Advancing equity in antimicrobial stewardship: How do we know if we are making progress?

Melinda M. Pettigrew, PhD
Dean and Mayo Chair
2024 MN Antibiotic Stewardship Conference
May 1, 2024

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

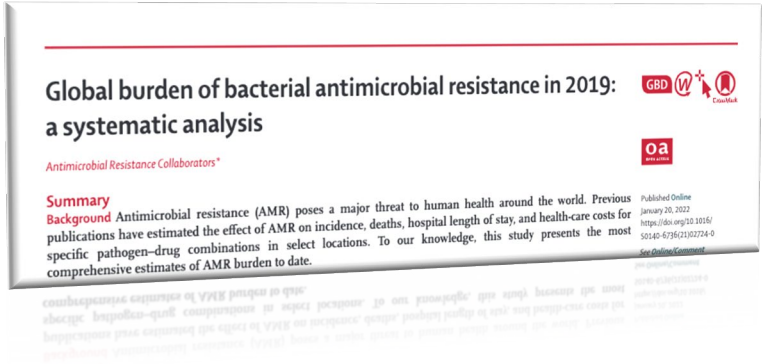
Topics to Consider

- Describe how social determinants of health contribute to disparities related to antimicrobial resistance
- Provide examples of goals, strategies, and challenges for measuring and achieving equitable enrollment and representation in antibiotic stewardship research and surveillance
- Discuss the ways in which a One Health framework can advance health equity

Antibiotics are essentially different than other drugs; they not only effect the individual to whom they are given but also the entire community through selection for resistance to their own action. Thus, their use resides at the intersection of personal and public health.

-Martin Blaser, Science, 2016

Antimicrobial Resistance (AMR): A Global Public Health Threat



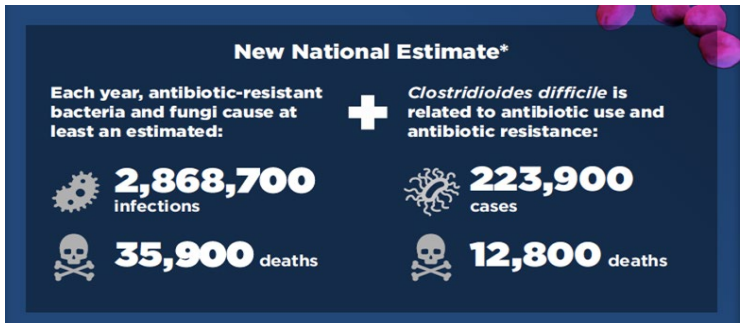
Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis

Antimicrobial Resistance Collaborators*

Summary

Background Antimicrobial resistance (AMR) poses a major threat to human health around the world. Previous publications have estimated the effect of AMR on incidence, deaths, hospital length of stay, and health-care costs for specific pathogen–drug combinations in select locations. To our knowledge, this study presents the most comprehensive estimates of AMR burden to date.

CDC Report on Antibiotic Resistance Threats in the US, 2019



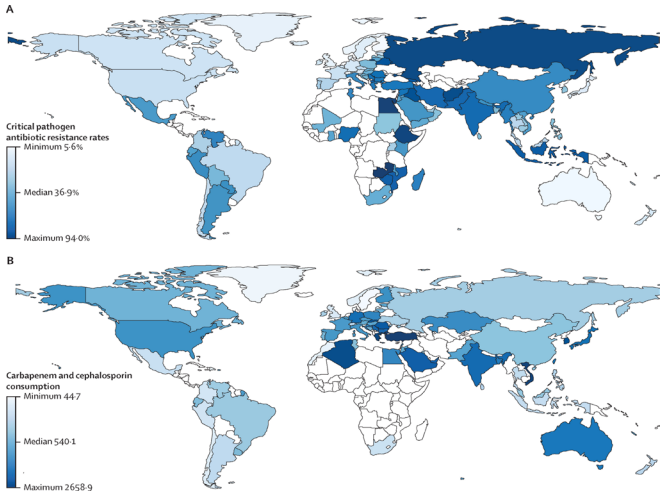
- 4.95 95% UI (3.62-6.57) million deaths associated w/AMR
- 1.27 95% UI (0.91-1.71) million deaths attributable to AMR
- Western sub-Saharan Africa has the highest burden ~27.3 deaths per 100,000
- Lower respiratory infections accounted for 1.5 million deaths associated with resistance

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Antimicrobial Resistance Collaborators (2022) *Lancet*, 399: P629-655

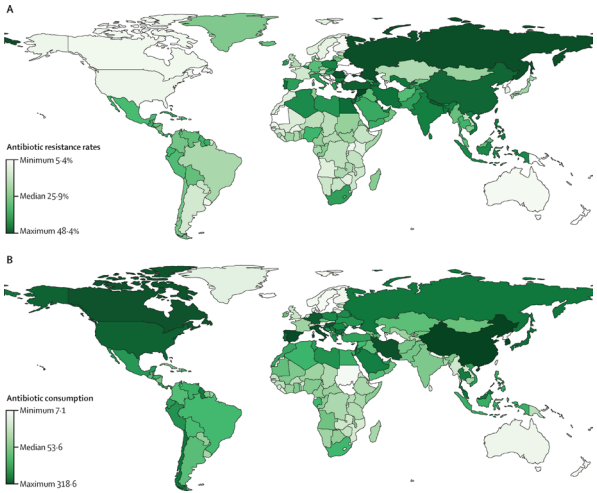
Antibiotic Use is an Important Driver of Resistance

Critical pathogen AMR rates, carbapenem and cephalosporin consumption



Pearson's correlation between AMR and consumption in humans, 0.30 (p=0·021)

AMR rates and antibiotic consumption in food-producing animals



Pearson's correlation between AMR and consumption in food-producing animals, 0.28 (p<0·0001)

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

The Lancet Planetary Health 2023 7e291-e303DOI: (10.1016/S2542-5196(23)00026-8)

Complex and Multifactorial Drivers of Antimicrobial Resistance

GLOBAL TRENDS

- Population growth
- Increasing travel
- Mobility (humans and animals)
- Political instability/war/conflict
- Climate change
- Deficits in the antibiotic pipeline

INEQUITIES

- Unequal/limited access to clean water
- Poor sanitation, hygiene, and infrastructure in low resource settings
- Environmental contamination/pollution (air, soil, water)

BEHAVIOR

Antibiotics are a public good, their use and misuse is driven by unsustainable economies in:

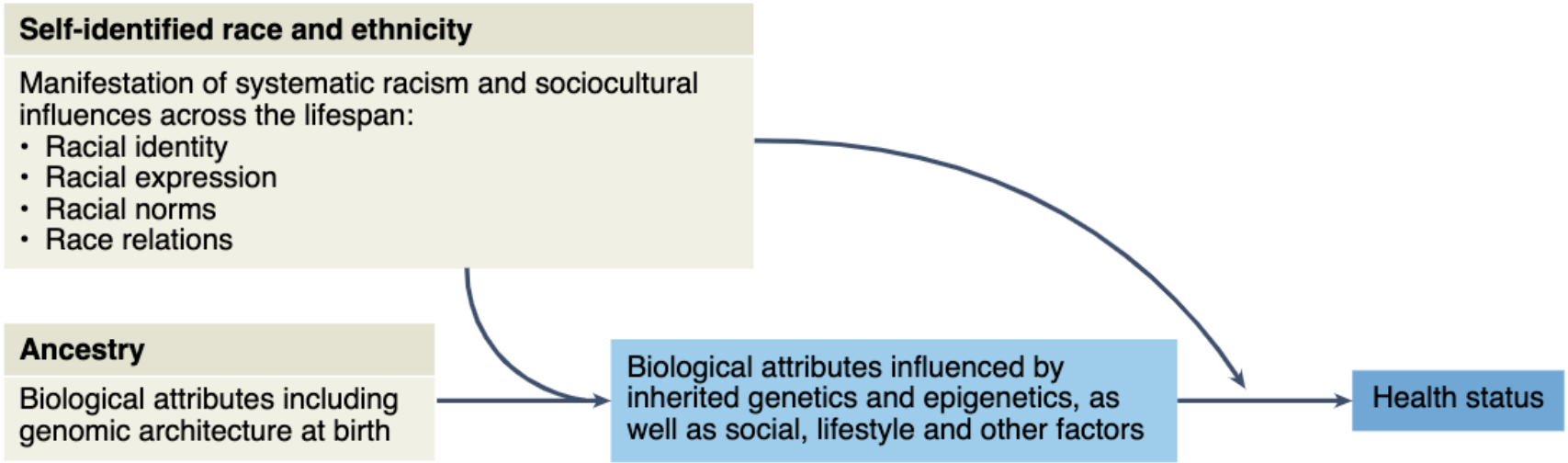
- Human health care
- Farming- livestock and crop production

