UWTASP tele-antimicrobial stewardship program | echo

November 5th, 2024

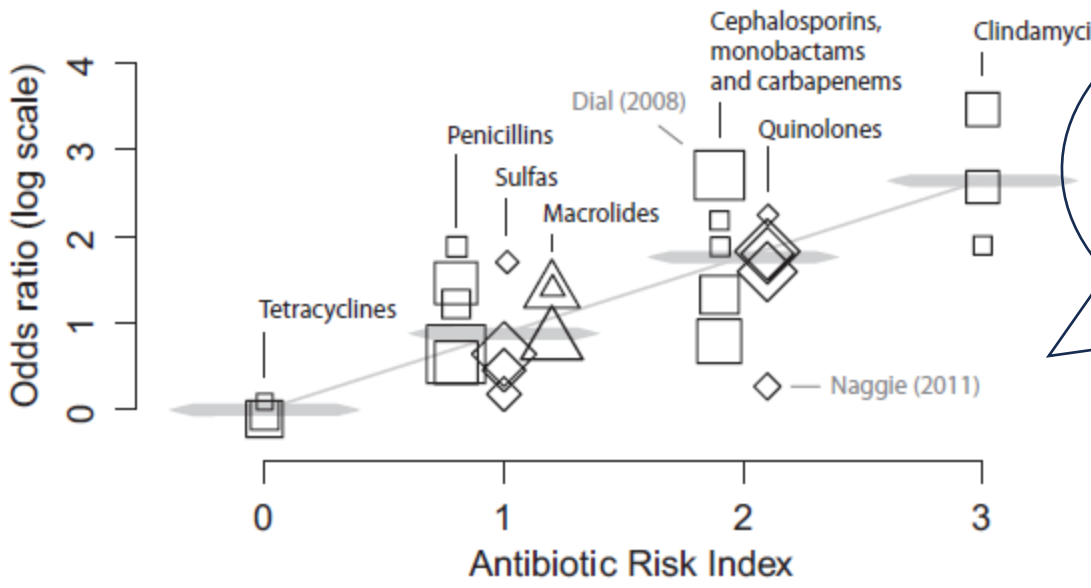
IDWeek 2024 Highlights

- Joanne Huang, PharmD
- Jeannie Chan, PharmD, MPH
- John Lynch, MD, MPH

Project ECHO

C. difficile risk: selection vs duration

- Mixed literature classifying “highest risk”
- Inherent bias in CDI studies
- Initial certainty of adequate coverage
- Most patients end up on more than one antibiotic



-Observational bias?
-Accuracy of identifying CDI?
-Other factors impacting microbiome diversity?

Brown Kaet al. Antimicrob Agents Chemother. 2013 May;57(5):2326-32.

Microbiome 101

- Healthy adult microbiome is comprised of 4 phylum:
  - Bacteroidetes/Firmicutes>Actinobacteria/Proteobacteria
- C difficile requires dysbiosis to cause active disease.
- Specific gut microbiota are required for short chain fatty acid metabolism (Actinobacteria and others)
- Specific gut microbiota are required for bile acid conversion. (Lachnospirales and others)

Bidell MR, Hobbs ALV, Lodise TP. Gut microbiome health and dysbiosis: A clinical primer. Pharmacotherapy. 2022 Nov;42(11):849-857.

Secondary bile acids = good
Primary bile acids = bad

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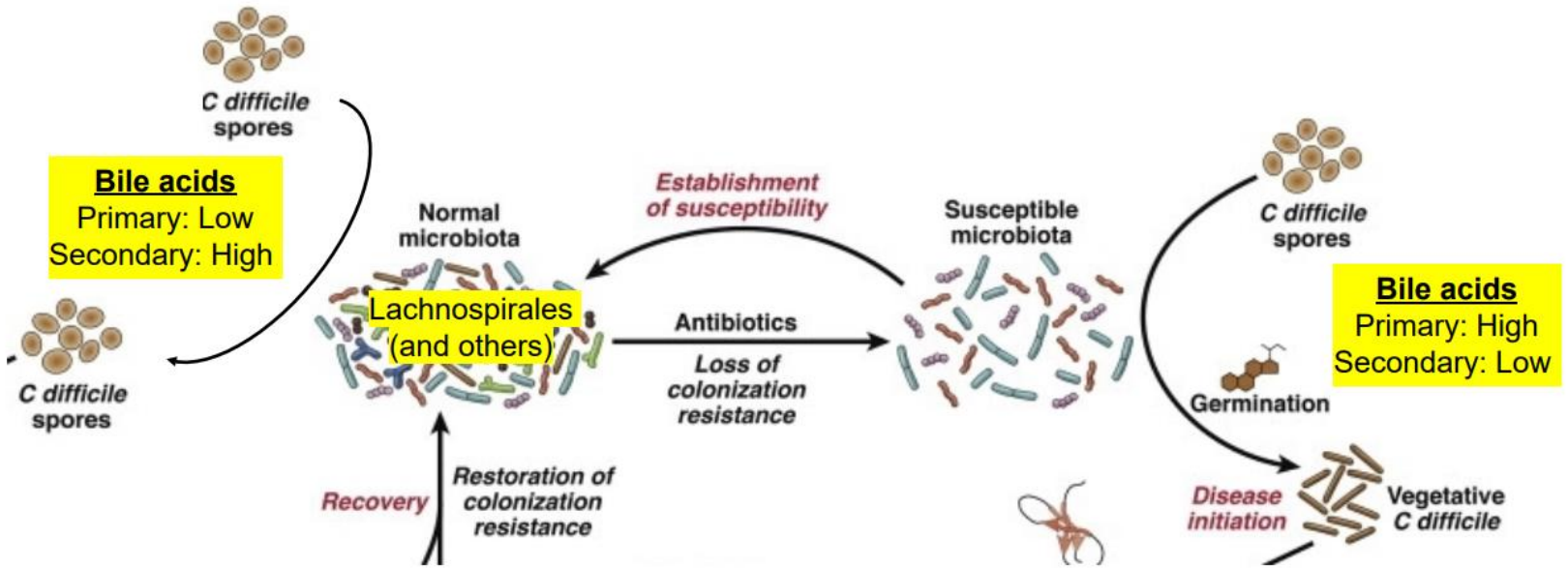

