

# INSPIRE Skin & Soft Tissue Infection Trial

*INtelligent Stewardship Prompts to Improve Rreal-time Empiric  
Antibiotic Selection for Patients*

ID Week

October 17, 2024



## Funding and Disclosures

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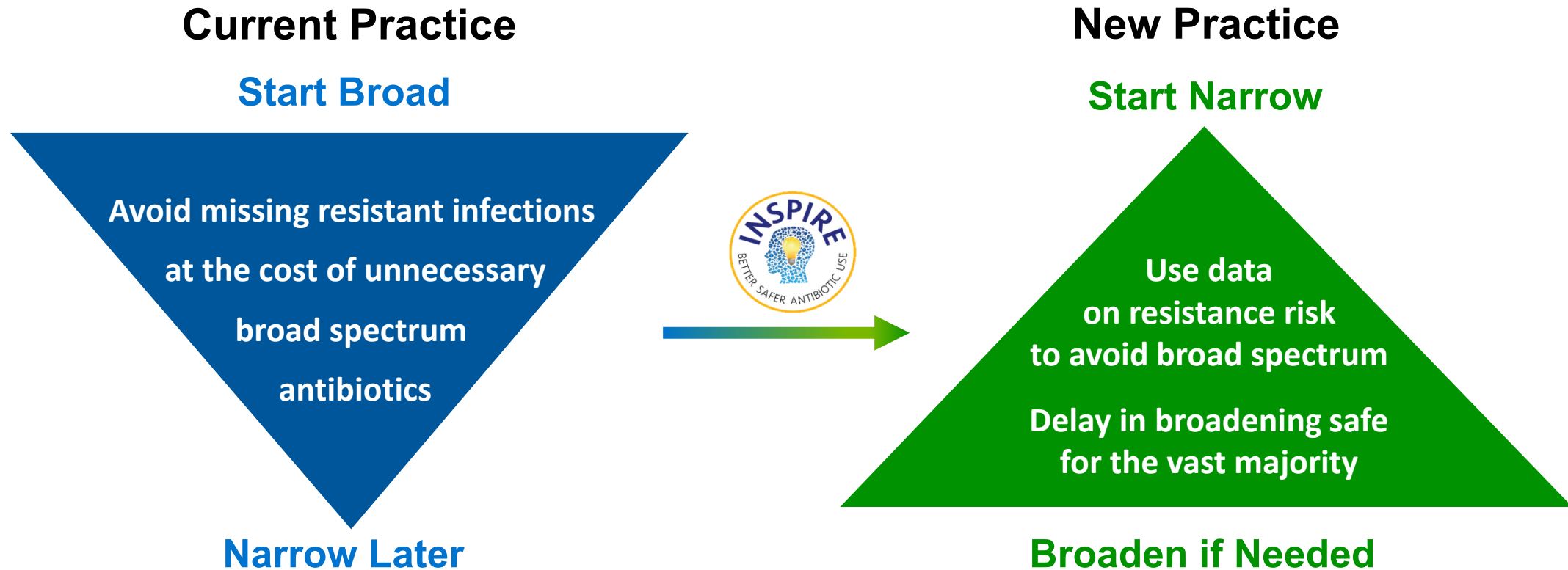
- No relevant disclosures
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- Supported in kind by HCA Healthcare and/or HCA Healthcare affiliated entities

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# Can We Change the Culture of Empiric Antibiotic Selection in Non-Critically Patients?

- More than 2.8 million antibiotic-resistant infections annually in US alone
- Overprescribing is a major contributor: 40% of inpatient antibiotics too broad



# Infections & Bacteria That Account for Antibiotic Use

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- **Most commonly treated infections in US hospitals**
  - Pneumonia<sup>1</sup>
  - Urinary tract infection (UTI)<sup>2</sup>
  - Abdominal infections<sup>3</sup>
  - **Skin/soft tissue infections**
- **Multidrug-resistant organisms physicians worry most about**
  - Methicillin resistant *Staphylococcus aureus* (MRSA)
  - *Pseudomonas* species
  - Extended-Spectrum Beta-Lactamase producing *Enterobacterales* (ESBL)
  - Vancomycin Resistant *Enterococci* (VRE)
  - Carbapenem Resistant *Enterobacterales* (CRE)

<sup>1</sup>Gohil SK, Stewardship Prompts to Improve Antibiotic Selection for Pneumonia: The INSPIRE Randomized Clinical Trial. JAMA. April 19, 2024. doi:10.1001/jama.2024.6248

<sup>2</sup>Gohil SK, Stewardship Prompts to Improve Antibiotic Selection for Urinary Tract Infection: The INSPIRE Randomized Clinical Trial. JAMA. April 19, 2024. doi:10.1001/jama.2024.6259

