Complexities of tracking AMR at the One Health Interface

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Assessing the Burden and Potential Strategies to Address Antimicrobial Resistance: A Workshop
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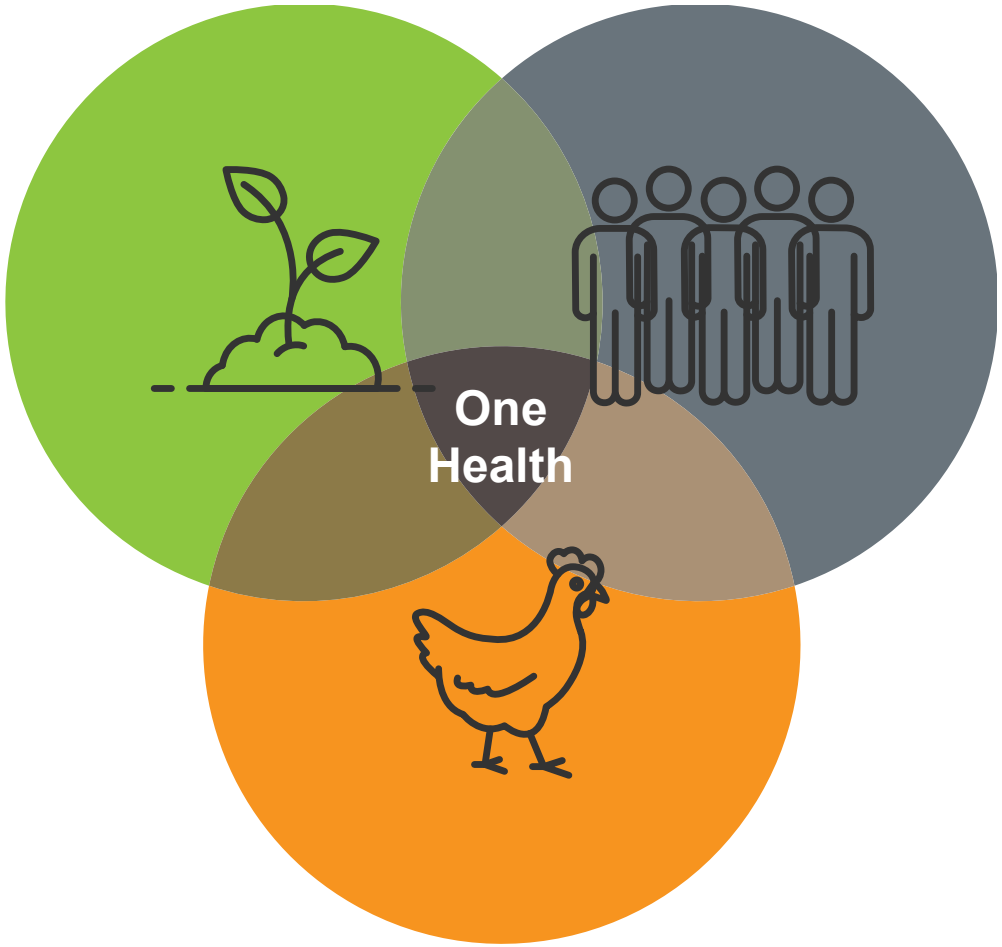
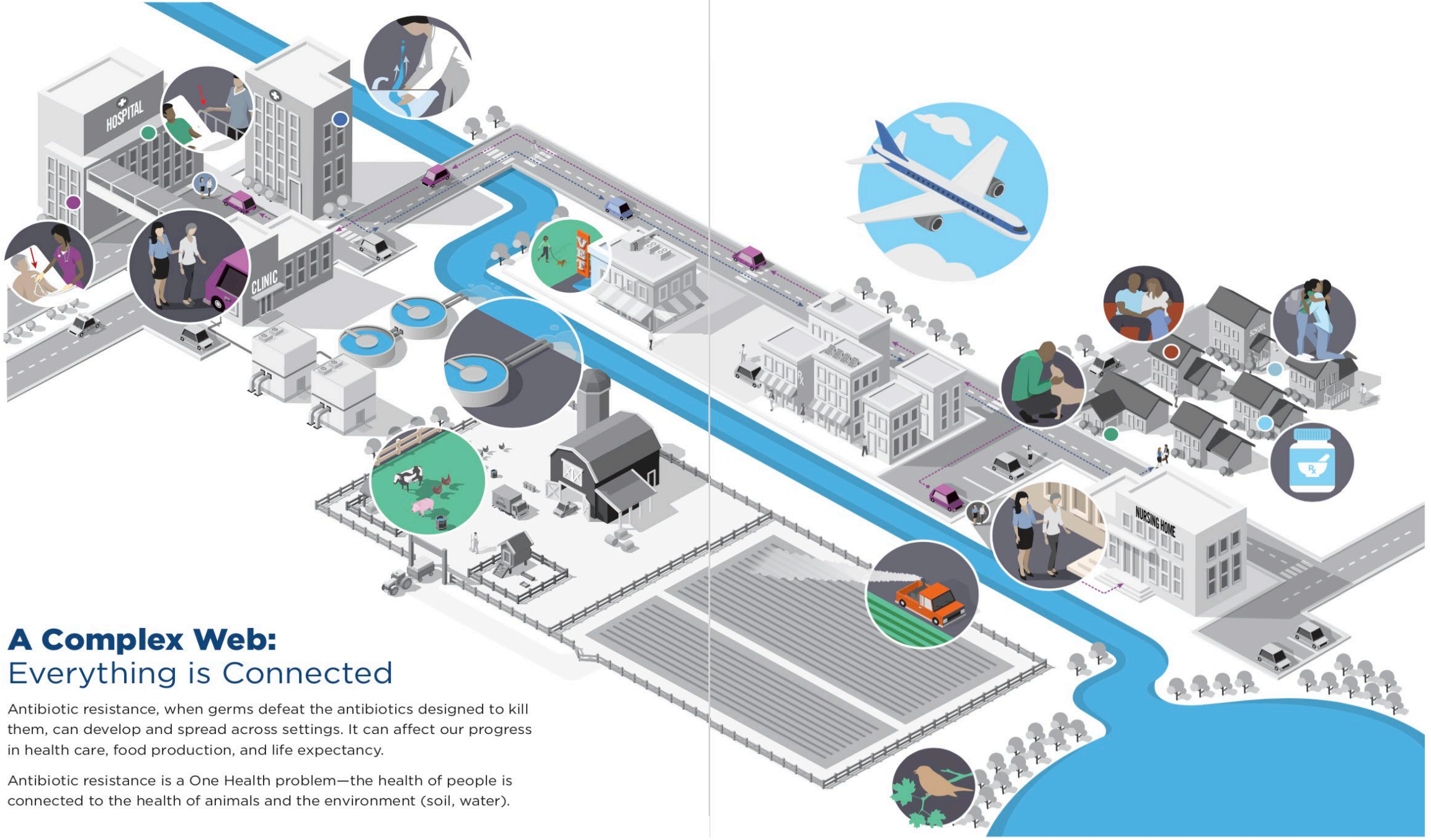
What Is "One Health?"