Britton RA, Young VB. Gastroenterology. 2014;146:1547-53.
Slide credit: Jinhee Jo Idweek 2024

Omadacycline preserved ratios of Actinobacteria and Firmicutes

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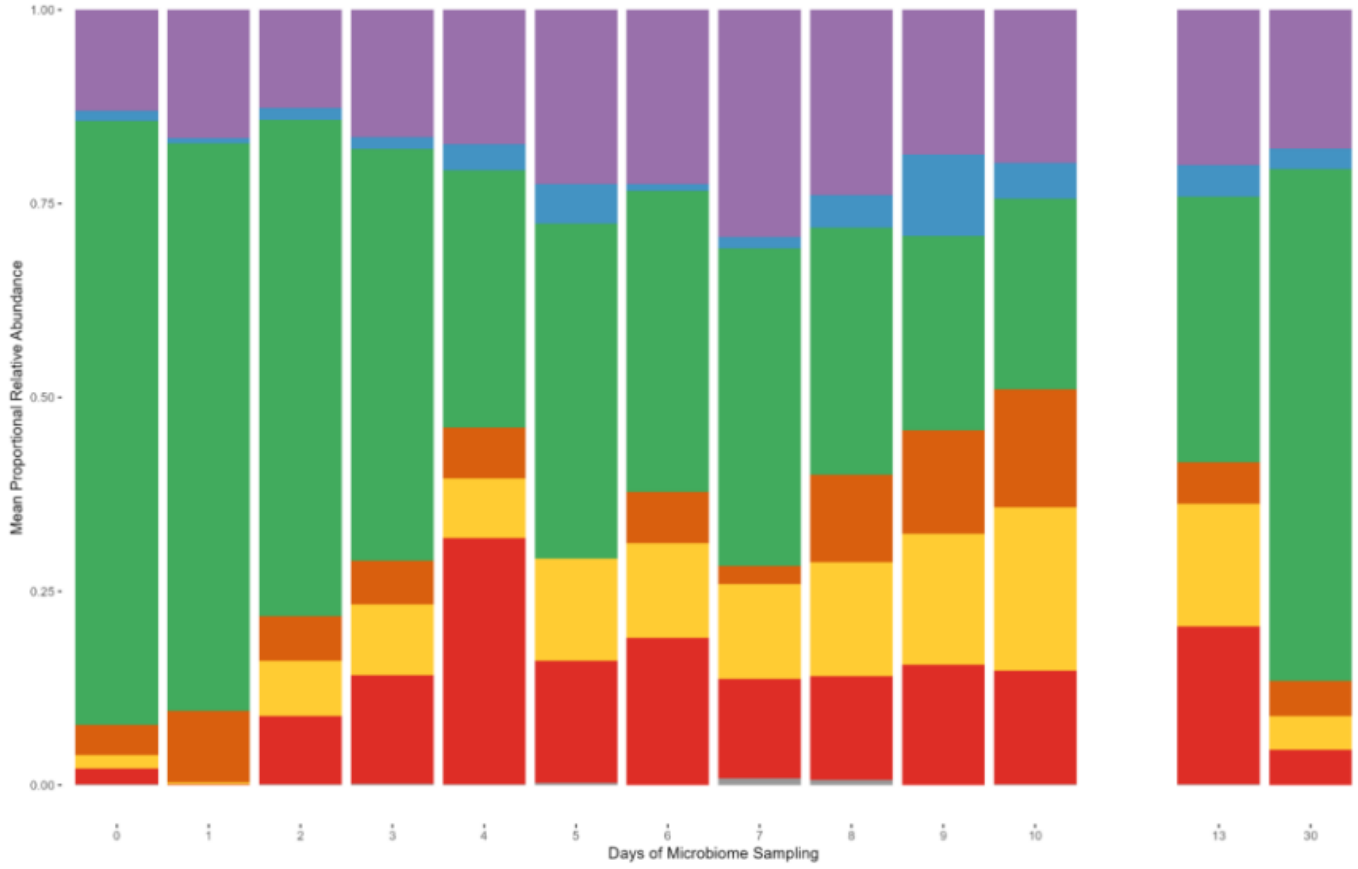
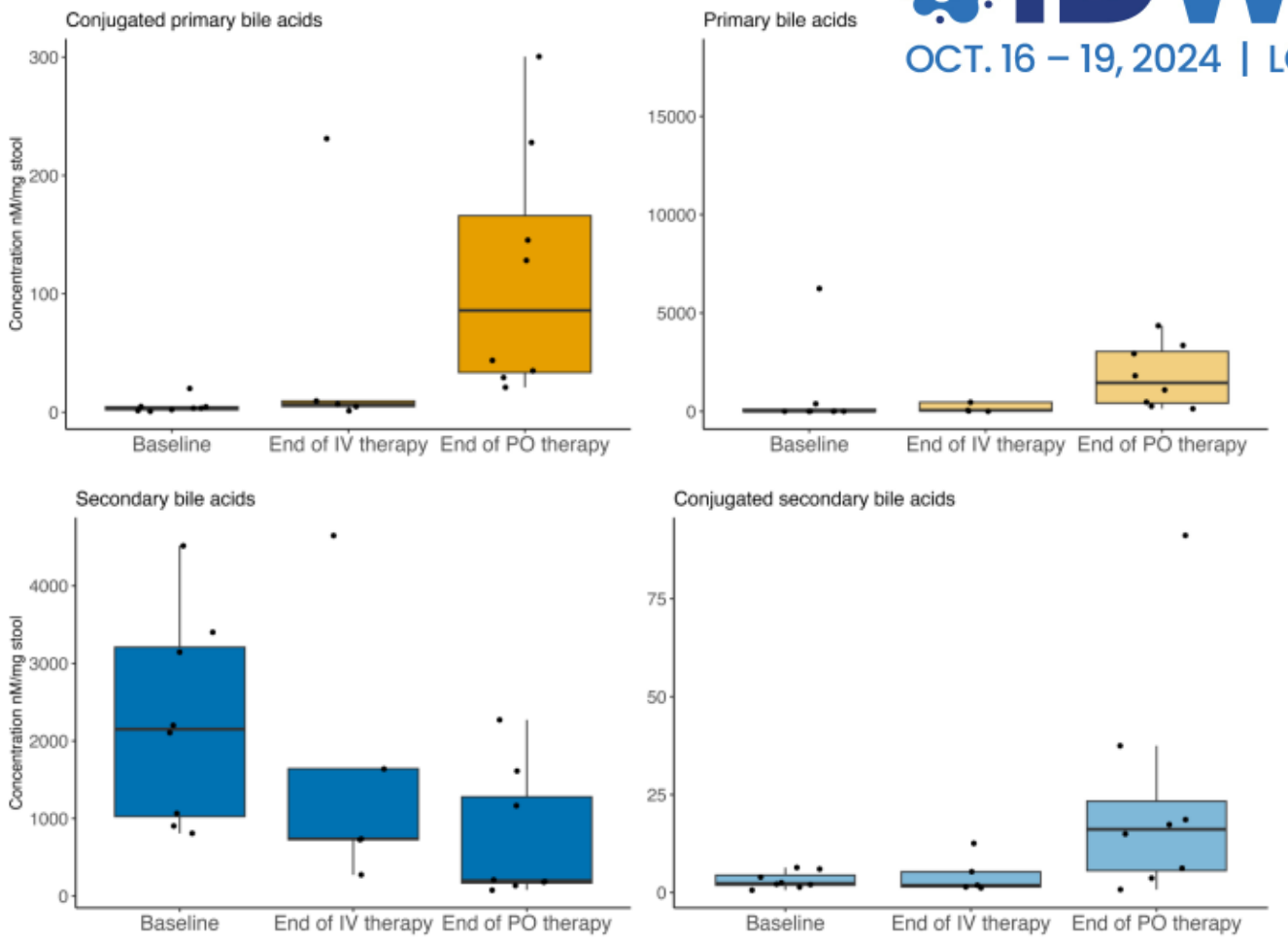


