

# INSPIRE Skin & Soft Tissue Infection Trial

I**N**telligent S**t**ewardship P**r**ompts to I**m**prove R**e**al-time E**m**piric  
A**n**tibiotic S**e**lection for P**a**tients

ID Week

October 17, 2024



# Funding and Disclosures

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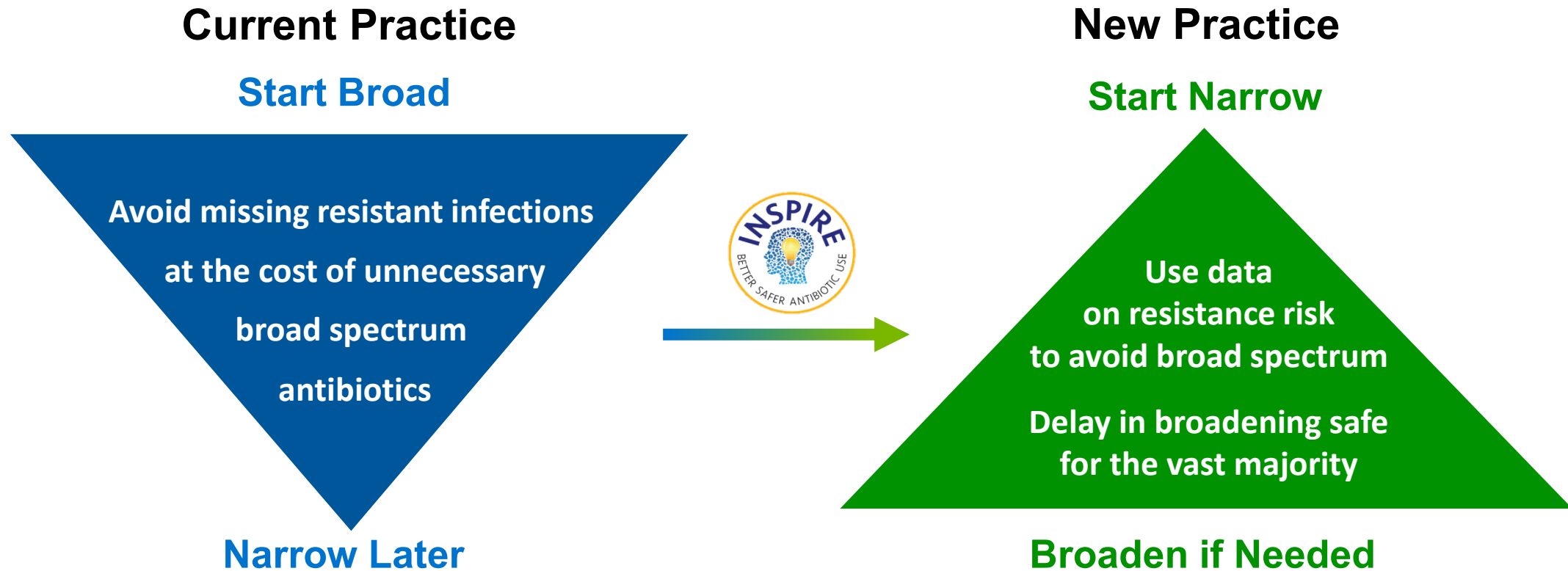
- No relevant disclosures
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# Can We Change the Culture of Empiric Antibiotic Selection in Non-Critically Patients?