INADEQUATE INVESTMENT

- Sewage collection and treatment
- Drinking water and hygiene
- Pharmaceutical industry
- Livestock biosecurity

Distinguishing Race from Genetic Ancestry

Self identified race and ethnicity (social construct) and genetic ancestry (genome) impact health in distinct ways



SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Rebbeck, TR et al. (2022) Nat. Med. 28:890-99

The Need for a Health Equity Lens: Race and Ethnicity Inequities in AMR-Related Morbidity and Mortality

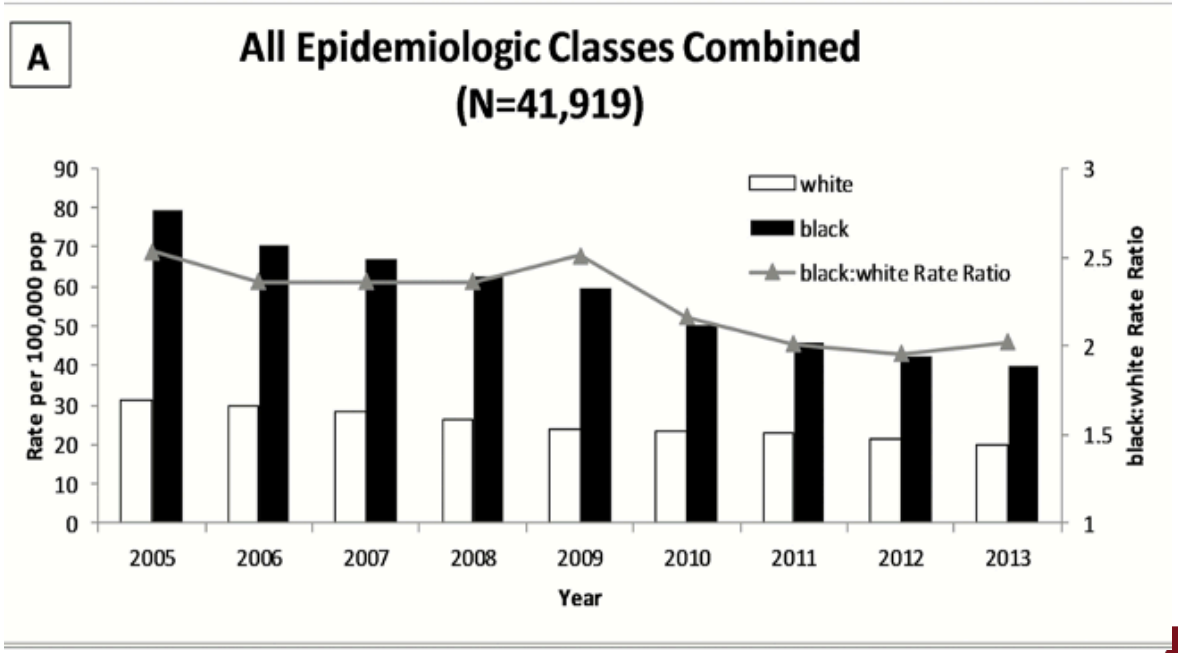
Race and ethnicity are social constructs, social determinants of health influence risk for AMR infections

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Nadimpalli, ML et al. (2021) Nat. Med. 27:187-88.

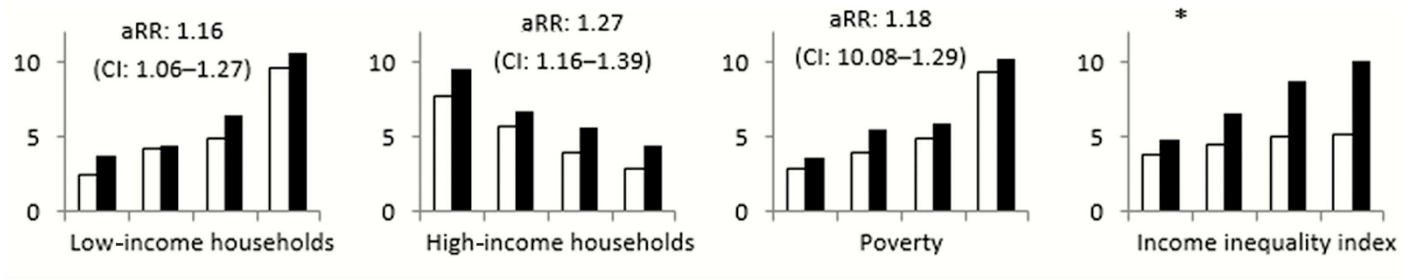
Racial disparities have been identified for invasive methicillin-resistant *Staphylococcus aureus* (MRSA)

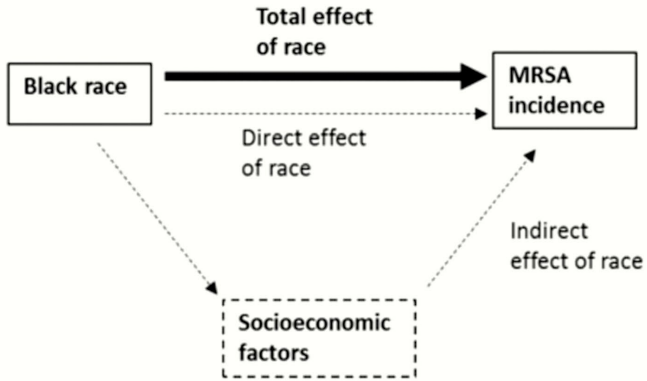
Unadjusted invasive MRSA rates by race, 2005–2014



Gualandi, N. et al (2018) Clin Infect Dis. 67: 1175–1181.

Socioeconomic factors help explain racial inequities in community-associated MRSA





Effect of race	Rate ratio	95% confidence interval
Total	1.68	1.53–1.84
Direct	1.05	.92–1.20
Indirect	1.60	1.44–1.78

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

See, I. et al (2017) Clin Infect Dis. 64: 597–604.

Diverse representation and reporting in randomized controlled trials (RCTs): Why is it important?

EDITORIAL

The Reporting of Race and Ethnicity in Medical and Science Journals
Comments Invited

Annette Flanagin, RN, MA; Tracy Frey, BA; Stacy L. Christiansen, MA; Howard Bauchner, MD

For many years and increasingly in the last year, *JAMA* and the JAMA Network journals have published many important articles addressing disparities and racism in medical educa- ternal review from leading scholars and researchers, who provided thoughtful input and represented diverse opinions (and yet, did not always agree with one another). This revised sec-

2023 omnibus spending bill includes the Diverse and Equitable Participation in Clinical Trials (DEPICT) Act

nature COMMUNICATIONS

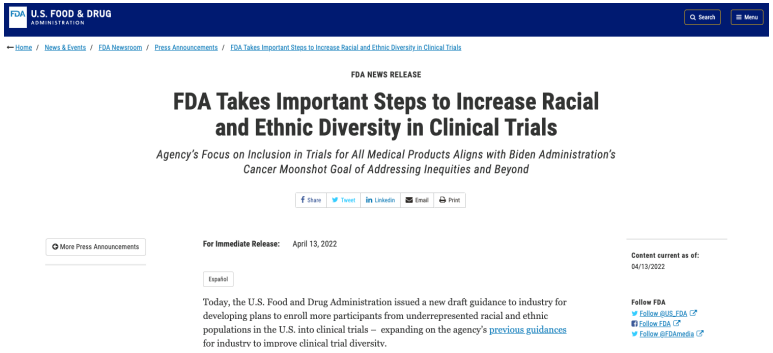
EDITORIAL

https://doi.org/10.1038/s41467-022-30398-1 OPEN

Check for updates

Raising the bar on sex and gender reporting in research

For nearly a decade, Nature Portfolio journals have asked for information about sex and gender in research studies, and more recently, we have also encouraged authors to use the Sex and Gender Equity in Research (SAGER) guidelines in their work. We are now updating our guidance and practice so that authors are more clearly and actively encouraged to report on select items within the SAGER guidelines.



