Title
Stewardship Prompts to Improve Antibiotic Selection for Pneumonia

Journal
JAMA, 331(23)

ISSN
0098-7484

Authors
Gohil, Shruti K
Septimus, Edward
Kleinman, Ken
et al.

Publication Date
2024-06-18

DOI
10.1001/jama.2024.6248

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 10, 2024. doi:10.1001/jama.2024.6248

Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: the INSPIRE Randomized Clinical Trial

Shruti K. Gohil, MD, MPH[1], Edward Septimus, MD[2], Ken Kleinman, ScD[3], Neha Varma, MPH[2], Taliser R. Avery, MS[2], Lauren Heim, MPH[1], Risa Rahm, PharmD[4], William S. Cooper, PharmD[4], Mandelin Cooper, PharmD[4], Laura E. McLean, MEd[4], Naoise G. Nickolay RPh[4], Robert A. Weinstein, MD[5], L. Hayley Burgess PharmD[4], Micaela H. Coady, MS[2], Edward Rosen, BA[2], Selsebil Sljivo, MPH[2], Kenneth E. Sands, MD, MPH[2,4], Julia Moody, MS[4], Justin Vigeant, BA[2], Syma Rashid, MD[1], Rebecca F. Gilbert BA[2], Kim N. Smith, MBA[4], Brandon Carver, BA[4], Russell E. Poland, PhD[2,4], Jason Hickok, MBA[4], S.G. Sturdevant, PhD[6], Michael S. Calderwood, MD, MPH[7], Anastasiia Weiland, MD[1], David W. Kubiak, PharmD[8], Sujan Reddy, MD, MSc[9], Melinda M. Neuhauser, PharmD, MPH[9], Arjun Srinivasan, MD[9], John A. Jernigan, MD, MS[9], Mary K. Hayden, MD[10], Abinav Gowda, BS[2], Katyuska Eibensteiner, BA[2], Robert Wolf, BS[2], Jonathan B. Perlin, MD, PhD[4,11], Richard Platt, MD, MSc[2], Susan S. Huang, MD, MPH[1]

Author Affiliations:
1) Division of Infectious Diseases, University of California, Irvine School of Medicine, Irvine, California, 2) Department of Population Medicine, Harvard Pilgrim Healthcare Institute, Harvard Medical School, Boston, Massachusetts, 3) Biostatistics and Epidemiology, University of Massachusetts, Amherst, Massachusetts, 4) HCA Healthcare, Nashville, Tennessee, 5) Rush University Medical Center, Cook County Health, Chicago, IL 6) National Institutes of Health, Bethesda, Maryland 7) Section of Infectious Disease and International Health, Dartmouth Hitchcock Medical Center, Lebanon, NH, 8) Brigham and Women's Hospital, Boston, Massachusetts, 9) Centers for Disease Control and Prevention, Atlanta, Georgia, 10) Rush University Medical Center, Chicago, IL 11) now with The Joint Commission, Oakbrook Terrace, Illinois

Corresponding Author:
Shruti K. Gohil, MD, MPH, University of California Irvine, School of Medicine 100 Theory, Irvine, CA 92617, skgohil@hs.uci.edu

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 10, 2024. doi:10.1001/jama.2024.6248

Key Points

Question: Can computerized provider order entry (CPOE) prompts that provide patient-specific risk estimates for multidrug-resistant organisms (MDROs) reduce empiric extended-spectrum antibiotic use in patients admitted with pneumonia?

Findings: In a cluster-randomized trial of 59 hospitals (n = 44,780 adults in the intervention period), CPOE prompts promoting standard-spectrum antibiotics for patients at low risk of infection with MDROs significantly reduced empiric extended-spectrum antibiotic use in hospitalized patients with pneumonia by 28.4%, without increasing intensive care unit transfers or length of stay.

Meaning: Real-time electronic health record–generated recommendations for standard-spectrum antibiotics using patient-specific risk for MDRO-associated infections can substantially and safely reduce empiric extended-spectrum antibiotic use in patients hospitalized for pneumonia.

Abstract

Importance: Pneumonia is the most common infection requiring hospitalization and is a major reason for overuse of extended-spectrum antibiotics. Despite low risk of multidrug-resistant organism (MDRO) infection, clinical uncertainty often drives initial antibiotic selection. Strategies to limit empiric antibiotic overuse for patients with pneumonia are needed.

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 10, 2024. doi:10.1001/jama.2024.6248

Objective: To evaluate whether computerized provider order entry (CPOE) prompts providing patient- and pathogen-specific MDRO infection risk estimates could reduce empiric extended-spectrum antibiotics for non–critically ill patients admitted with pneumonia.

Design, Setting, and Participants: Cluster-randomized trial in 59 US community hospitals comparing the effect of a CPOE stewardship bundle (education, feedback, and real-time MDRO risk-based CPOE prompts; n = 29 hospitals) vs routine stewardship (n = 30 hospitals) on antibiotic selection during the first 3 hospital days (empiric period) in non–critically ill adults (≥18 years) hospitalized with pneumonia. There was an 18-month baseline period from April 1, 2017, to September 30, 2018, and a 15-month intervention period from April 1, 2019, to June 30, 2020.

Intervention: CPOE prompts recommending standard-spectrum antibiotics in patients ordered to receive extended-spectrum antibiotics during the empiric period who have low estimated absolute risk (<10%) of MDRO pneumonia, coupled with feedback and education.

Main Outcome(s) and Measures: The primary outcome was empiric (first 3 days of hospitalization) extended-spectrum antibiotic days of therapy. Secondary outcomes included empiric vancomycin and antipseudomonal days of therapy and safety outcomes included days to intensive care unit (ICU) transfer and hospital length of stay. Outcomes compared differences between baseline and intervention periods across strategies.

Results: Among 59 hospitals with 96,451 (51,671 in the baseline period and 44,780 in the intervention period) adult patients admitted with pneumonia, the mean (SD) age of patients was 68.1 (17.0) years, 48.1% were men, and the median (IQR) Elixhauser comorbidity count was 4 (2-6). Compared with routine stewardship, the group using CPOE prompts had a 28.4%

reduction in empiric extended-spectrum days of therapy (rate ratio, 0.72 [95% CI, 0.66-0.78]; P < .001). Safety outcomes of mean days to ICU transfer (6.5 vs 7.1 days) and hospital length of stay (6.8 vs 7.1 days) did not differ significantly between the routine and CPOE intervention groups.

Conclusions and Relevance: Empiric extended-spectrum antibiotic use was significantly lower among adults admitted with pneumonia to non-ICU settings in hospitals using education, feedback, and CPOE prompts recommending standard-spectrum antibiotics for patients at low risk of MDRO infection, compared with routine stewardship practices. Hospital length of stay and days to ICU transfer were unchanged.

Trial Registration ClinicalTrials.gov Identifier: NCT03697070

Introduction

More than 1.5 million adults are hospitalized in the US annually for pneumonia, the most common infection-related condition for which patients are hospitalized.[1] Estimates suggest that about half of patients admitted with pneumonia unnecessarily receive extended-spectrum antibiotics.[2-5] Identifying effective strategies to curb antibiotic overuse is a national priority; to date strategies to improve prescribing for inpatient pneumonia have largely focused on shortening antibiotic duration or de-escalating extended-spectrum antibiotics after microbiologic tests return and patients are stabilized.[4,6,7] However, such strategies do not address unnecessary extended-spectrum antibiotics used before these results are available.[7] Since even brief exposure to extended-spectrum antibiotics can increase a patient's risk for multidrug-resistant organisms (MDRO), *Clostridioides difficile* infection, and other antibiotic-associated adverse effects, additional strategies are urgently needed.[3,8,9]

Currently, clinicians often prescribe vancomycin and/or antipseudomonal therapy for pneumonia at admission and deescalate to standard-spectrum antibiotics if nasal screening test results are negative for methicillin-resistant *Staphylococcus aureus* (MRSA) or if cultures do not reveal *Pseudomonas* or other MDROs.[6,10-12] Although most inpatients with pneumonia can be safely treated with standard-spectrum antibiotics, which do not cover *Pseudomonas* or MDROs, clinicians are reluctant to initially select them because of concern that the patient may be infected with an MDRO.[5,10,13-15] Real-time identification of patients with low risk for MDRO pneumonia might therefore reduce empiric extended-spectrum antibiotic exposure.[14] We evaluated whether the INSPIRE antibiotic stewardship bundle, consisting of computerized provider order entry (CPOE) prompts to use standard-spectrum antibiotics for patients at low risk for MDRO pneumonia, coupled with education and feedback, reduced empiric extended-spectrum antibiotic prescribing for patients hospitalized with pneumonia.

