

# **$\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations Show a High Degree of Cross-Resistance in Gram-Negative Bacteria, but Not to Cefiderocol**

Results from the  
SENTRY Antimicrobial Surveillance Program (2020–2024)

**#627** – Resistance Mechanisms and Epidemiology  
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# Disclosures

This research was conducted by Element Iowa City (JMI Laboratories) and funded by Shionogi.

Boudewijn L.M. DeJonge, Sean T. Nguyen, Chris Longshaw, Hidenori Yamashiro, and Yoshinori Yamano are employees of Shionogi.

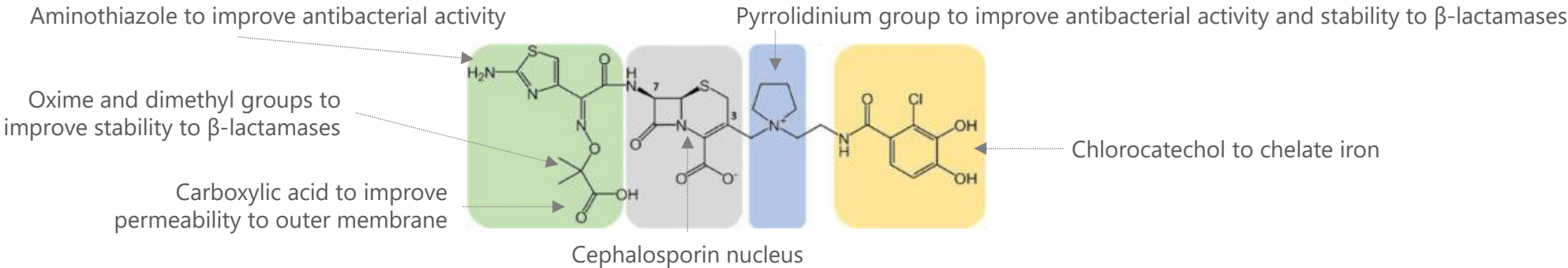
Rodrigo E. Mendes and Joshua Maher are employees of Element Iowa City.

# Introduction

- $\beta$ -lactam– $\beta$ -lactamase inhibitor combinations, such as ceftazidime-avibactam, meropenem-vaborbactam, ceftolozane-tazobactam, and imipenem-relebactam, are used to treat infections caused by carbapenem-resistant Enterobacterales and/or *P. aeruginosa*
- Resistance to these agents was assessed for isolates collected in a 5-year surveillance program, and the degree of cross-resistance among  $\beta$ -lactam– $\beta$ -lactamase inhibitor combinations and cefiderocol, a siderophore conjugated cephalosporin with good activity against carbapenem-resistant Gram-negative bacteria, was determined

Activity of cefiderocol against Gram-negative pathogens

| Enterobacterales  |                       |                              | <i>P. aeruginosa</i>                        |                              | <i>A. baumannii</i>                     | <i>S. maltophilia</i>          | Other resistance mechanisms |                          |
|-------------------|-----------------------|------------------------------|---------------------------------------------|------------------------------|-----------------------------------------|--------------------------------|-----------------------------|--------------------------|
| ESBLs and/or AmpC | Serine carbapenemases | Metallo- $\beta$ -lactamases | Serine $\beta$ -lactamases (including AmpC) | Metallo- $\beta$ -lactamases | Serine carbapenemases (OXA) and/or AmpC | L1 metallo- $\beta$ -lactamase | Porin channel mutations     | Efflux pump upregulation |
| ✓                 | ✓                     | ✓                            | ✓                                           | ✓                            | ✓                                       | ✓                              | ✓                           | ✓                        |