Actinobacteria

Firmicutes

Slide credit: Jinhee Jo Idweek 2024

Omadacycline preserved secondary bile acids



Slide credit: Jinhee Jo Idweek 2024

Conclusions

- Omadacycline preserved key microbiome taxa (Actinobacteria, Lachnospirales) supporting possible mechanisms of CDI protection.

The Journal of Infectious Diseases
MAJOR ARTICLE

Fecal Pharmacokinetics and Gut Microbiome Effects of Oral Omadacycline Versus Vancomycin in Healthy Volunteers

Jinhee Jo,[1] Chenlin Hu,[1] Khurshida Begum,[1] Weiqun Wang,[1] Thanh M. Le,[1] Samantha Agyapong,[1] Blake M. Hanson,[2] Hossaena Ayele,[2] Chris Lancaster,[1] M. Jahangir Alam,[1] Anne J. Gonzales-Luna,[1] and Kevin W. Garey[1,©]

[1]Department of Pharmacy Practice and Translational Research College of Pharmacy, University of Houston; and [2]UTHealth Houston School of Public Health, University of Texas Health Science Center at Houston, Houston, Texas

- Dysbiosis observed w/ vancomycin causes bile acid and microbiota imbalances – increased CDI risk?

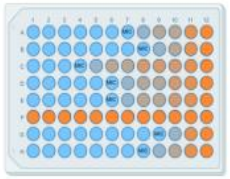
Aminopenicillins: Are They Still a Treatment Option for Ampicillin-Resistant Enterococcus Urinary Tract Infections?

Treatment Conundrums: *Not Always Black and White*

Navaneeth Narayanan, PharmD, MPH, BCIDP
Clinical Associate Professor | Rutgers Health
Infectious Diseases Pharmacist | RWJBarnabas Health
IDWeek 2024 | Los Angeles, CA

Are Aminopenicillins a Treatment Option for Ampicillin-Resistant *Enterococcus* UTI?

What does “resistance” really mean?



- CLSI Interpretative Category Definition

MIC is too high for drug concentrations to overcome/inhibit

Known resistance mechanism is likely present

Lack of reliable studies showing clinical efficacy

Serum Concentration

Antimicrobial Agent	MIC Breakpoints (µg/mL)	
	S	R
Ampicillin	≤8	≥16

Urine concentration that matters!

Translating a Translational Science: **Urine PK/PD**

PK/PD index	PK/PD Basics	PK/PD target
%*f*T>MIC		~30-50%

Why is it worth trying to translate plasma PK/PD into urine PK/PD?