Methods

Study Design and Intervention

The INSPIRE (Intelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection) Pneumonia Trial was a cluster-randomized trial comparing the effect of routine antibiotic stewardship vs INSPIRE CPOE stewardship bundle on empiric extended-spectrum antibiotic selection. The study population was non–critically ill adults (≥18 years) hospitalized with pneumonia at HCA Healthcare (hereafter referred to as HCA), the largest private community hospital system in the US. There was an 18-month baseline period (April 1, 2017-September 30, 2018), 6-month phase-in period (October 1, 2018-March 31, 2019), and 15-month intervention period (April 1, 2019-June 30, 2020). An analogous trial focusing on patients hospitalized with urinary tract infection is reported separately.[16]

Hospitals were randomly assigned to the routine or CPOE bundle group. The routine antibiotic stewardship group received educational materials and quarterly coaching calls to maintain stewardship activities for pneumonia per national guidance (Supplement 1). Routine stewardship activities included providing hospital guidelines and protocols for antibiotic selection, requiring a documented indication (reason) for antibiotics, and prospectively evaluating antibiotic use with clinician feedback to deescalate antibiotics after microbiologic test results returned.

In addition to routine stewardship activities, the CPOE bundle group received monthly coaching calls and the same educational material for maintaining national antibiotic stewardship guidance, plus (1) CPOE prompts recommending standard-spectrum instead of extended-spectrum antibiotics during the first 3 hospital days (empiric period) for patients with a low absolute risk (<10%) of MDRO pneumonia and (2) clinician education and feedback reports.

The CPOE algorithm and prompt were activated when extended-spectrum antibiotics (eTable 1 in Supplement 2) were ordered in a non–intensive care unit (ICU) location for an indication of pneumonia within 72 hours of admission (including antibiotics administered in the emergency department). The hospitals' order-entry system required documentation of an indication for all antibiotic orders. If the patient's estimated absolute MDRO risk was less than 10%, a prompt was triggered that recommended standard-spectrum antibiotics. The 10% threshold was recommended by an expert panel. Patient-specific estimates were recorded in the electronic health record in both study groups, but prompts were displayed only in the CPOE bundle group.

The CPOE algorithm and prompt were tailored to the specific extended-spectrum antibiotic ordered. For example, if vancomycin was ordered, the evaluation was for a less than 10% risk for pneumonia with MRSA; for cefepime, a less than 10% risk for *Pseudomonas* was evaluated; and for a carbapenem, a less than 10% combined risk of extended-spectrum β-lactamase–producing Enterobacterales (ESBLs) or resistant *Pseudomonas* was evaluated. These risks were obtained from recursive partitioning models that estimated absolute MDRO risk based on a retrospective dataset of patients admitted with pneumonia in 140 HCA hospitals (199,903 patients). Models assessed more than 50 variables, including each hospital's frequency of positive MDRO respiratory and blood culture results among patients with pneumonia and factors previously associated with risk of MDRO-associated pneumonia, such as demographics, health care exposures, antibiotic exposure, history or microbiologic evidence of MDROs (any body site), comorbidities, and admission laboratory values. Data were limited to information in the HCA health system. The modeling approach and factors associated with high risk of MDRO-associated pneumonia are provided in eTable 2 in Supplement 2.

The clinical workflow and prompts are shown in the eFigure in Supplement 2. The prompt provided a single-click option to substitute ceftriaxone (standard-spectrum) for the

extended-spectrum antibiotic. Clinicians could override (not accept) the recommendation and proceed with ordering extended-spectrum antibiotics.

Education for Both Study Groups. Education emphasized national standards for empiric pneumonia treatment, including updated guidance for community-acquired pneumonia released during this trial's intervention period, which emphasized empiric standard-spectrum antibiotics and use of nasal MRSA polymerase chain reaction testing for deescalating vancomycin for hospitalized patients with pneumonia.[6,10,17] Coaching calls emphasized the importance of avoiding competing interventions and polling questions monitored any new interventions. All educational content was developed by the investigative team, including presentations, handouts, and emails disseminated through existing hospital channels by local study champions and/or leadership (Supplement 1).

Education and Feedback in the CPOE Prompts Group. In addition to education provided to the routine stewardship group, the CPOE bundle group received education on how MDRO pneumonia risk estimates were calculated and the local frequency of positive MDRO culture results among patients with pneumonia. Additionally, lead investigators conducted 1-time site visits and additional webinars as requested. Investigators held coaching calls to support local education efforts. Feedback reports allowed local stewardship teams to monitor and provide feedback on extended-spectrum antibiotic prescribing for pneumonia at the hospital, department, and clinician levels as well as prompt response.

Hospital Recruitment and Study Cohort Definition

Hospitals were eligible to participate if they used the MEDITECH electronic health record (EHR) system and agreed to avoid new initiatives that could directly affect empiric antibiotic selection in non–critically ill patients with pneumonia. Hospitals sharing clinicians under a single antibiotic stewardship program were randomized as a single unit.

The analytic cohort was defined as patients with discharge claims codes for pneumonia that were accompanied by a "present on admission" indicator (eTable 3 in Supplement 2). This definition substantially overlaps with patients assigned an indication of pneumonia during antibiotic order entry and was selected to ensure full inclusion of patients with pneumonia independent of orders placed for a different indication. The cohort excluded individuals in prison and patients transferred to the ICU within 2 calendar days of admission. The Harvard Pilgrim Health Care Institute Institutional Review Board provided centralized oversight, with reliance agreements and operational committee approvals from participating hospitals. Individual informed consent was waived. This trial was registered with ClinicalTrials.gov (NCT03697070). Results are reported according to CONSORT guidelines.

Randomization

Hospitals were randomized in a 1:1 ratio to the routine stewardship or CPOE prompt intervention group for the INSPIRE pneumonia trial and the concurrent INSPIRE urinary tract infection trial.[16] Aggregated baseline hospital data from May 1, 2014, through March 31, 2017, were used to establish pairs of similar hospitals based on the following variables: (1) baseline extended-spectrum antibiotic days of therapy for pneumonia (primary and secondary outcomes), (2) baseline clinical practice (percentage of participants with cultures sent and time to first antibiotic dose), and (3) hospital patient case mix (annual pneumonia admissions, length of stay, ICU transfers, hospital baseline percentage of patients with pneumonia with culture results positive for MRSA and *Pseudomonas*, sex, Elixhauser comorbidity count [mean], percentage of admitted patients with select comorbidities, and percentage of vancomycin and antipseudomonal antibiotics given to patients calculated to have <10% absolute risk for MRSA or *Pseudomonas* pneumonia, respectively). Pairing was done by calculating the Mahalanobis distance between facilities across baseline values of weighted variables and choosing pairings

with the minimum mean within-pair distance.[18,19] Randomization was performed within these pairs.

Data Collection

Data obtained from the HCA centralized data warehouse included patient demographics, hospital unit location, any prior hospital/nursing home admissions and inpatient antibiotic exposures at the same hospital, and comorbid conditions. Race and ethnicity were included as collected in the HCA EHR to address population diversity and generalizability. Extended-spectrum antibiotics are shown in eTable 1 in Supplement 2. History of MDROs was obtained from any microbiology laboratory result from a body site yielding MRSA, vancomycin-resistant *Enterococci*, ESBL-producing Enterobacterales (ESBL), multidrug-resistant *Pseudomonas*, multidrug-resistant *Acinetobacter*, and carbapenem-resistant Enterobacterales (as defined in eTable 4 in Supplement 2). Designation of pneumonia due to an MDRO was based on positive results from blood or respiratory source (nares, sputum, trachea, bronchoalveolar lavage, or pleural fluid samples) cultures sent during the first 3 days of hospitalization and the associated emergency department stay.

Trial Outcomes

The primary outcome was extended-spectrum days of therapy in the first 3 calendar days of hospitalization, calculated as the summed number of different extended-spectrum antibiotics received per patient each calendar day in a non-ICU location, beginning at the time of admission. For convenience, this period was termed the *empiric period* and *empiric days* were calculated. For example, 2 different extended-spectrum antibiotics administered at least once during each of the first 3 days would yield 6 days of extended-spectrum therapy. The study had 97% (95% CI, 91%-99%) power to detect a 12.5% difference in extended-spectrum days of

therapy between the intervention and routine stewardship groups during the first 3 days (see the statistical analysis plan in Supplement 1).

