Multidrug-resistant Gram-negative Bacilli – Epidemiology & Decolonization Considerations

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Drug Development Considerations for the Prevention of Healthcare-Associated Infections—Virtual Public Workshop
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Overview

- Epidemiology
- Asymptomatic colonization
  - Risk factors and duration
  - Risk of infection and role in transmission
- Decolonization and pathogen reduction approaches

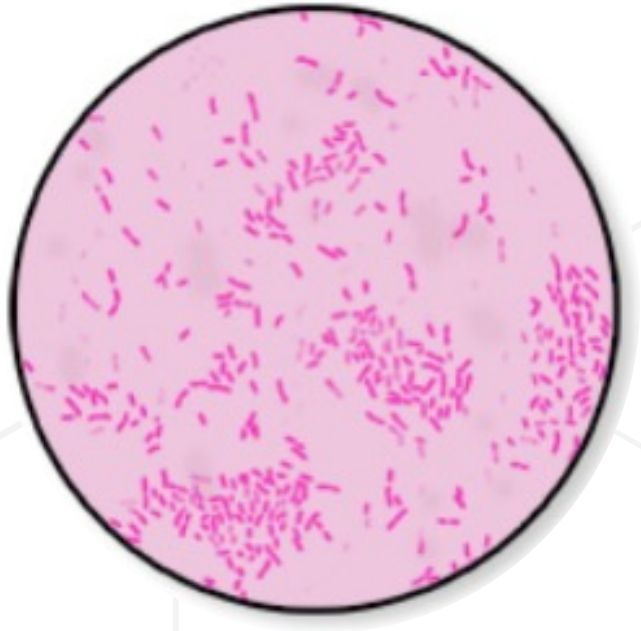
Drug development needs for MDR-gram-negative bacteria prevention:

- Novel approaches for decolonization and pathogen reduction
  - Of the gastrointestinal tract
  - Of other body sites (e.g., respiratory tract, wounds) in certain high-risk populations
- Systematic evaluation of these approaches to understand their impact on colonization, infection, and transmission
  - Including dosing, duration, pre-treatments, and target populations
  - Informed end points for defining and measuring decolonization
  - Evaluation with control groups, especially randomized controlled trials

THE PROBLEM

Gram-negative bacilli

- Cause diverse array of infections including pneumonia, bloodstream, urinary tract, wounds and surgical sites
- Responsible for >30% of healthcare-associated infections
  - Most infections caused by Enterobacterales and the lactose non-fermenters, *Pseudomonas* spp. and *Acinetobacter* spp.



Gram stain of gram-negative bacilli under microscope

Healthcare-associated MDR gram-negative bacilli: Urgent and serious threats

Carbapenem-Resistant Enterobacterales (CRE)

Extended-Spectrum β-Lactamase producing Enterobacterales (ESBL)

Multidrug-Resistant *Pseudomonas aeruginosa*

Carbapenem-Resistant *Acinetobacter* (CRA)

Enteric Organisms

- Enterobacterales has >70 genera, including
  - *Klebsiella* spp.
  - *Escherichia coli*
  - *Enterobacter cloacae*
  - *Citrobacter spp.*
  - *Proteus mirabilis*

Non-Enteric Organisms

Common features of healthcare-associated MDR-gram-negative bacilli threats

Carbapenem-Resistant Enterobacterales (CRE)

Extended-Spectrum β-Lactamase producing Enterobacterales (ESBL)

Multidrug-Resistant *Pseudomonas aeruginosa*

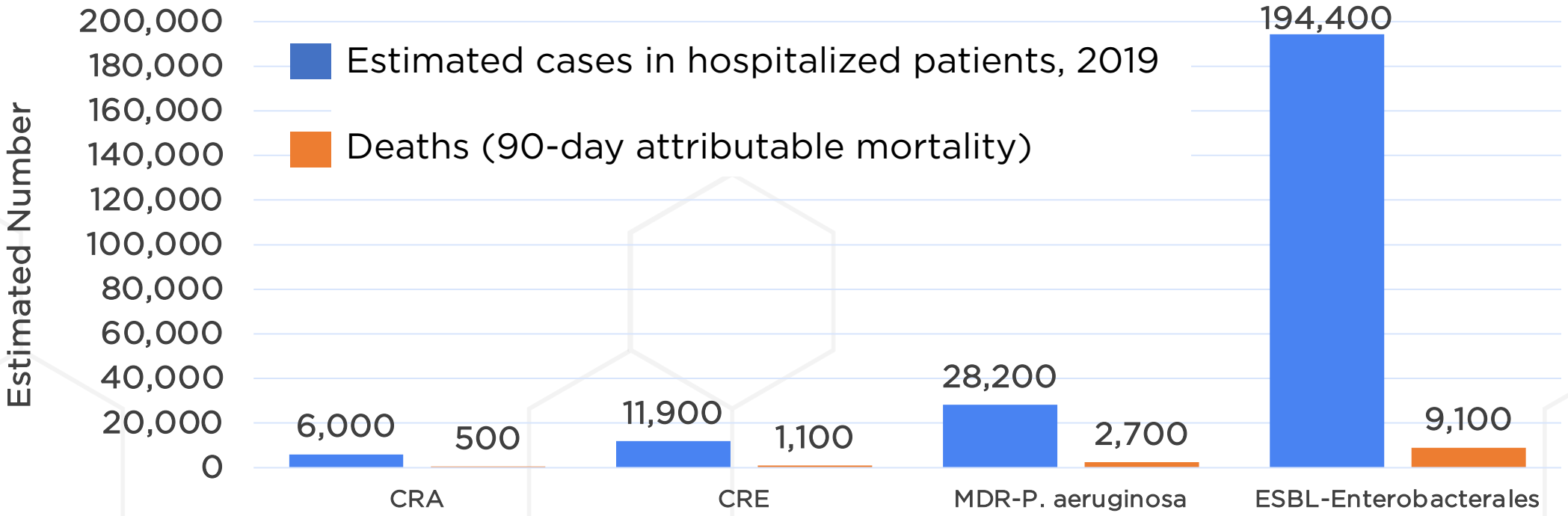
Carbapenem-Resistant *Acinetobacter* (CRA)