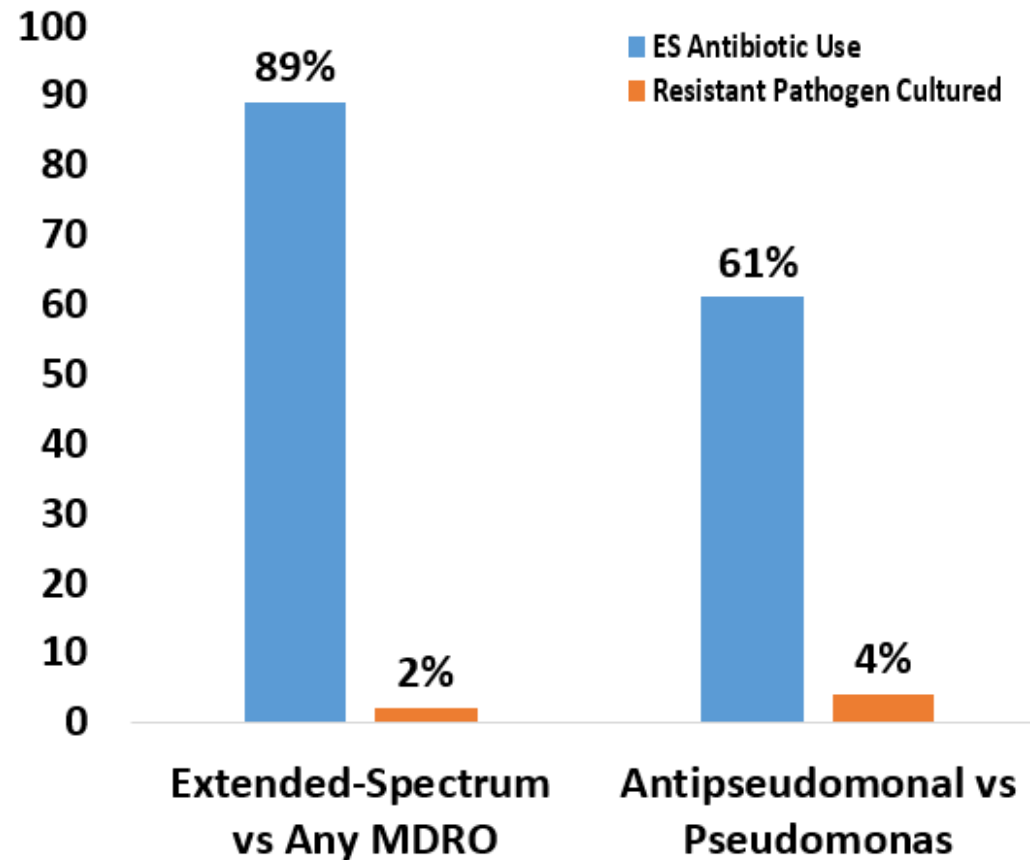
<sup>3</sup>Gohil SK, ID Week 2024 SHEA Featured Oral Abstract #444



# Empiric Antibiotic Selection in Skin & Soft Tissue Infections?

*Extended-spectrum use far exceeds resistance*

**Skin and Soft Tissue Infections <4% with Resistant Bacteria**



Among nearly 200,000 HCA Healthcare patients admitted with skin/soft tissue infection, 2017-2019

\*Abbreviations: MDRO=multidrug-resistant organism; MRSA=methicillin-resistant *Staphylococcus aureus*





# **INSPIRE Skin & Soft Tissue Infection Cluster Randomized Trial**

# INSPIRE Skin & Soft Tissue Infection Trial – Design

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*92-hospital, cluster-randomized trial*

## **Arm 1: Routine Care – 46 Hospitals**

- Standard-of-care antibiotic stewardship

## **Arm 2: INSPIRE Computerized Physician Order Entry (CPOE) Bundle Intervention – 46 Hospitals**

- Physician “CPOE smart prompts” for patient-specific resistant organism risk
- Recommends appropriate antibiotic choice
- Provider encouragement and feedback reports (by local study champions)

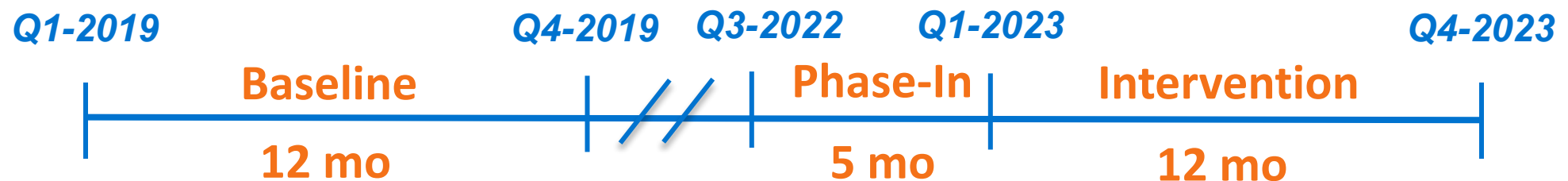
# INSPIRE Study Population and Timeline

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## Setting

- HCA Healthcare (largest private hospital system in the nation) – 200+
- Pragmatic – community hospitals
- Adults admitted for **Skin and Soft Tissue Infections**
- Excludes patients admitted to ICUs
- Focuses on first 3 days of admission

## Trial Timeline



## CPOE Prompt Activated Via Indication Screens

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- INSPIRE prompts activated when physicians select extended-spectrum antibiotics to treat skin/soft tissue infections
- Programmed to fire only in non-ICU locations
- Provides **absolute risk** of infection due to a multidrug-resistant organism:
  - ✓ Patient-specific
  - ✓ Infection syndrome-specific
  - ✓ Pathogen-specific
  - ✓ Hospital-specific

# What Antibiotics Are Considered “Extended-Spectrum”?

Category	Extended–Spectrum Antibiotics Included in CPOE Alerts <sup>1</sup>
Anti-Vancomycin Resistant <i>Enterococcus</i>	Daptomycin, Linezolid <sup>2</sup>
Antipseudomonals	Aztreonam, Cefepime, Ceftazidime, Piperacillin/Tazobactam
Anti-Extended Spectrum Beta Lactmase-producing <i>Enterobacterales</i>	Ertapenem, Imipenem, Meropenem, Ceftolozane/Tazobactam

<sup>1</sup>Anti-MRSA drugs Vancomycin and Ceftaroline not included (national guidelines support empiric MRSA coverage for purulence and local MRSA prevalence in skin/soft tissue infection was high). Fluoroquinolones not included as extended-spectrum.