U.S. FOOD & DRUG ADMINISTRATION

Search Menu

Home / News & Events / FDA Newsroom / Press Announcements / FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials

FDA NEWS RELEASE

FDA Takes Important Steps to Increase Racial and Ethnic Diversity in Clinical Trials

Agency's Focus on Inclusion in Trials for All Medical Products Aligns with Biden Administration's Cancer Moonshot Goal of Addressing Inequities and Beyond

Share Tweet LinkedIn Email Print

More Press Announcements

For Immediate Release: April 13, 2022

Español

Today, the U.S. Food and Drug Administration issued a new draft guidance to industry for developing plans to enroll more participants from underrepresented racial and ethnic populations in the U.S. into clinical trials — expanding on the agency's previous guidances for industry to improve clinical trial diversity.

Content current as of: 04/13/2022

Follow FDA
Follow @US_FDA
Follow FDA
Follow @FDAmedia

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Gualandi, N. et al (2018) Clin Infect Dis. 67: 1175–1181.
Flanagin, A. et al (2021) JAMA. 326: 621-27.

Historical benchmarks are needed to ensure that progress can be evaluated

Research Question

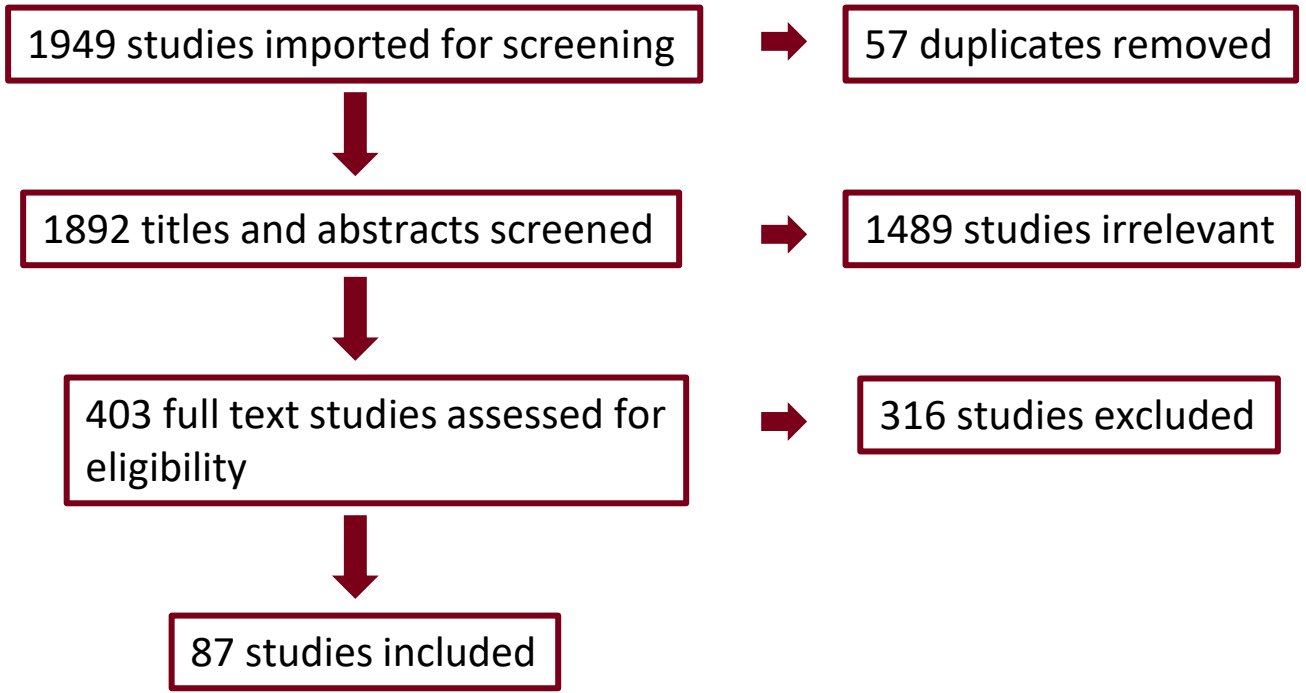
What is the status of demographic reporting and representation in the US-based randomized clinical trials (RCTs) of antibacterial drugs used to treat infections due to *S. aureus*?

- RCTs published 2000-2021 including registrational trials for FDA marketing approval and strategy trials designed to test antibiotics and/or treatment strategies
- Patients diagnosed with *S. aureus* infections where anti-staphylococcal antibiotics are used
  - Acute bacterial skin and skin structure infections (ABSSSIs)
  - Bloodstream infections (BSI)
  - Respiratory tract infections
  - *S. aureus* is a major pathogen

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Study Screening



SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

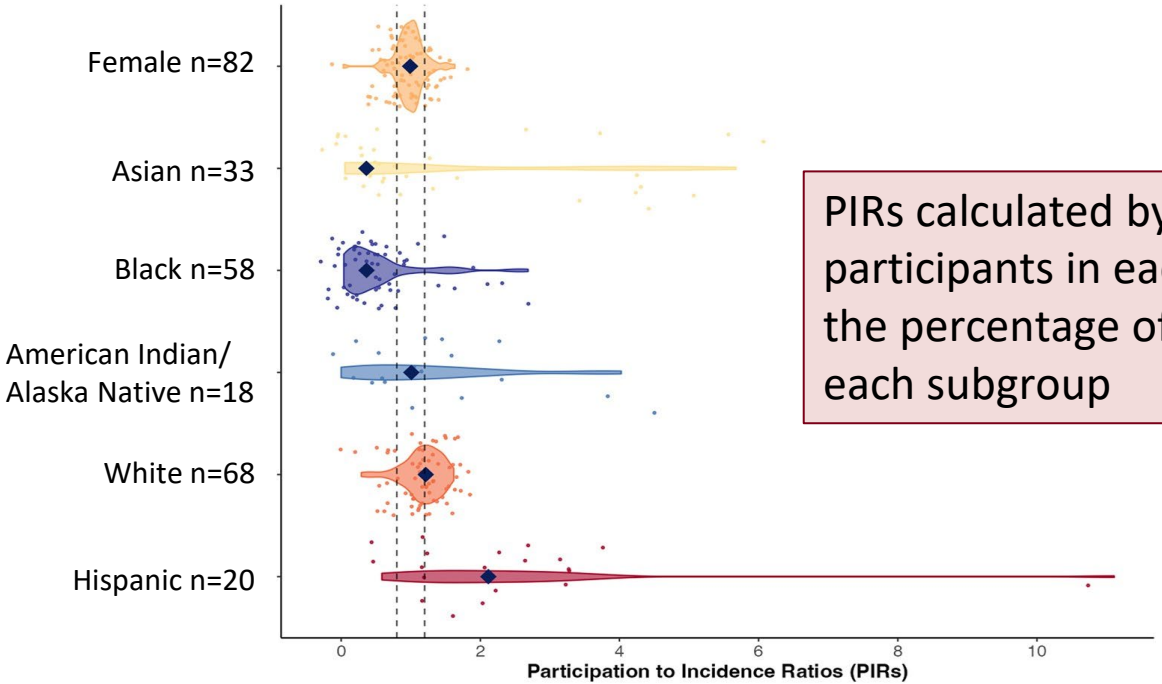
Demographic Breakdown and Reporting in *S. aureus* Trials (n=87)