Enteric Organisms

Non-Enteric Organisms

- Opportunistic pathogens that can colonize multiple mucosal surfaces
- Cause a variety of infections, most commonly urinary tract, wound, and bloodstream infections, and pneumonia
- In healthcare settings, transmitted via direct and indirect contact with infected or colonized individuals or contaminated healthcare environment

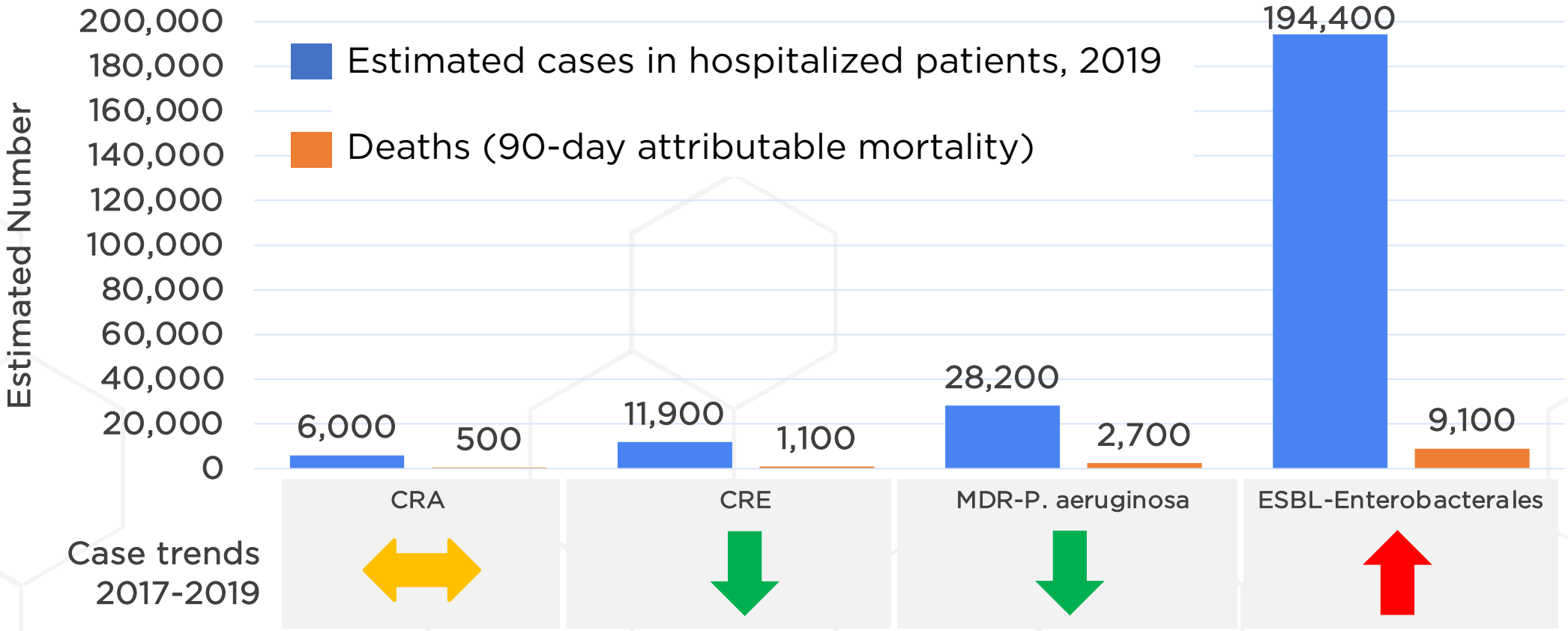
Estimated cases and deaths in hospitalized patients, 2019



