Effects of Code Sepsis Implementation on ED Sepsis Care (Code Sepsis)

STATISTICAL ANALYSIS PLAN
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Version 1.0

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EFFECTS OF CODE SEPSIS IMPLEMENTATION ON ED SEPSIS CARE (CODE SEPSIS) STATISTICAL ANALYSIS PLAN

Objective

Determine the effects of reorganizing emergency department (ED) sepsis care (Code Sepsis protocol) on door-to-antibiotic time for ED patients with sepsis.

Hypothesis

Early activation of a multidisciplinary, coordinated, team-based assessment and treatment protocol for patients with potential sepsis will decrease door-to-antibiotic time for ED patients with sepsis.

Study overview

To assess feasibility and test the preliminary effects of ED-based Code Sepsis teams on care delivery and patient outcomes, we will conduct a Phase 2a implementation trial involving Code Sepsis team activation in one ED while collecting contemporaneous control data at two other urban EDs (control sites). Application of pseudo-experimental analysis methods to collected data will facilitate causal inference.

Study phases and associated exposures

Phase	Patient ED arrival dates	Care received by patients	
		Control ED	Intervention EDs
Pre-intervention analysis	11/13/2018-11/12/2019	Standard care	Standard care
Post-intervention wash-in	11/13/2019-2/12/2020	Standard care	Code Sepsis protocol
Post-intervention analysis	2/13/2020-2/12/2021	Standard care	Code Sepsis protocol

Study design

Pragmatic pre/post single-center type III hybrid implementation/effectiveness trial with contemporaneous controls.

Inclusion/exclusion criteria

Cohort	Inclusion	Exclusion	Cohort eligibility indicator variable*
ED sepsis cohort *(primary analysis cohort)*	(1) Age ≥18 years (2) Arrival to an intervention or control ED during study period (3) Met all Sepsis-3 criteria in the ED • Acute organ failure in the ED defined by SOFA score while in the ED ,≥2 points above baseline • Suspected or confirmed infection while in the ED, based on having both: i. Administration of ,≥1 IV or IV-equivalent antibiotics while in the ED for suspected infection (i.e. antibiotics not given for prophylaxis) ii. Collection of ,≥1 body fluid cultures while in the ED	(1) Trauma patient (2) Subsequent eligible ED visit with sepsis after first eligible encounter during an analysis window	`cohort_sepsis`
All adult ED patients cohort	(1) Age ≥18 years (2) Arrival to an intervention or control ED during study period	(1) Trauma patient (2) Received antibiotics within 6 hours prior to study ED arrival (3) Subsequent eligible ED visit after first eligible encounter during an analysis window (4) Left ED without evaluation or treatment	`cohort_all`
Sepsis high-risk cohort	(1) Age ≥18 years (2) Arrival to an intervention or control ED during study period (3) First recorded temperature ≥38.0˚C (4) First-recorded vital sign data meets ≥2 of: a. Systolic blood pressure <90 mmHg b. Glasgow Coma Scale (GCS) score <15 c. Respiratory rate ≥22 breaths/min or oxygen saturation <85%	(1) Trauma patient (2) Received antibiotics within 6 hours prior to study ED arrival (3) Subsequent eligible ED visit after first eligible encounter during an analysis window (4) Left ED without evaluation or treatment	`cohort_risk`

Cohort	Inclusion	Exclusion	Cohort eligibility indicator variable*
Sepsis mimic cohort	(1) Age ≥18 years (2) Arrival to an intervention or control ED during study period (3) Primary ICD-10-CM discharge diagnosis code of venous thromboembolism or congestive heart failure and no ICD-10-CM discharge diagnosis code for infection in any position	(1) Trauma patient (2) Received antibiotics within 6 hours prior to study ED arrival (3) Subsequent eligible ED visit after first eligible encounter during an analysis window (4) Left ED without evaluation or treatment	`cohort_mimics`

* For analyses including all eligible encounters for a given cohort (i.e., ignoring exclusion criteria #3), the name of the indicator variable is appended with "`_sens`" (e.g. "`cohort_sepsis_sens`")

Primary exposure

The primary exposure is arrival to the ED at the intervention hospital during the post-intervention analysis period rather than the pre-intervention analysis period.