One Health is a collaborative, multisectoral, and transdisciplinary approach—working at the local, regional, national, and global levels—with the goal of achieving optimal health outcomes recognizing the interconnection between people, animals, plants, and their shared environment.



A Complex Web:
Everything is Connected

Antibiotic resistance, when germs defeat the antibiotics designed to kill them, can develop and spread across settings. It can affect our progress in health care, food production, and life expectancy.

Antibiotic resistance is a One Health problem—the health of people is connected to the health of animals and the environment (soil, water).

SOURCE: https://www.cdc.gov/drugresistance/pdf/threats-report/2019-ar-threats-report-508.pdf

Clinical breakpoints and the interpretations (i.e. – S/I/R) associated with them are recommendations developed by organizations to assist in the interpretation of the success of treatment with an antimicrobial for a specific condition using a specific dosing regimen in a specific species

Table 1. USCAST MIC breakpoints compared to three other antimicrobial agent susceptibility breakpoint determining organizations (SDO), when testing the fluoroquinolone class compounds (modified from the current USCAST Quinolone Report).

Organism/Antimicrobial	MIC breakpoints in µg/mL by criteria organization (Susceptible/Resistant)			
	CLSI[a]	USA-FDA	EUCAST[b]	USCAST
Enterobacteriaceae				
Ciprofloxacin	≤0.25 / ≥2	≤1 / ≥4[c]	≤0.25 / >0.5[b]	≤0.25 / ≥1
Delafloxacin	-	≤0.25 / ≥1	≤0.12 / >0.12 (*E.coli* only)	≤0.25 / ≥1
Levofloxacin	≤0.5 / ≥2	≤2 / ≥8[d]	≤0.5 / >1	≤0.5 / ≥2

Building a common language for antimicrobial resistance between human and animal health

The problems:

1) Clinical breakpoints for the same bacterial species differ between humans and animal species and thus are not ideal for One Health comparisons

2) Veterinary Medicine has very limited validated breakpoints

When “R” means different things

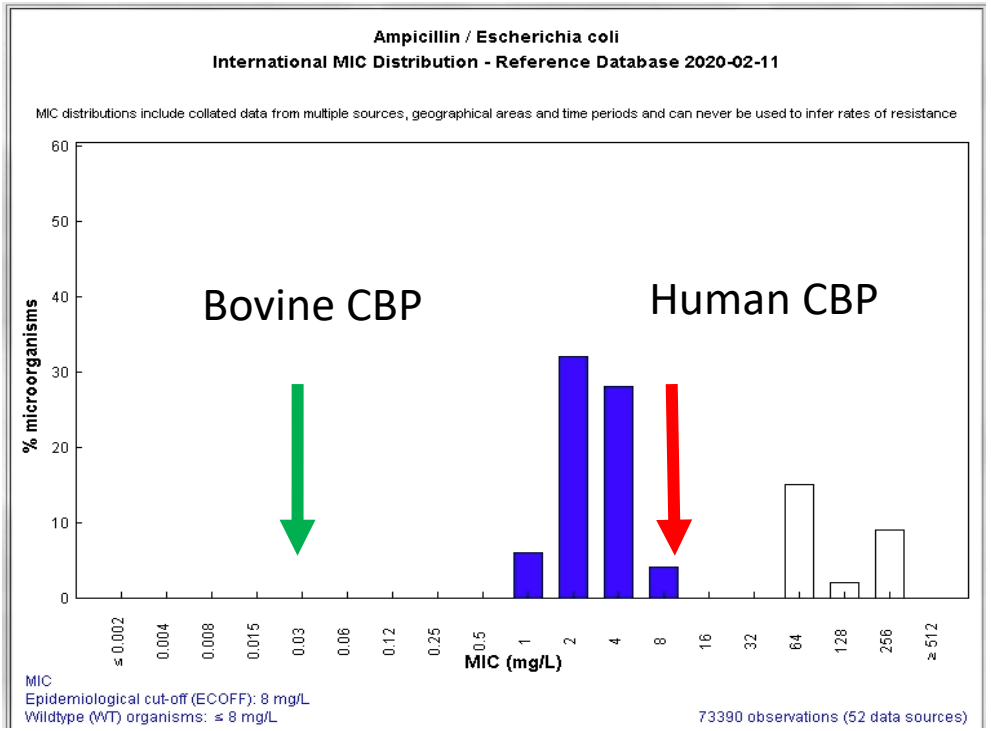
Clinical breakpoints can differ substantially between species!

