

# Geographic shifts in antibacterial drug clinical trial enrollment Implications for generalizability

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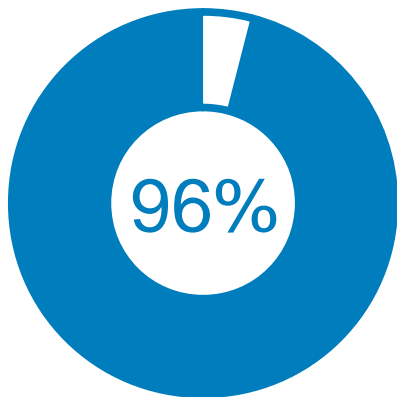
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# Drug clinical trials are increasingly globalizing

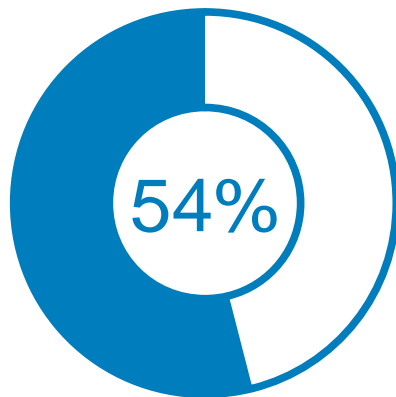


## US-based investigators

1990



2007



**56.9%**

of subjects in drug trials  
were enrolled from outside  
the US in 2008



# Antibacterial drug applications increasingly include non-US data



## Labels for several recently approved antibacterial drugs

“The majority of the patients (99%) were from Eastern Europe; 3 patients were from the United States.”

“There were no patients enrolled within the United States.”

“The majority of sites were in Eastern Europe [...]; 3 patients were enrolled in the US.”

# Speculated drivers for enrollment changes



## Cost

Significant savings outside US and Western Europe



## Differences in clinical practice and recruitment

Prior antibacterial drug therapy and length of hospitalization for IV drug administration

Lack of interest among investigators in some regions



## Emerging markets

Expansion of sales into new regions

How is antibacterial drug trial enrollment changing?

What impact does changing enrollment have on trial generalizability?



# Methods



## Identified New Drug Applications (NDAs) for antibacterial drugs

- Included Phase 3 trials started after January 1, 2001, with electronic subject-level data
  - Four small trials targeting a specific organism or resistance phenotype were excluded



### Geography

Regions assigned by country



### Demographics

Age, sex, race, etc.