Exposure parameter	***Description***	***Exposure variable***
Intervention site	Presentation to ED at intervention or control hospital	`intervention_site`
Analysis phase	Presentation to ED during pre-intervention analysis period or post-intervention analysis period. *Encounters presenting during the wash-in period have a missing variable for this variable.*	`analysis_phase (value missing if wash-in period)`
Study phase	Presentation to ED during pre-intervention analysis period, wash-in period, or post-intervention analysis period. *This variable is not used for primary differences-in-differences analyses.*	`study_phase`

Outcomes & analyses

Primary outcome

Outcome	***Analysis cohort***	***Description***	***Outcome variable***
Door-to-antibiotic time	Sepsis cohort	Time (minutes) from ED arrival to administration of first IV (or equivalent) antimicrobial while in the ED	`abx_elapsed`

Secondary outcomes

Outcome	Analysis cohort	Description	Outcome variable
Door-to-antibiotic time ≤3 hours	Sepsis cohort	Time (minutes) from ED arrival to administration of first IV (or equivalent) antimicrobial while in the ED less than or equal to 180 minutes	`abx_lt3h`
30-day mortality	Sepsis cohort	Key clinical/secondary outcome	`mort_30d`
1-year mortality	Sepsis cohort		`mort_1y`
In-hospital mortality	Sepsis cohort		`mort_hosp`
Hospital charges	Sepsis cohort		`hosp_charges`
Hosp. length of stay (days)	Sepsis cohort		`los_hosp`

Safety outcomes

Outcome	Analysis cohort	Description	Outcome variable
Antibiotic utilization	All patient cohort	Receipt of IV or equivalent antibiotics within 24 hours of ED arrival	`abx_24h`
Antibiotic utilization	Sepsis high-risk cohort	Receipt of of receiving IV or equivalent antibiotics within 24 hours of ED arrival	`abx_24h`
Potential adverse effect of antibiotics	Sepsis cohort	Antibiotic-related adverse event (a discharge diagnosis code consistent with anaphylaxis or with an adverse reaction to antibiotics)	`icd10_ae_summary`
Potential adverse effect of antibiotics	All patient cohort	Antibiotic-related adverse event (a discharge diagnosis code consistent with anaphylaxis or with an adverse reaction to antibiotics)	`icd10_ae_summary`
New-onset *C difficile*	Sepsis cohort*	New positive stool test for *Clostridium difficile* colitis between 72 hours and 90 days after ED arrival * Excludes patients with a positive *C. difficile* assay in the 14 days preceding ED arrival or within 72 hours following ED arrival	`cdiff_72h_new_analysis (missing if ineligible)`

Outcome	*Analysis cohort*	*Description*	*Outcome variable*
New-onset *C difficile*	All patient cohort*	New positive stool test for *Clostridium difficile* colitis between 72 hours and 90 days after ED arrival * Excludes patients with a positive *C. difficile* assay in the 14 days preceding ED arrival or within 72 hours following ED arrival	`cdiff_72h_new_analysis (missing if ineligible)`
Antibiotic overtreatment rate	Sepsis mimic cohort	Receipt of antibiotics in the ED among ED patients with a primary hospital discharge diagnosis of congestive heart failure or venous thromboembolism	`abx_ed`
False-positive presumptive infection diagnosis rate	Sepsis cohort	Final adjudicated infection status is "not infected" among ED patients meeting sepsis criteria	`uninfected`
Antibiotic spectrum	Sepsis cohort*	Total antibiotic spectrum score for all IV or equivalent antibiotics administered in first 24 hours using antibiotic spectrum scoring system developed by Stenehjem et al. (Clin Infect Dis 2016;63:1273-1280). Individual antibiotics have spectrum scores of 1 to 5, with the total score resulting from summation of the spectrum scores for each unique antibiotic administered during the first 24 hours. Minimum total 24-hour score is therefore 1 (administration of a single, minimum-spectrum antibiotic), with no maximum score. * Patients receiving no antibiotics (only antivirals or antifungals) are excluded from analysis.	`abx_24h_score_total (missing if ineligible)`

Outcome	Analysis cohort	Description	Outcome variable
Antibiotic spectrum	All patient cohort receiving antibiotics*	Total antibiotic spectrum score for all antibiotics administered in first 24 hours using antibiotic spectrum scoring system developed by Stenehjem et al. (Clin Infect Dis 2016;63:1273-1280). Individual antibiotics have spectrum scores of 1 to 5, with the total score resulting from summation of the spectrum scores for each unique antibiotic administered during the first 24 hours. Minimum total 24-hour score is therefore 1 (administration of a single, minimum-spectrum antibiotic), with no maximum score. * Patients receiving no antibiotics (only antivirals or antifungals) are excluded from analysis.	`abx_24h_score_total (missing if ineligible)`
Antibiotic spectrum	Sepsis high-risk patients treated with antibiotics*	Total antibiotic spectrum score for all antibiotics administered in first 24 hours using antibiotic spectrum scoring system developed by Stenehjem et al. (Clin Infect Dis 2016;63:1273-1280). Individual antibiotics have spectrum scores of 1 to 5, with the total score resulting from summation of the spectrum scores for each unique antibiotic administered during the first 24 hours. Minimum total 24-hour score is therefore 1 (administration of a single, minimum-spectrum antibiotic), with no maximum score. * Patients receiving no antibiotics (only antivirals or antifungals) are excluded from analysis.	`abx_24h_score_total (missing if ineligible)`