# Materials and Methods

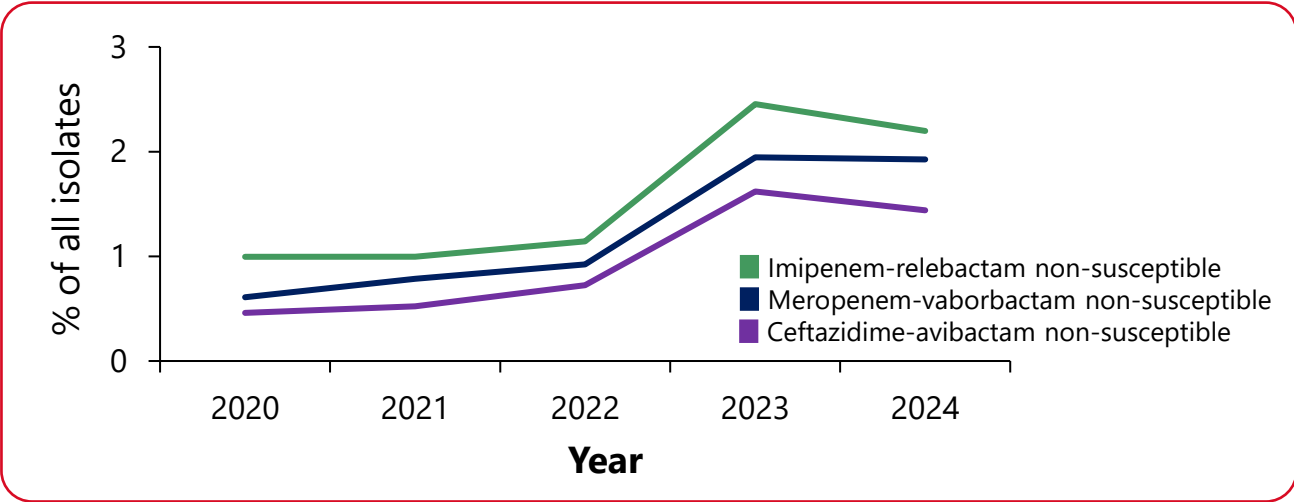
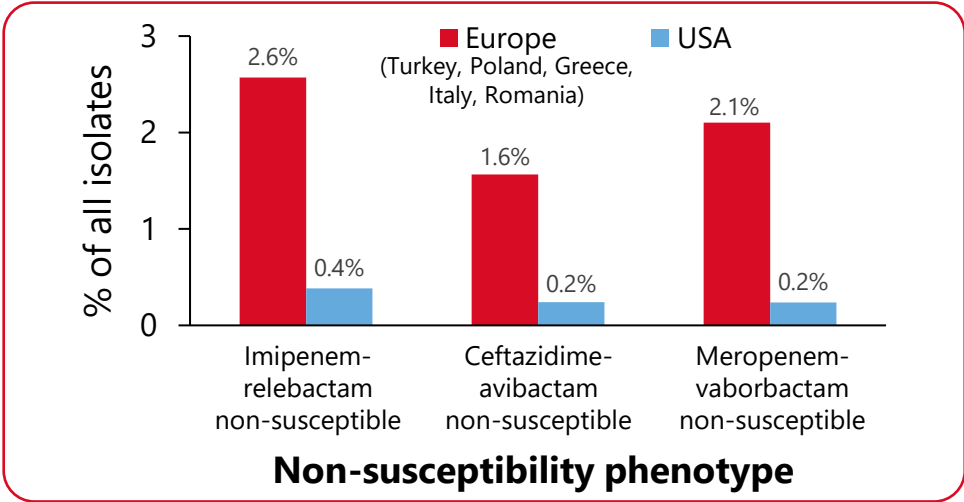
- 40,048 Enterobacterales and 11,757 *P. aeruginosa* isolates were collected between 2020 and 2024 in Europe and the USA as part of the SENTRY Antimicrobial Surveillance Program
- Minimum inhibitory concentrations were determined by broth microdilution according to CLSI procedures using cation-adjusted Mueller–Hinton broth (CAMHB) for  $\beta$ -lactam– $\beta$ -lactamase inhibitor combinations and iron-depleted CAMHB for cefiderocol
- Non-susceptibility to  $\beta$ -lactam– $\beta$ -lactamase inhibitor combinations was assessed with CLSI breakpoints
- Susceptibility to cefiderocol was assessed according to 2025 CLSI, FDA, and EUCAST breakpoints