NEJM 1974

SERUM VERSUS URINARY ANTIMICROBIAL CONCENTRATIONS IN CURE OF URINARY-TRACT INFECTIONS

THOMAS A. STAMEY, M.D., WILLIAM R. FAIR, M.D., MARY M. TIMOTHY, MARCIA A. MILLAR, GLADYS MIHARA, AND YVONNE C. LOWERY

*"We conclude that **cure of urinary infections** depends upon **antimicrobial concentrations in the urine** rather than in the serum..."*

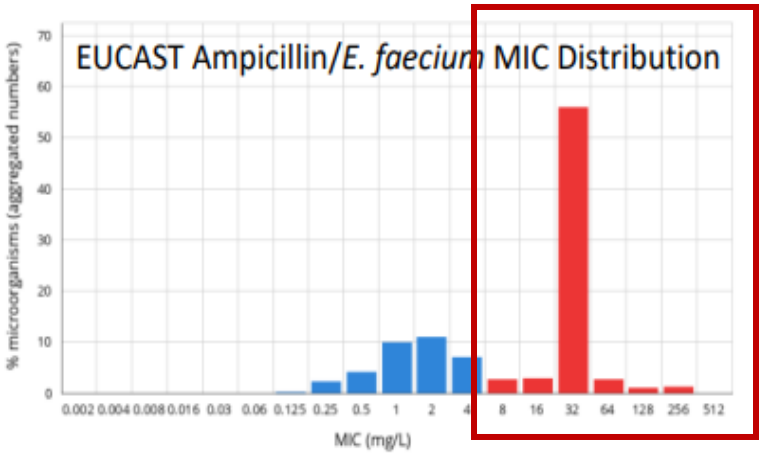
Moxifloxacin	Nitrofurantoin
↑ plasma [ ]	↓ plasma [ ]
↓ urine [ ]	↑ urine [ ]
Tx for UTI? ⊘	**Tx for UTI?** ✓

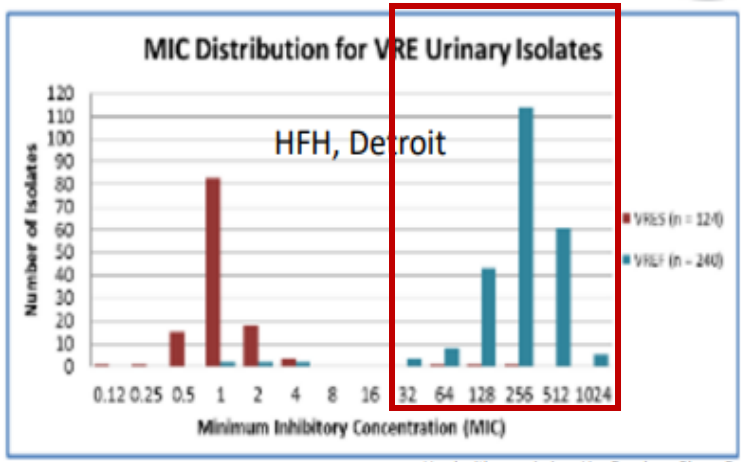
https://www.eucast.org/publications-and-documents/consultations

Amoxicillin achieves high urinary concentration

Translating a Translational Science: Urine PK/PD

Microbiology

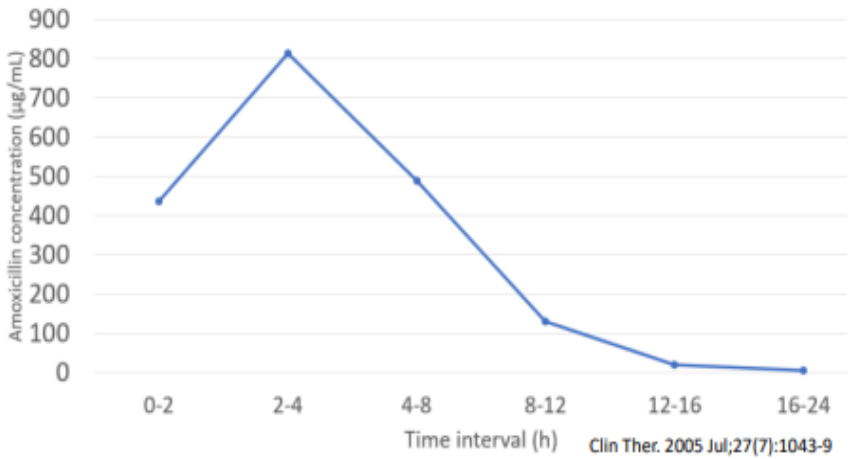




Used with permission: Lisa Dumkow, PharmD

Pharmacokinetics

Mean amoxicillin concentration (µg/mL) of sustained-release amoxicillin-clavulanic acid 2000/125 mg in healthy volunteers (n=12)



Clin Ther. 2005 Jul;27(7):1043-9

Study	Avg. Urine Conc. for AMOXICILLIN
Sutherland (1972)	250 mg (0-6 h): **580** µg/mL 500 mg (0-6 h): **1,100** µg/mL
Bodey (1972)	250 mg (0-6 h): **482** µg/mL 500 mg (0-6 h): **1,579** µg/mL 1000 mg (0-6 h): **3,313** µg/mL
Cole (1978)	250 mg (0-2 h): **432** µg/mL (2-4 h): **516** µg/mL (4-6 h): **94** µg/mL

Am J Health-Syst Pharm. 2022;79:1056-106

Clinical Evidence Gold Standard

FDA Guidance

Uncomplicated Urinary Tract Infections: Developing Drugs for Treatment
Guidance for Industry

We recommend the following inclusion and exclusion criteria:

- Patients should be adult females and, if appropriate, adolescent females with evidence of pyuria (see section III.B.2., Clinical Microbiology Considerations) and at least two of the following signs or symptoms of uUTI:
  - Dysuria
  - Urinary frequency
  - Urinary urgency
  - Suprapubic pain

Urinary symptoms

The primary efficacy endpoint should be based on a responder outcome of clinical and microbiologic response.