Process outcomes

Outcome	Analysis cohort	Description	Outcome variable
Code Sepsis activation rate	All ED patients*†	Percentage of ED patients at intervention site with a Code Sepsis activation during post-intervention analysis phase	`cs_yn`
Code Sepsis sensitivity	Sepsis patients*†	Percentage of ED patients at intervention site with a sepsis during post-intervention analysis phase for whom Code Sepsis was activated	`cs_yn`
Code Sepsis PPV for sepsis	All ED patients*†	Percentage of Code Sepsis activations during post-intervention analysis phase who met sepsis criteria in the ED	`sepsis_yn (among patients with cs_yn = 1)`

Outcome	*Analysis cohort*	*Description*	*Outcome variable*
Code Sepsis PPV for infection	All ED patients*†	Percentage of Code Sepsis activations during post-intervention analysis phase who had infection on final assessment	`infected (measured among patients with cs_yn == 1)`
Door-to-Code Sepsis time	All ED patients*†	Time from ED arrival to Code Sepsis activation	`cs_elapsed`

* Restricted to subset of cohort patients presenting to intervention hospital during post-intervention analysis phase.
† Analyses will use all patients meeting criteria for cohort but disregard the exclusion for subsequent eligible encounter. Sensitivity analyses will be based on the cohort excluding subsequent eligible encounters.

Data analysis

Analyses for causal inference regarding primary, secondary and safety outcomes will employ a quasi-experimental method called *difference-in-difference* (DID) analysis to control for secular trends and confounding of unknown individual factors associated with the outcome of interest. The DID approach will provide an estimate of the effect of the Code Sepsis intervention on primary, secondary, and safety outcomes by comparing the intervention and control hospitals during the pre- and post-implementation periods (Figure 1).

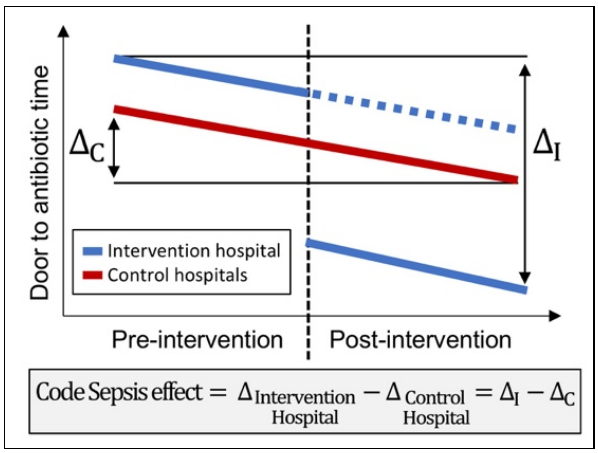

Figure 1. Difference-in-differences analysis

For the primary outcome, DID analysis will use multivariable linear regression to compare the adjusted mean door-to-antibiotic time (primary outcome) at the intervention hospital pre- versus post-implementation of the Code Sepsis protocol using the measured change at contemporaneous control non-intervention hospitals to control for pre-/post-intervention changes not attributable to protocol implementation after adjustment for potential confounders.

The following equation will be used to estimate the adjusted mean differential change in the primary outcome, door to antibiotic time:

$$Y_{igt} = \beta_0 + \beta_1 Int_g + \beta_2 Post_t + \boldsymbol{\beta_3}(Int_g * Post_t) + \beta_4 Cov$$

Where Y_{igt} is the door-to-antibiotic time for patient i treated at an intervention or non-intervention ED g at pre- or post-intervention time t. Int is a binary indicator for the subject being treated at an intervention hospital; $Post$ is a binary indicator the post-intervention period; and Cov represents a vector of patient-level covariates. The β_3 parameter from the regression model presented above estimates the adjusted mean differential change in door-to-antibiotic time observed in the Code Sepsis intervention hospital compared to the control hospital. We will consider the Code Sepsis intervention to have had an impact if β_3 is statistically significant and different from zero.