Ampicillin *E. coli* CBP in humans

- ≤8 μg/mL = S
  - Ampicillin sodium given IV four times daily

Ampicillin *E. coli* CBP in cattle

- ≤0.03 μg/mL = S
  - Ampicillin trihydrate given IM once daily
  - All isolates will test resistant even if “wild-type”



Current bovine-specific clinical breakpoints (systemic)

Antibiotics routinely tested via AST for bovine isolates	Bacterial species				
	M. haemolytica	*P. multocida*	*H. somni*	*E. coli*	All other *
Ampicillin	Yes	Yes	Yes	Yes	
Ceftiofur	Yes	Yes	Yes		
Danofloxacin	Yes	Yes			
Enrofloxacin	Yes	Yes	Yes		
Florfenicol	Yes	Yes	Yes		
Gamithromycin	Yes	Yes	Yes		
Penicillin	Yes	Yes	Yes		
Spectinomycin	Yes	Yes	Yes		
Tetracycline	Yes	Yes	Yes		
Tildipirosin	Yes	Yes	Yes		
Tilmicosin	Yes				
Tulathromycin	Yes	Yes	Yes		

Specific to <u>body site</u>, <u>drug dosages and routes</u> used in calculations – (almost) all respiratory

Current as of Vet01S 5th ed and Vet09 1st ed

Current porcine-specific clinical breakpoints (systemic)

Antibiotics routinely tested via AST for porcine isolates	Bacterial species				
	Salmonella Cholerasuis	*Strep. suis*	*Bordetella bronchiseptica*	*P. multocida*	*APP*
Ampicillin		Yes	Yes	Yes	Yes
Ceftiofur	Yes	Yes		Yes	Yes
Enrofloxacin		Yes		Yes	Yes
Florfenicol	Yes	Yes	Yes	Yes	Yes
Penicillin		Yes		Yes	
Tetracycline		Yes		Yes	Yes
Tiamulin					Yes
Tildipirosin			Yes	Yes	Yes
Tilmicosin				Yes	Yes
Tulathromycin			Yes	Yes	Yes

Specific to <u>body site</u>, <u>drug dosages and routes</u> used in calculations – all <u>respiratory</u>

Current as of Vet01S 5th ed and Vet09 1st ed

What AST is commonly performed?

Location from which culture was taken	Number of ASTs performed	Most common isolates (number in parenthesis)
Respiratory tract	4588	*M. haemolytica* (1729) *P. multocida* (1477) *H. somni* (943) *Salmonella* sp. (309) *B. trehalosi* (74)
Gastrointestinal tract/fecal	2621	*E. coli* (2090) *Salmonella* sp. (478)
Other (eye, CNS, joint, etc.)	1205	--
TOTAL	15577 (includes multiple sites)	*E. coli* (5259) *M. haemolytica* (2847) *Salmonella* sp. (2447) *P. multocida* (2500) *H. somni* (1453) All others (2101)

Most commonly performed AST at the ISU VDL 2003-2018 for bovine samples

The need:

Create a common language between human and animal health in evaluating antimicrobial resistance

How do we interpret AST?

Food Animal Susceptibility
#20453* Final Result S.SD --> Salmonella species group D

Antimicrobial	MIC
Ampicillin	>16.0000
Ceftiofur	>8.0000
Chlortetracycline	>8.0000
Clindamycin	>16.0000
Danofloxacin	0.5000
Enrofloxacin	0.5000
Florfenicol	4.0000
Gentamicin	<=1.0000
Neomycin	>32.0000
Oxytetracycline	>8.0000
Penicillin	>8.0000
Spectinomycin	64.0000
Sulfadimethoxine	>256.0000
Tiamulin	>32.0000
Tilmicosin	>64.0000
Trimethoprim/Sulphamethoxazole	<=2.0000
Tulathromycin	32.0000
Tylosin (Tartrate/Base)	>32.0000