Demographic characteristic	N	%* (N=38,080)
Participants with sex data	**37,059**	**97.3**
Female	14,388	38.8
Male	22,671	61.2
Participants with race data	**31,402**	**82.5**
Asian	2,091	6.7
Black/African American	3,767	12.0
American Indian/Alaskan Native	117	0.4
White	22,426	71.4
Multi-racial	210	0.7
Unknown race	1,308	4.2
Other	1483	4.8
Participants with ethnicity data	**8,024**	**21.1**
Hispanic/Latino	1,596	19.9
Non-Hispanic/Non-Latino	6,428	80.1

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

Participant to Incidence Ratios (PIRs) for Demographic Subgroups



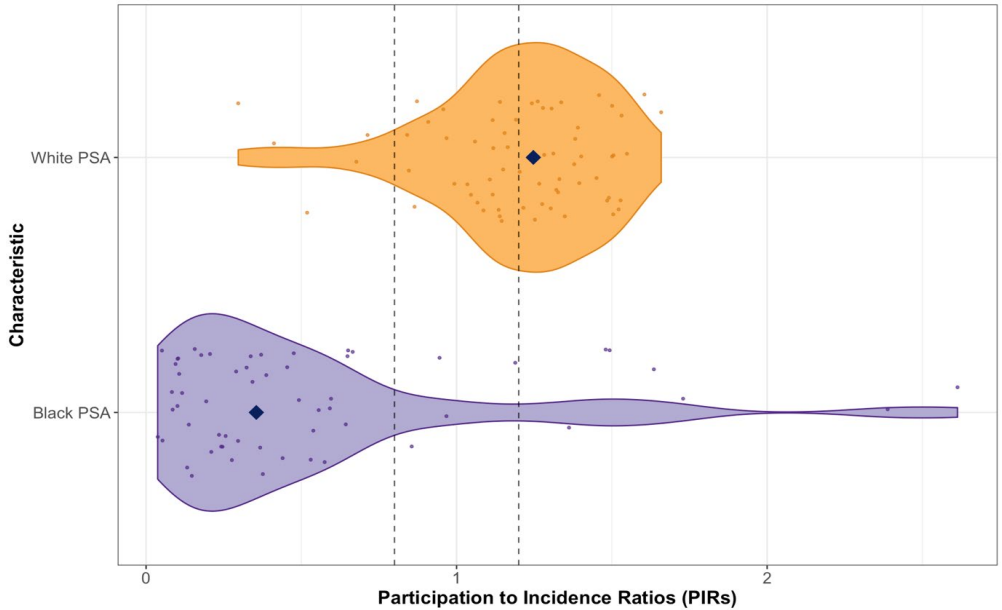
PIRs calculated by dividing the percentage of participants in each demographic subgroup by the percentage of incident MRSA infections in each subgroup

Underrepresentation defined as a PIR <0.8, overrepresentation as PIR >1.2

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

Definitions and incidence change over time, surveillance data are not readily available for many populations



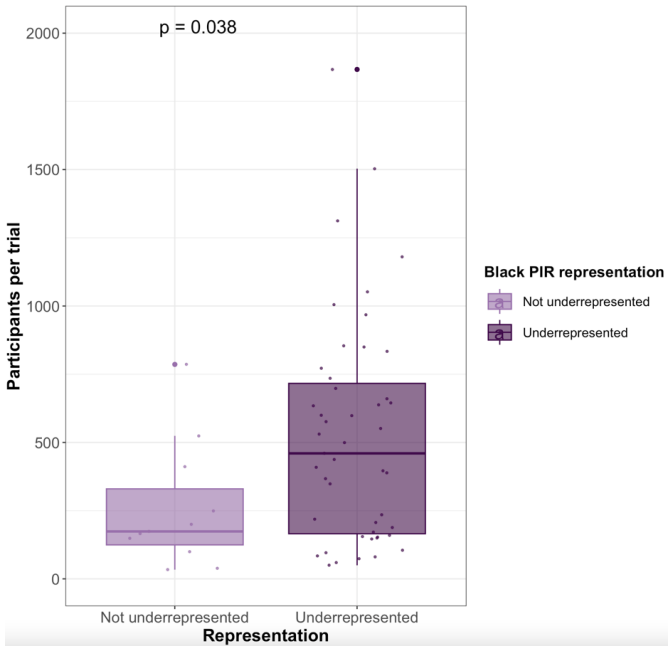
Probabilistic Sensitivity Analysis (PSA) for PIRs for Black and White participants across a range of values from CDC MRSA report data

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

Factors Associated with Underrepresentation of Black Participants in RCTs

Study sample size comparison by Black representation for the PIR



Underrepresentation of Black participants associated with:

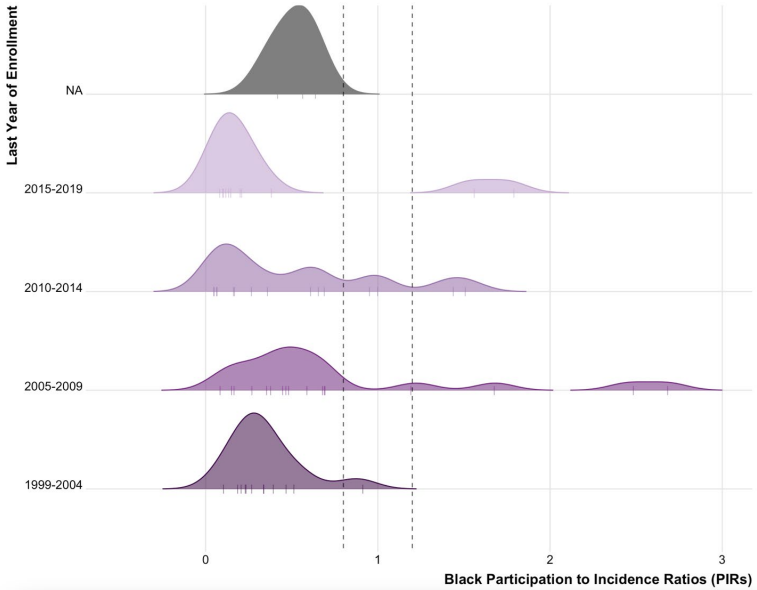
- larger study size
- international sites
- industry sponsorship
- Black participants were more likely to be underrepresented in phase 2/3 vs. phase 4 trials [OR, 4.57; 95% CI: (1.14–18.3)]

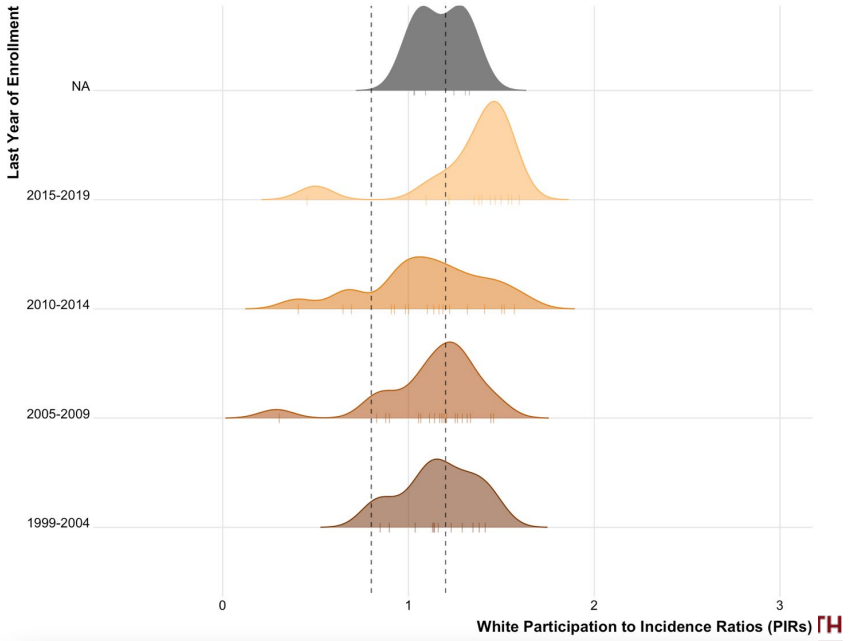
SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

Participation has not significantly changed over time…

Temporal distribution of Black and White participants by the last year of enrollment





UNIVERSITY OF MINNESOTA

Kwon, J. et al (2024) Clin Infect Dis. ciae049, https://doi.org/10.1093/cid/ciae049.