The 2 secondary outcomes were days of therapy of the following subsets of extended-spectrum agents: vancomycin and antipseudomonal. Antibiotics administered in the emergency department were counted toward antibiotic days of therapy if given on the first hospital day. Because patients initially admitted to a non-ICU location who were subsequently transferred to an ICU on hospital day 1 or 2 were excluded, their antibiotic days were not included. However, patients transferred to the ICU on hospital day 3 had all empiric antibiotics counted, including those given in the ICU.

Three prespecified safety outcomes were assessed for the duration of the hospital stay: (1) days to antibiotic escalation, defined as hospital days from standard-spectrum antibiotic initiation until switch to extended-spectrum antibiotic (including those received after ICU transfer); (2) days to ICU transfer, defined as days from admission until ICU transfer; and (3) length of stay in days.

Statistical Analysis

Unadjusted as-randomized outcomes were assessed using generalized linear mixed-effects models assessing differences in empiric extended-spectrum days of therapy between intervention vs baseline periods across the groups (difference in differences). Random effects accounted for clustering within hospital and period. Data from the phase-in period were excluded from all analyses. The unit of analysis was the patient. Patients with multiple admissions contributed 1 randomly selected admission. The primary outcome was assessed with 2-tailed significance at $\alpha = .05$ and the 2 secondary outcomes were each assessed with 2-tailed significance at $\alpha = .025$ to account for multiple comparisons.

Each safety outcome was assessed using as-randomized unadjusted proportional hazards models with random effects to account for clustering by hospital and period. To

maximize detection of safety risks, each safety outcome was assessed with 1-tailed significance at $\alpha = .05$.

Adjusted analyses accounted for age, sex, race and ethnicity, Medicaid insurance, antibiotic or nursing home exposure in the last year, mean Elixhauser comorbidity count, and history of MDRO. Race and ethnicity were included given prior evidence of association with risk for pneumonia, MDRO, and predisposing chronic pulmonary conditions.[20-22] All analyses were performed using SAS version 9.4 (SAS Institute) or R version 4.0.0 (R Foundation). The a priori statistical analytic plan is provided in Supplement 1.

Three sets of sensitivity analyses were completed, none of which were prespecified. First, all outcomes were reevaluated after including patients transferred to the ICU after the first admission day (the original analysis evaluated those transferred after the second admission day). Second, to account for the competing risk of death for safety outcomes, patients who died were counted as having transferred to the ICU and having had an antibiotic escalation on the day of death; for length of stay, each patient who died was assigned a length of stay of 30 days (99th percentile of hospitalization length in the baseline period). Third, to provide a clinically relatable metric for primary and secondary outcomes, these outcomes were reevaluated after redefining them as extended-spectrum doses per patient during the empiric period.

Results

Patient Characteristics

Fifty-nine hospitals were randomized to either the routine antibiotic stewardship group (30 hospitals; 47,029 patients) or the CPOE bundle group (29 hospitals; 49,422 patients) (Figure 1). Patient characteristics by group and period are provided in Table1. The routine stewardship group had 25,031 patients during the baseline period and 21,998 during the intervention period; the CPOE bundle intervention group had 26,640 patients during the

baseline period and 22,782 during the intervention period. Study groups were well-balanced overall. Compared with routine stewardship, the CPOE bundle group had a higher percentage of patients of Hispanic ethnicity (19.7% vs 16.3%), with diabetes (37.7% vs 36.9%), and with neurologic disorders (27.9% vs 25.5%), although the percentage with chronic pulmonary disease was higher in the routine stewardship group (48.9% vs 47.1%).

The percentage of patients with respiratory or blood cultures sent during the empiric period (first 3 days of hospitalization) and associated emergency department stay during baseline was 86.1% (21,544/25,031) for the routine stewardship group and 86.6% (23 078/26,640) for the CPOE bundle group; for the intervention period, the percentages were 86.6% (19,047/21,998) for the routine stewardship group and 85.8% (19,552/22,782) for the CPOE bundle group. Of patients with respiratory or blood cultures sent during the empiric period, the percentage with cultures positive for a pathogen requiring extended-spectrum antibiotics during baseline was 3.5% (764/21,544) for the routine stewardship group and 3.3% (767/23,078) for the CPOE bundle group; during the intervention period, the percentages were 3.9% (740/19,047) for the routine stewardship group and 3.4% (657/19,552) for the CPOE bundle group (eTable 5 in Supplement 2). Specifically, cultures were positive for MRSA or *Pseudomonas* in less than 2% of patients across both study groups in the baseline and intervention periods. MDRO pneumonia prevalence for all 59 hospitals is provided in eTable 6 in Supplement 2.

Antibiotic Prescribing and MDRO Risk Estimation

Receipt of any empiric extended-spectrum antibiotic was 51.5% (12,901/25,030) during the baseline period and 50.1% (11,014/21,998) during the intervention period for the routine stewardship group and 50.0% (13,338/26,640) for the baseline period and 38.1% (8,691/22,782) during the intervention period for the CPOE bundle group. Reductions in monthly extended-spectrum days of therapy in the CPOE bundle group were evident by 3 months into

the phase-in period (Figure 2A-B; eTable 7 in Supplement 2). These reductions continued during the COVID-19 pandemic in the last 4 months of the trial, with a COVID-19 positivity rate of 39 per 1000 admissions in the routine stewardship group and 41 per 1000 admissions in the CPOE bundle group.

The INSPIRE algorithm classified more than 96% of patients with pneumonia in both stewardship groups as low risk; less than 2% of these patients subsequently had an MDRO-positive culture (eTable 8 in Supplement 2).

Primary and Secondary Trial Outcomes.

For the primary outcome, empiric extended-spectrum days of therapy per 1000 empiric days was 633.0 during the baseline period and 615.2 during the intervention period for the routine stewardship group. For the CPOE bundle group, extended-spectrum days of therapy decreased from 613.9 during the baseline period to 428.5 during the intervention period. The overall rate ratio (RR) when clustering by hospital and period was 0.72 (95% CI, 0.66-0.78; $P < .001$) for the primary outcome (Table 2, Figure 3A), indicating a 28.4% (95% CI, 22.2%-34.1%; $P < .001$) significantly lower rate of empiric extended-spectrum days of therapy in the CPOE bundle group compared with routine stewardship. Secondary outcomes of vancomycin and antipseudomonal days of therapy showed similar reductions (Table 2, Figure 3A).

Sensitivity Analyses. Point estimates remained nearly identical for all outcomes after adjusted and sensitivity analyses (eTables 9-10 in Supplement 2). Notably, there was a 32% reduction in empiric extended-spectrum antibiotic doses per patient, from 3.3 (83,613/25,030) during the baseline period to 3.3 (72 536/21 998) during the intervention period for the routine stewardship group vs 3.3 (87 710/26 640) during the baseline period and 2.2 (51 145/22 782) during the intervention period for the CPOE bundle group (eTable 10 in Supplement 2).

Safety Outcomes

In the routine vs CPOE bundle groups, the percentage of patients transferred to the ICU was 6.9% vs 6.7% and the percentage requiring antibiotic escalation was 11.9% vs 10.8% (eTable 11 in Supplement 2). There were no significant differences between the groups for the safety outcomes of ICU transfer or hospital length of stay (Table 2, Figure 3B). Time to antibiotic escalation (from standard- to extended-spectrum antibiotics) was 18.1% longer in the CPOE bundle group compared with the routine stewardship group (overall hazard ratio, 0.82 [95% CI, 0.69-0.97]; $P = .02$). Hazard ratios for all safety outcomes remained nearly identical in sensitivity analyses (eTable 12 in Supplement 2).

Monitoring of CPOE Prompt and Competing Interventions

Auditing of the CPOE algorithm showed that the automated system was working as intended when extended-spectrum antibiotics were ordered for a pneumonia indication, with prompt activation if the relevant MDRO(s) risk was less than 10% in the CPOE bundle group. The reduction in prescribing of extended-spectrum antibiotics in the CPOE bundle group consisted largely of (1) a reduction in clinicians' initial choice of extended-spectrum antibiotics (26.1% [5,937/22,782] in the CPOE bundle hospitals vs 35.5% [7,807/21,998] in the routine stewardship hospitals) during the intervention period and (2) a change from extended- to standard-spectrum antibiotic therapy in 12.5% (591/4,718) of patients who encountered the real-time prompt. The percentage of patients for whom pneumonia was chosen as the indication for antibiotic use among those with pneumonia as a discharge diagnosis was similar in the routine (80.4% [17,690/21,998]) and CPOE bundle (80.0% [18,234/22,782]) groups.