CRA: Carbapenem-resistant *Acinetobacter*; CRE: Carbapenem-resistant Enterobacterales (*E. coli, Klebsiella* spp., *Enterobacter* spp.); MDR: multidrug-resistant; ESBL: Extended-spectrum β-lactamase-producing Enterobacterales (*E. coli* and *Klebsiella* spp. excluding *K. aerogenes*)

https://www.cdc.gov/drugresistance/pdf/covid19-impact-report-508.pdf

Estimated cases and deaths in hospitalized patients, 2019 (case trends)



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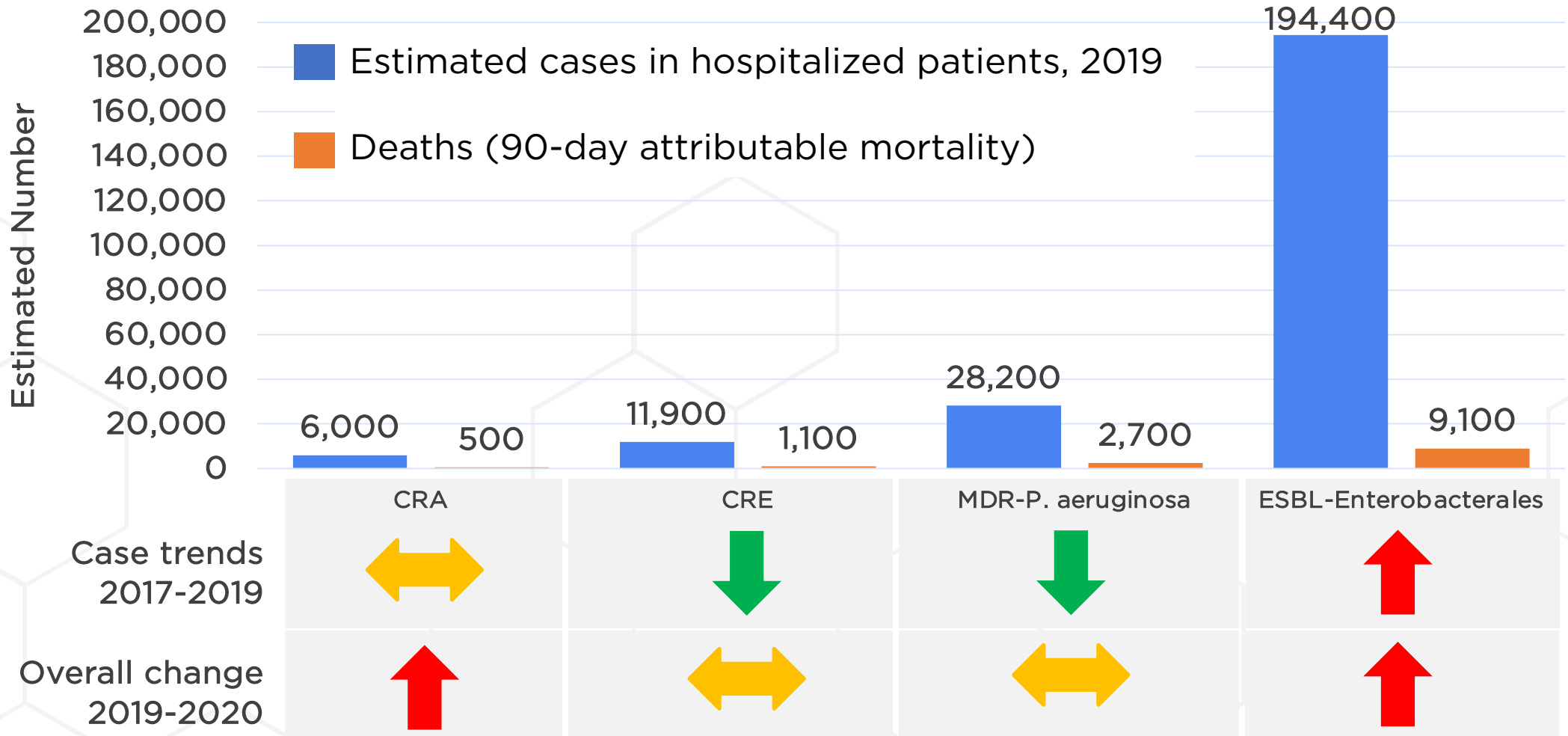
Estimated cases and deaths in hospitalized patients, 2019 (overall)



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Epidemiology of ESBL-Enterobacterales and CRE infections differs