Clinical Infectious Diseases

EDITORIAL COMMENTARY

Robust Performance Metrics for Assessing Equitable Clinical Trial Participant Enrollment: Can We Get There?

Evangeline Green[1] **and Jasmine R. Marcelin**[2,*]

[1]Internal Medicine Residency, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA; and [2]Division of Infectious Diseases, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska, USA

Keywords. clinical trial participants; diversity; pharmacoequity; health equity; equitable enrollment.

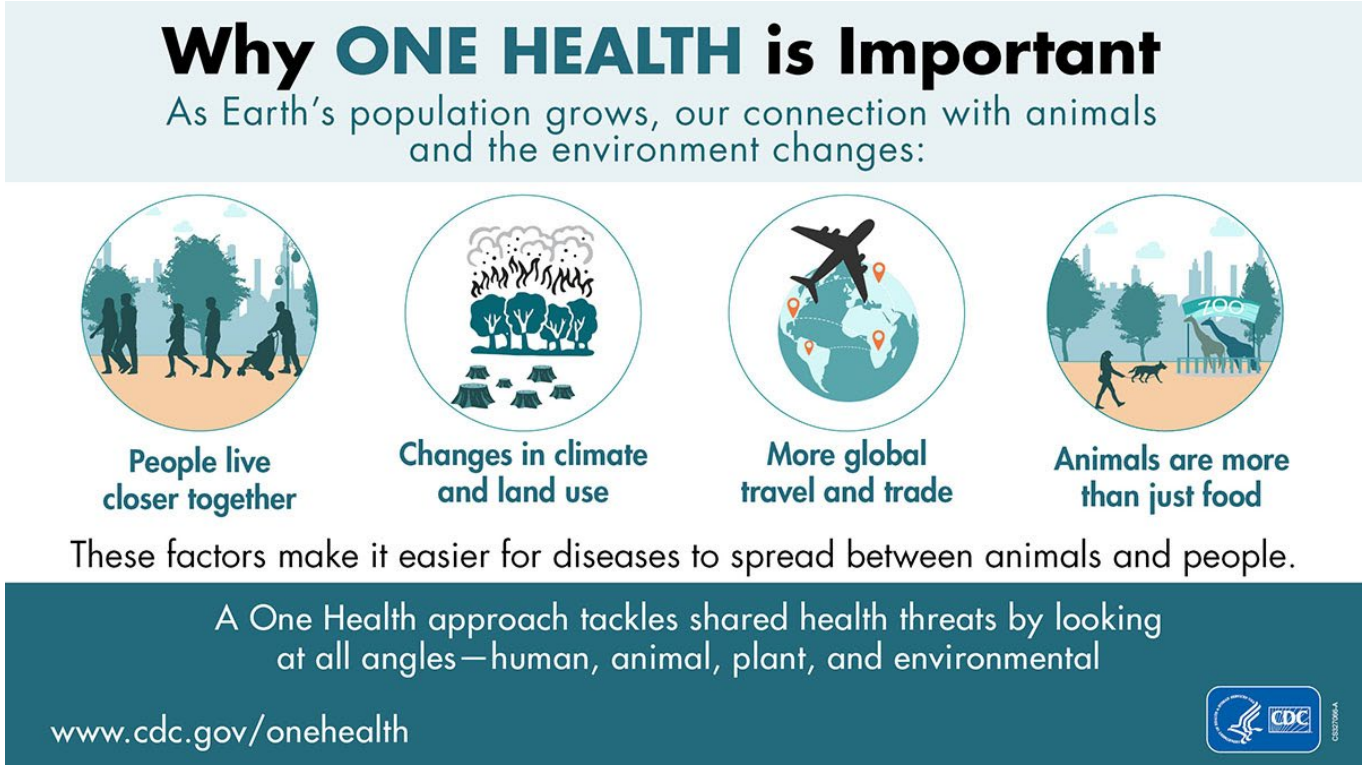
Discussion: How do we ensure that we are achieving appropriate enrollment?

- Should we use US census or incidence data to compare demographic proportions?
- How do we explain that American Indian/Alaskan Native groups are adequately represented, and Hispanic populations are overrepresented?
- Can we accurately calculate PIRs?
  - US vs. international settings
  - Challenges with surveillance data, disease incidence must be known
- What other factors explain inequities in trial participation?

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Clinical Infectious Diseases, 2024; ciae047

Antibiotic Resistance is a One Health Issue



SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

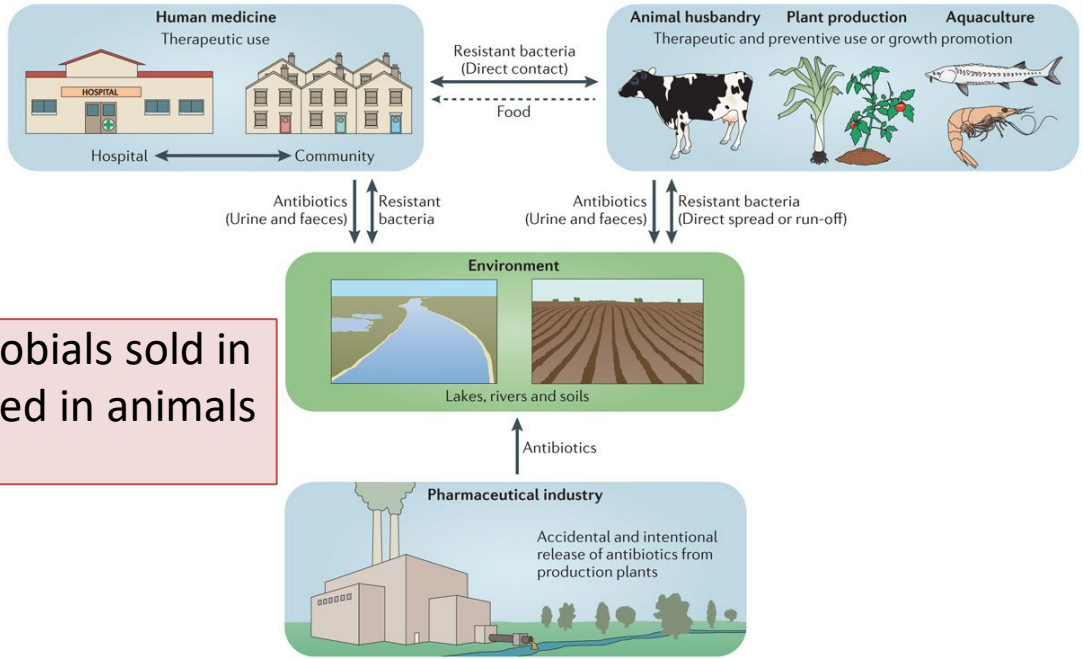
Health equity has historically been discussed and reserved for human health

"An equity approach to One Health asks us to look at systematic processes that make unfair or unjust access or opportunities to benefit from the determinants of health across species and generations"

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Stephen, C (2020) *Animals Health and Society*.https://doi.org/10.1201/9780429320873

Ecology of Antibiotics and Antibiotic Resistance



The majority of antimicrobials sold in the United States are used in animals raised for food

20-80% of antibiotics are released into the environment, sub-MIC concentrations are found in humans, farms, and in the environment