### Clinical characteristics

Comorbidities, medical history, and disease severity



### Microbiology

Species and resistance phenotypes



### ABSSSI

Acute bacterial skin and skin structure infections



### cIAI

Complicated intra-abdominal infections



### CABP

Community-acquired bacterial pneumonia

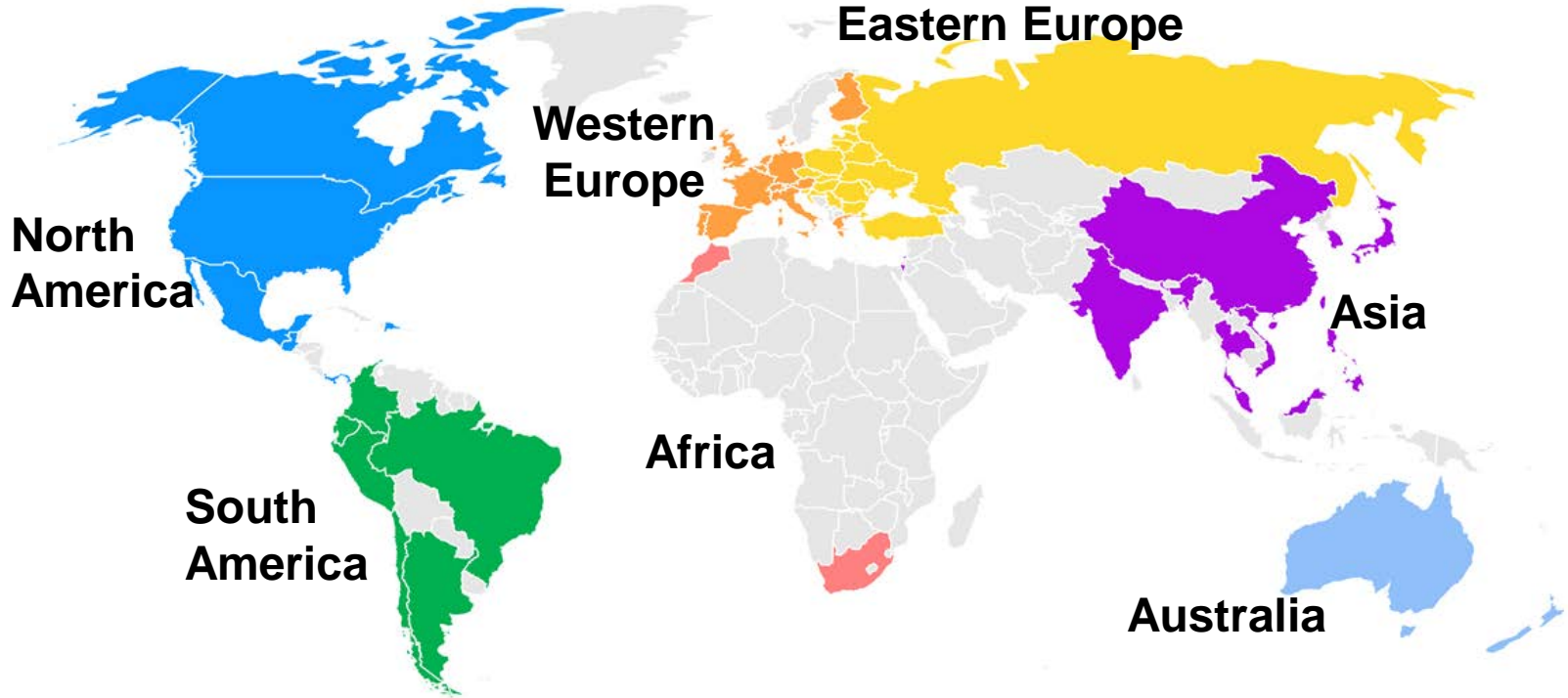


### cUTI

Complicated urinary tract infections



Subjects assigned to one of 7 regions  
Regional assignments influenced heavily by sponsor designations