The parallel trend assumption will be tested using the approach outlined by Callaway and Sant'Anna.[1] This approach allows for testing the parallel trend assumption after conditioning on covariates. This approach is

limited in that it only considers the control and treated groups during the pre-implementation phase. If the pre-test of parallel trends assumption fails, then we will weight the gamma regression model with propensity scores. As demonstrated by Stuart *et. al*,[2] this will balance the covariates amongst the four study groups defined by their treatment status as well as time (pre vs post). We will leverage the covariate balancing propensity score (CBPS) library in R to generate propensity scores. This weighting approach can recover treatment effects in that it allows for adjustments due to observed baseline covariates that differ either across groups or over time. Covariates that will be used in generating propensity scores will include age; sex; weighted Elixhauser comorbidity score; English language preference; first-available heart rate, temperature, systolic blood pressure, and respiratory rate; acute physiology score; ED arrival at nightime (10 pm to 6:59 am), ED arrival on weekend (midnight Saturday to 11:59 pm Sunday), SARS-CoV-2 test result (positive, negative, or not performed during ED-associated hospitalization or within 14 days preceding ED arrival); and insurance type. For analyses involving a cohort of patients with sepsis, propensity score covariates will additionally include arrival to ED via ambulance; presentation from a long term care facility; serum lactic acid level checked and ≥2 mmol/dL; ED SOFA score; and ED-diagnosed infection source.

In order to account for the right skew known to exist in door-to-antibiotic time we will use generalized linear gamma regression to estimate the DID. Evaluation of secondary outcomes will employ an analogous approach using multivariable linear, Poisson, logistic, or gamma regression as appropriate. Data from the wash-in phase will be excluded from DID analyses. All multivariable models will be adjusted for demographic and clinical parameters with known or plausible associations with both outcomes and treatment hospital, presentation before or after Code Sepsis implementation, and/or Code Sepsis activation as well as select precision variables as detailed below. Analyses for secondary, safety, and heterogeneity of treatment effect outcomes will not be adjusted for multiple comparisons and will therefore be considered hypothesis generating.

Statistical significance will be set to $p < 0.05$. All analyses will be conducted with R.

Primary and secondary outcome analysis covariates

Variables listed below will be included in multivariable adjusted analyses for primary and secondary outcomes listed above. Variables are also included in any associated subgroup and sensitivity analyses for these outcomes. For heterogeneity of treatment effect analyses, where continuous variables are categorized or dichotomized, the corresponding adjustment variable will also be categorized analogously in the adjustment model and for creation of the interaction term.

- Age (**`age,`** `continuous`)
- Female sex (**`sex,`** `binary`)
- Presentation from a long-term care facility (**`snf,`** `binary`)
- Weighted Elixhauser comorbidity score (**`elixhauser_vw,`** `continuous`)
- Arrival to ED via ambulance (**`arrival_mode,`** `binary`)
- English is preferred language (**`english_preferred_yn,`** `binary`)
- First-available temperature in ED (**`vs_temp_cat,`** `categorical, reference group = 1 [temp 36–38˚C]`)
- First-available systolic blood pressure in ED (**`vs_sbp,`** `continuous`)
- Acute physiology score (**`aps_24h,`** `continuous`)
- ED SOFA score (**`sofa_ed,`** `continuous`)

- ED-diagnosed infection source (**`source_ed_final_simpler`**, `categorical, reference group = 1 [pneumonia]`)