Andersson and Hughes (2014) *Nat Rev Microbiol*. 12: 465-78

Colistin Resistance: A Cautionary Tale

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Lancet Infect Dis 2016; 16: 161-68

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia*

EXPERT REVIEW OF ANTI-INFECTIVE THERAPY, 2016
VOL. 14, NO. 9, 785–788
http://dx.doi.org/10.1080/14787210.2016.1216314

Taylor & Francis
Taylor & Francis Group

EDITORIAL

On the path to untreatable infections: colistin use in agriculture and the end of 'last resort' antibiotics

Richard R. Watkins[a,b], Tara C. Smith[c] and Robert A. Bonomo[d,e,f,g]

[a]Department of Internal Medicine, Northeast Ohio Medical University, Rootstown, OH, USA; [b]Division of Infectious Diseases, Cleveland Clinic Akron General Medical Center, Akron, OH, USA; [c]Department of Biostatistics, Environmental Health Sciences, and Epidemiology, College of Public Health, Kent State University, Kent, OH, USA; [d]Medicine and Research Services, Louis Stokes Cleveland VA Medical Center, Cleveland, OH, USA; [e]Department of Medicine, Case Western Reserve University School of Medicine, Cleveland, OH, USA; [f]Department of Pharmacology, Case Western Reserve University School of Medicine, Cleveland, OH, USA; [g]Department of Molecular Biology and Microbiology, Case Western Reserve University School of Medicine, Cleveland, OH, USA

ARTICLE HISTORY Received 30 June 2016; Accepted 20 July 2016; Published online 1 August 2016

GERMINATION *A Blog by Maryn McKenna*

Apocalypse Pig: The Last Antibiotic Begins to Fail

POSTED SAT, 11/21/2015

A pig being home-raised for a festival in China. PHOTOGRAPH BY CLEMSON, FLICKR (CC).

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

January 1, 2017: U.S. FDA banned medically important antibiotics for growth promotion

- FDA guidance prohibits the over-the-counter sale of medically important antimicrobials for use in farming
- 54% of antimicrobials used in US animal agriculture are medically important
- ~1/3 of antibiotics approved for use in animals lack restrictions on prescription duration
- Tylosin phosphate (macrolide) frequently given in feed to prevent liver abscesses
- Ionophores are still used for growth promotion and are the second most widely used class of antibiotics in animals in the United States

https://www.fda.gov/animal-veterinary/cvm-updates/fda-releases-annual-summary-report-antimicrobials-sold-or-distributed-2020-use-food-producing

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

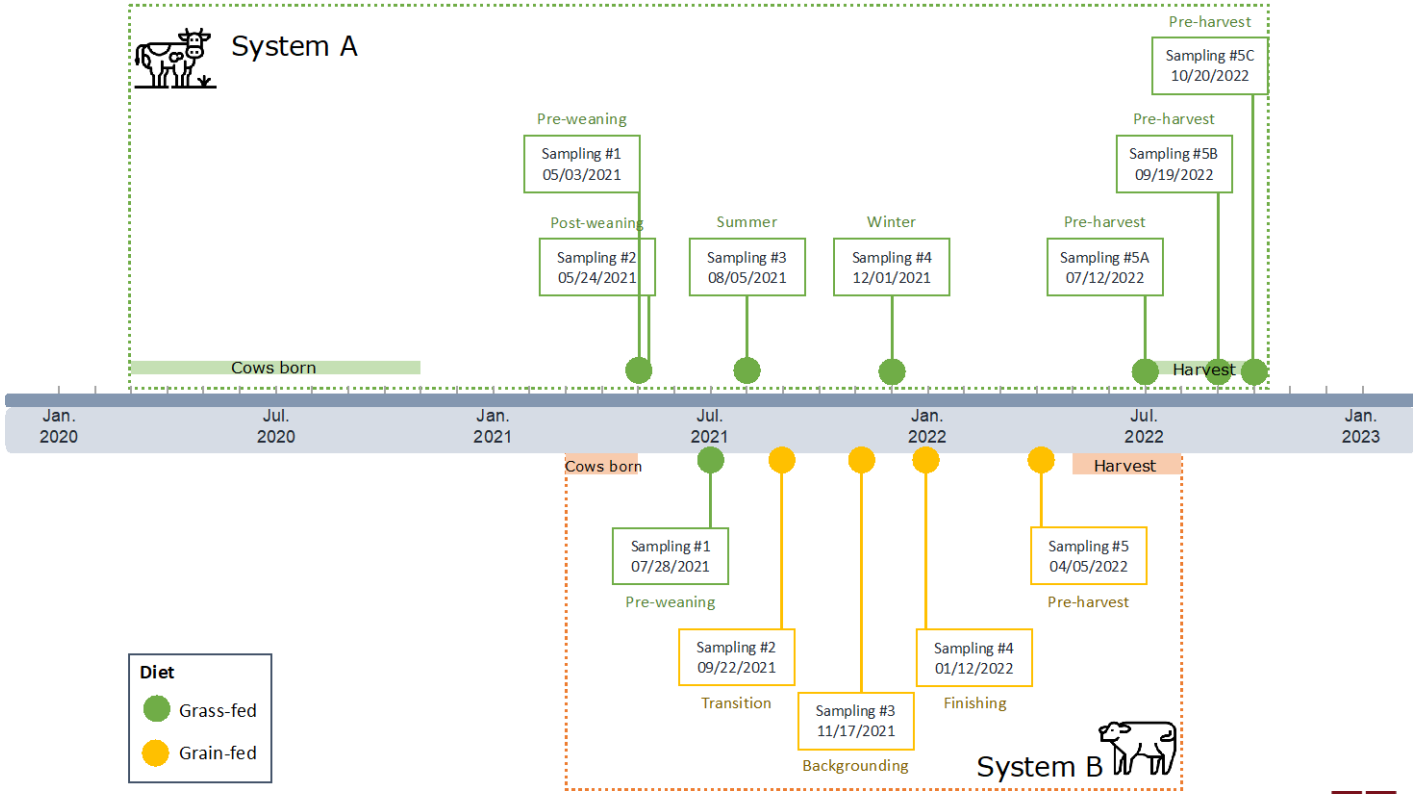
Comparison of the digestive tract resistome in cattle raised in grass-fed vs. conventional production systems

- Grass-fed diets have been recommended over grain-fed diets as a way to reduce AMR
- Antimicrobial resistance could concentrate in animal-specific pathogens and the extent of spillover into humans is a subject of debate