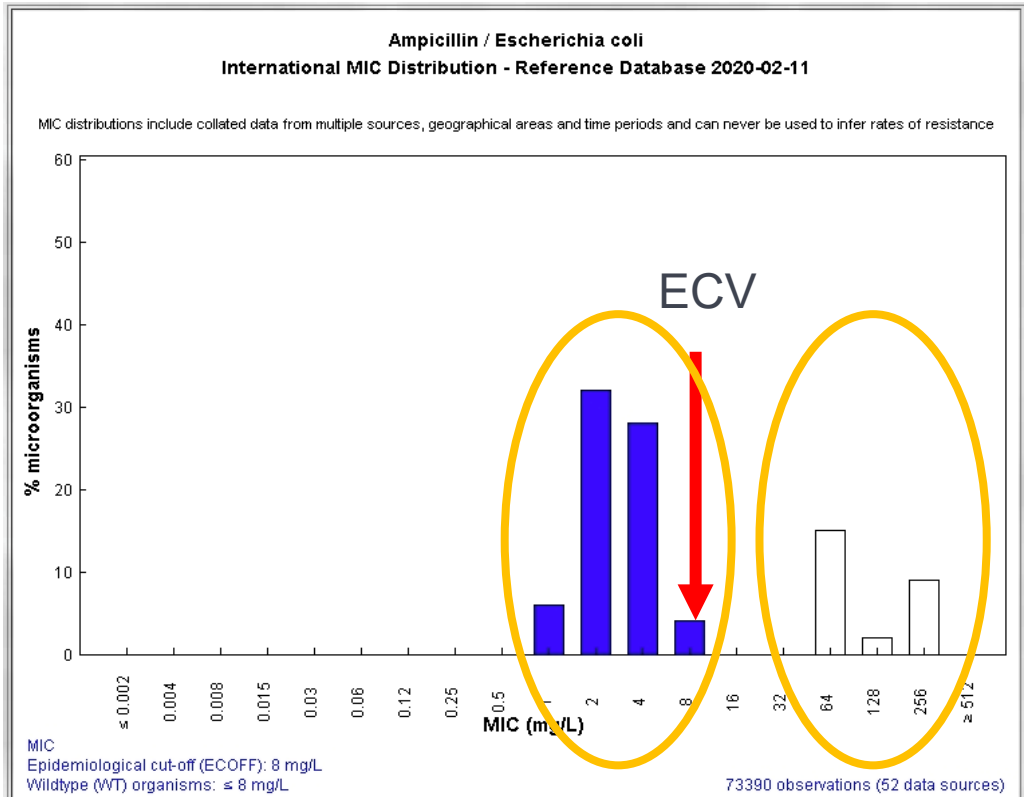
Option 1 – utilize clinical breakpoints to generate a susceptible/intermediate /resistant interpretation from the MIC for clinician to direct antimicrobial therapy
—animal species specific
—drug formulation/dosing specific

Option 2 – utilize epidemiologic cutoff values (ECV) to determine if the bacterial isolate has acquired resistance to antimicrobial of interest
—independent of host
—independent of drug pharmacology

ECVs create a common language between human and animal health!

Epidemiologic cutoff values (ECV)

- "Bacteriologic" definition of susceptible vs resistant
- ECV is determined from MIC values from bacterial population
- Independent of drug or host factors
- Applies to all bacteria of that species regardless of where it came from



https://mic.eucast.org/Eucast2/

Implications

Use Caution when Interpreting

- In most cases, unless the antimicrobial resistance data is derived from raw MIC data using standard operating procedures, or uses ECV based interpretations, it is not comparable across One Health sectors
- “Resistance” as defined by clinical breakpoints does not equal the acquisition of acquired resistance mechanisms
- Frequently the easiest data streams have significant bias
    - For instance, diagnostic laboratory specimens that are often easiest to access in low and high resource areas are often submitted only after one or more treatment failures

Use Caution when Interpreting

Antimicrobial consumption and resistance in bacteria from humans and food-producing animals

Fourth joint inter-agency report on integrated analysis of antimicrobial agent consumption and occurrence of antimicrobial resistance in bacteria from humans and food-producing animals in the EU/EEA

JIACRA IV – 2019–2021

- *"Although ecological studies are particularly useful for generating hypotheses, they cannot establish causation, no matter how strong the associations discerned, since traditional criteria for causality are not met. The findings of ecological analyses, such as those presented in this report, are not causal assessments. Therefore, it cannot be excluded that, while detecting a statistically significant association, concomitant phenomena were observed without any causal relationship. It is important to take this into account when interpreting the results of the analyses presented in this report."*

Connect

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