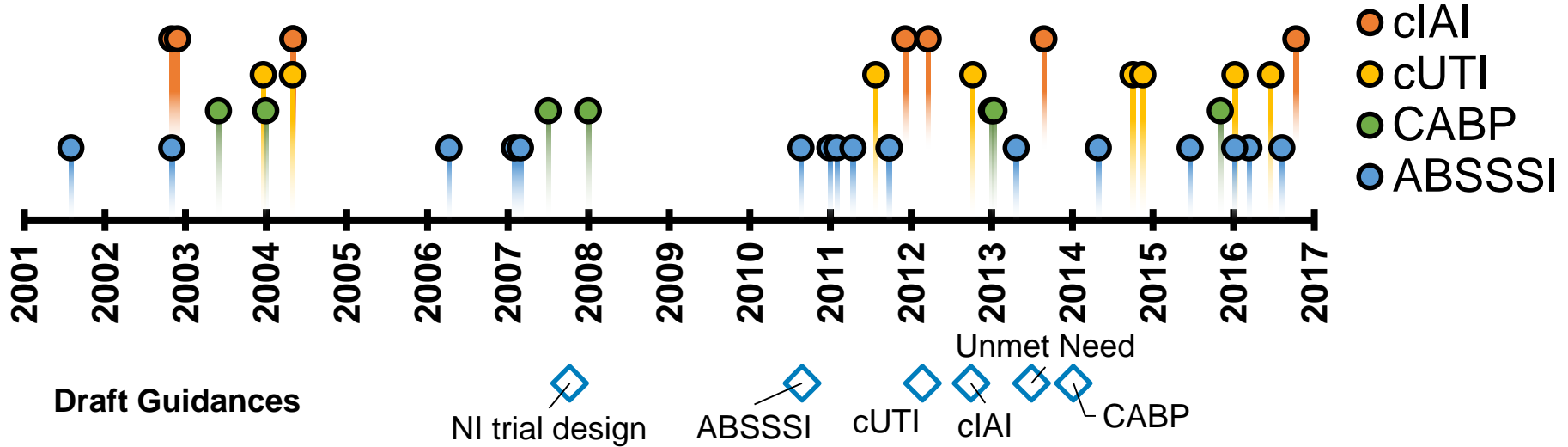




# Timeline of included trials

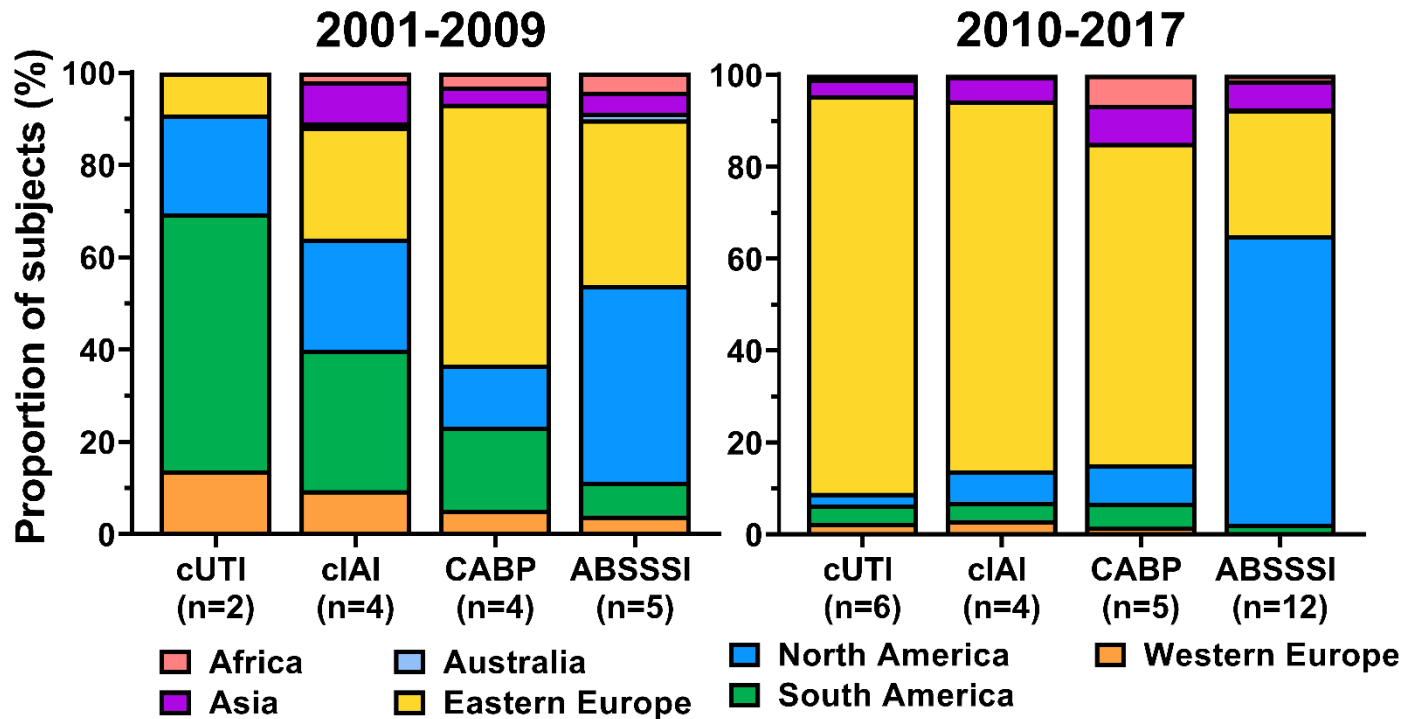


42 Phase 3 trials identified  
29,282 subjects from 57 countries

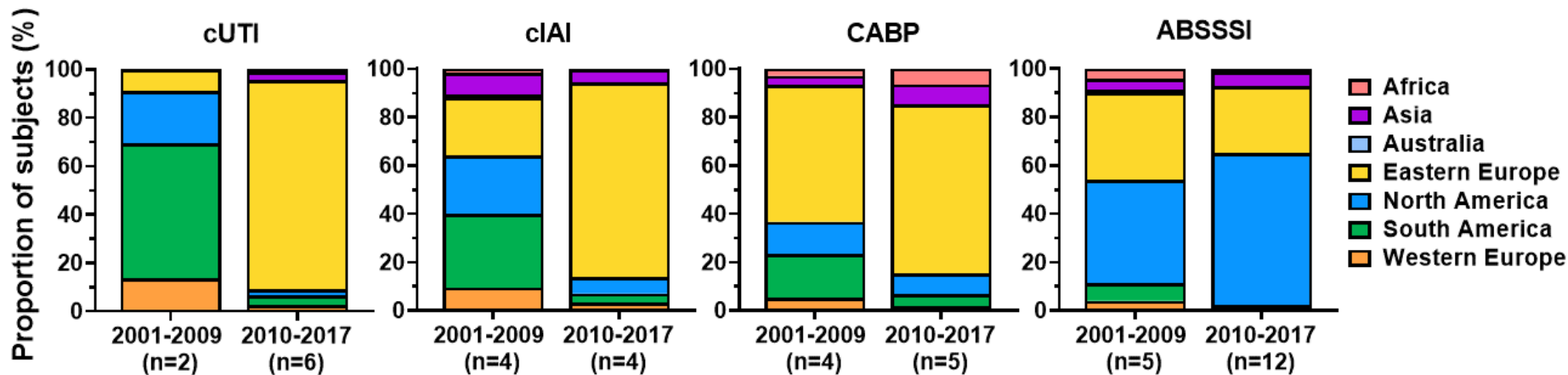


Trials initiated 2001-2009 were compared with those 2010-2017 to analyze enrollment trends

# Enrollment is increasing in Eastern Europe Except in ABSSSI trials



# Enrollment is increasing in Eastern Europe Except in ABSSSI