<sup>2</sup>Both oral and intravenous (IV) formulations

# INSPIRE Prompt Approach

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- Risk estimate and guidance *tailored to drug and pathogen*.
  - If cefepime ordered → returns *Pseudomonas* risk
  - If meropenem ordered → returns ESBL or *Pseudomonas* risk
- Real-time, patient-specific.
  - MD orders cefepime for skin and soft tissue infection indication
  - Prompt pulls patient characteristics from EHR to generate risk estimate
  - Prompt recommends cefazolin if *Pseudomonas* skin and soft tissue infection risk is < 10%

# INSPIRE Skin & Soft Tissue Infection Risk Models

- Based on >195,000 HCA patients with skin/soft tissue infection, 2017-2019
- Used recursive partitioning to identify algorithm for MDRO infection
- Evaluated >60 variables: demographics, comorbidities, prior antibiotics, nursing home, hospitalization, admission labs, prior MDRO

MDRO SST Infection Model	Elements Predictive of Absolute Risk $\geq 10\%$
VRE	No risk factors predicted $\geq 10\%$ risk
<i>Pseudomonas</i>	History of <i>Pseudomonas</i>
ESBL (no <i>Pseudomonas</i> )	History of ESBL, Facility %ESBL of all SST
ESBL (with <i>Pseudomonas</i> )	History of ESBL/ <i>Pseudomonas</i> , Facility %ESBL of all SST
CRE	No risk factors predicted $\geq 10\%$ risk

VRE – Vancomycin Resistant *Enterococci*, ESBL – Extended-Spectrum Beta Lactamase producing *Enterobacterales*; CRE – Carbapenem Resistant *Enterobacterales*.

# INSPIRE Prompt Provides Patient-Specific Risk Estimates

- Example: Physician orders cefepime for **skin/soft tissue (SST) infection** and risk of *Pseudomonas* SST infection calculated to be low (<10%)
- No prompt if risk  $\geq 10\%$

**\*\* PROVIDER PROMPT \*\***

Cefepime is NOT recommended for EMPIRIC therapy because this patient's risk of *Pseudomonas* skin and soft tissue infection is **< 10%**

CEFAZOLIN is recommended.

This risk is calculated based on known patient and hospital factors at admission. This recommendation does not account for positive cultures this admission or allergies, and does not replace clinical judgment.

Do you wish to REPLACE this order with the recommended CEFAZOLIN?