ESBL

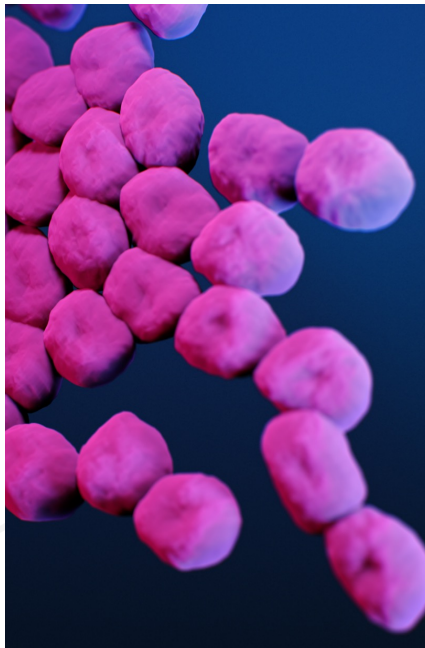
- Endemic
- ~Half occur in people who have not had recent inpatient exposures or invasive procedures
- Risk factors in community include recent antibiotic therapy, international travel
  - Food and water are increasingly recognized reservoirs in community

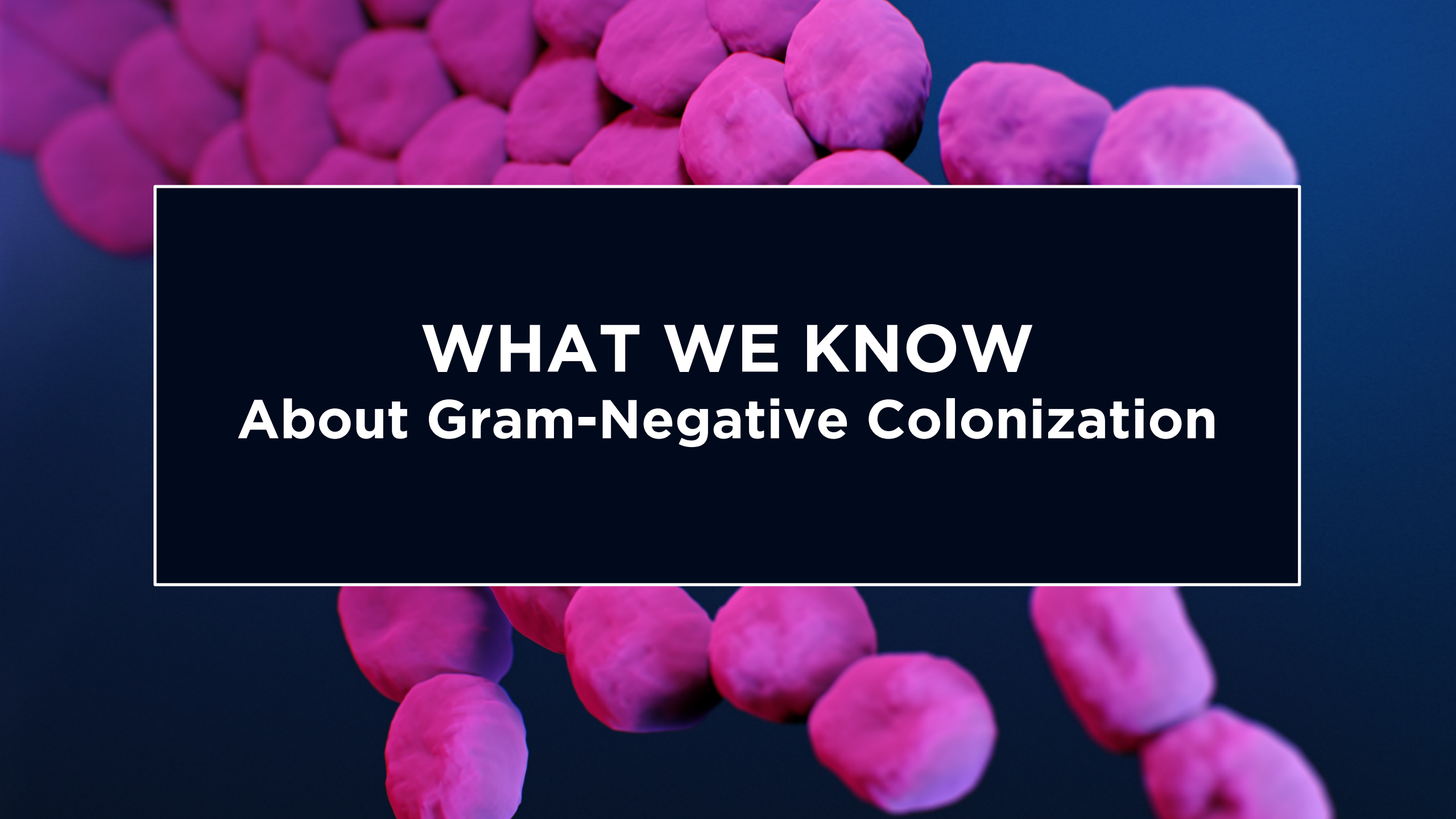
CRE

- Emerging
- Primarily occur in patients with extensive healthcare exposures
  - Risk factors for acquisition include indwelling devices, severe underlying illness, long-term care facility admission, antibiotic exposure
- Patient-to-patient transmission accounts for majority of cases
  - Wastewater plumbing recognized reservoir in healthcare facilities