- 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

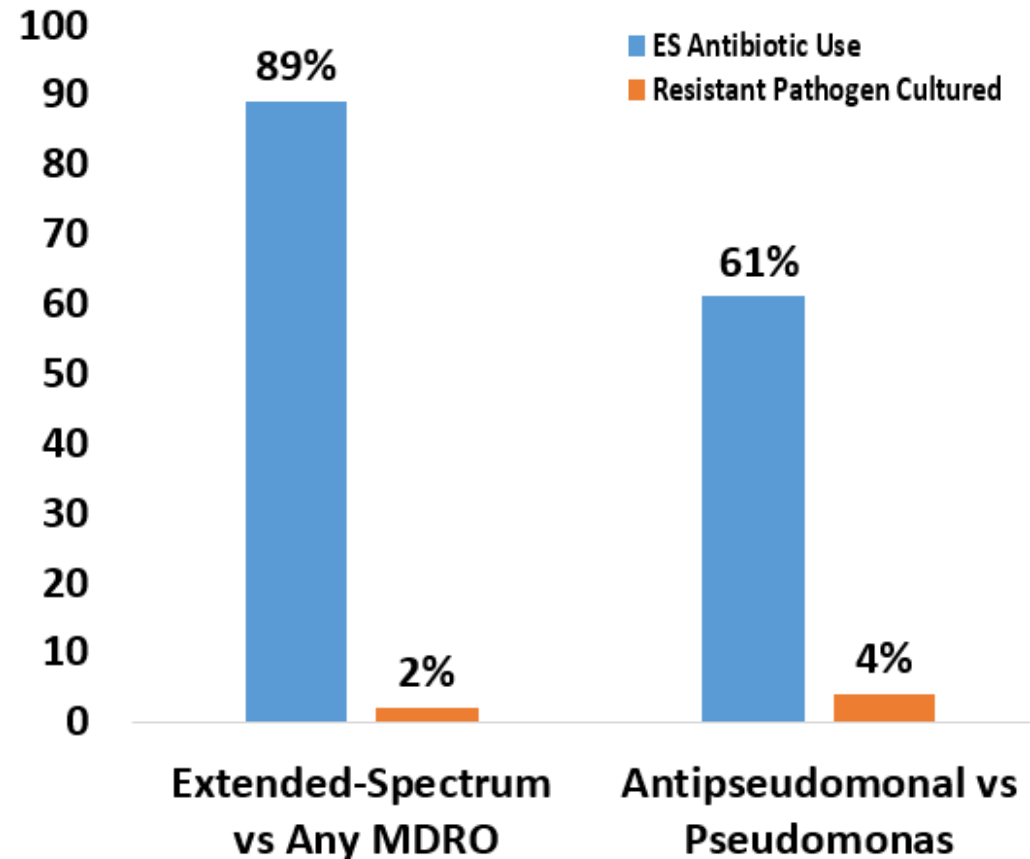
<sup>3</sup>Gohil SK, ID Week 2024 SHEA Featured Oral Abstract #444



# 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)



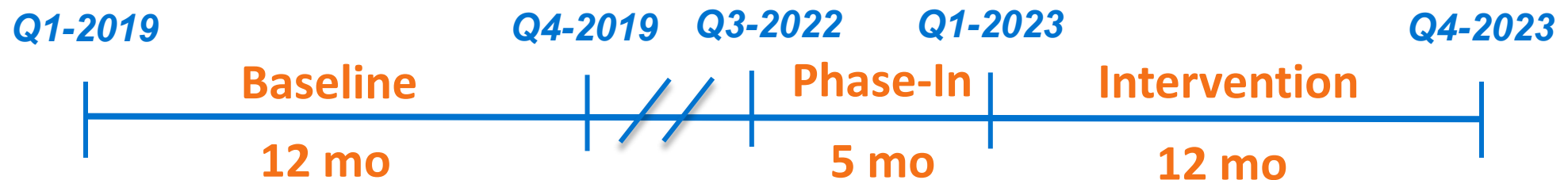
# INSPIRE Study Population and Timeline

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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> |
|-------------------------------------------------------------------------------|--------------------------------------------------------------------|
| <b>Anti-Vancomycin Resistant <i>Enterococcus</i></b>                          | Daptomycin, Linezolid <sup>2</sup>                                 |
| <b>Antipseudomonals</b>                                                       | Aztreonam, Cefepime, Ceftazidime, Piperacillin/Tazobactam          |
| <b>Anti-Extended Spectrum Beta Lactmase-producing <i>Enterobacterales</i></b> | 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