trials



# Impacts on generalizability



## Geography

Shifts in enrollment toward Eastern Europe or North America



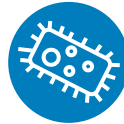
## Demographics

Age, sex, race, etc.



## Clinical characteristics

Comorbidities, medical history, and disease severity



## Microbiology

Species and resistance phenotypes

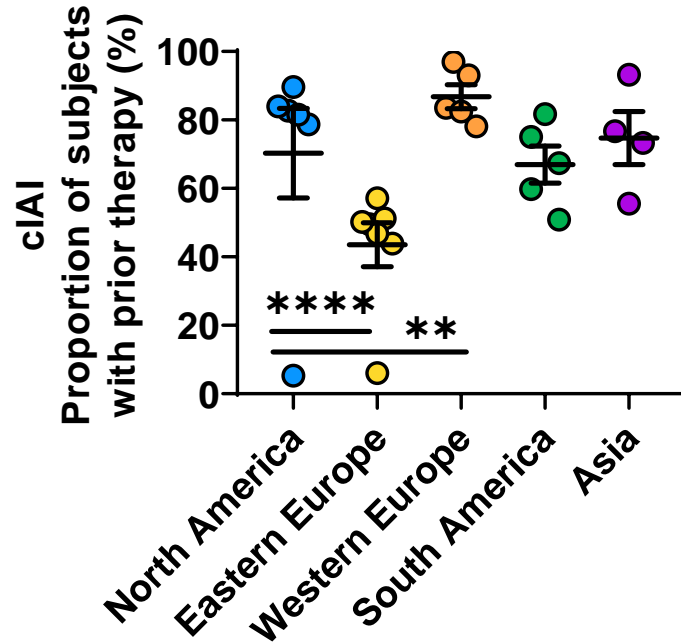
Subject-level NDA data used to investigate differences among regions