- **Clinical and microbiologic response:** Resolution of the symptoms of uUTI (see section III.B.1., Clinical Trial Designs, Populations, and Enrollment Criteria) present at trial entry (and no new symptoms) and the demonstration that the bacterial pathogen found at trial entry is reduced to fewer than 10^3 CFU/mL on urine culture (microbiologic response) assessed at a fixed time point after randomization that is based on the duration of investigational antibacterial drug therapy and half-life of the investigational drug.

Clinical + Microbiologic response

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/uncomplicated-urinary-tract-infections-developing-drugs-treatment-guidance-industry

Uncertainty of clinical evidence

So, what's the rub? *Dealing with uncertainty*

- Small sample size → underpowered
- Varying infection and outcome definitions
- Missing outcome data (lack of f/u testing)
- Selection bias
- Confounding by indication

Conclusion

Uncomplicated cystitis only
No concomitant bacteremia
Not severely ill (not in ICU)

Suppress AST results for urine VRE isolates
Add comment (**HFH example**: *Ampicillin IV or amoxicillin orally are predictably reliable for treatment of uncomplicated enterococcal UTI*)

PK/PD evidence is rough but compelling enough – leans in favor of AP treatment for amp-R enterococcal cystitis

Clinical evidence has low-moderate certainty but biologically plausible, consistent signal, real-world use

Risk with implementation is likely low and may provide simplification for clinical micro lab

Diagnostic Stewardship: order (and treat) the urine culture ONLY if there is a ***true*** clinical indication

ADAPTATIONS OF MICROBIAL POPULATIONS IN THE ARCTIC

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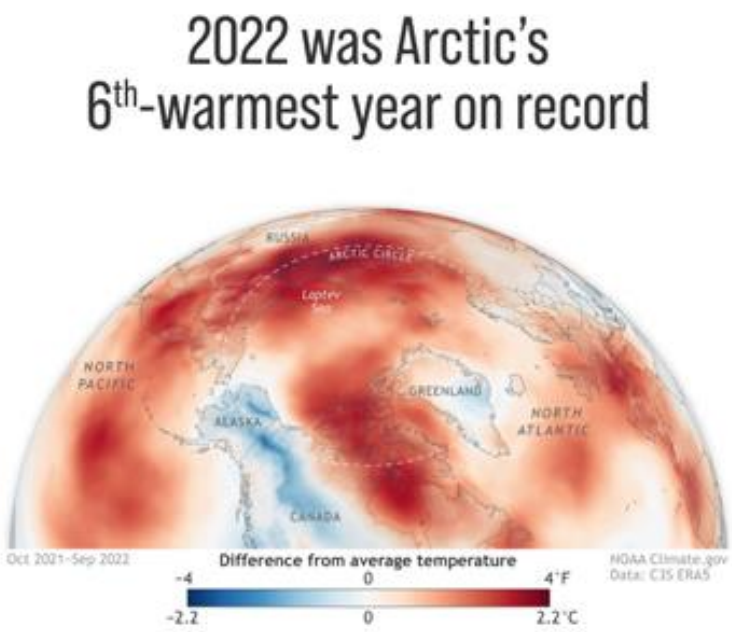
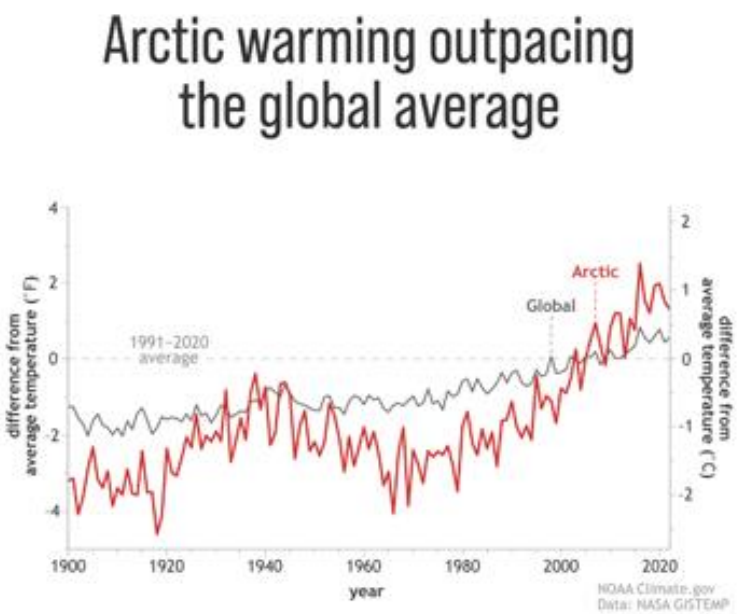
What do we really know about infectious diseases and climate changes in Arctic areas?