Epidemiology of MDR-*P. aeruginosa* and *A. baumannii*

- **Biofilm formation important attribute**
  - Colonization of indwelling medical devices
  - Persistent wound and respiratory tract colonization
  - Can contribute to persistent contamination of shared medical equipment
- **Risk factors:** antibiotic exposure, mechanical ventilation, indwelling medical devices, longer duration of hospitalization
- **Occur almost exclusively in patients with substantial healthcare exposure**
  - Including patients with chronic underlying conditions resulting in dysbiosis, such as cystic fibrosis
- **Very limited treatment options**, particularly for carbapenem-resistant *A. baumannii*

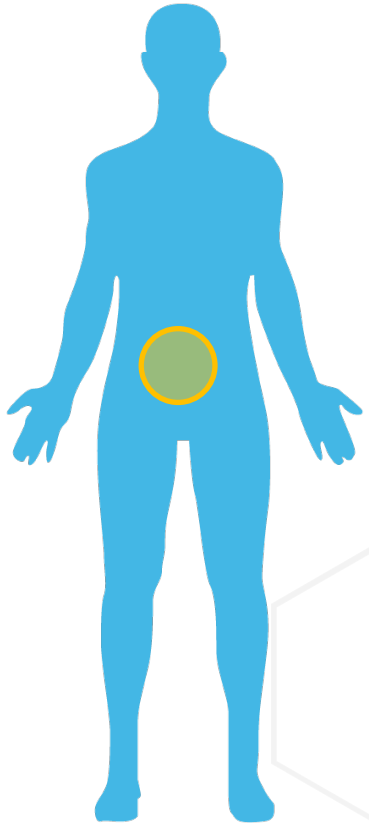




WHAT WE KNOW
About Gram-Negative Colonization

Asymptomatic colonization with MDR-Enterobacterales

- **Gastrointestinal tract is primary colonization site**
- **Duration of colonization is prolonged**, exact estimates vary
  - 35% remained colonized with ESBL-Enterobacterales/CRE at 1 year[1]
  - Median time to decolonization: 144 days[2], 295 days[3], 265 days[4]
  - Community dwellers decolonize at higher rates and more rapidly[1]
  - Some strains associated with increased duration of colonization
    - ESBL-producing ST 131 E. coli



[1]Bar-Yoseph H, et al. J Antimicrob Chemother. 2016;71(10):2729–2739.
[2]O'Fallon, E, et al. Clinical Infectious Diseases. 2009;48(10):1375-1381.
[3]Zimmerman, FS, et al. American Journal of Infection Control. 2009;41(3):190-194.
[4]Haverkate, MR, et al. Open forum infectious diseases. 2016;3(4):ofw178.
[5]Overdevest, I, et al. Euro Surveill. 2016;21(42):pii=30376.

Risk of infection after colonization with MDR-Enterobacterales

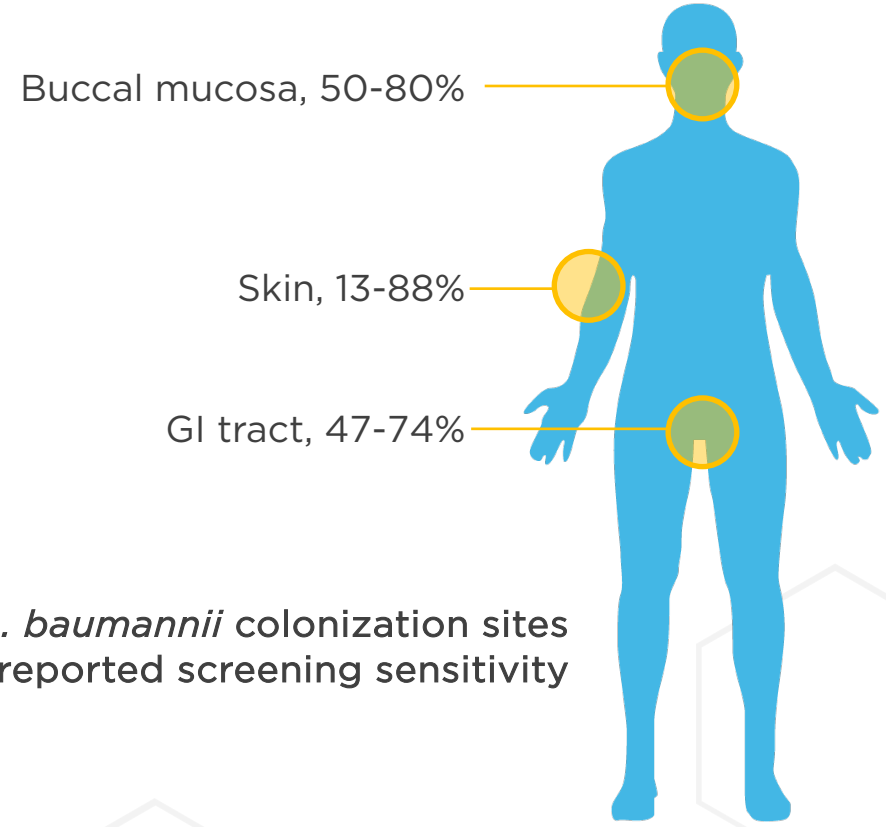
- **Colonization associated with higher risk of infection**
  - Colonized ICU patients: 2-10-fold increased risk of CRE infection[1,2]
  - 95% of ESBL-Enterobacterales infections in ICU patients occur in those with history of colonization[3]