Data were pooled across entire study period, not divided by date

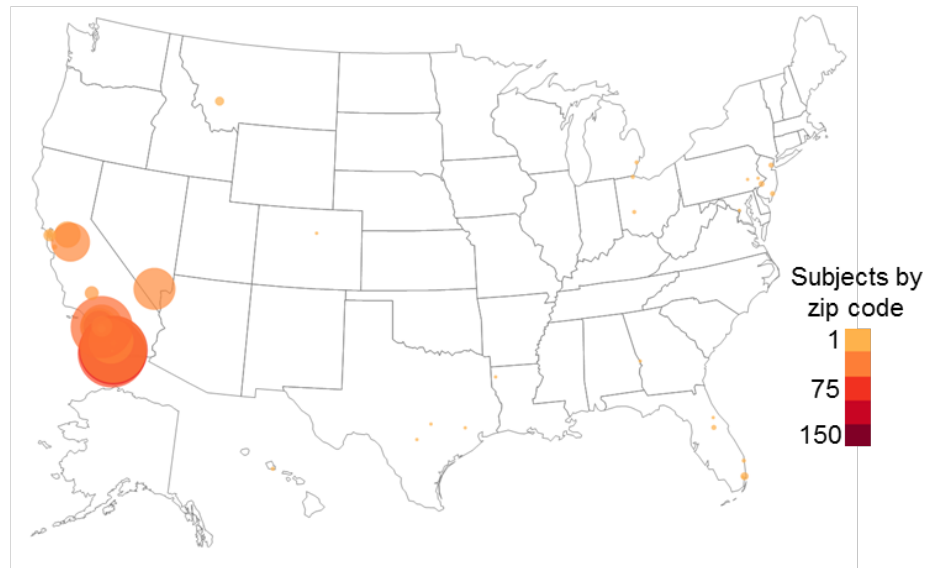
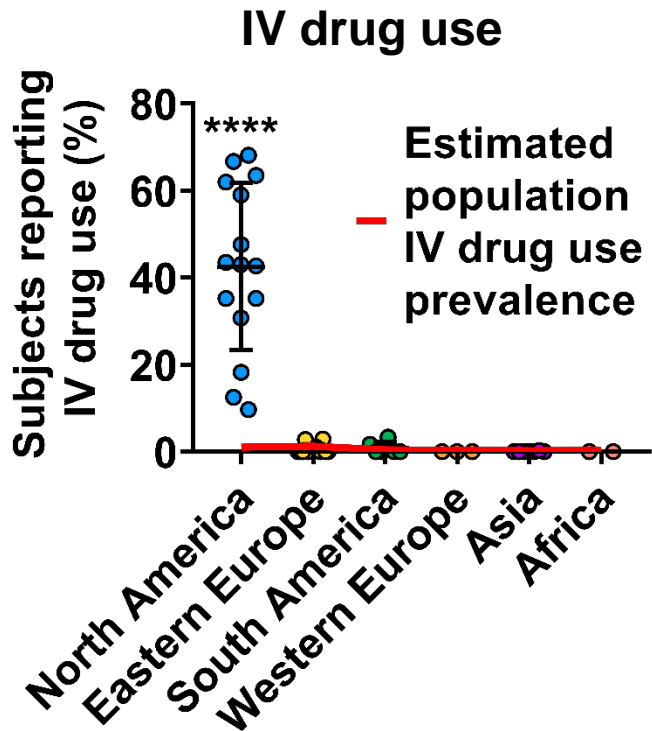
# Eastern European subjects receive less prior antibacterial drug therapy



## Prior antibacterial drug therapy



# North American ABSSSI subjects are disproportionately IV drug users



\*\*p<0.01, \*\*\*\*p<0.0001, random effects model

# Impacts on generalizability



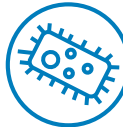
**Geography**  
Regions assigned by country