# Prevalence of Enterobacterales Non-Susceptible to $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations

Percentage of ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam non-susceptible Enterobacterales isolates

| Enterobacterales isolates (n)                                     | % of total | 3 most prevalent species                                                         |
|-------------------------------------------------------------------|------------|----------------------------------------------------------------------------------|
| All (n=40,048)                                                    | 100        | <i>E. coli</i> (44.1%), <i>K. pneumoniae</i> (20.1%), <i>P. mirabilis</i> (5.7%) |
| Ceftazidime-avibactam non-susceptible (n=381) <sup>a</sup>        | 1.0        | <i>K. pneumoniae</i> (69.2%), <i>E. cloacae</i> (12.9%), <i>E. coli</i> (5.8%)   |
| Meropenem-vaborbactam non-susceptible (n=495) <sup>a</sup>        | 1.2        | <i>K. pneumoniae</i> (83.2%), <i>E. cloacae</i> (6.9%), <i>E. coli</i> (4.9%)    |
| Imipenem-relebactam non-susceptible (n=567/36,442) <sup>a,b</sup> | 1.6        | <i>K. pneumoniae</i> (73.7%), <i>E. cloacae</i> (8.5%), <i>E. coli</i> (5.7%)    |

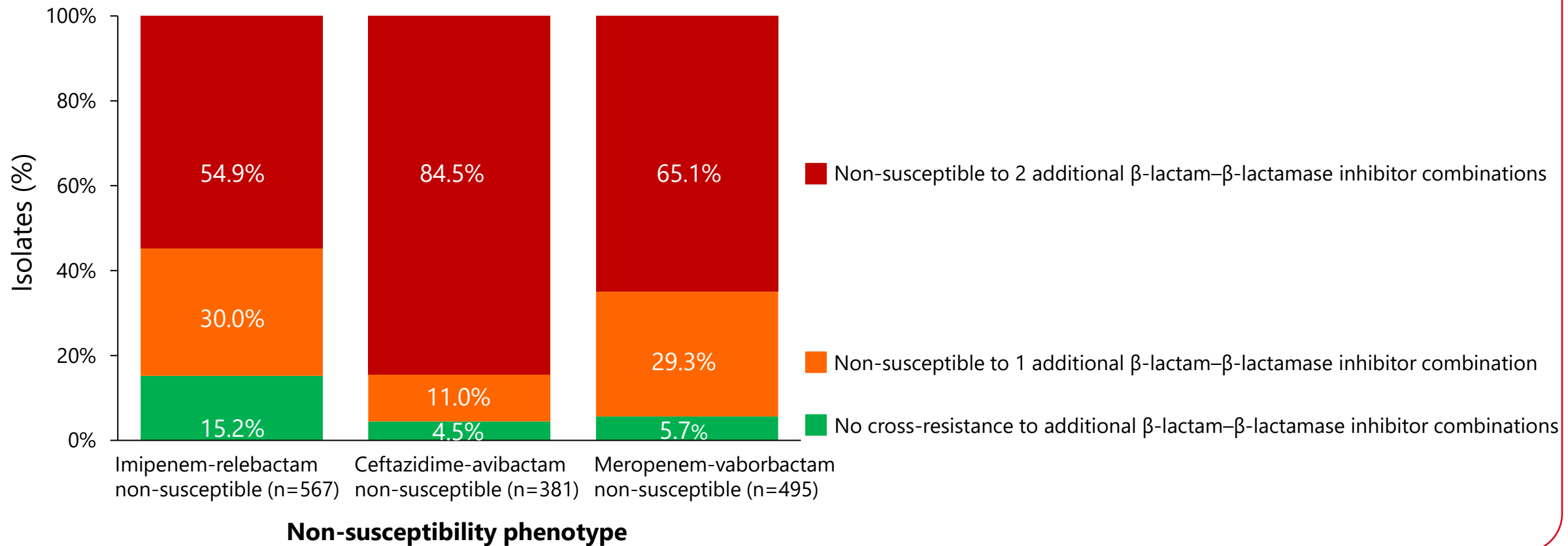
<sup>a</sup>Non-susceptibility based on CLSI breakpoints; <sup>b</sup>*Morganella*, *Proteus*, and *Providencia* spp. were excluded due to the intrinsic resistance of these species.