Patient & syndrome-specific risk estimate

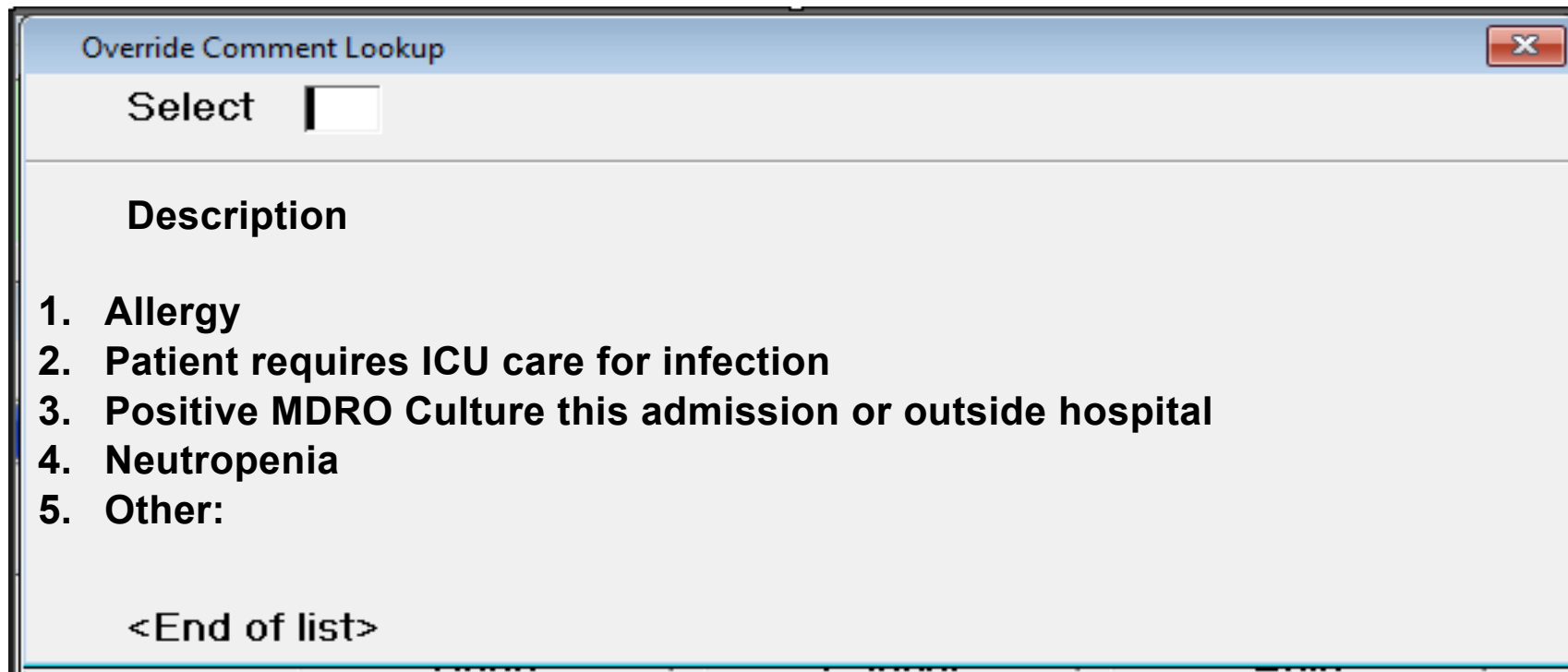
Returns to order screen

Next screen asks reason to keep cefepime

Taken to cefazolin order screen

## Override Screen and Options

- Alert supports, but does not replace clinical judgment
- Clinicians choosing to override must give a reason:



The screenshot shows a software dialog box titled "Override Comment Lookup" with a close button (X) in the top right corner. Below the title bar, there is a "Select" label followed by a small, empty rectangular input field. A horizontal line separates this from the main content area, which is headed "Description". Under "Description", there is a numbered list of five options: "1. Allergy", "2. Patient requires ICU care for infection", "3. Positive MDRO Culture this admission or outside hospital", "4. Neutropenia", and "5. Other:". At the bottom of the list, the text "<End of list>" is displayed.

Override Comment Lookup

Select

**Description**

1. Allergy
2. Patient requires ICU care for infection
3. Positive MDRO Culture this admission or outside hospital
4. Neutropenia
5. Other:

<End of list>

# INSPIRE Skin & Soft Tissue Infection Trial Outcomes

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## Primary Outcome

- Extended-spectrum antibiotic days of therapy during first 3 days of admission

## Secondary Outcomes

- Antipseudomonal days of therapy during first 3 days of admission

## Safety Outcomes

- Days to ICU transfer
- Length-of-stay

# Statistical Analysis

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- Main results are as-randomized, unadjusted, admission level
- **Primary/secondary outcomes:** generalized linear mixed effects model (GLIMMIX)
  - Multivariable regression model
  - Compares intervention to baseline rates between arms, accounting for clustering within hospital and period
- **Safety Outcomes:** Proportional hazards models with shared frailties to account for clustering within hospital and period (baseline vs intervention)
- Adjusted analyses



# INSPIRE Skin & Soft Tissue Infection Trial

## Results

# INSPIRE Trial Participants

- 92 hospitals in 15 states
- Non-ICU intervention period patients admitted with **Skin/Soft Tissue Infection: 60,725**