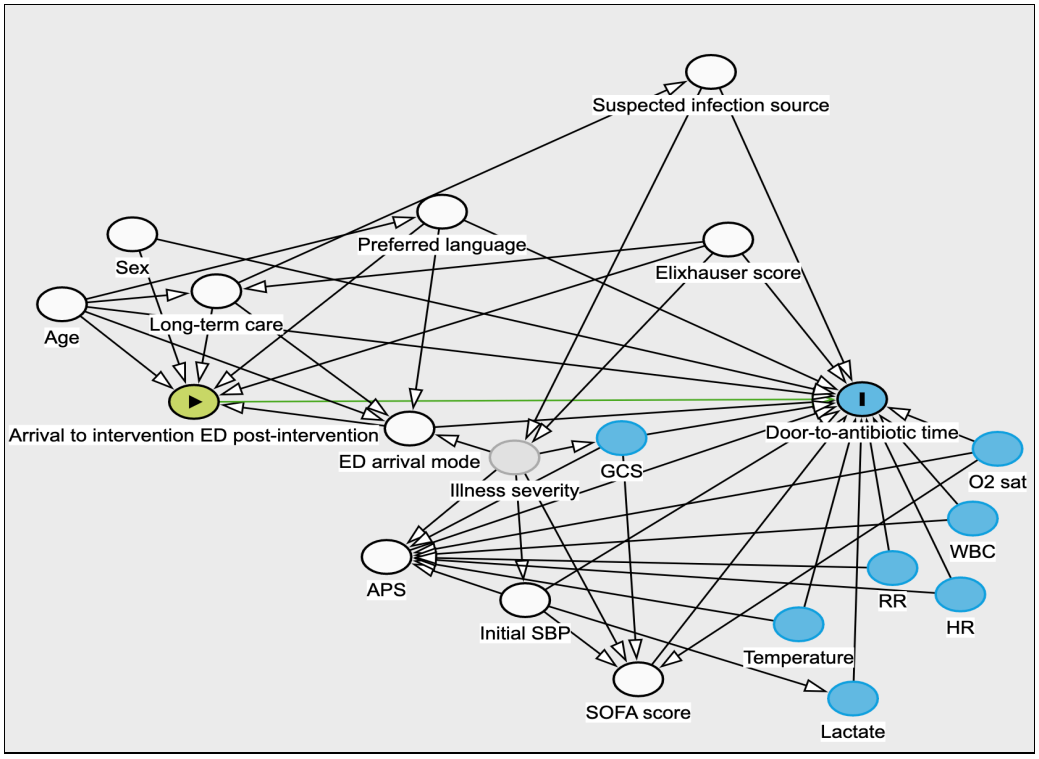

Figure 2. Adjustment variables for primary & secondary multivariable analyses. The primary exposure is intervention ED arrival post-intervention and the primary outcome is door-to-antibiotic time. White symbols indicate potential confounders or precision variables included in the multivariable model, gray symbols represent an unobserved variable, and blue symbols (other than the outcome) represent an ancestor of outcome not included in the multivariable model.

Safety outcome analysis covariates

Variables listed below are included in multivariable analyses for primary and secondary outcomes listed above. Variables are also included in any associated subgroup, heterogeneity of treatment, and sensitivity analyses.

- Age (**`age`**, `continuous`)
- Female sex (**`sex`**, `binary`)
- Weighted Elixhauser comorbidity score (**`elixhauser_vw`**, `continuous`)
- Insurance (**`insurance`**, `categorical`)
- First-available temperature in ED (**`vs_temp_cat`**, `categorical`)
- First-available systolic blood pressure in ED (**`vs_sbp`**, `continuous`)
- Acute physiology score (**`aps_24h`**, `continuous`)