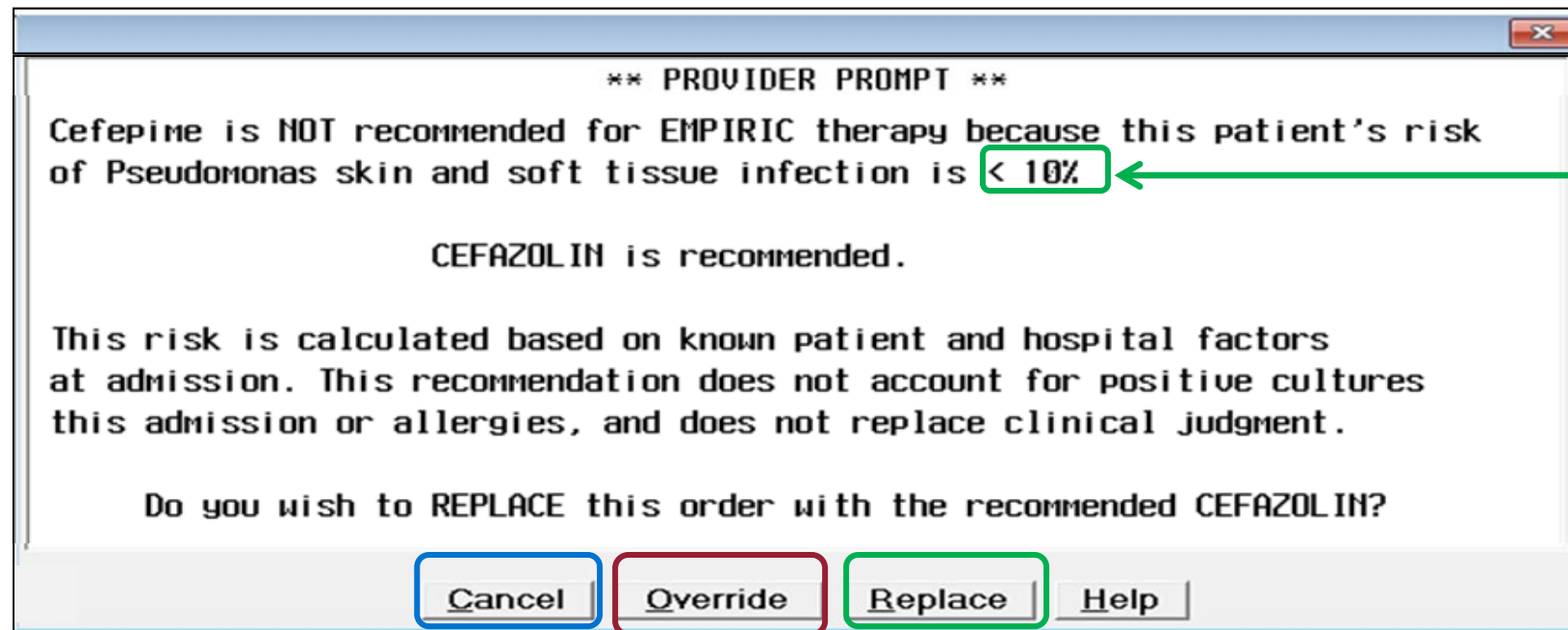
- Based on >195,000 HCA patients with skin/soft tissue infection, 2017-2019
- Used recursive partitioning to identify algorithm for MDRO infection
- Evaluated >60 variables: demographics, comorbidities, prior antibiotics, nursing home, hospitalization, admission labs, prior MDRO

| 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  $\geq 10\%$



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:

Override Comment Lookup

Select

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**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**