**Demographics**  
Age, sex, race, etc.



**Clinical characteristics**  
Comorbidities and disease severity

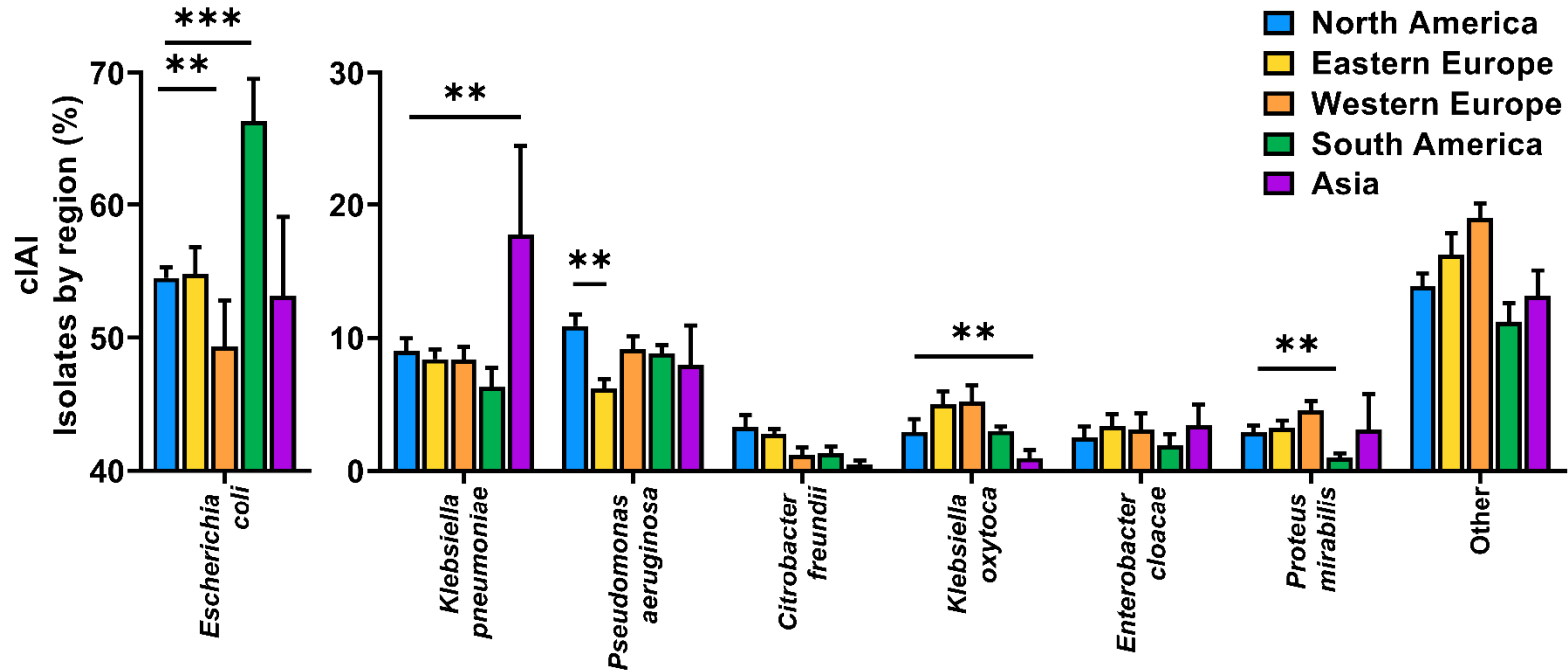


**Microbiology**  
Species and resistance phenotypes

Subject-level NDA data used to investigate demographic differences among regions  
Analyzed regional differences for [cIAI](#), cUTI (Gram-negative aerobes) and ABSSSI (all organisms)  
Used FDA-recognized breakpoints to identify resistant isolates

# cIAI microbiology is similar worldwide

## *K. pneumoniae* elevated in Asia

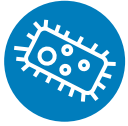


**Gram-negative species prevalence**

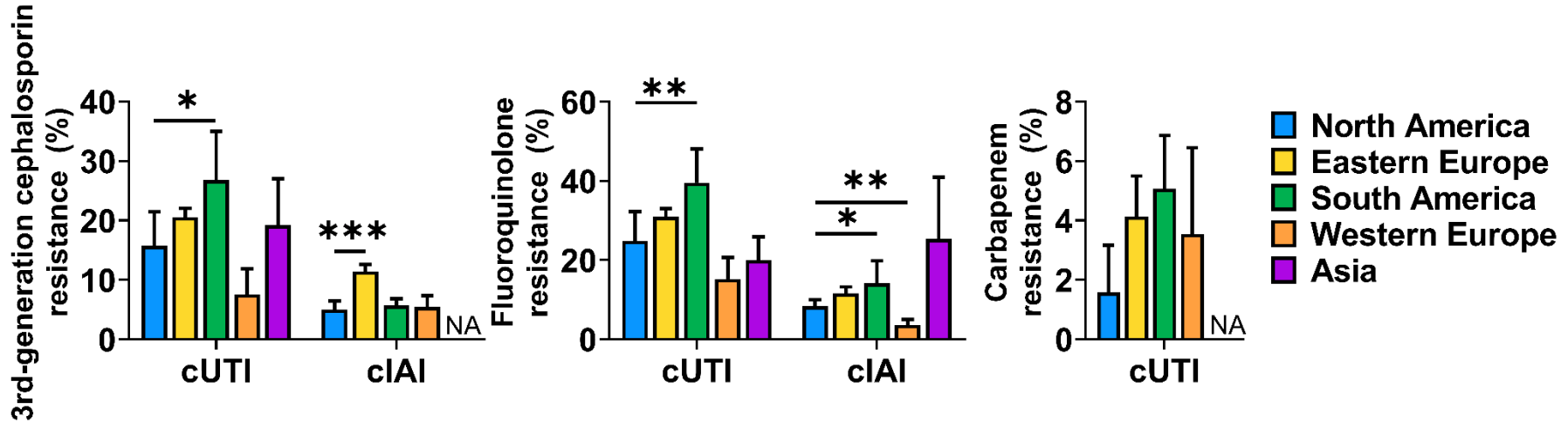
n=8 trials  
 Mean ± SEM  
 \*p<0.05, \*\*p<0.01, \*\*\*p<0.001, random effects model