Of the 39 proposed changes in antibiotic stewardship practices reported by hospitals in both study groups, 2 conflicted with the trial protocol and were not implemented.

Discussion

Pneumonia is a leading cause of hospitalization and unnecessary use of extended-spectrum antibiotics, with an estimated 750,000 hospitalized adults receiving extended-spectrum antibiotics annually in the US. [1-4, 12,15,24,25] The CPOE bundle intervention resulted in a rapid, sustained, and safe reduction of empiric extended-spectrum antibiotic use for non–critically ill patients hospitalized with pneumonia. This trial focused on reducing use of extended-spectrum agents before microbiology results were available. Importantly, reductions were achieved without a change in the safety outcomes of ICU transfer or length of stay.

Data from HCA's extensive network of community hospitals show that MRSA and *Pseudomonas* each accounted for less than 2% of inpatients with pneumonia. This may be an overestimate because organism recovery from nonsterile respiratory sites may represent colonization rather than the source of infection. Thus, most patients with pneumonia do not need extended-spectrum antibiotics, as further supported by equivalence in safety outcomes across study groups.

The patient-, pathogen-, and infection-specific prompts may have changed empiric prescribing of antibiotics in several important ways. First, the prompt shifted initial prescriptions from extended- to standard-spectrum antibiotic therapy, possibly by giving clinicians a clearer sense of the relatively low risk of resistant pathogens in the overall population. Second, for the remaining low-risk patients in whom extended-spectrum antibiotics remained the initial choice, the prompts provided guidance and reassurance to change an initial choice away from extended-spectrum antibiotic therapy. Third, providing each hospital's prevalence of MDROs among patients hospitalized with pneumonia is nationally recommended but rarely operationalized. Fourth, because most antibiotics that are initiated in the emergency department are continued throughout hospitalization, initial choices likely influenced extended-spectrum antibiotic prescribing across multiple hospital locations. [26, 27] Fifth, the automated nature of the prompt sustained the intervention and maintained lower extended-spectrum antibiotic use even

during pandemic-associated disruptions. Sixth, documentation of each patient's estimated MDRO risk in the EHR may have helped mitigate potential medicolegal concerns by recording the patient's low estimated risk at the time of prescribing. This helped reassure clinicians that empiric selection of standard-spectrum antibiotics was justified based on available data, even if cultures subsequently grew an MDRO. Finally, setting the threshold for classifying a patient as "low risk" for MDRO infection at less than 10% addressed variability in clinician tolerance for risk.

Limitations

There are several limitations in this study. First, the trial was performed in private community hospitals and applicability to other settings is unknown. Second, culture results were included without regard for specimen quality, likely overestimating the proportion of pneumonia classified as being caused by MDRO pathogens. Third, a threshold of MDRO risk greater than 10% could have been a safe and more effective stewardship intervention.[28] Fourth, the INSPIRE pneumonia prompts were implemented simultaneously with urinary tract infection prompts. Although concurrent prompts for urinary tract infection could have improved adoption of the pneumonia prompt through increased familiarity with prompt processes, it is also possible that concurrent prompts could have negatively affected adoption through alert fatigue. Fifth, it is not possible to separate the effect of the prompt itself from the effects of education and feedback, although the rapid reduction in extended-spectrum antibiotic use suggests that the prompt played a prominent role because education and feedback campaigns generally require more time to effect change.[29-31] Sixth, updated pneumonia treatment guidelines released during the trial emphasizing empiric standard-spectrum antibiotic use may have affected temporal trends; notably, education on this new guidance was disseminated to both study groups, yet reductions were only seen in the INSPIRE CPOE bundle stewardship group.

Conclusions

Empiric extended-spectrum antibiotic use was significantly lower among adults admitted with pneumonia to non-ICU settings in hospitals using education, feedback, and real-time CPOE prompts recommending standard-spectrum antibiotics for patients at low risk of MDRO infection, compared with routine stewardship practices. Hospital length of stay and days to ICU transfer were unchanged.

Author Contributions:

Dr Gohil had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Gohil, Septimus, Kleinman, Rahm, M. Cooper, Nickolay, Weinstein, Burgess, Sands, Gilbert, Poland, Hickok, Calderwood, Reddy, Neuhauser, Srinivasan, Jernigan, Hayden, Perlin, Platt, Huang.

Acquisition, analysis, or interpretation of data: Gohil, Septimus, Kleinman, Varma, Avery, Heim, W. Cooper, McLean, Weinstein, Coady, Rosen, Sljivo, Moody, Vigeant, Rashid, Smith, Carver, Poland, Sturdevant, Weiland, Kubiak, Gowda, Eibensteiner, Wolf, Platt, Huang.

Drafting of the manuscript: Gohil, Septimus, Kleinman, Varma, Avery, Rosen, Huang.

Critical review of the manuscript for important intellectual content: Gohil, Septimus, Kleinman, Varma, Heim, Rahm, W. Cooper, M. Cooper, McLean, Nickolay, Weinstein, Burgess, Coady, Sljivo, Sands, Moody, Vigeant, Rashid, Gilbert, Smith, Carver, Poland, Hickok, Sturdevant, Calderwood, Weiland, Kubiak, Reddy, Neuhauser, Srinivasan, Jernigan, Hayden, Gowda, Eibensteiner, Wolf, Perlin, Platt, Huang.

Statistical analysis: Gohil, Kleinman, Varma, Avery, M. Cooper, Rosen, Sturdevant.

Obtained funding: Septimus, Sands, Poland, Perlin, Platt, Huang.

Administrative, technical, or material support: Gohil, Septimus, Varma, Avery, Heim, Rahm, W. Cooper, M. Cooper, McLean, Nickolay, Weinstein, Burgess, Coady, Sljivo, Sands,

Moody, Vigeant, Rashid, Gilbert, Smith, Carver, Poland, Hickok, Weiland, Kubiak, Reddy, Neuhauser, Jernigan, Hayden, Gowda, Eibensteiner, Wolf, Perlin, Huang.

Supervision: Gohil, Septimus, Kleinman, W. Cooper, McLean, Smith, Hickok, Perlin, Platt, Huang.

Conflict of Interest Disclosures:

Dr Platt reported contracts to his academic department from GlaxoSmithKline, Pfizer, Janssen, and the US Food and Drug Administration and grants from the National Institutes of Health. Dr Huang reported conducting clinical studies in which participating nursing homes and hospital patients received contributed antiseptic product from Xttrium Laboratories and Medline Industries. No other disclosures were reported.

Funding/Support:

Funding for this study was provided by the Centers for Disease Control and Prevention (SHEPheRD Task Order 200-2011-42037). Support for HCA's participation in the study was provided in kind by HCA.

Role of the Funder/Sponsor:

Role of the Funder/Sponsor: The CDC and HCA had a role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication

Disclaimer:

The views expressed in this publication represent those of the author(s) and do not necessarily represent the official views of CDC nor HCA nor any affiliated entities.

Data Sharing Statement:

See Supplement 3.