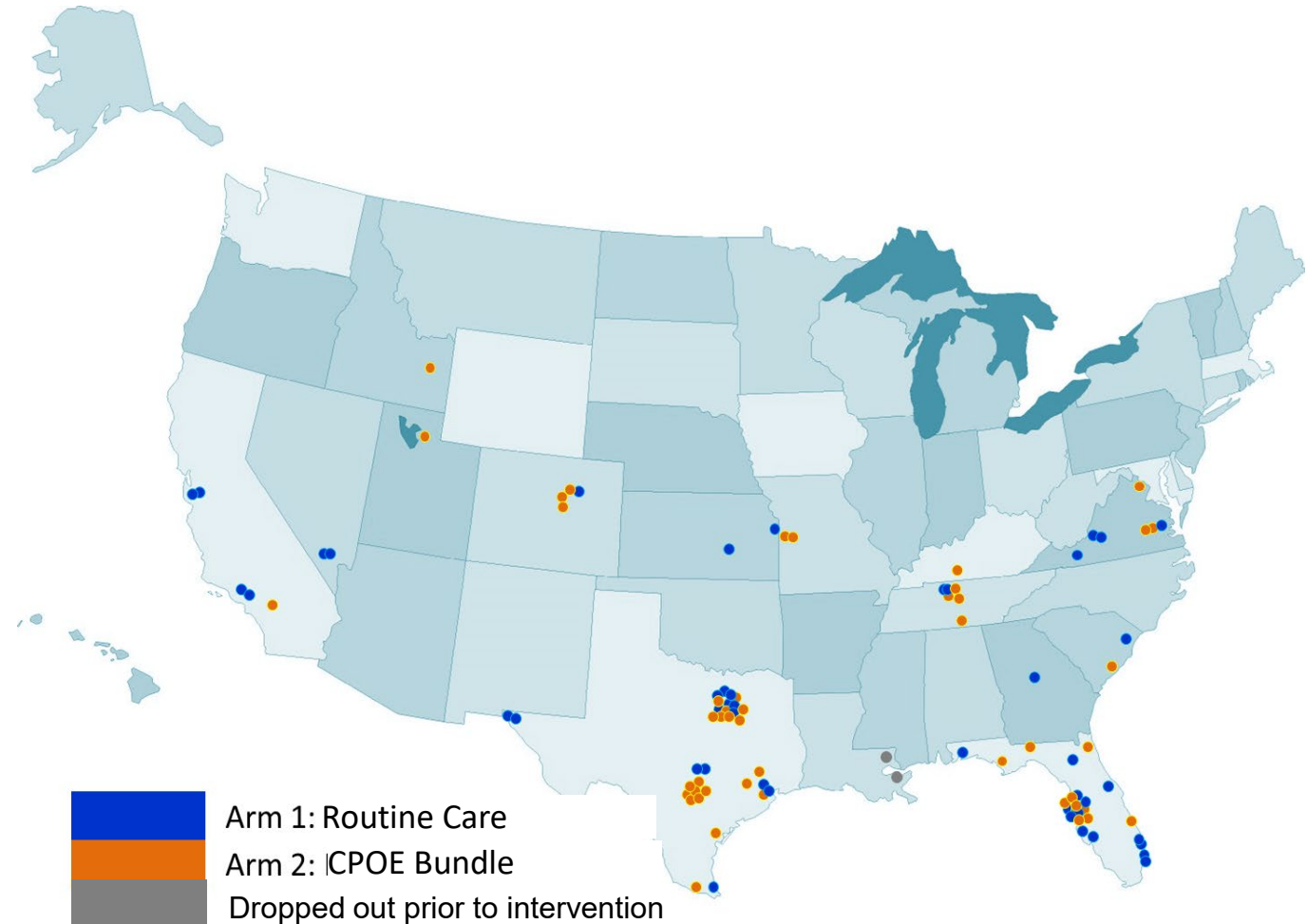
## **Results**

# 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)