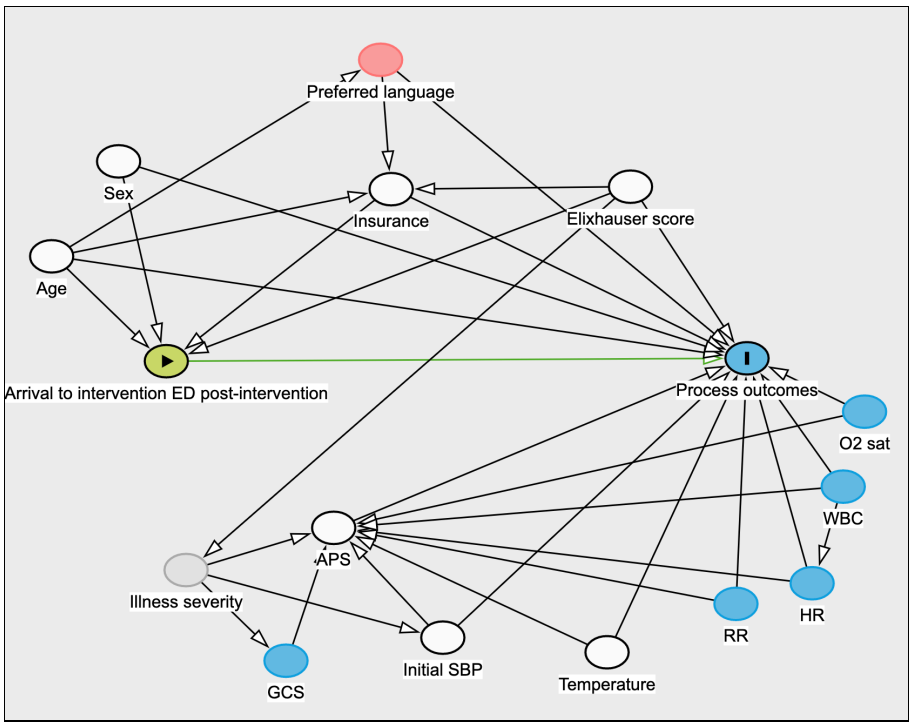

Figure 3. Adjustment variables for safety outcome multivariable analyses. The primary exposure is arrival to the intervention ED post-intervention. White symbols indicate potential confounders or precision variables included in the multivariable model, red variables indicate potential confounders not required for the minimal adjustment set, gray symbols represent an unobserved confounder, and blue symbols (other than the outcome) represent an outcome ancestor not included in the multivariable model.

Heterogeneity of treatment effect for primary outcome

Potential heterogeneity of treatment effect (HTE) will be evaluated using a differences-in-differences-in-differences approach adding interaction terms for subgroups versus study phase and versus control/intervention ED, and a three-way interaction between subgroup, study phase, and control/intervention ED. Subgroup results will be considered descriptive and will be referenced to the overall treatment effect from the primary analysis. The subgroup analyses are not confirmatory, hence no corrections for multiple comparisons will be made.

The following are predefined subgroups for HTE analyses:

- Age (<65 years vs ≥65 years)
- Sex (male vs female)
- Presence of hypotension on ED arrival (SBP <90 or MAP <65)
- Arrival to hospital via ambulance
- Source of infection
- APS quartiles

We will use the following DID formula for HTE analyses:

$$Y_{igts} = \beta_0 + \beta_1 Int_g + \beta_2 Post_t + \beta_3 Sub_s + \beta_4(Int_g * Post_t) + \beta_5(Post_t * Sub_s) + \boldsymbol{\beta_6}(Post_t * Int_g * Sub_s) + \beta_7 Cov$$

Where Y_{igts} is the door-to-antibiotic time for patient i treated at an intervention of non-intervention ED g at pre- or post-intervention time t from the cohort subgroup s. Int is a binary indicator for the subject being treated at an intervention hospital; $Post$ is a binary indicator the post-intervention period; Sub is a binary indicator (or group indicator in the case of APS quartiles) of the subgroup; and Cov represents a vector of hospital- and patient-level covariates. The β_6 parameter from the regression model presented above estimates the effect measure modification for door-to-antibiotic time in pre-specified subgroups. We will consider the Code Sepsis intervention to have had an impact on the subgroup if β_6 is statistically significant and different from zero.

Sensitivity analyses

Key sensitivity analysis: To augment causal inference from the primary analysis and evaluate for the possibility of non-parallel trends in the primary outcome at intervention versus control hospitals during the pre-intervention phase, we will perform a sensitivity analysis evaluating the adjusted primary outcome (door-to-antibiotic time) with a multi-group interrupted time series analysis. The following segmented regression suggested by Ryan et.al.[3] will be used to estimate the effect of the Code Sepsis intervention on door-to-antibiotic time:

$$Y_{igt} = \beta_0 + \beta_1 Time + \beta_2(Time * Int_g) + \beta_3 Post_t + \boldsymbol{\beta_4}(Int_g * Post_t) + \beta_5 Cov$$

Where Y_{igt} is the door-to-antibiotic time for patient i treated at an intervention or non-intervention ED g at pre- or post-intervention time t. $Time$ is a continuous variable indicating the bi-weekly count from the start of the observation period; Int is a binary indicator for the subject being treated at an intervention hospital; $Post$ is a binary indicator for the post intervention period. The β_4 parameter from the regression model is interpreted in nearly the same manner as the primary outcome, in that it estimates the adjusted differential change in door-to-antibiotic time between the control and CodeSepsis hospitals. This model allows for the trends to differ between the intervention and control hospitals during the pre-intervention phase. We will consider the Code Sepsis intervention of have had an impact if β_4 is statistically significant and different from zero.

In order to account for the right skew known to exist in door-to-antibiotic time we will use generalized linear gamma regression to estimate the DID. Data from the wash-in phase will be excluded from the sensitivity analysis.