REFERENCES

1. Kennedy JL, Haberling DL, Huang CC, et al. Infectious Disease Hospitalizations: United States, 2001 to 2014. Chest 2019;156(2):255-268. DOI: 10.1016/j.chest.2019.04.013.
2. Magill SS, O'Leary E, Ray SM, et al. Antimicrobial Use in US Hospitals: Comparison of Results From Emerging Infections Program Prevalence Surveys, 2015 and 2011. Clin Infect Dis 2021;72(10):1784-1792. DOI: 10.1093/cid/ciaa373.
3. Centers for Disease Control and Prevention (CDC). Antibiotic Resistance Threats in the United States, 2019. (https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf) Accessed September 16. 2023.
4. Vaughn VM, Flanders SA, Snyder A, et al. Excess Antibiotic Treatment Duration and Adverse Events in Patients Hospitalized With Pneumonia: A Multihospital Cohort Study. Ann Intern Med 2019;171(3):153-163. DOI: 10.7326/M18-3640.
5. Klompas M. Overuse of Broad-Spectrum Antibiotics for Pneumonia. JAMA Intern Med 2020;180(4):485-486. DOI: 10.1001/jamainternmed.2019.7251.
6. Deshpande A, Richter SS, Haessler S, et al. De-escalation of Empiric Antibiotics Following Negative Cultures in Hospitalized Patients With Pneumonia: Rates and Outcomes. Clin Infect Dis 2021;72(8):1314-1322. DOI: 10.1093/cid/ciaa212.
7. Core Elements of Hospital Antibiotic Stewardship Programs. Centers for Disease Control and Prevention. (https://www.cdc.gov/antibiotic-use/core-elements/hospital.html) Accessed September 16. 2023.
8. Baggs J, Fridkin SK, Pollack LA, Srinivasan A, Jernigan JA. Estimating National Trends in Inpatient Antibiotic Use Among US Hospitals From 2006 to 2012. JAMA Intern Med 2016;176(11):1639-1648. DOI: 10.1001/jamainternmed.2016.5651.
9. Tamma PD, Avdic E, Li DX, Dzintars K, Cosgrove SE. Association of Adverse Events With Antibiotic Use in Hospitalized Patients. JAMA Intern Med 2017;177(9):1308-1315. (In eng). DOI: 10.1001/jamainternmed.2017.1938.
10. Metlay JP, Waterer GW, Long AC, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med 2019;200(7):e45-e67. DOI: 10.1164/rccm.201908-1581ST.
11. Lew KY, Ng TM, Tan M, et al. Safety and clinical outcomes of carbapenem de-escalation as part of an antimicrobial stewardship programme in an ESBL-endemic setting. J Antimicrob Chemother 2015;70(4):1219-25. (In eng). DOI: 10.1093/jac/dku479.
12. Jones BE, Ying J, Stevens V, et al. Empirical Anti-MRSA vs Standard Antibiotic Therapy and Risk of 30-Day Mortality in Patients Hospitalized for Pneumonia. JAMA Intern Med 2020;180(4):552-560. DOI: 10.1001/jamainternmed.2019.7495.
13. Krockow EM, Colman AM, Chattoe-Brown E, et al. Balancing the risks to individual and society: a systematic review and synthesis of qualitative research on antibiotic prescribing behaviour in hospitals. J Hosp Infect 2019;101(4):428-439. DOI: 10.1016/j.jhin.2018.08.007.
14. Webb BJ, Jones B, Dean NC. Empiric antibiotic selection and risk prediction of drug-resistant pathogens in community-onset pneumonia. Curr Opin Infect Dis 2016;29(2):167-77. (In eng). DOI: 10.1097/QCO.0000000000000254.

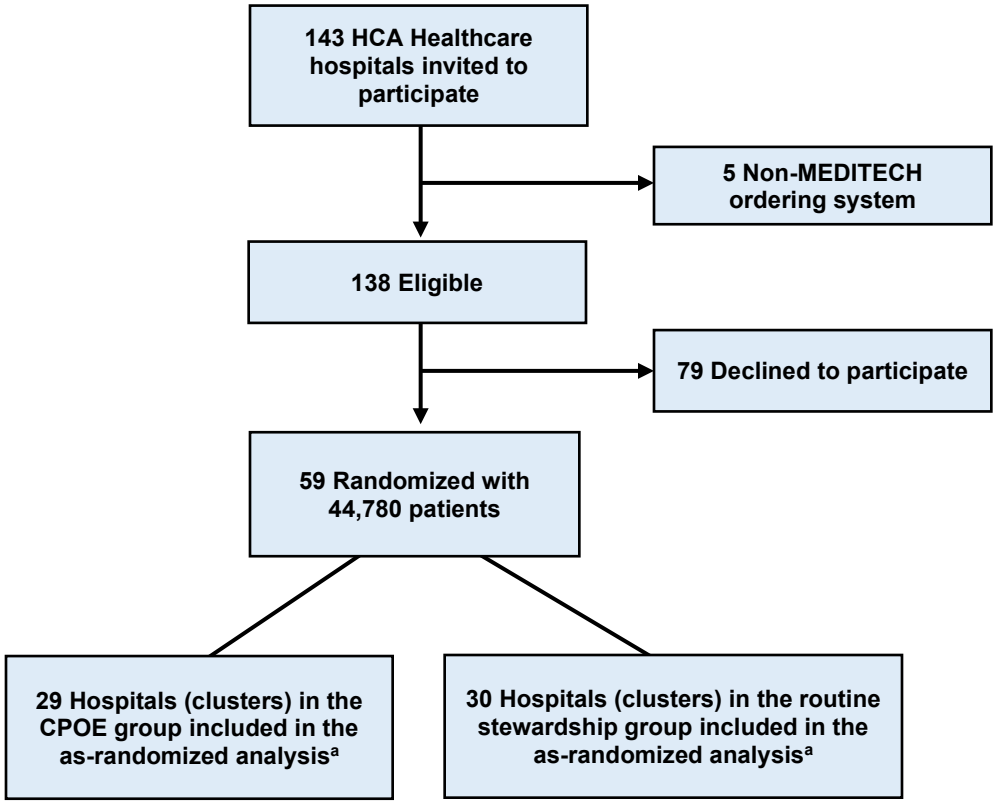
15. Self WH, Wunderink RG, Williams DJ, et al. Staphylococcus aureus Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes. Clin Infect Dis 2016;63(3):300-9. (In eng). DOI: 10.1093/cid/ciw300.
16. Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 19, 2024. doi:10.1001/jama.2024.6259 .
17. Parente DM, Cunha CB, Mylonakis E, Timbrook TT. The Clinical Utility of Methicillin-Resistant Staphylococcus aureus (MRSA) Nasal Screening to Rule Out MRSA Pneumonia: A Diagnostic Meta-analysis With Antimicrobial Stewardship Implications. Clin Infect Dis 2018;67(1):1-7. DOI: 10.1093/cid/ciy024.
18. Mahalanobis P. On the generalised distance in statistics. Proceedings of the National Institute of Sciences of India. 1936.
19. Sturdevant SG, Huang SS, Platt R, Kleinman K. Matching in cluster randomized trials using the Goldilocks Approach. Contemp Clin Trials Commun 2021;22:100746. DOI: 10.1016/j.conctc.2021.100746.
20. Gontjes KJ, Gibson KE, Lansing BJ, Mody L, Cassone M. Assessment of race and sex as risk factors for colonization with multidrug-resistant organisms in six nursing homes. Infect Control Hosp Epidemiol 2020;41(10):1222-1224. DOI: 10.1017/ice.2020.215.
21. Nadimpalli ML, Chan CW, Doron S. Antibiotic resistance: a call to action to prevent the next epidemic of inequality. Nat Med 2021;27(2):187-188. DOI: 10.1038/s41591-020-01201-9.
22. Hausmann LR, Ibrahim SA, Mehrotra A, et al. Racial and ethnic disparities in pneumonia treatment and mortality. Med Care 2009;47(9):1009-17. DOI: 10.1097/MLR.0b013e3181a80fdc.
23. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. *Med Care*. 1998;36(1):8-27. doi:10.1097/00005650-199801000-00004
24. Jones BE, Sarvet AL, Ying J, et al. Incidence and Outcomes of Non-Ventilator-Associated Hospital-Acquired Pneumonia in 284 US Hospitals Using Electronic Surveillance Criteria. JAMA Netw Open 2023;6(5):e2314185. DOI: 10.1001/jamanetworkopen.2023.14185.
25. Gupta AB, Flanders SA, Petty LA, et al. Inappropriate Diagnosis of Pneumonia Among Hospitalized Adults. JAMA Intern Med 2024. DOI: 10.1001/jamainternmed.2024.0077.
26. Kiyatkin D, Bessman E, McKenzie R. Impact of antibiotic choices made in the emergency department on appropriateness of antibiotic treatment of urinary tract infections in hospitalized patients. J Hosp Med 2016;11(3):181-4. (In eng). DOI: 10.1002/jhm.2508.
27. Jones T, Dodds Ashley, E, Johnson, MD, Moehring, RW, Sarubbi, C, Wrenn, R. Do Antibiotic Choices Made in the ED Influence Inpatient Therapy? Open Forum Infectious Diseases;6(Supplement_2):Page S354. DOI: https://doi.org/10.1093/ofid/ofz360.870.
28. Daneman N, Low DE, McGeer A, Green KA, Fisman DN. At the threshold: defining clinically meaningful resistance thresholds for antibiotic choice in community-acquired pneumonia. Clin Infect Dis 2008;46(8):1131-8. DOI: 10.1086/529440.
29. Shafat T, Shimoni O, Nikonov A, Nesher L. The Kinetics of an Antibiotic Stewardship Intervention: A Quasi-Experimental Study. Infect Dis Ther 2021;10(1):613-619. DOI: 10.1007/s40121-021-00403-z.

30. Wojcik G, Ring N, McCulloch C, Willis DS, Williams B, Kydonaki K. Understanding the complexities of antibiotic prescribing behaviour in acute hospitals: a systematic review and meta-ethnography. Arch Public Health 2021;79(1):134. DOI: 10.1186/s13690-021-00624-1.
31. Ranji SR, Steinman MA, Shojania KG, Gonzales R. Interventions to reduce unnecessary antibiotic prescribing: a systematic review and quantitative analysis. Med Care 2008;46(8):847-62. DOI: 10.1097/MLR.0b013e318178eabd.