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

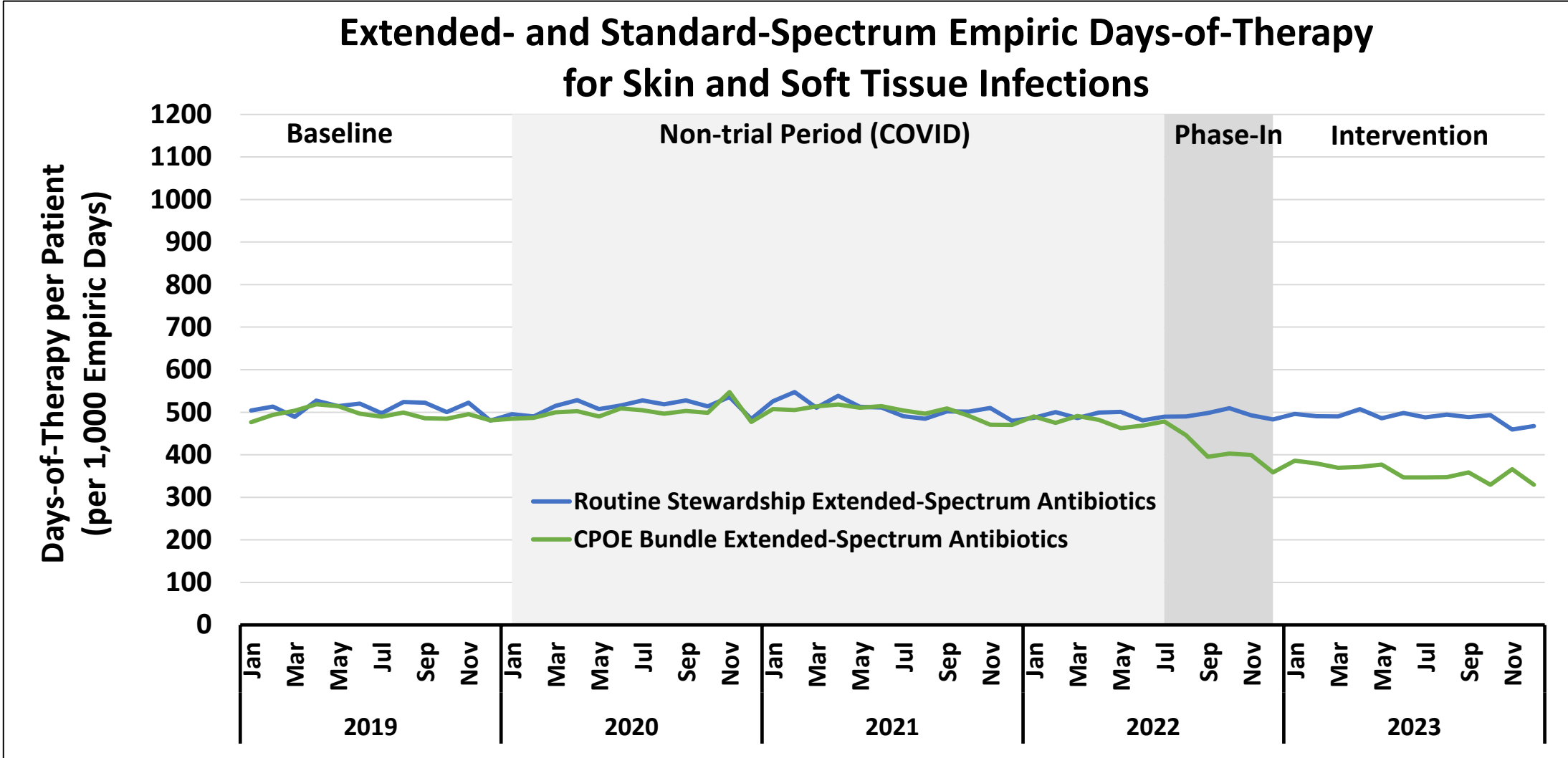
# INSPIRE Participants - MDRO History (Intervention Period)