- *Other primary outcome sensitivity analyses*:
  - Repeat primary analysis among patients in "sepsis high-risk" cohort who received antibiotics in the ED.
  - Repeat primary analysis in the dataset comprising all *encounters* (≥1 encounter per patient) meeting sepsis criteria between ED arrival and ED departure, using generalized linear models with a random effect for patient to account for non-independence.
  - Missing data sensitivity analyses as described in the "Missing Data" section

Missing data

Patients with missing outcome data will be excluded from the analyses for that outcome exposure. Exposure data (study hospital and study phase) is expected to be 100% non-missing. Data is also expected to be 100% non-missing for all eligible encounters for covariates for primary/secondary outcome multivariable models. However, if this is not the case for primary and secondary outcome analyses, we will apply the following approaches based on multiple imputation using chained equations (10 datasets, results combined using Rubin's rules):

- 100% of eligible encounters with complete data: perform complete case analysis.
- ≥95% of eligible encounters with complete data: perform complete case analysis for the main outcome reporting/interpretation multivariable analysis; use multiple imputed data as a sensitivity analysis.
- <95% of eligible encounters with complete data: use multiple imputed data for the main outcome reporting/interpretation multivariable analysis; perform complete case analysis as a sensitivity analysis.

For safety outcomes, there is expected to be missingness for some prespecified covariates for patients included in "all ED" and "sepsis mimic" cohorts.

- 100% of eligible encounters with complete data: perform complete case analysis.
- ≥95% of eligible encounters with complete data: perform complete case analysis for the main outcome reporting/interpretation multivariable analysis; use multiple imputed data as a sensitivity analysis.
- <95% of eligible encounters with complete data: use multiply imputed data for the main outcome reporting/interpretation multivariable analysis; perform complete case analysis as a sensitivity analysis.

Where performed, multiple imputation models will be performed separately for primary/secondary vs safety outcomes. Variables included in the model will include each outcome (within the outcome class), study site, study phase, all covariates (within the outcome class), and additional potentially-informative variables identified based on expert opinion and literature review. We will use predictive mean matching using five nearest neighbors for imputation of continuous variables and logistic regression with bootstrap for binary variables.

Power

It was estimated that the intervention ED provides care for 1,650 sepsis patients annually (approximately 4.5 sepsis patients per day) and the control EDs together care for a total of 2,200 sepsis patients annually (approximately 6 sepsis patients per day). Estimated control door-to-antibiotic time for ED sepsis patients was an average 170 (±75) minutes based on 2013-2017 data from study hospitals, with approximately 5-10% of patients receiving antibiotics within 1 hour of ED arrival. Based on these assumptions, we estimated 90% power to detect a difference-in-differences change of 16 minutes or more in door-to-antibiotic time associated with Code Sepsis implementation, with the measurement population being all ED sepsis patients. Power calculations employed Monte Carlo simulations.

References

1. Callaway B, Sant'Anna PHC. Difference-in-differences with multiple time periods. *J Econometrics.* 2021;225(2):200-230.
2. Stuart EA, Huskamp HA, Duckworth K, et al. Using propensity scores in difference-in-differences models to estimate the effects of a policy change. *Health Serv Outcomes Res Methodol.* 2014;14(4):166-182.
3. Ryan AM, Kontopantelis E, Linden A, Burgess JF, Jr. Now trending: Coping with non-parallel trends in difference-in-differences analysis. *Stat Methods Med Res.* 2019;28(12):3697-3711.
4. Textor J, van der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GT. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol.* 2016;45(6):1887-1894.

Appendix

Code for directed acyclic graphs

Code used to generated directed acyclic graphs via Dagitty web application (http://www.dagitty.net/dags.html).[4]

Primary and secondary analyses

```
dag {
"Arrival to intervention ED post-intervention" [exposure,pos="-1.196,0.491"]
"Door-to-antibiotic time" [outcome,pos="1.007,0.477"]
"ED arrival mode" [adjusted,pos="-0.485,0.630"]
"Elixhauser score" [adjusted,pos="0.565,-0.356"]
"Illness severity" [latent,pos="-0.139,0.781"]
"Initial SBP" [adjusted,pos="-0.104,1.525"]
"Long-term care" [adjusted,pos="-1.122,-0.086"]
"O2 sat" [pos="1.453,0.736"]
"Preferred language" [adjusted,pos="-0.378,-0.501"]
"SOFA score" [adjusted,pos="0.269,1.938"]
"Suspected infection source" [adjusted,pos="0.536,-1.411"]
APS [adjusted,pos="-0.561,1.300"]
Age [adjusted,pos="-1.631,-0.018"]
GCS [pos="0.214,0.680"]
HR [pos="1.331,1.495"]
Lactate [pos="0.977,2.039"]
RR [pos="1.106,1.680"]
Sex [adjusted,pos="-1.399,-0.383"]
Temperature [pos="0.798,1.651"]
WBC [pos="1.406,1.039"]
"Arrival to intervention ED post-intervention" -> "Door-to-antibiotic time"
"ED arrival mode" -> "Arrival to intervention ED post-intervention"
"ED arrival mode" -> "Door-to-antibiotic time"
"Elixhauser score" -> "Arrival to intervention ED post-intervention"
"Elixhauser score" -> "Door-to-antibiotic time"
"Elixhauser score" -> "Illness severity"
"Elixhauser score" -> "Long-term care"
"Illness severity" -> "ED arrival mode"
"Illness severity" -> "Initial SBP"
"Illness severity" -> "SOFA score"
"Illness severity" -> APS
"Illness severity" -> GCS
"Initial SBP" -> "Door-to-antibiotic time"
"Initial SBP" -> "SOFA score"
```