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 10, 2024. doi:10.1001/jama.2024.6248

INSPIRE Pneumonia Trial Tables/Figures

Figure 1. Hospital Recruitment and Randomization in the INSPIRE Pneumonia Trial



MEDITECH is a hospital electronic health record system. CPOE indicates computerized provider order entry; INSPIRE, Intelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection.

[a]All analyses are as-randomized because all hospitals remained in the trial until end of intervention (no hospital withdrawals after enrollment). There was a median (IQR) of 1,679 (1,019-2,319) patients per hospital in the CPOE bundle group and 1,544 (1,204-1,971) in the routine stewardship group.

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA.* Published online April 10, 2024. doi:10.1001/jama.2024.6248

Table 1: Characteristics of Patients with Pneumonia During Baseline and Intervention Periods

Patient Characteristics	BASELINE (18 months)		INTERVENTION (15 months)	
	CPOE Bundle N (%)	Routine Stewardship N (%)	CPOE Bundle N (%)	Routine Stewardship N (%)
Patients	**26,640**	**25,031**	**22,782**	**21,998**
Mean Age (SD)	68.9 (16.7)	68.1 (17.0)	68.0 (17.0)	67.4 (17.3)
Age Categorized				
18-44	2,443 (9.2)	2,585 (10.3)	2,415 (10.6)	2,546 (11.6)
45-54	2,445 (9.2)	2,430 (9.7)	2,055 (9.0)	2,072 (9.4)
55-64	4,591 (17.2)	4,279 (17.1)	4,024 (17.7)	3,742 (17.0)
65-74	6,039 (22.7)	5,675 (22.7)	5,140 (22.6)	5,107 (23.2)
75-84	6,232 (23.4)	5,745 (23.0)	5,296 (23.2)	4,990 (22.7)
≥85	4,890 (18.4)	4,317 (17.2)	3,852 (16.9)	3,541 (16.1)
Sex[a]				
Male	12,852 (48.4)	11,869 (47.6)	10,966 (48.2)	10,545 (48.1)
Female	13,710 (51.5)	13,085 (52.3)	11,768 (51.7)	11,400 (51.8)
Race				
Black	3,194 (12.0)	2,985 (11.9)	2,908 (12.8)	2,848 (12.9)
White	20,387 (76.5)	18,178 (72.6)	17,205 (75.5)	15,415 (70.1)
Other[b]	1,781 (6.7)	969 (3.9)	1,304 (5.7)	898 (4.1)
Unknown	1,278 (4.8)	2,899 (11.6)	1,365 (6.0)	2,837 (12.9)
Hispanic/Latino Ethnicity	5,308 (19.9)	3,947 (15.8)	4,489 (19.7)	3,587 (16.3)
Insurance Type				
Medicare	18,982 (71.3)	17,441 (69.7)	15,658 (68.7)	15,001 (68.2)
Medicaid	2,670 (10.0)	2,190 (8.7)	2,430 (10.7)	2,019 (9.2)
Commercial	2,790 (10.5)	2,984 (11.9)	2,512 (11.0)	2,695 (12.3)
Other (e.g. Self-pay, Free care)	2,198 (8.3)	2,416 (9.7)	2,182 (9.6)	2,283 (10.4)
Antibiotic & Healthcare Exposures in Year Prior to Admission[c]				
Emergency Department Visit	13,599 (51.0)	11,999 (47.9)	11,217 (49.2)	10,363 (47.1)
Hospitalization	9,888 (37.1)	8,976 (35.9)	8,121 (35.6)	7,727 (35.1)
Antibiotics	7,957 (29.9)	7,211 (28.8)	6,468 (28.4)	6,233 (28.3)
Nursing Home Stay	3,425 (12.9)	2,821 (11.3)	2,625 (11.5)	2,368 (10.8)
Hours to First Antibiotics (Current Admission)[d]				
Median (IQR)	2.5 (1.0-4.5)	2.0 (1.0-4.5)	1.5 (1.0-1.5)	1.5 (0.5-1.5)
History of Pathogen Requiring Extended Spectrum Antibiotics – Any[e]	2,645 (9.9)	2,379 (9.5)	2,329 (10.2)	2,125 (9.7)
MRSA	1,665 (6.3)	1,471 (5.9)	1,396 (6.1)	1,291 (5.9)
Pseudomonas	836 (3.1)	792 (3.2)	771 (3.4)	707 (3.2)
ESBL	795 (3.0)	651 (2.6)	729 (3.2)	687 (3.1)
CRE[f]	184 (0.7)	184 (0.7)	133 (0.6)	131 (0.6)

VRE	182 (0.7)	192 (0.8)	164 (0.7)	125 (0.6)
Elixhauser Comorbidities[g]				
Hypertension	18,246 (68.5)	16,867 (67.4)	16,120 (70.8)	15,474 (70.3)
Chronic Pulmonary Disease	12,613 (47.3)	12,109 (48.4)	10,741 (47.1)	10,747 (48.9)
Diabetes	9,734 (36.5)	8,950 (35.8)	8,597 (37.7)	8,113 (36.9)
Heart Failure	8,605 (32.3)	8,121 (32.4)	7,806 (34.3)	7,515 (34.2)
Anemias	7,934 (29.8)	7,945 (31.7)	7,159 (31.4)	7,189 (32.7)
Neurological Disorders	7,154 (26.9)	6,314 (25.2)	6,367 (27.9)	5,618 (25.5)
Kidney Disease	6,638 (24.9)	6,095 (24.3)	5,965 (26.2)	5,819 (26.5)
Obesity	4,316 (16.2)	4,680 (18.7)	4,229 (18.6)	4,596 (20.9)
Solid Tumor	2,364 (8.9)	2,309 (9.2)	2,215 (9.7)	2,198 (10)
Alcohol and Drug Abuse	1,854 (7.0)	1,682 (6.7)	1,818 (8.0)	1,625 (7.4)
Liver Disease	1,423 (5.3)	1,410 (5.6)	1,598 (7.0)	1,584 (7.2)
Hematologic Malignancy	704 (2.6)	643 (2.6)	655 (2.9)	568 (2.6)
Elixhauser Count[h]				
Median (IQR)	4 (2.0-5.0)	4 (2.0-5.0)	4 (3.0-6.0)	4 (3.0-6.0)

Abbreviations: CRE = carbapenem-resistant Enterobacterales; ESBL = extended-spectrum β-lactamase-producing Enterobacterales; MRSA = methicillin-resistant *Staphylococcus aureus*; VRE = vancomycin-resistant *Enterococci*.

[a]The numbers for sex may not equal the group totals because some patients had missing or unknown sex.

[b]Other race category included: Asian, Hawaiian, Native American, or Multiracial.

[c]Health care exposures limited to those documented within a prior inpatient or emergency department visit in the HCA Healthcare electronic medical record.

[d]Hours to first antibiotics includes first dose of any antibiotics administered in the emergency department or inpatient wards from 2 days prior to date of admission up to 3 days of hospitalization.

[e]History of multidrug-resistant pathogen included any prior growth of pathogen requiring extended-spectrum antibiotics, including *Pseudomonas* or multidrug-resistant organisms: MRSA, ESBL producer, and VRE. Includes MRSA polymerase chain reaction test positivity and MRSA *International Statistical Classification of Diseases and Related Health Problems, Tenth* Revision diagnosis codes.

