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Reporting Summary

Nature Portfolio wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Portfolio policies, see our Editorial Policies and the Editorial Policy Checklist.

Statistics

For all statistical analyses, confirm that the following items are present in the figure legend, table legend, main text, or Methods section.

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ A statement on whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistical parameters including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No specialized software was used for data collection.
Data analysis	The TREWS early warning system described in this study is available from Bayesian Health, New York, New York. The underlying source code is proprietary intellectual property and is not available. Code for the primary statistical analyses and development of the high-risk cohort can be found at https://github.com/royadams/adams_et_al_2022_code.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
- For clinical datasets or third party data, please ensure that the statement adheres to our policy

The data are not publicly available because they are from electronic health records approved for limited use by Johns Hopkins University investigators. Making the data publicly available without additional consent, ethical, or legal approval might compromise patients' privacy and the original ethical approval. To perform additional analyses using this data, researchers should contact AWW or SS to apply for an IRB-approved research collaboration and obtain an appropriate data use agreement.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	The sample used was a convenience sample including all data available from the deployment of the tool under study, however, a post-hoc power analysis performed using the multiple logistic regression test in G*Power gave power 0.993 at the alpha=0.05 level.
Data exclusions	No data was excluded beyond the inclusion criteria stated in the paper.
Replication	Due to the cost and time involved in deploying a clinical decision support tool and gathering electronic medical record data no attempts were made to replicate this prospective cohort study. However, we tested the robustness of our analyses by repeating the primary analysis (adjusted comparison of patient outcomes between arms) under five modifications to the analysis or population. First, to ensure that our conclusions were not dependent on our choice of statistical method, we repeated the analysis using an alternative method, inverse probability of treatment weighting. We used logistic regression for the probability of treatment model and we stabilized and truncated weights at the 1st and 99th weight percentiles to reduce estimation variance. Second, because a patient's problem list reflects real-time diagnoses made by providers, it is less reliable than final diagnoses which reflect all information from a patient's stay. Similarly, clinicians may not always mark a present on arrival diagnosis as such. We tested the sensitivity to these issues by replacing ICD-10 codes in the patient's problem list with final diagnosis ICD-10 codes. Final diagnosis codes are more comprehensive but may include information from well after the patient's alert, leading to potential over-adjustment. Third, because we included each patient encounter separately in our data, we wished to ensure that our conclusions were not overly sensitive to a few patients with multiple encounters. We tested this sensitivity by repeating the analysis using only the first encounter for each patient. Fourth, the COVID-19 pandemic impacted both characteristics of patients in our data and the care those patients received. We tested the sensitivity to inclusion of data during the COVID-19 pandemic by repeating the analysis using only patients admitted before April 1, 2020. Finally, the list of antibiotics used to determine the time of first antibiotic administration was intentionally inclusive. To ensure that our results are not sensitive to the specific antibiotics included, we repeated the analysis using a restricted list of antibiotics that removes some antibiotics that are either unlikely to be used to treat sepsis or unlikely to be used on adult patients. The restricted list removes amoxicillin, azithromycin, cefotaxime, dapsone, erythromycin, neomycin, and rifampin from the antibiotics listed in Extended Data Table 5. These sensitivity analyses did not change the direction or significance of our findings.
Randomization	The study was not randomized and thus covariate adjustment was used. The relationship between antibiotics timing and patient outcomes may be confounded by several aspects of patient presentation. We adjusted for a range of patient variables to account for potential confounding. Similar to previous studies, we adjusted for patient age, documented sex, comorbidity history, and measurements taken during the current encounter. To account for differences due to pre-existing conditions and patient history, we adjusted for the patient's Charlson Comorbidity Index (CCI) as well as individual indicators for a history of diabetes (with and without complications), dementia, malignant tumors, or metastatic solid tumors. These conditions were identified from International Classification of Diseases, Tenth Revision (ICD-10) codes included in the patient's medical history. To account for differences in treatment arising from patient presentation at the current visit, we adjusted for several sepsis-relevant labs, vital signs, and treatments including systolic blood pressure, Glasgow Coma Score (GCS) below 15 (indicating any abnormal mental activity), temperature, white blood cell count, lactate above 2 mmol/L, and indicators for vasopressors and mechanical ventilation. We additionally adjusted for composite measures of acute patient severity including individual SOFA score components and APACHE II score. For labs and vital signs, we used the most recent measurement taken in the 24 hours prior to the alert and imputed a normal value if no measurement was observed during this period. SOFA and APACHE II scores were calculated using the worst measurements from the 24 hours prior to the alert. In cases where the alert occurred within 12 hours of presentation to the ED or admission to an in-patient unit (whichever came first), we used the worst measurements recorded within 12 hours of presentation/admission to allow for lab processing and recording delays. In addition to the variables used in previous studies, we included several additional patient and hospital related variables. In medically complex patients, clinicians may wish to obtain more information on the patients before ordering antibiotics. To account for this, we further adjusted for the presence of several comorbidities that may obscure a sepsis diagnosis including metastatic cancer, end stage renal disease, congestive heart failure, acute liver disease, gastrointestinal bleeding, and chronic obstructive pulmonary disease. These comorbidities were identified from ICD-10 codes listed as part of the patient's problem list and marked as present on arrival. Additionally, for ED patients, we adjusted for whether or not the trauma team was activated upon arrival. To account for differences in clinical practice between hospitals, we included an indicator for the admitting hospital. Finally, we included a binary indicator for presentation at the hospital after April 1, 2020, to account for differences in treatment patterns arising from the COVID-19 pandemic.
Blinding	This study was observational and thus no blinding was used.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	6,877 patient encounter involving 6,264 unique patients were included in the primary analysis. The average age was 66.0 (std 17.2) and 47.0% were document as male. The average Charlson Commorbidity Index was 6.5 (std 4.0) and, at the time of the alert, the average APACHE II score was 11.8 (std 7.7) and the average SOFA score was 4.1 (std 3.4). 95.7% presented at the emergency department, 1.3% were discharged directly from the emergency department, and 44.8% were admitted to the ICU during the encounter. 42.1% met the criteria for septic shock during the encounter. For additional details, see Table 1 and Supplementary Table 1.
Recruitment	This study used electronic health records gathered naturally over the course of patient care and thus patients were not directly recruited to the study. A waiver of consent was obtained from the Johns Hopkins University internal review board (IRB No. 00252594).
Ethics oversight	The Johns Hopkins University internal review board (IRB No. 00252594).

Note that full information on the approval of the study protocol must also be provided in the manuscript.