- Percentages of isolates non-susceptible to  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations were low
- Prevalence was higher in Europe
- Percentages were trending upwards

# Cross-Resistance Among $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations in Enterobacterales

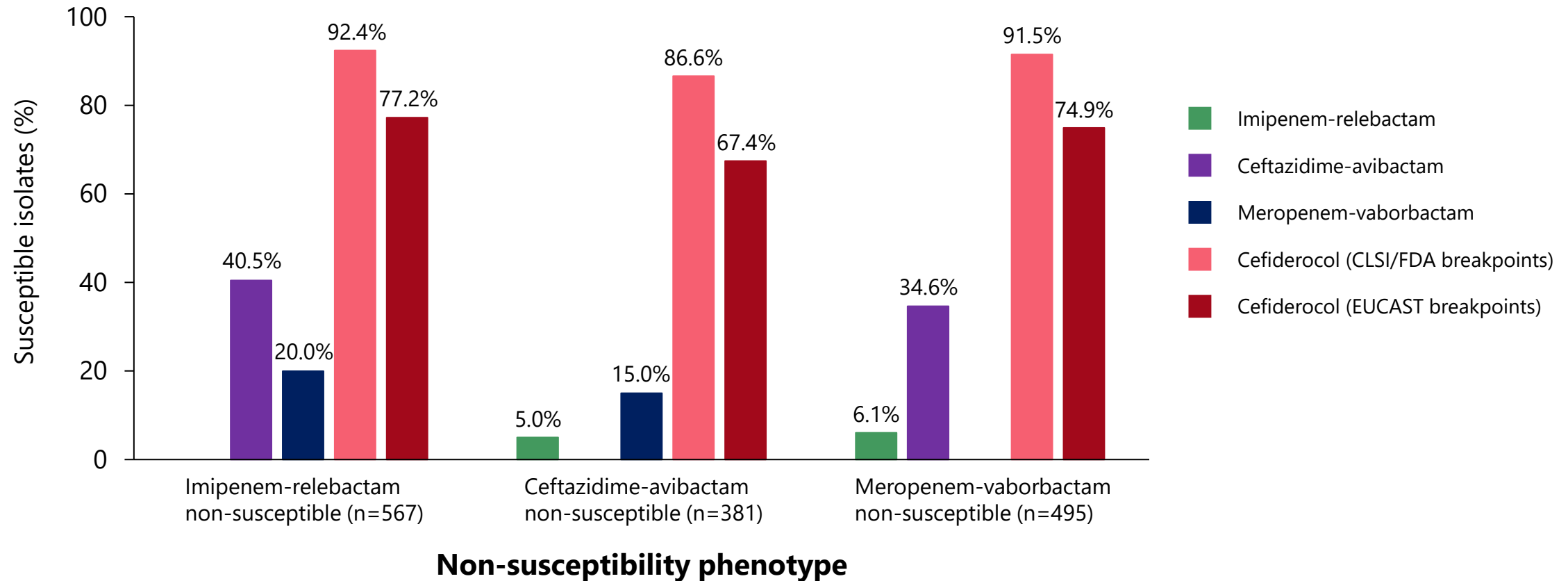
**Cross-resistance among  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations**



- The majority of isolates were non-susceptible to other  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations

# Activity Against Enterobacterales Isolates Non-Susceptible to $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations

## Susceptibility for isolates non-susceptible to $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations



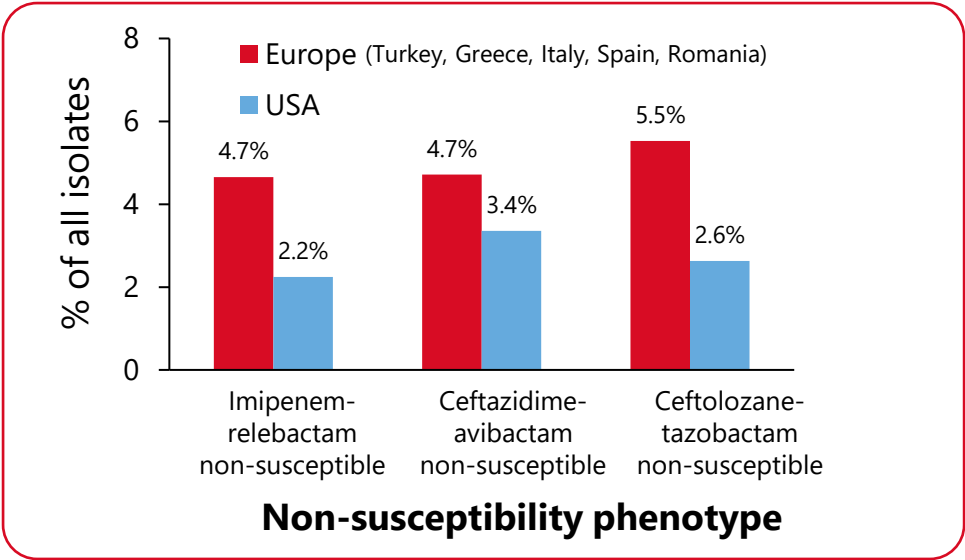
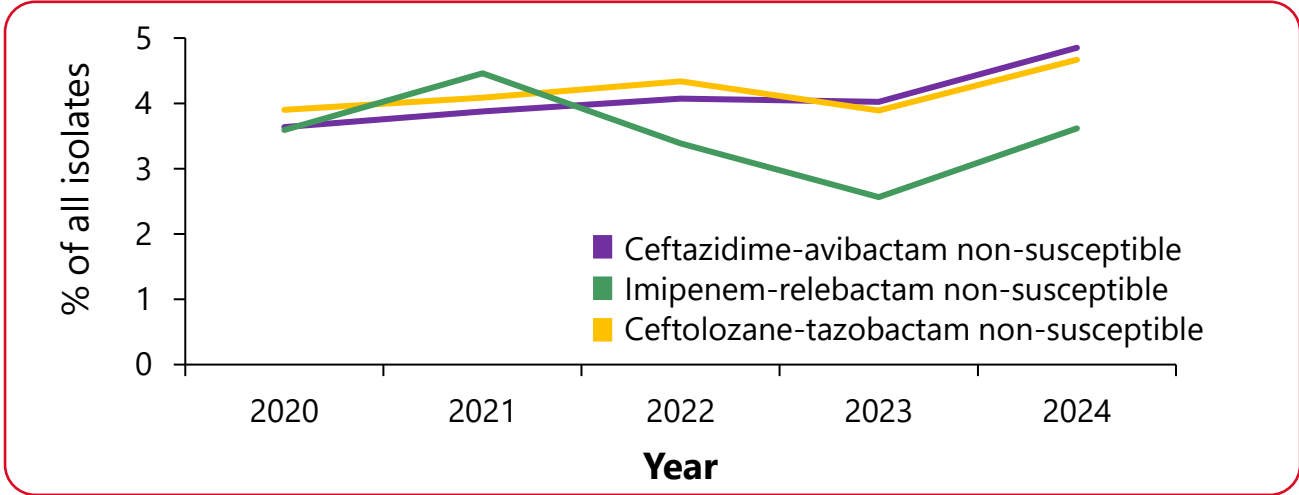
- Cefiderocol retains good activity against isolates non-susceptible to  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations

# Prevalence of *P. aeruginosa* Non-Susceptible to $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations

Percentage of ceftazidime-avibactam-, ceftolozane-tazobactam-, and imipenem-relebactam-non-susceptible *P. aeruginosa* isolates

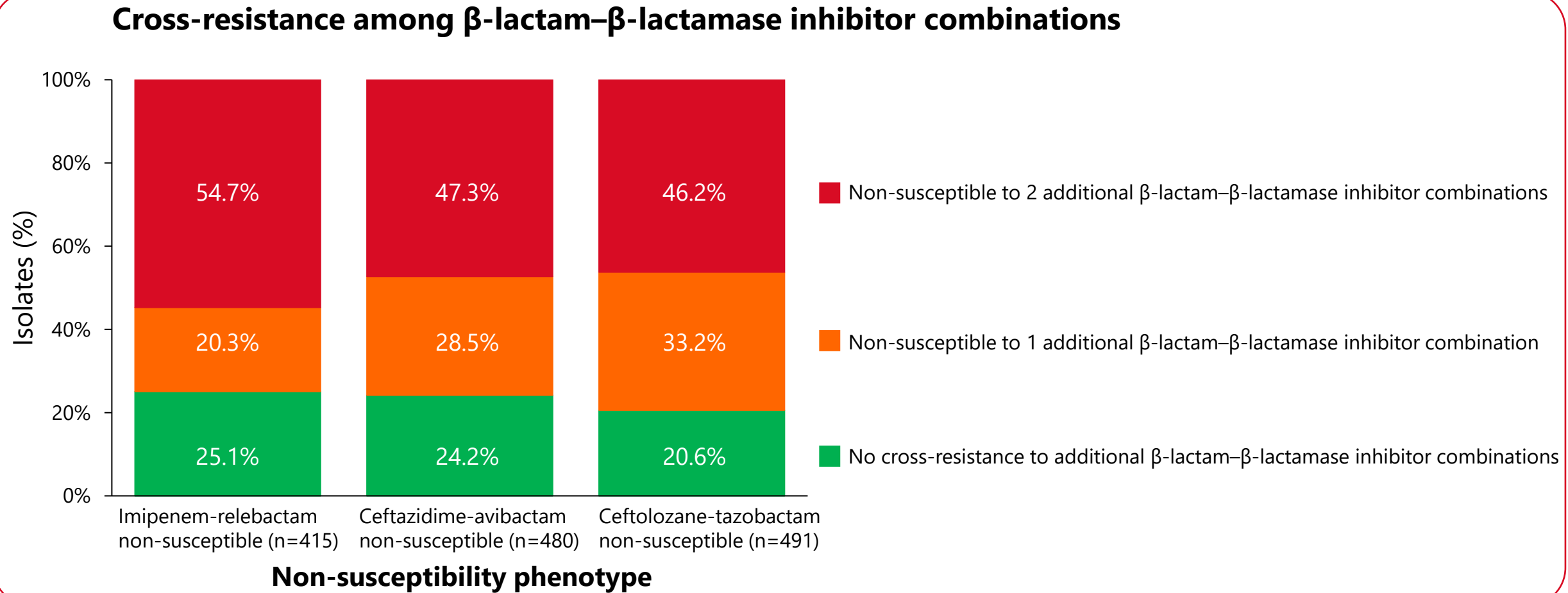
| <i>P. aeruginosa</i> isolates (n)                           | % of total |
|-------------------------------------------------------------|------------|
| All (n=11,757)                                              | 100        |
| Ceftazidime-avibactam non-susceptible (n=480) <sup>a</sup>  | 4.1        |
| Ceftolozane-tazobactam non-susceptible (n=491) <sup>a</sup> | 4.2        |
| Imipenem-relebactam non-susceptible (n=415) <sup>a</sup>    | 3.5        |

<sup>a</sup>Non-susceptibility based on CLSI breakpoints.