## Arm 1: Routine Care

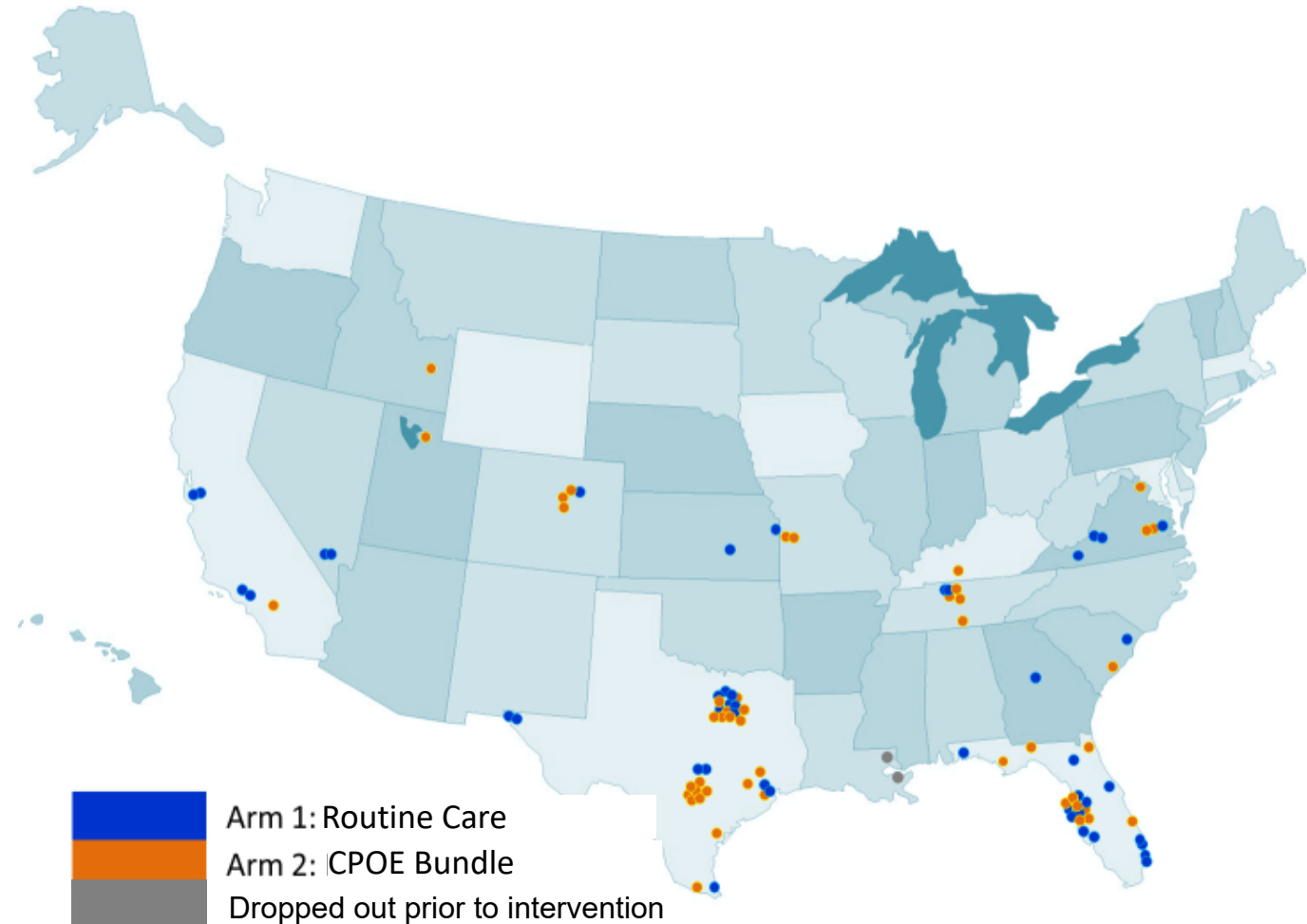
46 Hospitals

Skin & Soft Tissue Infection Trial: **N = 31,337**

## Arm 2: CPOE Bundle

44 Hospitals

Skin & Soft Tissue Infection Trial: **N = 29,388**



## Participant Characteristics (Intervention Period)

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Characteristics	Skin & Soft Tissue Infection	
	Routine (N=31,116)	CPOE Bundle (N=29,432)
Mean Age	59	58
Female	43%	42%
Non-White	25%	29%
Hispanic	20%	22%
Medicaid Insured	30%	30%
Hospitalization - Past Year	35%	37%
Antibiotic use - Past Year	31%	32%
Nursing Home Visit - Past Year	8%	9%
Length of Stay (mean days)	7.5	7.3
Comorbidity Score <sup>1</sup>	3	3

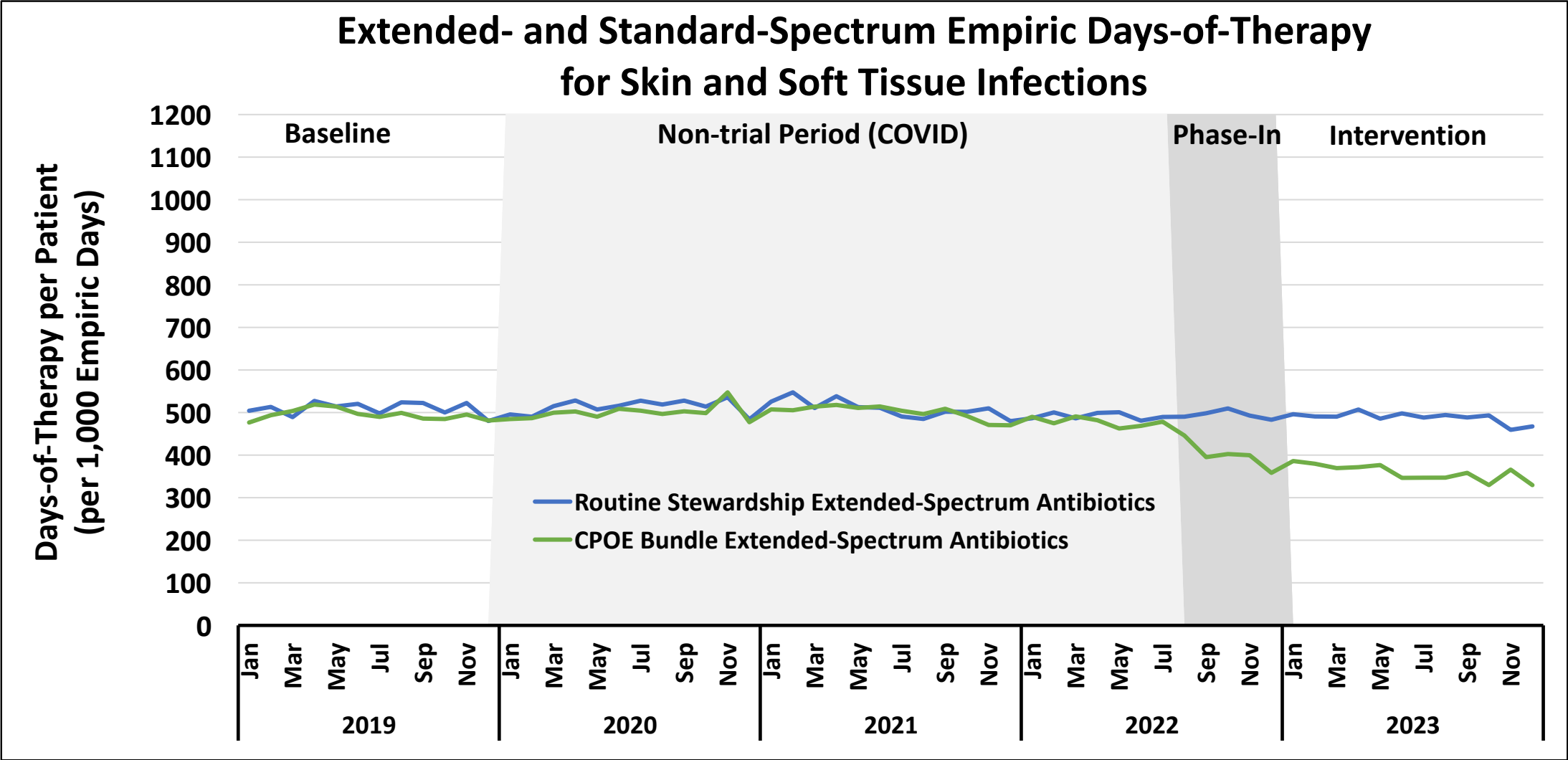
# INSPIRE Participants - MDRO History (Intervention Period)