"Initial SBP" -> APS
"Initial SBP" -> Lactate
"Long-term care" -> "Arrival to intervention ED post-intervention"
"Long-term care" -> "ED arrival mode"
"Long-term care" -> "Suspected infection source"
"O2 sat" -> "Door-to-antibiotic time"
"O2 sat" -> "SOFA score"
"O2 sat" -> APS
"Preferred language" -> "Arrival to intervention ED post-intervention"
"Preferred language" -> "Door-to-antibiotic time"
"Preferred language" -> "ED arrival mode"
"SOFA score" -> "Door-to-antibiotic time"
"Suspected infection source" -> "Door-to-antibiotic time"
"Suspected infection source" -> "Illness severity"
APS -> "Door-to-antibiotic time"
Age -> "Arrival to intervention ED post-intervention"
Age -> "Door-to-antibiotic time"
Age -> "ED arrival mode"
Age -> "Long-term care"
Age -> "Preferred language"
GCS -> "Door-to-antibiotic time"
GCS -> "SOFA score"
GCS -> APS
HR -> "Door-to-antibiotic time"
HR -> APS
Lactate -> "Door-to-antibiotic time"
RR -> "Door-to-antibiotic time"
RR -> APS
Sex -> "Arrival to intervention ED post-intervention"
Sex -> "Door-to-antibiotic time"
Temperature -> "Door-to-antibiotic time"
Temperature -> APS
WBC -> "Door-to-antibiotic time"
WBC -> APS
}

Safety analyses

```
dag {
"Arrival to intervention ED post-intervention" [exposure,pos="-1.196,0.491"]
"Elixhauser score" [adjusted,pos="0.565,-0.356"]
"Illness severity" [latent,pos="-1.121,1.505"]
"Initial SBP" [adjusted,pos="-0.147,1.833"]
"O2 sat" [pos="1.453,0.736"]
"Preferred language" [pos="-0.383,-0.972"]
"Process outcomes" [outcome,pos="1.007,0.477"]
APS [adjusted,pos="-0.561,1.300"]
Age [adjusted,pos="-1.631,-0.018"]
GCS [pos="-0.742,1.945"]
HR [pos="1.254,1.569"]
Insurance [adjusted,pos="-0.343,-0.344"]
RR [pos="0.965,1.669"]
Sex [adjusted,pos="-1.377,-0.479"]
Temperature [adjusted,pos="0.476,1.904"]
WBC [pos="1.372,1.100"]
"Arrival to intervention ED post-intervention" -> "Process outcomes"
"Elixhauser score" -> "Arrival to intervention ED post-intervention"
"Elixhauser score" -> "Illness severity"
"Elixhauser score" -> "Process outcomes"
"Elixhauser score" -> Insurance
"Illness severity" -> "Initial SBP"
"Illness severity" -> APS
"Illness severity" -> GCS
"Initial SBP" -> "Process outcomes"
"Initial SBP" -> APS
"O2 sat" -> "Process outcomes"
"O2 sat" -> APS
"Preferred language" -> "Process outcomes"
"Preferred language" -> Insurance
APS -> "Process outcomes"
Age -> "Arrival to intervention ED post-intervention"
Age -> "Preferred language"
Age -> "Process outcomes"
Age -> Insurance
GCS -> APS
HR -> "Process outcomes"
HR -> APS
Insurance -> "Arrival to intervention ED post-intervention"
Insurance -> "Process outcomes"
RR -> "Process outcomes"
```

RR -> APS
Sex -> "Arrival to intervention ED post-intervention"
Sex -> "Process outcomes"
Temperature -> "Process outcomes"
Temperature -> APS
WBC -> "Process outcomes"
WBC -> APS
WBC -> HR
}

Version changes

Version	Modification	Rationale
1.0	Original version	N/A