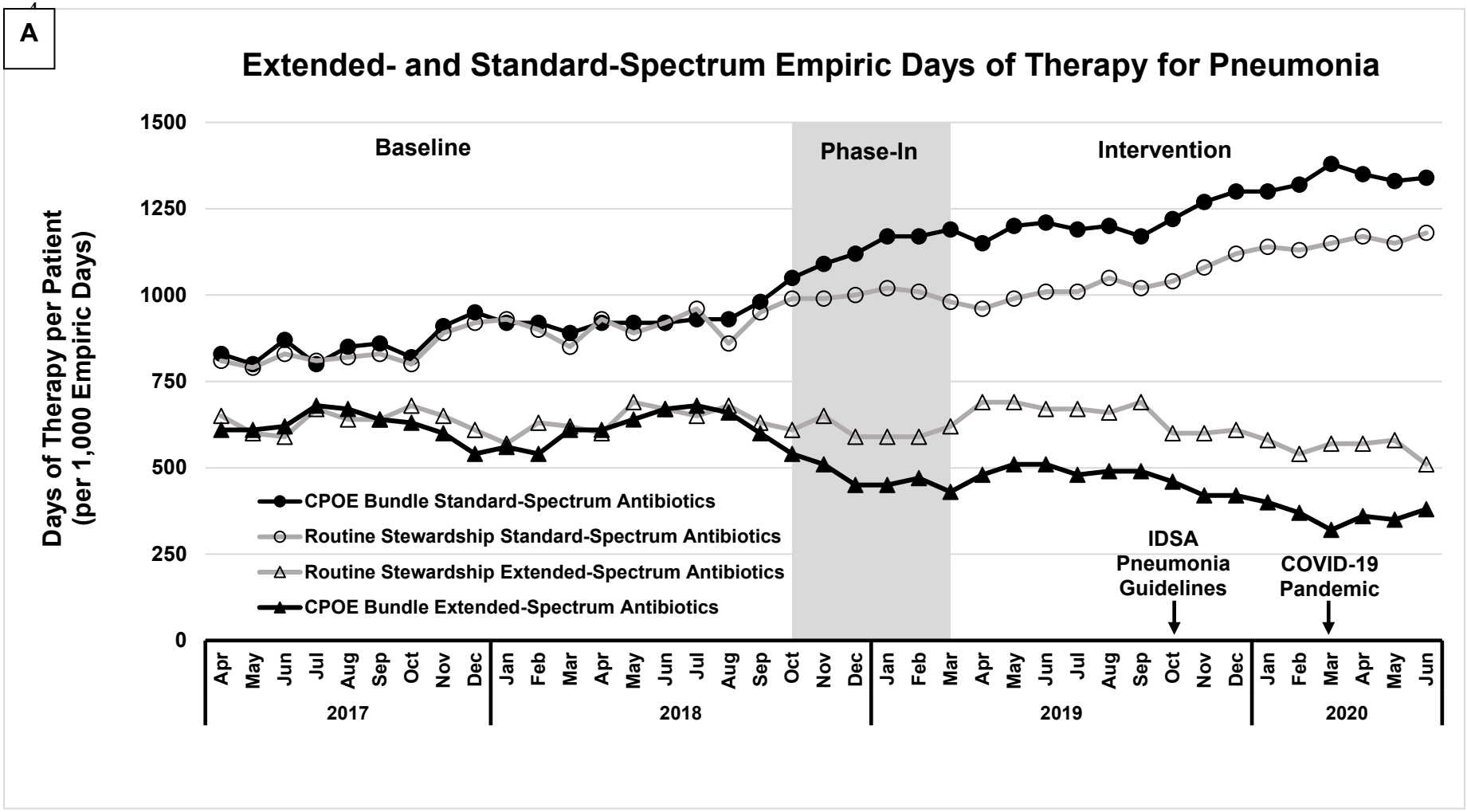
[f]Includes carbapenem-resistant Enterobacterales, *Acinetobacter,* and *Pseudomonas*.

[g]Selected from Elixhauser comorbidity conditions (Elixhauser, Anne, et al. Medical Care, 36 (1):8-27, 1998); chronic pulmonary disease includes pulmonary circulation disease; Diabetes includes with and without chronic complications; Anemias includes anemias due to nutritional and iron deficiencies; Liver disease includes mild, moderate, and severe; Kidney disease includes moderate and severe; Neurologic disease includes dementia, cerebrovascular disease, paralysis, neurologic disorders affecting movement, seizures and epilepsy, and other neurological diseases; Solid tumor includes with and without metastases; and hematologic malignancy includes lymphoma and leukemia.

[h]Elixhauser count is the sum of each comorbid condition (among 38) as available in the electronic health record for each patient.

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA*. Published online April 10, 2024. doi:10.1001/jama.2024.6248

Figure 2A-B: Monthly Empiric Extended- and Standard-Spectrum Antibiotic Days of Therapy in the Computerized Provider Order Entry (CPOE) Bundle vs Routine Stewardship Across the Baseline and Intervention Periods



Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA*. Published online April 10, 2024. doi:10.1001/jama.2024.6248

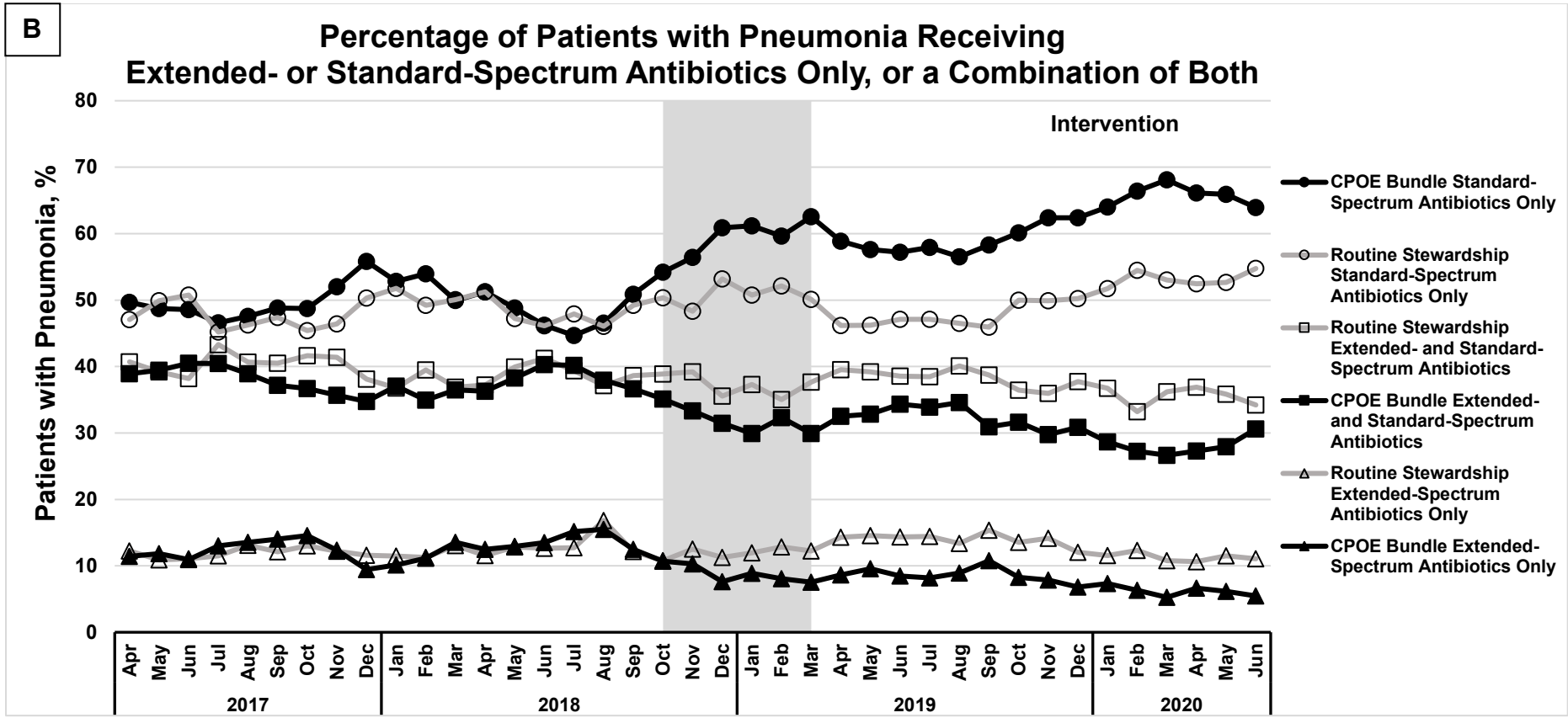


Figure 2: (A) Temporal trends in empiric (hospital days 1-3) extended and standard-spectrum days-of-therapy show sustained reductions in monthly extended-spectrum and increases in standard-spectrum antibiotic days-of-therapy in the intervention group that was evident early in the phase-in period. Effects persisted despite arrival of the COVID-19 pandemic. (**B)** Temporal trends in percent of patients with pneumonia who received either extended-spectrum only, standard-spectrum only, or a combination of both (mutually exclusive categories) during the empiric period. Percent of patients receiving standard-spectrum only in the intervention group increased while the percent receiving extended-spectrum only or combination of both decreased. In both study groups, there was a secular trend showing increased standard-spectrum use after updated national guidance in October 2019.