- **CRE risk of infection among colonized, hospitalized patients**
  - Estimated 16.5% in meta-analysis (typical range: 7.6%-44%)[4]
    - Mortality in patients with infection: 30-75%
  - Higher abundance of KPC-*K. pneumoniae* in gut associated with increased risk of KPC-*K. pneumoniae* bacteremia[5]

[1]McConville TH, et al. PLoS ONE. 2017;12(10):e0186195.
[2]Dickstein, Y, et al. Journal of Hospital Infection. 2016;94(1):54-59.
[3]Detsis, M, et al. Critical Care Medicine. 2017;45(4):705-714.
[45]Tischendorf, J, et al. American Journal of Infection Control. 2016; 44(5):539-543
[5]Shimasaki T, et al. Clin Infect Dis. 2019;68(12):2053-2059.

Asymptomatic colonization with MDR-*P. aeruginosa* or *A. baumannii*

- **No gold standard screening site**
  - Colonize skin, upper and lower respiratory tract, wounds, and digestive tract
- **Prolonged carriage, estimates vary**
  - Carbapenem-resistant *A. baumannii*: 17% colonized after ≥6 months
  - Carbapenem-resistant *P. aeruginosa*: median persistence of 42 days in hospitalized kidney transplant patients



CR-*A. baumannii* colonization sites and reported screening sensitivity

Nutman, A, et. al. Clinical Microbiology and Infection. 2016;22 949.e5e949.e7
Nutman A, et al. Infection Control & Hospital Epidemiology. 2020;41: 965–967.
Doi Y, et al.. J Clin Microbiol. 2011;49:154e8.
Freire, MP, et al. Journal of Hospital Infection. 2021;115:83-92.
Marchaim, D, et. al. Journal of Clinical Microbiology. 2007;45:1551-1555.

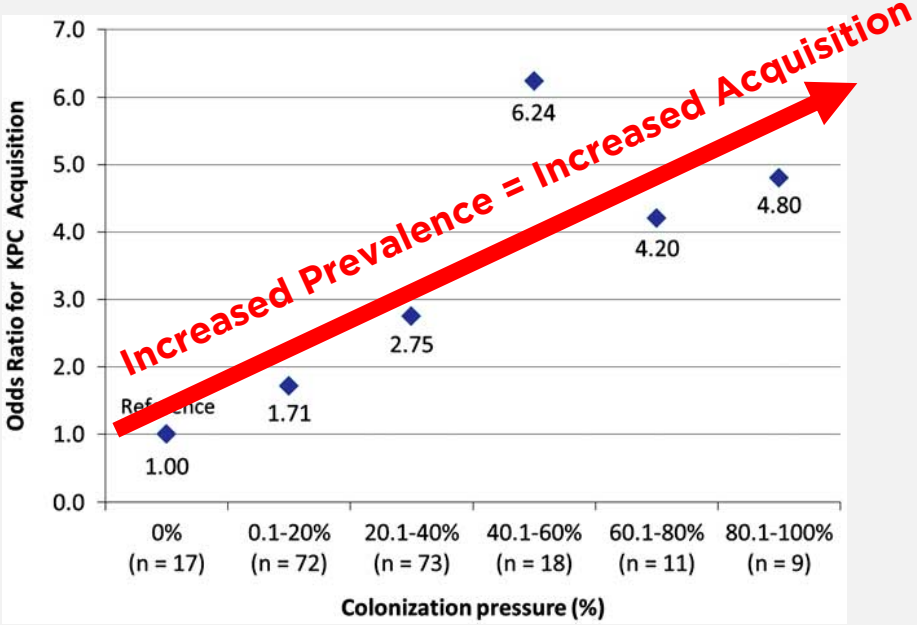
Risk of infection after colonization with MDR-*P. aeruginosa* or *A. baumannii*

- Colonization precedes infection with same strains
  - Patients with CR-*A. baumannii* bloodstream infections colonized with same strain in gut[1]
  - Among patients colonized with *P. aeruginosa* at ICU admission
    - 23%[2]-43%[3] developed infection during their hospitalization
    - Risk of clinical culture >6-times higher than those not colonized[2]

[1] Thom, K, et al. American Journal of Infection Control. 2010;38(9):751-753.
[2]Harris, A, et al. Infection Control & Hospital Epidemiology. 2016;:37(5):544-548.
[3]Hoang S, et al. PLoS ONE. 2018;13(3):e0193300.