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

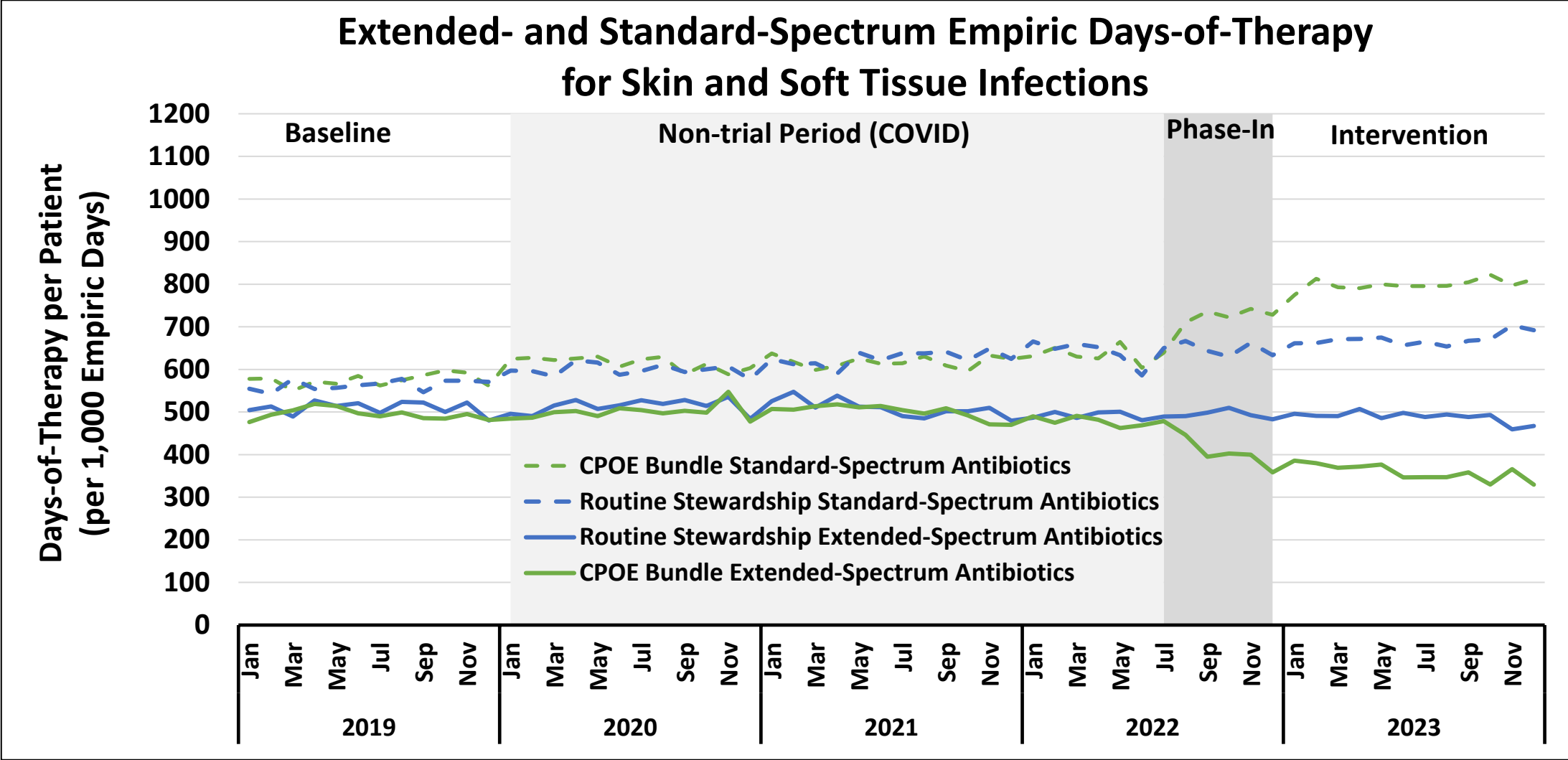
# Empiric Extended-Spectrum Use Across Study Period – Skin & Soft Tissue Infection