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

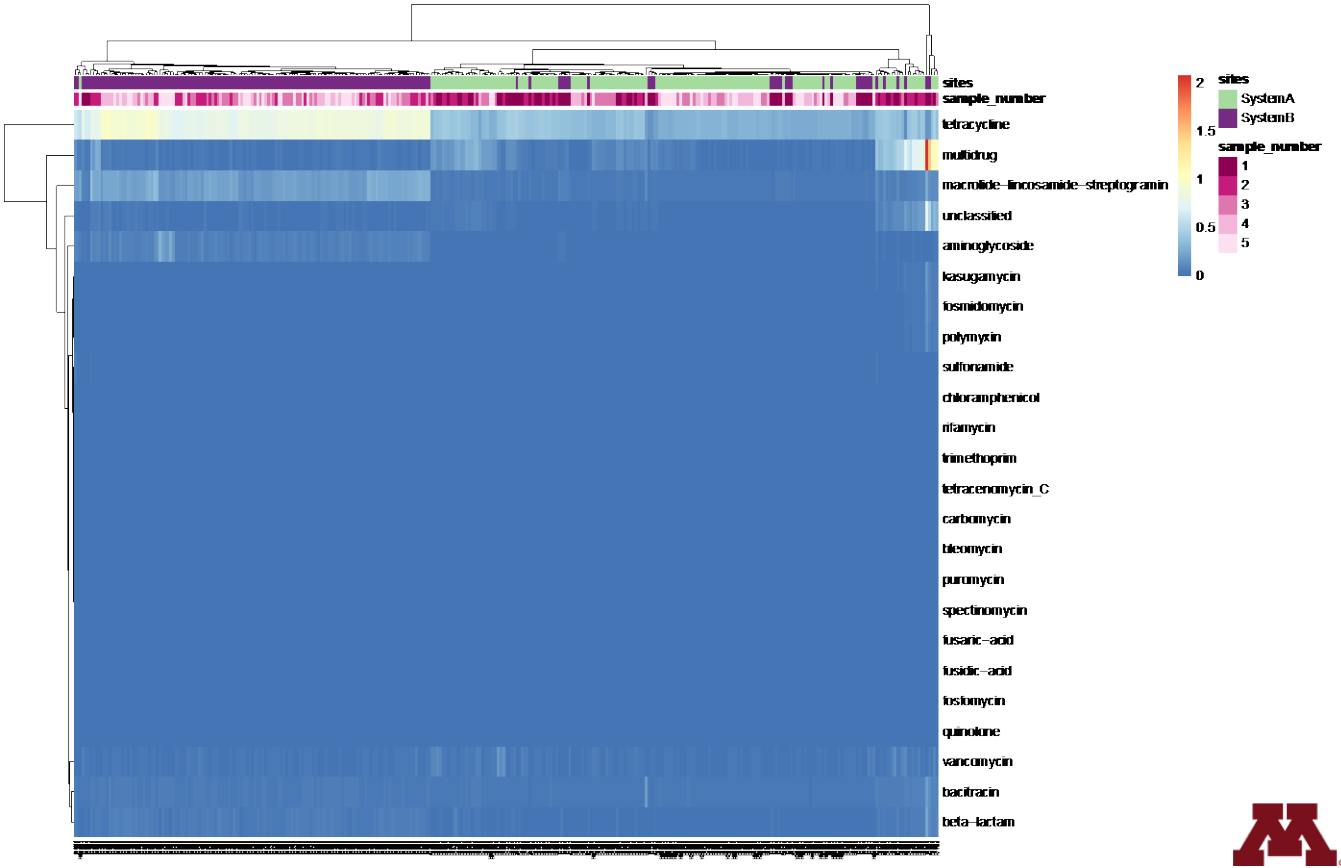
Kwon, J et al. 2024; *Submitted*.

Sampling Scheme Timeline for Cattle by System



Kwon, J et al. 2024; *Submitted*.

Antibiotic Resistance Genes (ARGs) Cluster by System



SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J et al. 2024; *Submitted*.

Cattle Characteristics

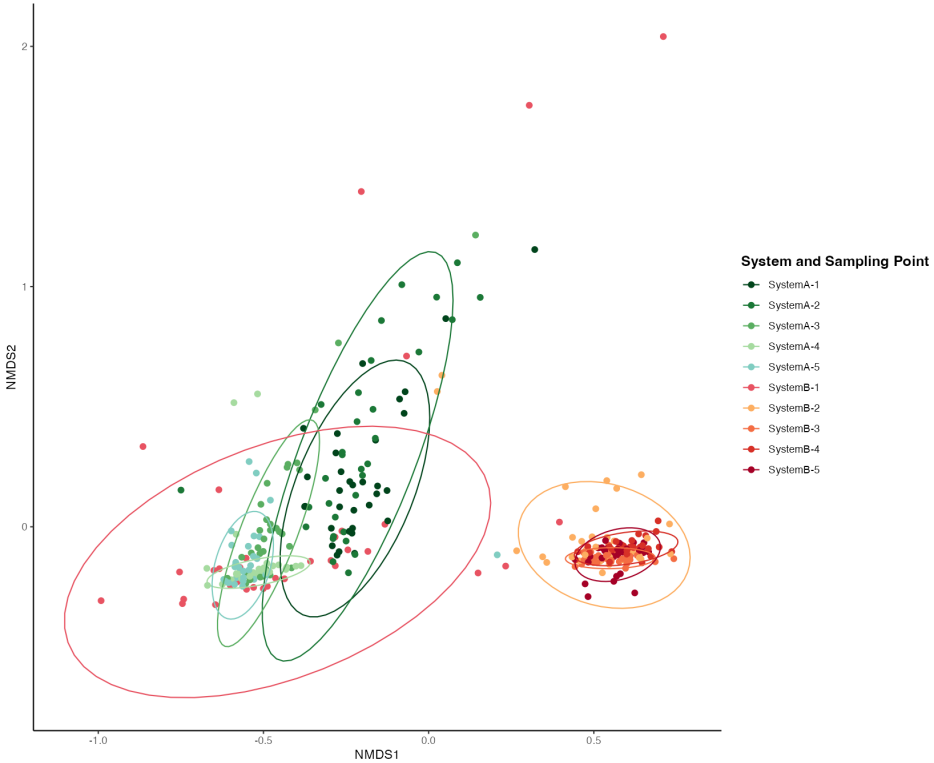
	S1	S2	S3	S4	S5
System A					
Age days (range)	259 (170, 414)	280 (191, 435)	353 (264, 508)	471 (382, 626)	694 (605, 849)
Weight lbs. (range)	416 (234, 558)	461 (248, 598)	447 (236, 616)	517 (254, 704)	639 (392, 840)
Diet	Pre-weaning	Grazing	Grazing	Bale grazing	Grazing
No. received/ sequenced	33	33	33	33	30
System B					
Age days (range)	126(587, 146)	182 (143, 202)	238 (199, 258)	294 (255, 314)	377 (338, 397)
Weight lbs. (range)	353 (260, 466)	431 (302, 540)	623 (484, 762)	831 (678, 988)	1,173 (996,1355)
Diet	Pre-weaning	Transition*	Backgrounding*	Finishing*	Finishing*
No. received/ sequenced	34	33	33	33	33

*Rumensin (ionophore) supplement

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J et al. 2024; *Submitted*.

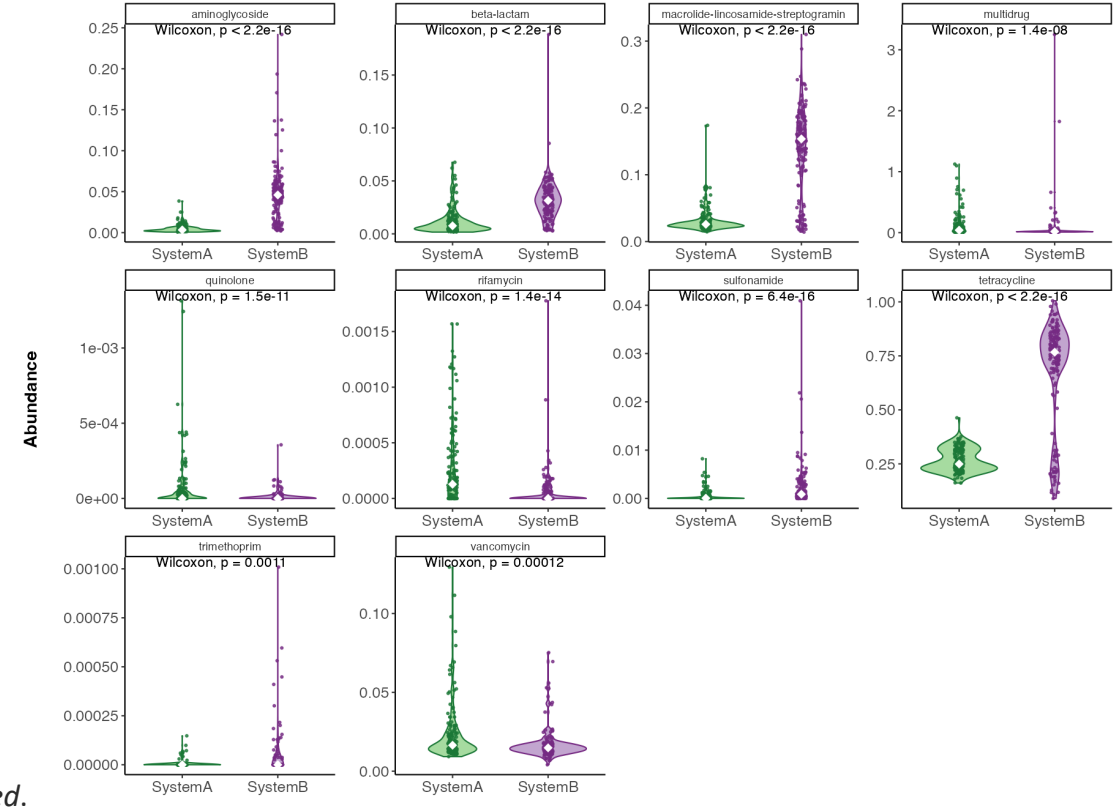
Beta-diversity of Type-level Antibiotic Resistance Genes (ARGs) by System and Sampling Point



- System B-1 pre-weaning samples overlap with System A samples
- Clear distinction between system A and B 2-5 samples
- Clustering by the system was confirmed using PERMANOVA ($P < 0.001$; $n = 4000$ permutations)

Kwon, J et al. 2024; *Submitted*.