Transmission from colonized individuals

- Risk of acquisition increases with higher colonization prevalence, even when multiple interventions[1] in place
  - Long-term acute care hospitals: 1% increase in colonization pressure associated with 2% increase in acquisition risk for KPC-*K. pneumoniae*

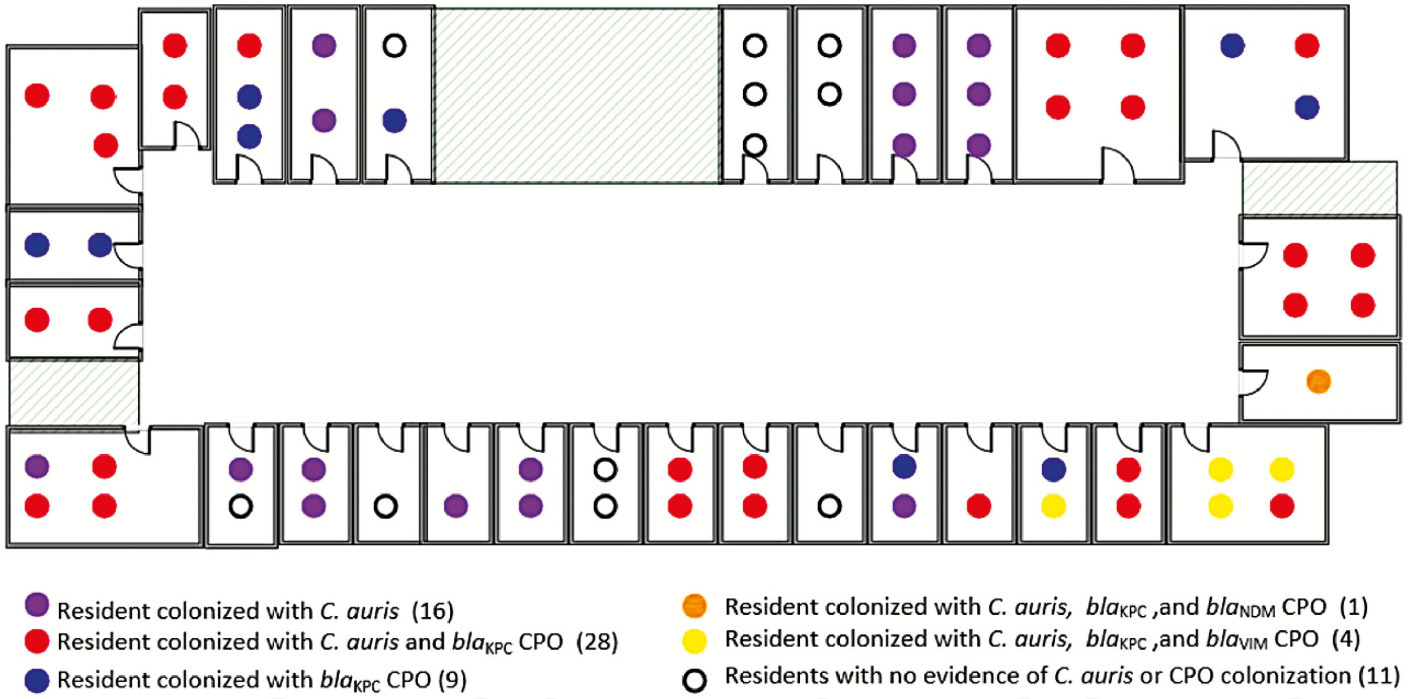


[1]Interventions:
- active surveillance,
- daily chlorhexidine bathing,
- contact isolation and geographic separation of KPC-carriers,
- healthcare personnel education

Okamoto, K, et al. Infection Control & Hospital Epidemiology. 2017;38(6):670-677.

Transmission from colonized individuals (continued)

- High-acuity, long-term care settings associated with high prevalence of patients colonized with ≥1 resistant gram-negative



Candida auris, carbapenemase-producing-CRE, and carbapenemase-producing-*P. aeruginosa* colonization among residents at a ventilator-capable skilled nursing facility

Pacilli, M, et al. Clinical Infectious Diseases. 2020;71(11):e718–e725.