	Skin & Soft Tissue Infection	
Patient Characteristic	Routine (N=31,116)	CPOE Bundle (N=29,432)
History of Any MDRO	18.5%	19.3%
MRSA	14.0%	14.3%
VRE	1.1%	1.1%
<i>Pseudomonas</i>	5.0%	5.4%
ESBL	3.8%	4.2%
CRE	0.2%	0.3%
MDR Gram Negative Rods*	0.9%	0.9%

\*MDR Gram Negative Rods – includes MDR *Enterobacteriaceae*, MDR/carbapenem resistant *Pseudomonas*, *Acinetobacter*.  
 Abbreviations: MDRO – multidrug resistant organism; MRSA - Methicillin Resistant *Staphylococcus aureus*; ESBL – Extended Spectrum Beta Lactamase producer; VRE – Vancomycin Resistant *Enterococci*; CRE – Carbapenem Resistant *Enterobacteriaceae*; MDR- Multi-Drug Resistant

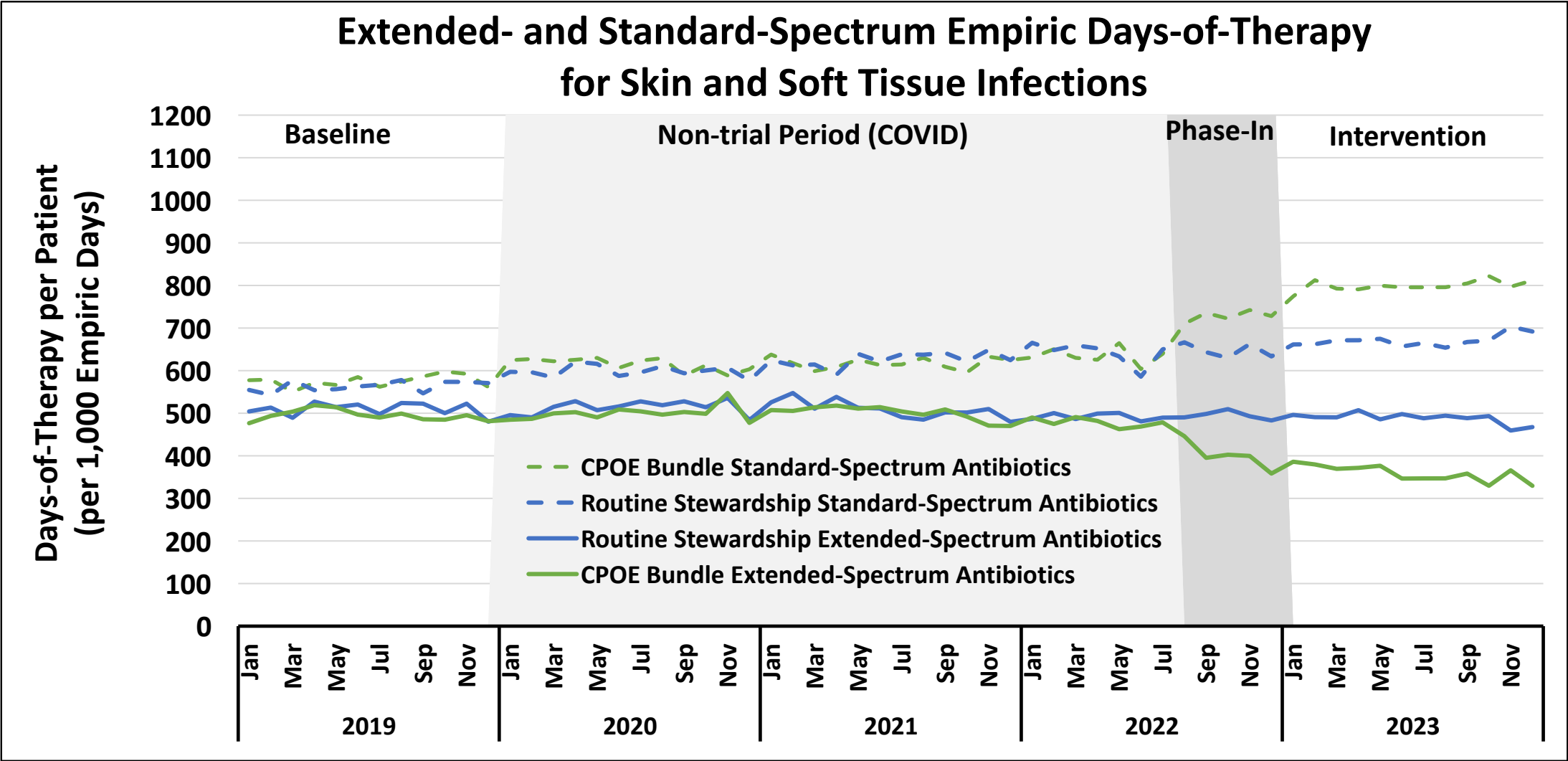
# Empiric Extended-Spectrum Use Across Study Period – Skin & Soft Tissue Infection