- Percentages of isolates non-susceptible to  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations were low
- Prevalence was higher in Europe than in the USA
- Percentages appear to show upward trends

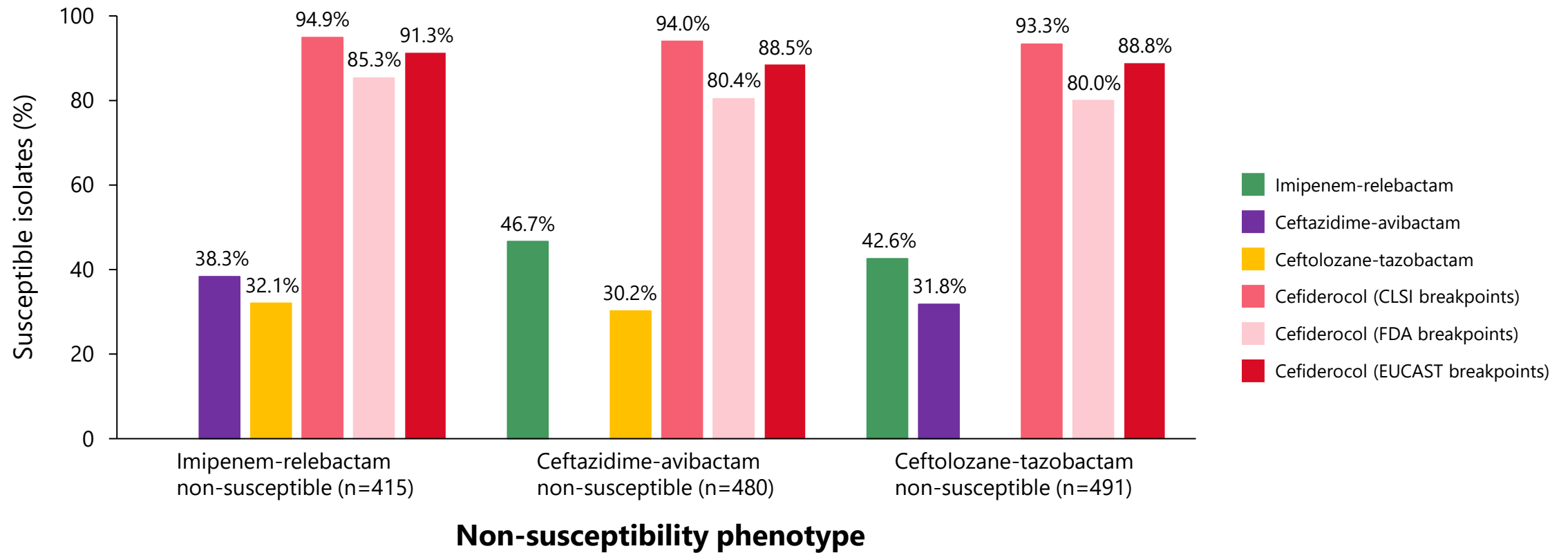
# Cross-Resistance Among $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations in *P. aeruginosa*



- The majority of these isolates were non-susceptible to other  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations

# Activity Against *P. aeruginosa* Isolates Non-Susceptible to $\beta$ -Lactam- $\beta$ -Lactamase Inhibitor Combinations

## Susceptibility for isolates non-susceptible to $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations



- Cefiderocol retains good activity against isolates non-susceptible to  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations

# Conclusions

- Resistance to  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations in Europe and USA remains low (~1–4%), more so for Enterobacterales (<2%) than for *P. aeruginosa* (~4%)
  - Percentages are higher in Europe compared with the USA
  - Percentages showed an increasing trend over time
- $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations show a high degree of cross-resistance in Enterobacterales and *P. aeruginosa*, but cefiderocol remained active against these highly resistant isolates
- Given the high degree of cross-resistance among  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations and the good activity of cefiderocol against these isolates, cefiderocol should be considered as a treatment option when pathogens non-susceptible to any of the  $\beta$ -lactam- $\beta$ -lactamase inhibitor combinations are encountered or suspected