Anders Koch, MD, PhD, MPH
Professor (adjunct)
University of Greenland, Nuuk, Greenland
&
Senior consultant
Statens Serum Institut & Rigshospitalet University Hospital
Copenhagen, Denmark

Anders could not attend, so lecture done by Jay Butler from Alaska Dept of Health and Social Services

Climate Changes in the Arctic





National Oceanic and Atmospheric Administration
U.S. Department of Commerce

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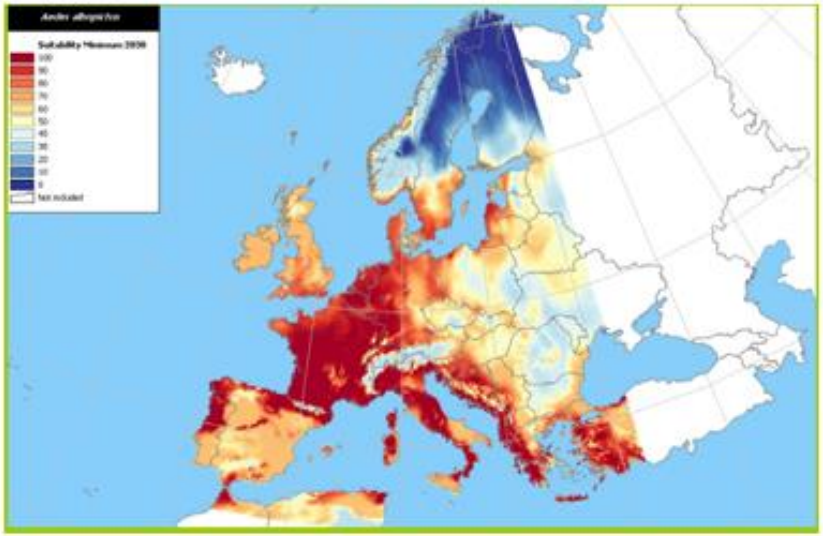
Climate Sensitive Infections

- Infections that **depend in some way on the natural environment for their spread or persistence**
  - Transmitted by arthropod vectors, water or soil, or
  - Use wildlife as a reservoir

- **Zoonotic infections** that may be transferred between humans and animals are particularly central. More than 70 % of current human infections are zoonotic, as are many of the emerging infections



Sensitivity of North Ecosystems

- Low biodiversity and highly specialized species – low possibilities to adapt
- Examples of species expanding north of importance for infectious diseases:
- **Common tick** (*Ixodes ricinus*) passed 70° N and to higher altitudes (2011)
- **Taiga tick** (*Ixodes persulcatus*) passed the traditional northern boundary at 62° (2003)
- **Roedeer** (*Capreolus capreolus*) of importance for ticks to feed on

Impact on Humans

- *Vibrio parahaemolyticus*
- Cholera-like bacterium
- 2004 Alaska Outbreak in cruise ship
- Local oisters
- Warming of local waters
- Northernmost appearance of *Vibrio parahaemolyticus* in the world

- *Coxiella burnetii*
- Bacterium in ruminants
- Never described in the Arctic
- 2007 East Greenland male infected
- Result of climate changes?

Koch et al. *Emerg Inf Dis* 2010

- *Francisella tularensis*
- Intracellular bacterium
- Hares and rabbits
- Ticks and deer flies
- Northwards expansion
- Increased attention to tularemia in health system?

McLaughlin et al. *NEJM* 2005

Impact on Humans/Animals

- Spore forming bacterium

- Early 20th Century
  - 40.000-60.000 animal cases annually
  - 10.000-20.000 human cases
  - 25% mortality

- 1941
  - Last know outbreak of Anthrax in Siberia

- 2011
  - Russian researchers warn of re-emergence of Anthrax in Yakutia due to warming of grounds with >200 burial grounds of cattle died of Anthrax

- Summer 2016
  - Heatwave in Yamal tundra
  - Outbreak of Anthrax due to thawing of a reindeer carcass died 75 years ago
  - 72 Yamal nomads sick, 1 boy and >2.300 reindeer died

H5N1 Risk in Farm Workers

The Colorado Experience

Oct. 18, 2024

Rachel Herlihy, MD, MPH
State Epidemiologist and Deputy Chief Medical Officer
Colorado Department of Public Health and Environment

COLORADO
Department of Public Health & Environment

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Timeline (Colorado)

January 2022

USDA detects H5N1 in wild birds.*

February 2022

USDA confirmed outbreak of H5N1 in a commercial turkey flock in Indiana.*

Late March 2022

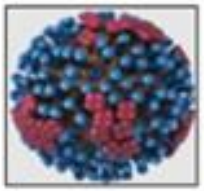
H5N1 detected in wild goose in Colorado.*

Mid April 2022

H5N1 detected in commercial chicken flock in Colorado.*

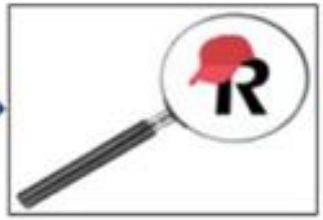
Late April 2022

Colorado resident tests positive for H5N1 using RT-PCR.**



May 2022 - March 2024

Ongoing surveillance of high risk individuals.***



Late March 2024

H5N1 detected in lactating dairy cattle in Texas.*

Late April 2024

Dairy cattle in Colorado confirmed to have H5N1.*

July 2024

Egg layer facilities in Colorado confirmed to have H5N1.