# Resistance phenotypes differ worldwide



Resistance phenotypes among **Enterobacteriaceae** in cUTI and cIAI trials  
 FDA-recognized breakpoints used to assess susceptibility  
 3<sup>rd</sup>-generation cephalosporins, carbapenems, and fluoroquinolones



n=8 trials for each cUTI and cIAI

Mean ± SEM

\*p<0.05, \*\*p<0.01, \*\*\*p<0.001, random effects model

# Conclusions



## Enrollment trends differ by indication

- cUTI, cIAI, and CABP trials increasingly enrolled from Eastern European sites
- ABSSSI trials are dominated by North American enrollment



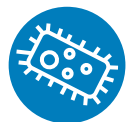
## Demographic characteristics did not differ significantly for most comparisons

- Higher BMI among North American subjects
  - Consideration in review of drug exposure data collected elsewhere



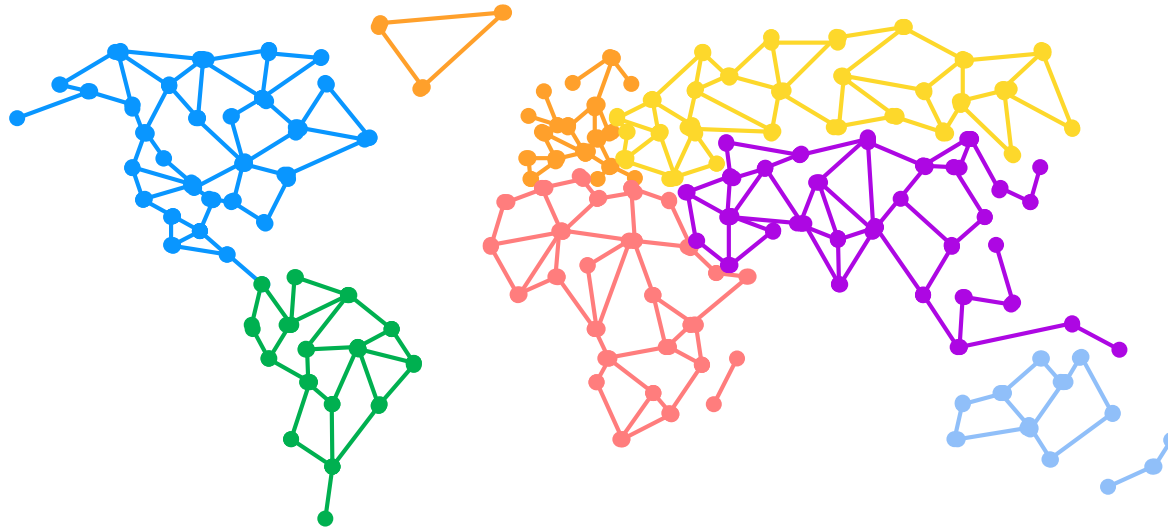
## Certain clinical characteristics vary by region

- Large differences in disease severity were not detected in this analysis
- Eastern European subjects exhibited the least prior antibacterial drug therapy
  - Differences in standards of care or in enrollment efficiency
- North American ABSSSI subjects disproportionately reported IV drug use
  - Differences in infection type and microbiology



## Microbiology is broadly similar among regions, with regional enrichment for some species and resistance phenotypes

- Differences could be used to guide future site selection



Demographic, clinical, and microbiological similarities lessen generalizability concerns for antibacterial drug trials

US participation is still important, given known and unknown regional differences



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