- 27% crude absolute reduction with INSPIRE CPOE bundle

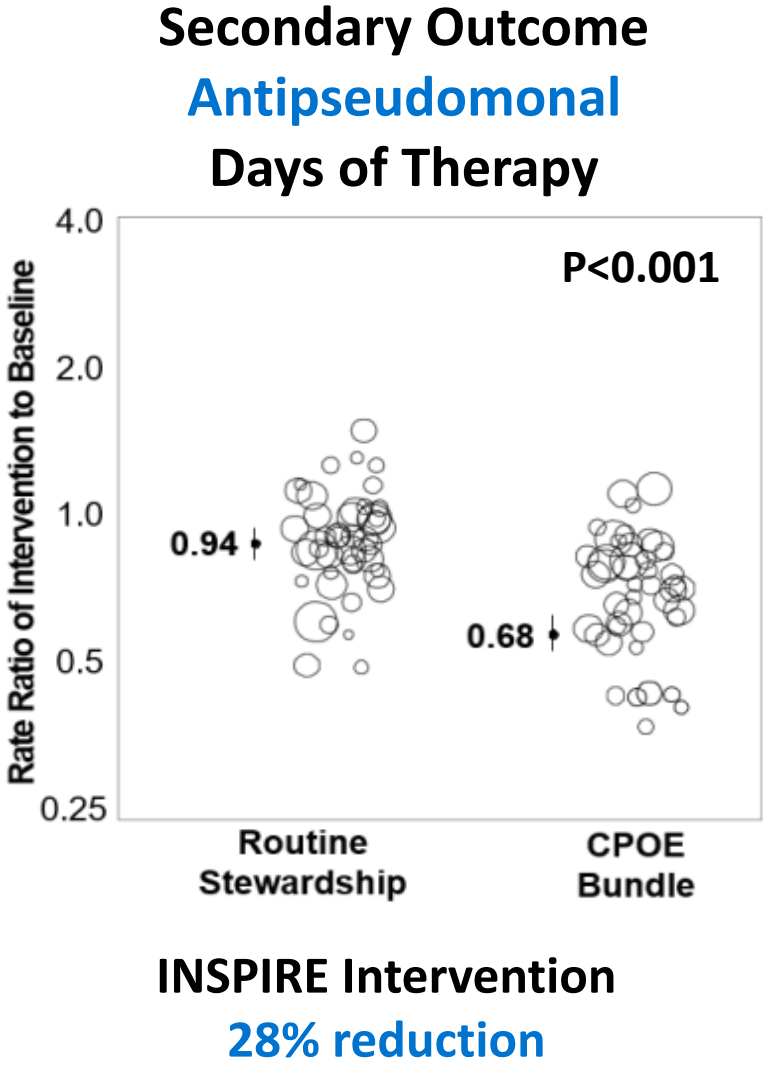
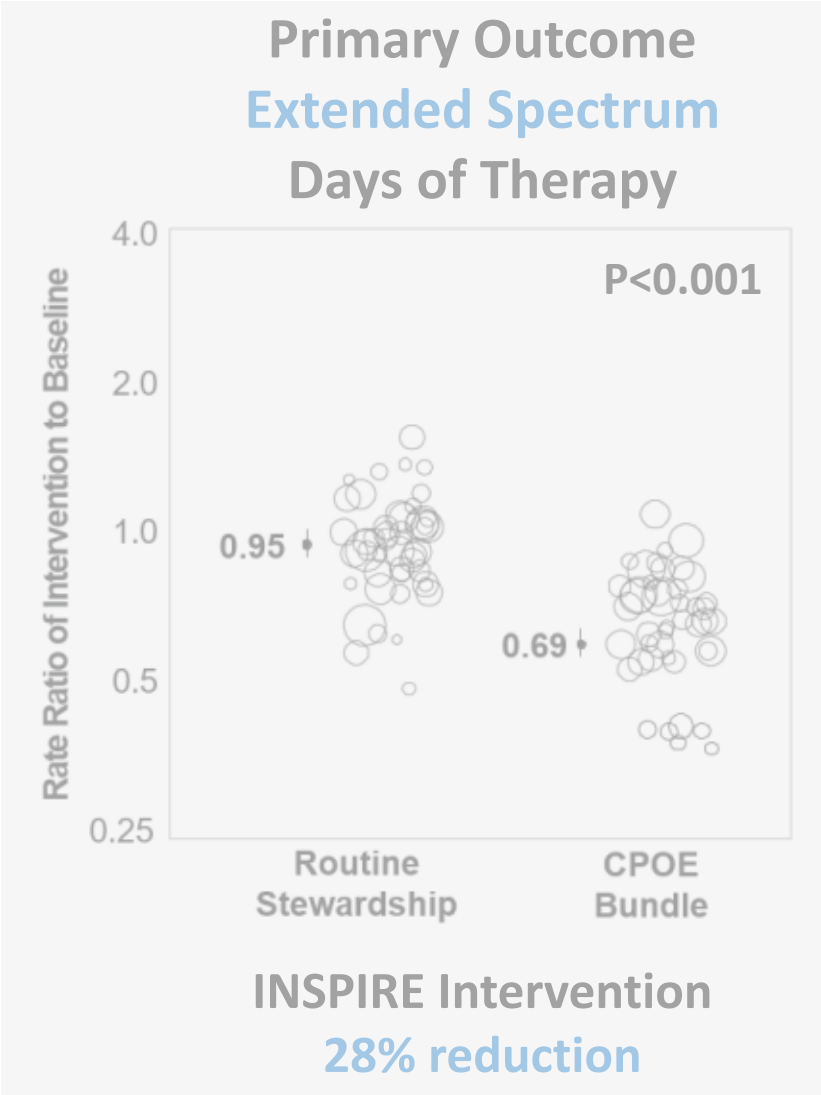