*Image from USDA
**Image from CDC
*** Image from REDCap

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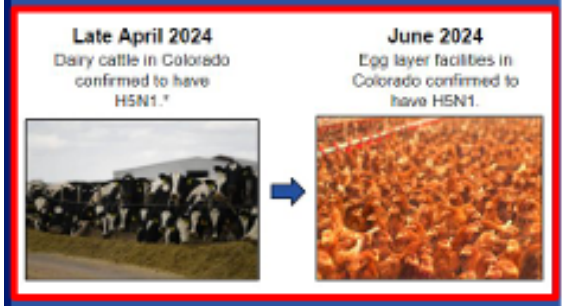
Department of Public Health & Environment

Timeline (Colorado)

Colorado cases H5N1 2.3.4.4b B3.13



Dairy Cattle:

- 64 confirmed positive herds *(63 released from QT)*

Poultry:

- 2 backyard flocks confirmed positive
- 3 commercial flocks confirmed positive - **3.3M birds**

Domestic Cats:

- 6 confirmed positive

Human Cases:

- 10 confirmed positive

COLORADO
Department of Public Health & Environment

Public Health Response

1. Initial producer interview - worker exposures and practices
2. Site visit
   a. Coordination with state and federal agriculture agency partners
   b. Observe workspaces
   c. Provide information to workers on risk and risk reduction
   d. Delivery of PPE (masks, goggles, face shields, gloves)
   e. Test symptomatic workers, offer oseltamivir
3. Establish monitoring for worker health

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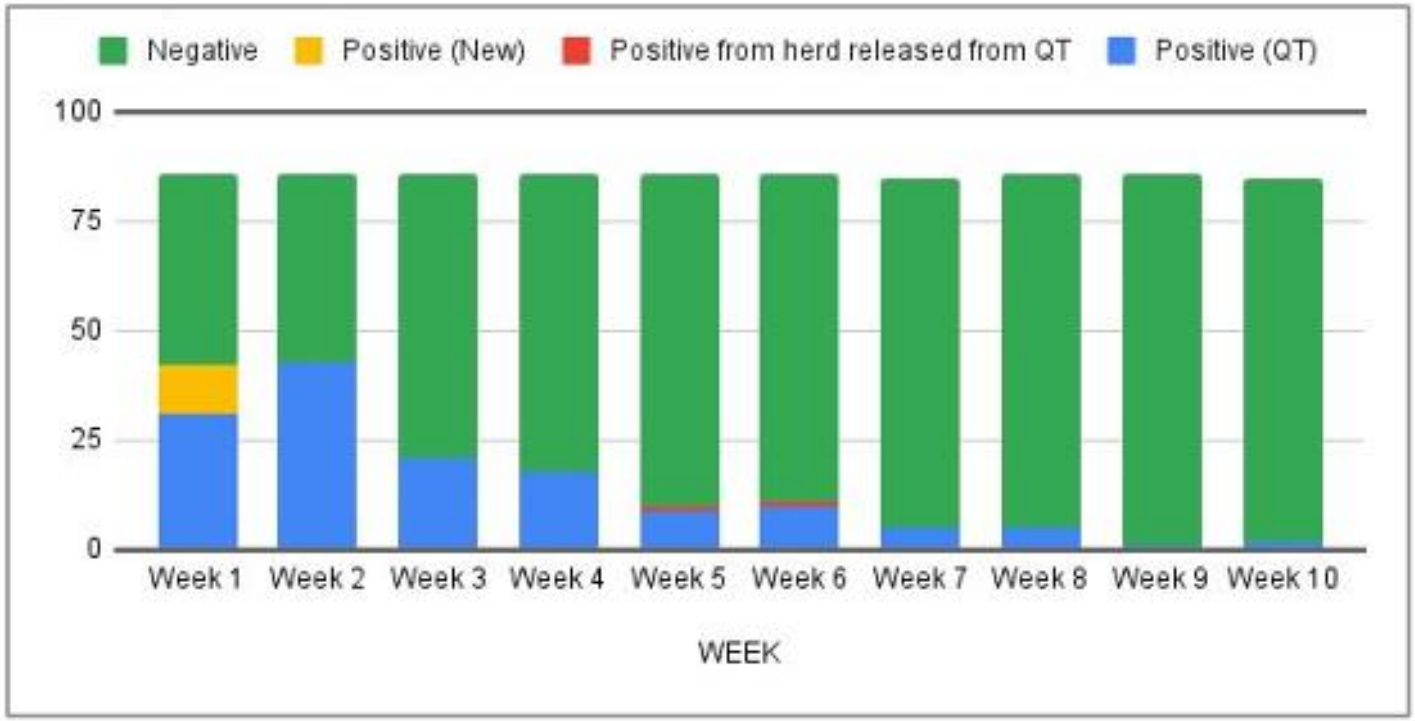
Colorado Bulk Tank Testing



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Department of Agriculture

PPE Use on Dairy Farms

- Use varied by work duties, including whether someone worked with sick cows.
- Overall reported PPE was high for some items:
  - Gloves 88%
  - Rubber boots or boot covers 71%
  - Head covers 69%
  - Eye protection 76%
- Reported mask use was low, with roughly half of workers reporting respirator or other mask use after H5N1 was detected.
- PPE use while working with sick cows increased after H5N1 was detected on surveyed farms (mean of 28%); eye protection use while milking cows increased the most (40%).