Addressing MDR-Enterobacterales colonization

Approaches	Findings
Skin antisepsis	▪ CHG bathing reduces skin concentrations of CRE,[1] may reduce CRA skin burden[2] ▪ Higher CHG MICs for CRE than for gram-positive bacteria
Non-absorbable oral antibiotics for selective digestive decontamination	▪ Multiple RCTs: SDD reduced GI carriage rate of ESBLs, CRE, and CRAB during high-risk periods[2] ▪ Temporary effect ▪ Risk of increased resistance
Probiotics	▪ In 2 RCTs probiotic administration did not alter MDR-Enterobacterales acquisition or loss[3,4]
Fecal microbiota transplant	▪ Case studies and uncontrolled studies ▪ Meta-analysis of 3 studies estimated 46% (95% CI: 20%-74%) patients decolonized antibiotic resistant organisms 1-month post-FMT[5]
Bacteriophage therapy	▪ Case reports of successful treatment of *Acinetobacter*, *P. aeruginosa*, and Enterobacterales infections at multiple anatomic sites, including CF patient populations [6]

[1]Lin, M.Y. Infection Control & Hospital Epidemiology. 2014;35(04):440-442; [2]Tacconelli, E, et al., Clinical Microbiology and Infection. 2019; 25:807-817;. [3]Kwon, J, et al. Infection Control & Hospital Epidemiology. 2015;36(12):1451-1454.; [4]Rauseo, A, et al. Infection Control & Hospital Epidemiology. 2022;43:167–173.; [5]Tavoukjian, V, Journal of Hospital Infection. 2019;102:174e188.; [6]Abedon, ST, et al., Pharmaceuticals 2021, 14, 1157.

WHAT WE NEED

Summary of MDR-gram-negative bacilli

- **Highly antibiotic resistant organisms** with limited treatment options
- **Colonization increases risk of infection,** transmission, opportunities to develop new, higher risk resistant strains, and potential for healthcare pathogens to move into the community
- Current methods to prevent transmission can **slow but do not stop spread** of these organisms
- **MDR-GNB decolonization can positively impact patient outcomes and public health** by reducing infections, days under infection control isolation, and emergence of new strains that are more virulent or more transmissible
  - **Currently no FDA-approved decolonization agents**

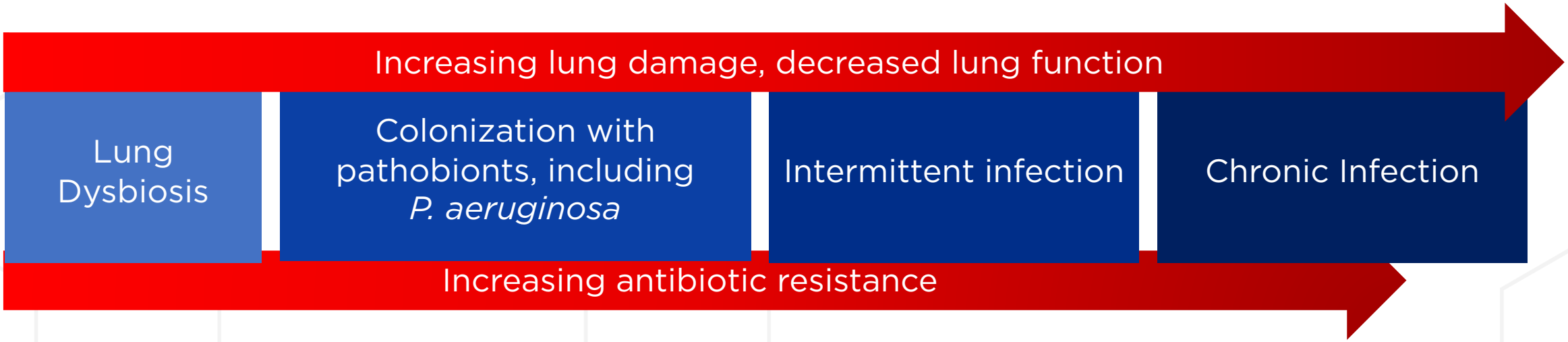
Critical Needs

- **Novel approaches for decolonization and pathogen reduction**
- **Systematic evaluation of decolonization approaches**
  - Including dosing, duration, pre-treatments, and target populations
  - Informed end points for defining and measuring decolonization
  - Evaluation with control groups, especially randomized controlled trials
  - Inform impact on colonization, infection, and transmission of clinically relevant multidrug-resistant gram-negative bacilli

Supplementary Slides

P. aeruginosa colonization in Cystic Fibrosis patients

- 90% of deaths in CF patients are attributed to pulmonary dysfunction directly associated with chronic infection



Rossi, E., La Rosa, R., Bartell, J.A., Marvig, R.L., Haagensen, J.A., Sommer, L.M., Molin, S. and Johansen, H.K., 2021. Pseudomonas aeruginosa adaptation and evolution in patients with cystic fibrosis. Nature Reviews Microbiology, 19(5), pp.331-342.