Gohil SK, Septimus E, Kleinman K, et al. Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. *JAMA*. Published online April 10, 2024. doi:10.1001/jama.2024.6248

Table 2: Primary, Secondary, & Safety Outcomes in the INSPIRE Pneumonia Trial

Effectiveness Outcomes	CPOE Bundle			Routine Stewardship			Overall Rate Ratio Difference-in-Differences	P-value[c]
	Baseline Days-of-Therapy Raw Rate[a]	Intervention Days-of-Therapy Raw Rate[a]	Rate Ratio (95% CI)[b]	Baseline Days-of-Therapy Raw Rate[a]	Intervention Days-of-Therapy Raw Rate[a]	Rate Ratio (95% CI)[b]		
Primary Outcome								
Extended-spectrum days-of-therapy	613.9 (46,993/76,522)	428.5 (27,971/65,272)	0.68 (0.64-0.72)	633.0 (45,595/72,033)	615.2 (38,690/62,892)	0.94 (0.89-1.00)	0.72 (0.66-0.78)	<.001
Secondary Outcomes								
Vancomycin days-of-therapy	235.4 (18,019/76,552)	161.4 (10,534/65,272)	0.68 (0.64-0.72)	241.4 (17,390/72,033)	219.1 (13,778/62,892)	0.89 (0.84-0.94)	0.77 (0.71-0.83)	<.001
Antipseudomonal days-of-therapy	342.4 (26,210/76,552)	240.1 (15,670/65,272)	0.67 (0.62-0.72)	356.7 (25,696/72,033)	360.7 (22,683/62,892)	0.98 (0.91-1.06)	0.68 (0.61-0.75)	<.001
Safety Outcomes	**CPOE Bundle**			**Routine Stewardship**			**Overall Hazard Ratio Difference-in-Differences**	**P-value[f]**
	Baseline Mean (SD) Days-to-Event[d]	**Intervention** Mean (SD) Days-to-Event[d]	**Hazard Ratio (95% CI)[e]**	**Baseline** Mean (SD) Days-to-Event[d]	**Intervention** Mean (SD) Days-to-Event[d]	**Hazard Ratio (95% CI)[e]**		
Length-of-Stay	6.9 (6.4)	7.1 (6.9)	1.00 (0.96-1.03)	6.9 (5.8)	6.8 (5.9)	1.04 (1.00-1.07)	0.96 (0.91-1.01)	0.13
Days-to-ICU Transfers	6.6 (5.4)	7.1 (5.9)	1.06 (0.95-1.19)	6.7 (5.6)	6.5 (5.2)	1.02 (0.92-1.14)	1.04 (0.89-1.21)	0.62
Days-to-Antibiotic Escalations	5.5 (4.2)	6.1 (5.9)	0.81 (0.73-0.91)	5.4 (3.9)	5.3 (3.8)	0.99 (0.88-1.12)	0.82 (0.69-0.97)	0.02

Abbreviations: CPOE = computerized provider order entry, INSPIRE = Intelligent Stewardship Prompts to Improve Real-time Empiric Antibiotic Selection

[a] Days-of-therapy rate calculated per patient per empiric day (first 3 days of hospitalization) expressed with multiplier 1,000 empiric days. [b]Rate ratios represent group-specific comparisons of intervention to baseline. [c]Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within hospitals and period. *P*-value assessed at 2-tailed significance set at α = 0.05 for null hypothesis that the relative rate ratio in each arm is not different for primary outcome; α=0.025 for secondary outcomes to account for multiple comparisons. [d]Days-to-event is defined as mean days calculated within a single admission. Days to intensive care unit (ICU) transfer is the days from admission to date of first ICU transfer among those requiring transfer on hospital day 3 through discharge. Days-to-antibiotic escalation is the days from admission to date of first change in antibiotics from standard-spectrum to extended-spectrum among those who were started on standard-spectrum in the empiric period (first 3 days of hospitalization). Length of stay is calculated as days from admission to date of hospital discharge among those discharged alive. [e]Hazard ratios represent group-specific comparisons of intervention to baseline. [f]Results are based on unadjusted proportional hazards models that accounted for clustering within hospitals and period. *P*-value for the difference in hazard ratio between periods.

Figure 3: Effect of Computerized Provider Order Entry (CPOE) Bundle Intervention versus Routine Stewardship on Trial Effectiveness and Safety Outcomes

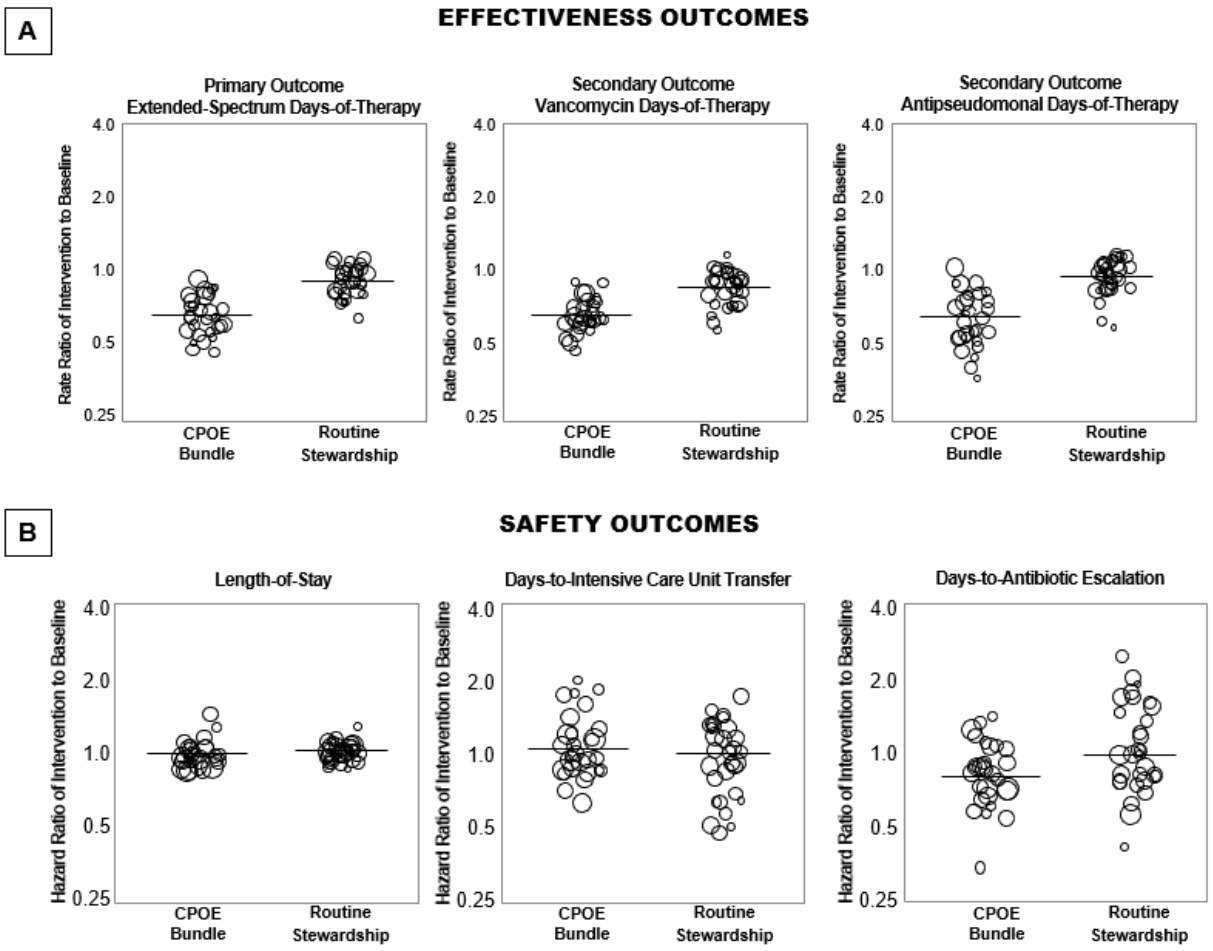


Figure 3: (A) Shown are group-specific relative rate ratios of intervention to baseline periods (indicated by horizontal lines) for primary and secondary outcomes. Results are based on unadjusted generalized linear mixed-effects models that accounted for clustering within hospitals and period. Bubble plots of raw rate ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown. The area of the bubble indicates the relative number of patients contributing data to the trial. **(B)** Shown are group-specific hazard ratios of intervention to baseline periods (indicated by horizontal lines) for safety outcomes. Results are based on proportional hazards models that accounted for clustering within hospitals and period. Bubble plots of raw hazard ratios (predicted random effects or exponentiated frailties) from individual hospitals relative to their group effects are shown. The area of the bubble indicates the relative number of patients contributing data to the trial.