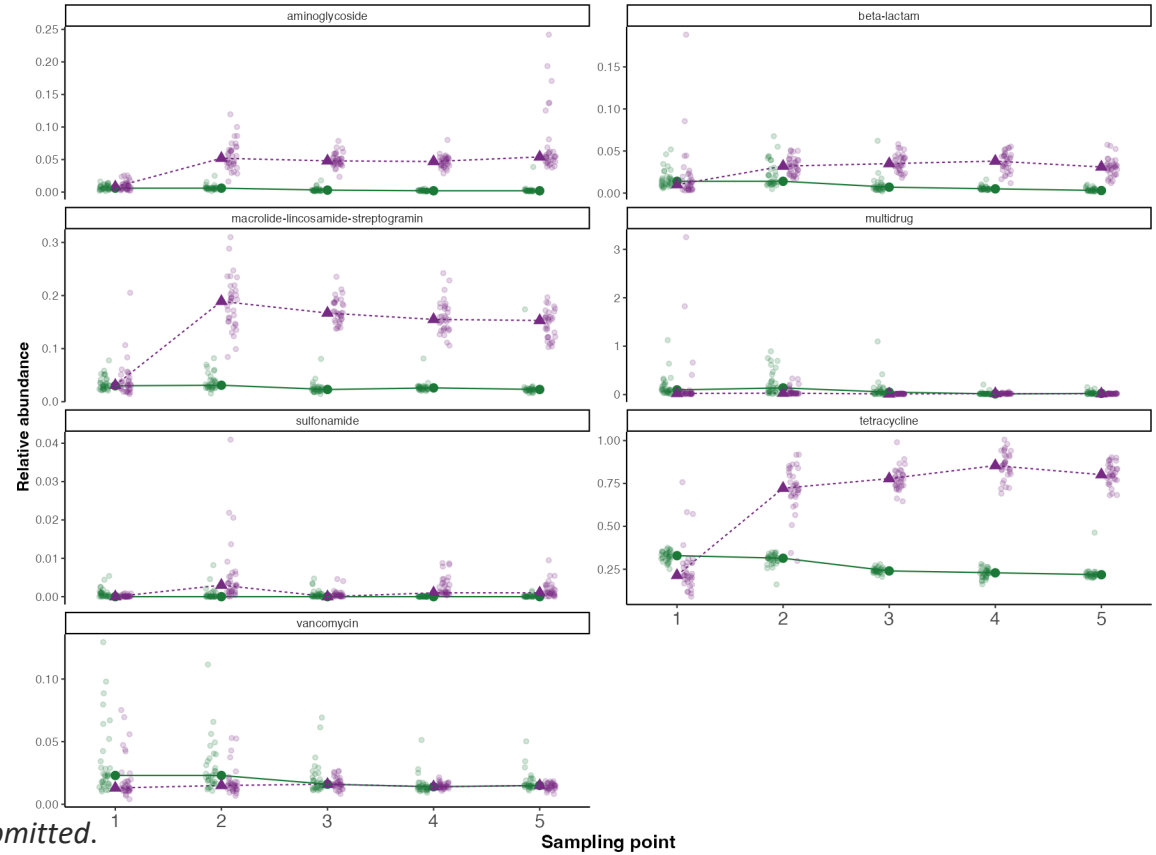
Abundance of Type Level Antibiotic Resistance Genes for Clinically Relevant Antibiotics



Kwon, J et al. 2024; *Submitted*.

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

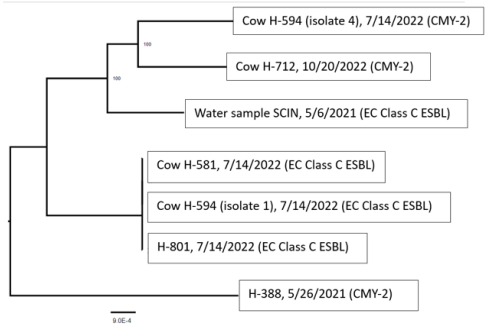
Temporal trends in Select ARGs by System



Kwon, J et al. 2024; *Submitted*.

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Extended Spectrum Beta-lactamase (ESBL) *E. coli*



- ESBL *E. coli* isolates were recovered from five steer from system A at three different time points
- Three isolates were ST23, which has been identified in agricultural products (e.g., chicken) and as a cause of urinary tract infections and bloodstream infections in humans
- Carriage of ESBL-*E. coli* appears to be transient and was not detected in system A cattle or any carcass samples
- Potential human pathogens such as *Salmonella enterica*, *Enterococcus faecalis*, and *C. difficile* were not identified by shotgun metagenomic sequencing

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA

Kwon, J et al. 2024; *Submitted*.

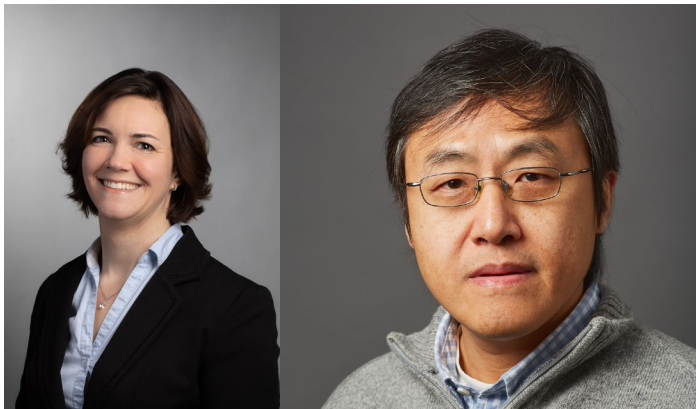
Discussion

- These and other data show that the cattle fecal resistome is usually dominated by ARGs for tetracycline and macrolide antibiotics
- Specific farm management practices may provide a path to reduce AMR
- Reductions in the use of antibiotics in agriculture will have to be part of a multifaceted approach to reduce resistance
- The veterinary and medical challenges that arise from AMR need to be considered along with the ethical treatment of animals and the need to sustainably and affordably feed the human population
- Future studies should focus on the development of risk and ranking models for ARGs and consider the impact of ionophore use on the microbiota and resistome

Questions?

Thank you!

- Green Acres Foundation
- OSU/Eastern Agricultural Research Station
- Cattle
- Marília Chiavegato
- Yong Kong
- Windy Tanner
- Keli Sorrentino
- Martina Wade
- Jiye Kwon
- Yale Center for Genome Analysis



Financial Support

- Research reported in this presentation was supported by:
  - The National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Numbers HHSN27200018, HHSN27200022, HHSN27200011, HHSN27200006, and UM1AI104681
  - Green Acres Foundation
- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Green Acres Foundation

ARLG
Antibacterial Resistance Leadership Group

SCHOOL OF PUBLIC HEALTH
UNIVERSITY OF MINNESOTA