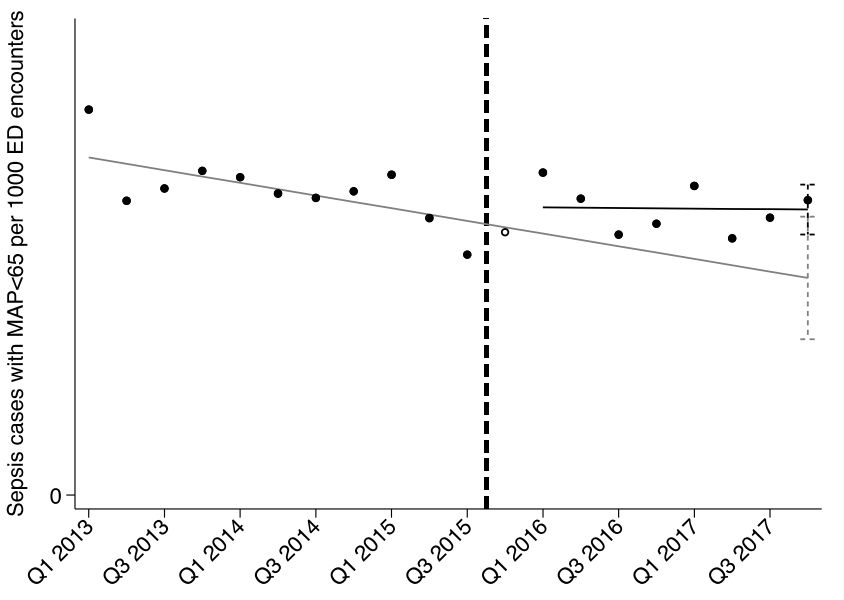
ED: emergency department; MAP: mean arterial pressure



Supplement Figure 4. Change in case counts indexed to ED encounters.



Supplement Figure 5. Change in ED encounters with blood cultures, indexed to ED encounters.



Supplement Figure 6. Change in case counts with presenting hypotension, indexed to ED encounters.

I. Evaluation for unmeasured confounding

We used the Stata `evalue` package to estimate E-values based on the risk difference in Q4 2017 for the process measure with the greatest effect (lactate measurement within 3 hours) and the clinical outcome with the greatest meaning (in-hospital mortality). The results of these E-value analyses are described below and suggest that the observed changes in lactate measurement could be explained by an unobserved confounder that was more than twice as common across groups and associated with lactate measurement with the same strength, but not by weaker confounders. In order to shift the upper confidence limit to demonstrate a mortality benefit, there would have to be an unbalanced confounder that was twice as common in either group and associated with mortality with an odds ratio of 2. For reference, none of the observed patient characteristics in Table 1 differed by nearly that degree between groups. The single comorbidity with the strongest association with mortality was metastatic cancer, with an odds ratio of 2.6, but it was well balanced (6.1% pre SEP-1 and 6.4% after SEP-1). It therefore seems unlikely that the lack of improvement in mortality is due to unmeasured confounding.

Risk difference for lactate measurement is +23.7
E-value to move this point estimate to a risk difference of 0 is 2.4

Risk difference for inpatient mortality is +0.1% with upper confidence limit of +1.1%
E-value to move this to a point estimate of -0.4% (absolute risk benefit of -0.4%, relative risk reduction of 10%) is 1.5
E-value to move this to a point estimate of -1% (absolute risk benefit of 1%, relative risk reduction of 25%) is 2.0
E-value to move the upper confidence limit of the mortality risk difference to 0 is 1.8

X. Missingness in SOFA score categories

Our approach of assuming missing data to be normal is consistent with widely cited studies that use EHR data to define sepsis (5,6). We examined some information on missingness for several of the subscores in the appendix, and our results are consistent with reported rates of missingness in other studies. For example, all patients had at least one recorded variable for the respiratory subscore, 99.8% had at least one recorded variable for the cardiovascular subscore, but only 14.8% had a recorded Glasgow coma scale, which is consistent with other data used to derive and validate sepsis definitions and phenotypes.

XI. Supplement references

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