- 27% crude absolute reduction with INSPIRE CPOE bundle

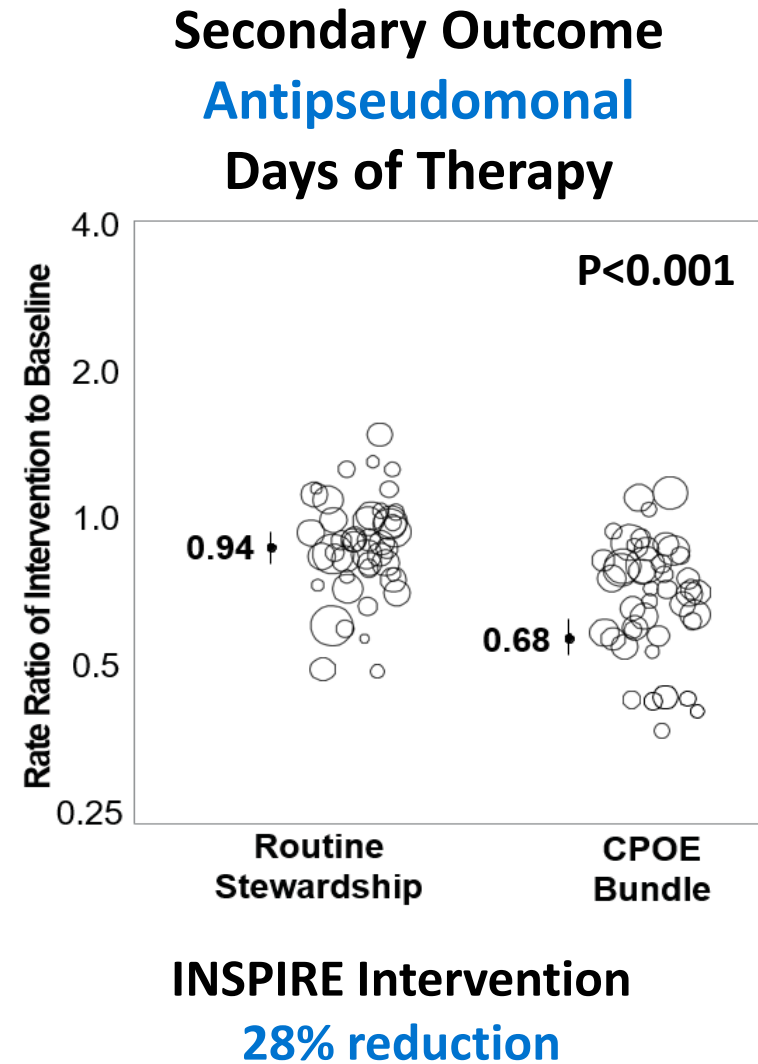
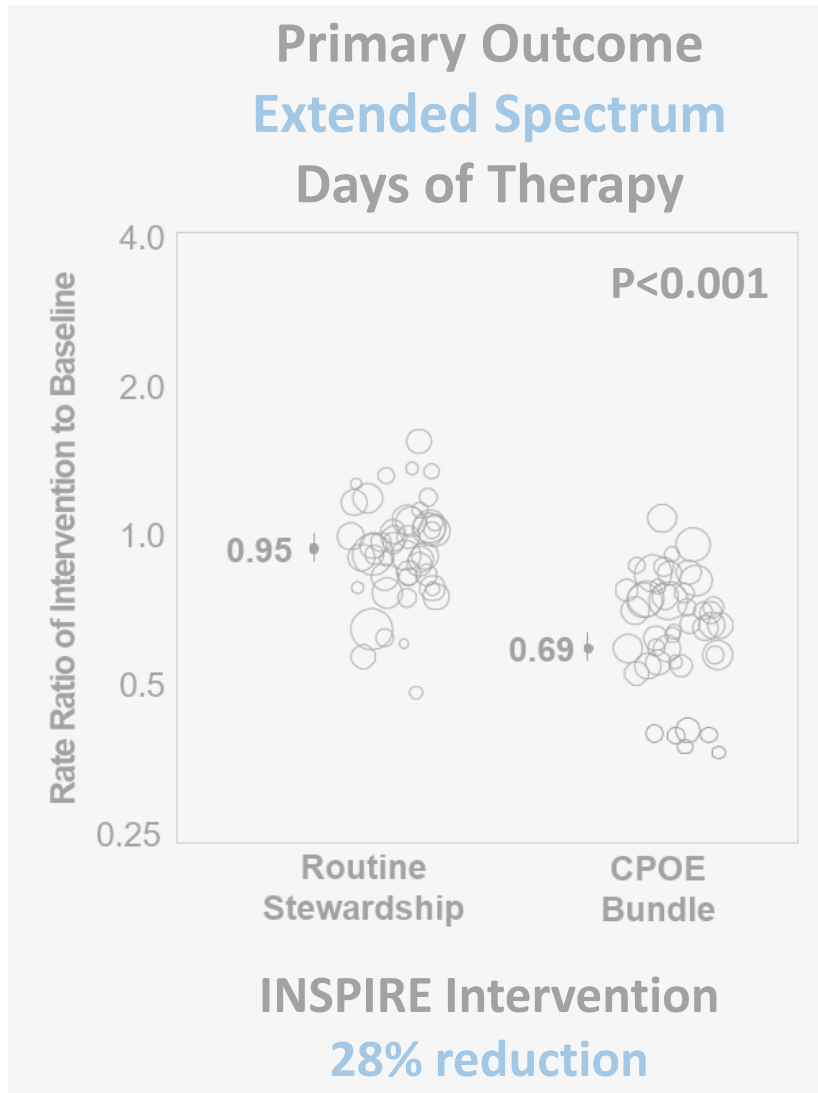


# Empiric Extended-Spectrum Use Across Study Period – Skin & Soft Tissue Infection

- 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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