CDC Protect Yourself From H5N1 When Working With Farm Animals
https://www.cdc.gov/bird-flu/situation-summary/inhumans.html

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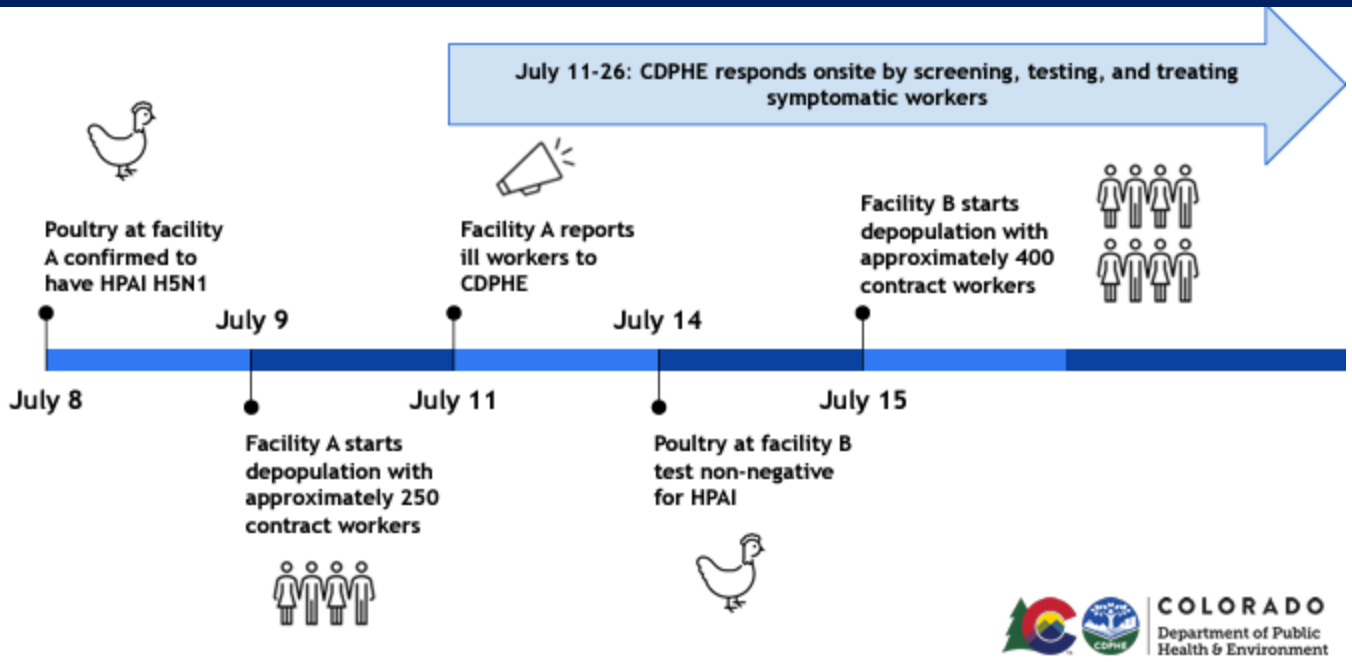
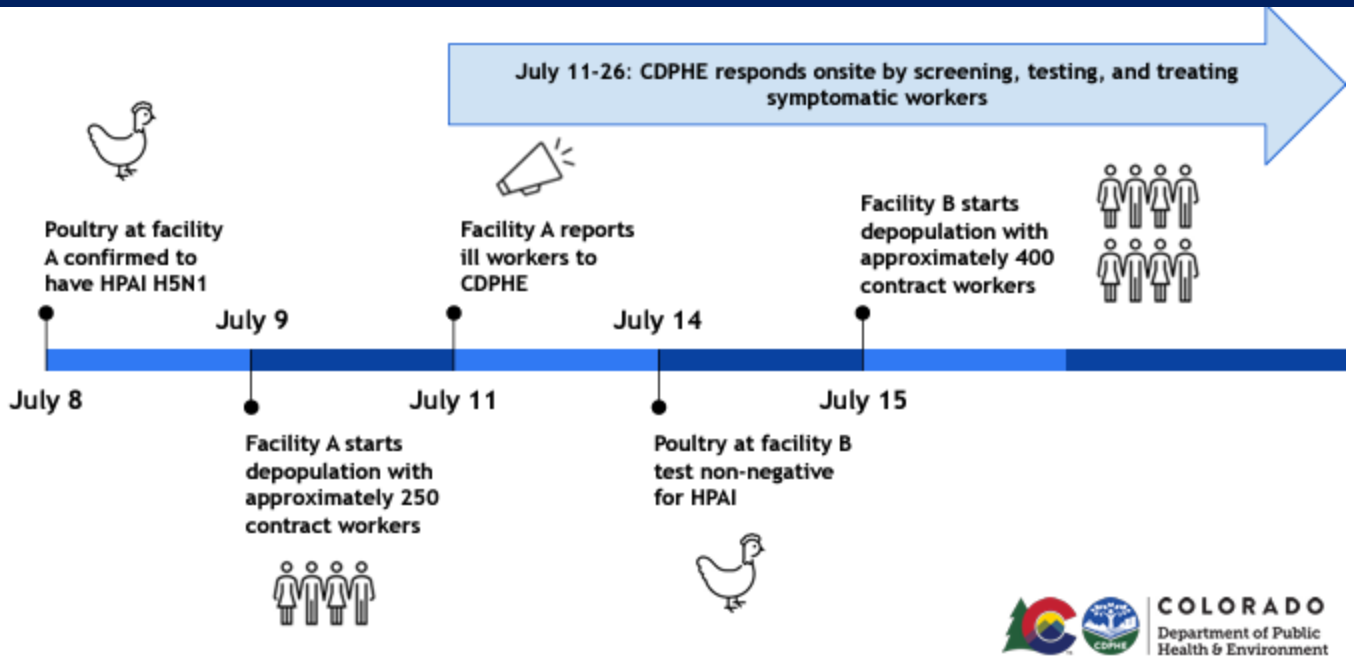
Colorado Poultry Farms



Colorado Poultry Farms



Characteristic	Facility A (N = 265)	Facility B (N = 398)
Number symptomatic, n (%)	65 (25%)	44 (11%)
Influenza A(H5) positive	6 (9%)	3 (7%)
COVID-19 positive	1 (2%)	18 (41%)