# Empiric Extended-Spectrum Use Across Study Period – Skin & Soft Tissue Infection

- 27% crude absolute reduction with INSPIRE CPOE bundle



# INSPIRE Skin & Soft Tissue Infection Trial Effectiveness Outcomes – As Randomized



# Safety Outcomes – Skin & Soft Tissue Infection Trial

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- Days to ICU Transfer
  - No difference between groups
  - HR (CI) = 1.14 (0.97-1.34),  $p = 0.11$
- Length of Stay
  - No difference between groups
  - HR (CI) = 0.99 (0.94-1.04),  $p = 0.77$

# Limitations

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- Effect of individual components of bundle unknown
  - Need for education and feedback components by site-based pharmacist and physician champion is unknown
- Requires CPOE capability and live link to electronic health record
- Lower alert thresholds could have spared additional ES antibiotic use

# Summary

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- Real-time, personalized prompts can reduce empiric extended-spectrum use
- Benefits of automated approach:
  - Reduction despite disruptions in hospital operations (e.g., weather, COVID-19)
  - Active hospital-wide, nights/weekends
  - Risk documented in EHR may address clinician medical-legal concerns

# INSPIRE Skin & Soft Tissue Infection Trial Hospital Participants

## Arm 1 Facilities

CJW Medical Center – Chippenham, Johnston Willis Campuses	HCA Florida Northwest Hospital	LewisGale Medical Center	Southern Hills Hospital & Medical Center
Overland Park Regional Medical Center	HCA Florida Oak Hill Hospital	Good Samaritan Hospital	Regional Medical Center of San Jose
Grand Strand Medical Center	HCA Florida Pasadena Hospital	Medical City Alliance	St. David's North Austin Medical Center
HCA Florida Bayonet Point Hospital	HCA Florida Sarasota Doctors Hospital	Medical City Dallas	St. David's Round Rock Medical Center
HCA Florida Blake Hospital	HCA Florida South Tampa Hospital	Medical City Denton	Sunrise Hospital & Medical Center
HCA Florida Englewood Hospital	HCA Florida West Tampa Hospital	Medical City Frisco	The Medical Center of Aurora
HCA Florida Fort Walton-Destin Hospital	HCA Florida Trinity Hospital	Medical City Las Colinas	TriStar Centennial Medical Center
HCA Florida JFK North Hospital	HCA Houston Healthcare Kingwood	Medical City McKinney	TriStar Southern Hills Medical Center
HCA Florida Kendall Hospital	HCA Houston Healthcare Southeast	Medical City Plano	Valley Regional Medical Center
HCA Florida Lake City Hospital	Las Palmas Medical Center	Menorah Medical Center	Wesley Medical Center
HCA Florida Mercy Hospital	Lee's Summit Medical Center	Orange Park Medical Center	Wesley Woodlawn Hospital & ER
Los Robles Hospital & Medical Center	LewisGale Hospital Montgomery	Fairview Park Hospital	West Hills Hospital & Medical Center
Del Sol Medical Center	LewisGale Hospital Pulaski	Oviedo Medical Center	

## Arm 2 Facilities

Corpus Christi Medical Center – Bay Area, Doctors, Heart Hospital	HCA Florida Brandon Hospital	Medical City North Hills	Eastern Idaho Regional Medical Center
Henrico Doctors' Hospital – Forest, Parham, Retreat Campuses	HCA Florida Capital Hospital	Medical City Weatherford	St. David's Medical Center
Rio Grande Regional Hospital Main Campus	HCA Florida Fawcett Hospital	Methodist Hospital   Northeast	HCA Houston Healthcare Clear Lake
HCA Florida Gulf Coast Hospital	HCA Houston Healthcare Conroe	Centerpoint Medical Center	Swedish Medical Center
HCA Florida Largo Hospital	HCA Houston Healthcare Mainland	Methodist Hospital	Trident Medical Center
HCA Florida Lawnwood Hospital	HCA Houston Healthcare Pearland	Methodist Hospital   Texsan	TriStar Greenview Regional Hospital
HCA Florida Memorial Hospital	HCA Houston Healthcare West	North Suburban Medical Center	TriStar Hendersonville Medical Center
HCA Florida Northside Hospital	Methodist Hospital   Metropolitan	Ogden Regional Medical Center	TriStar Horizon Medical Center
HCA Florida South Shore Hospital	Medical City Arlington	Parkridge East Hospital	TriStar StoneCrest Medical Center
HCA Florida St. Lucie Hospital	Medical City Fort Worth	Parkridge Medical Center	HCA Florida St. Petersburg Hospital
Riverside Community Hospital	Medical City Lewisville	Research Medical Center	Tulane Medical Center
Methodist Hospital   Specialty and Transplant	Sky Ridge Medical Center	Reston Hospital Center	Lakeview Regional Medical Center

# INSPIRE Investigative Team



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