Antimicrobial Stewardship Collaborative of South Carolina

One Health: Antibiotic use in Agriculture (and how it relates to humans)

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UNIVERSITY OF South Carolina

South Carolina Center for Rural and Primary Healthcare

Project ECHO

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Objective

Apply the current standards for outpatient antimicrobial stewardship practice when solving complex patient or system challenges and improving antibiotic prescribing in ambulatory care settings.

Understanding how antimicrobial prescribing impacts the world around us

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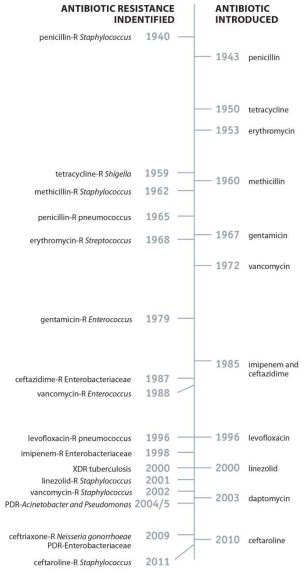

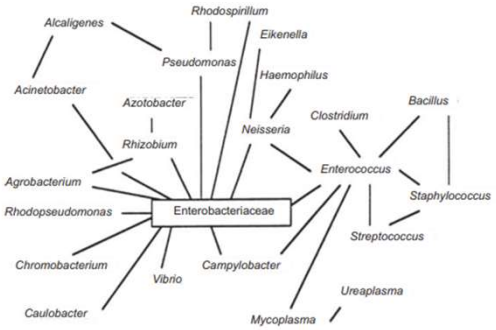

Figure 2
Genetic exchange among bacterial species. This process demonstrates the importance of bacterial reservoirs of resistance, including both pathogenic and nonpathogenic organisms (39).

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"The time may come when penicillin can be bought by anyone in the shops…then there is danger that the ignorant man may easily underdose himself and by exposing his microbes to nonlethal quantities of the drug make them resistant."

Alexander Fleming, when accepting his Nobel Prize for the discovery of penicillin

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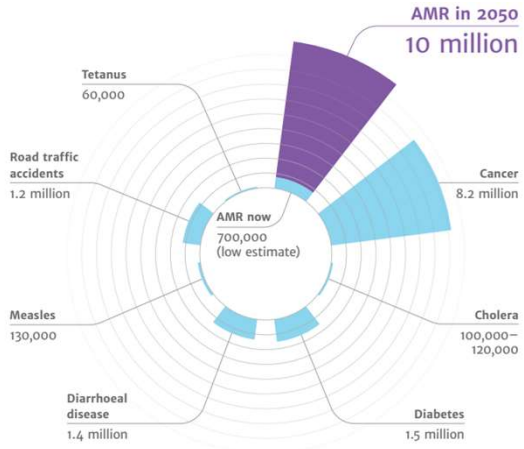

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O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. The Review on Antimicrobial Resistance 2016; CC BY 4.0.

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CDC: *Antibiotic Resistance Threats in the United States* (2019)

- Antimicrobial resistance (AMR) one of the greatest public health challenges currently
- 2018: 2 million people infected with AMR infections; 23,000 died
- Costs the US healthcare system $21-34 billion dollars/year

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Why agriculture?

- 1950s: low doses of antibioics given to livestock causes them to gain weight faster
  - Low doses
  - Unknown mechanism
- Industrial food animal production (IFAP)
- Concentrated animal feeding operations (CAFO)
  - Treat animal diseases
  - Prevent/control spread of disease
- Applied as pesticides
- Industry: reduces the cost of producing animals, therefore the cost of food is kept low(er)

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CAFO

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Humans, animals, and plants

- Carbapenems are reserved for human use only, but otherwise broad overlap
  - Some abx are only used in veterinary medicine due to toxicity in humans (ionophores, flavophosphlipols)
  - Tetracyclines, streptomycin treat infections in apples and pears ("fire blight" *Erwinia amylovora)*
  - Antifungals broadly used to cover massive crops like wheat
- Use varies in animals
  - Metaphylaxis: giving abx to healthy animals who are grouped together with diseased animals
    - Some consider this "therapeutic" use

Collignon PJ, McEwen SA. One Health: Its importance in helping to better control antimicrobial resistance. Tropical Medicine and Infectious Disease. 2019; 4(22).

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Growth promotion

- Highly controversial
- Administered to health animals for >2 weeks
  - Chickens: may be up to 36 days
- Sub-therapeutic doses improve "production"
- Colistin, fluoroquinolones, macrolides
- Benefits are likely quite small
- WHO advocates against using antimicrobials for growth promotion

Collignon PJ, McEwen SA. One Health: Its importance in helping to better control antimicrobial resistance. Tropical Medicine and Infectious Disease. 2019; 4(22).

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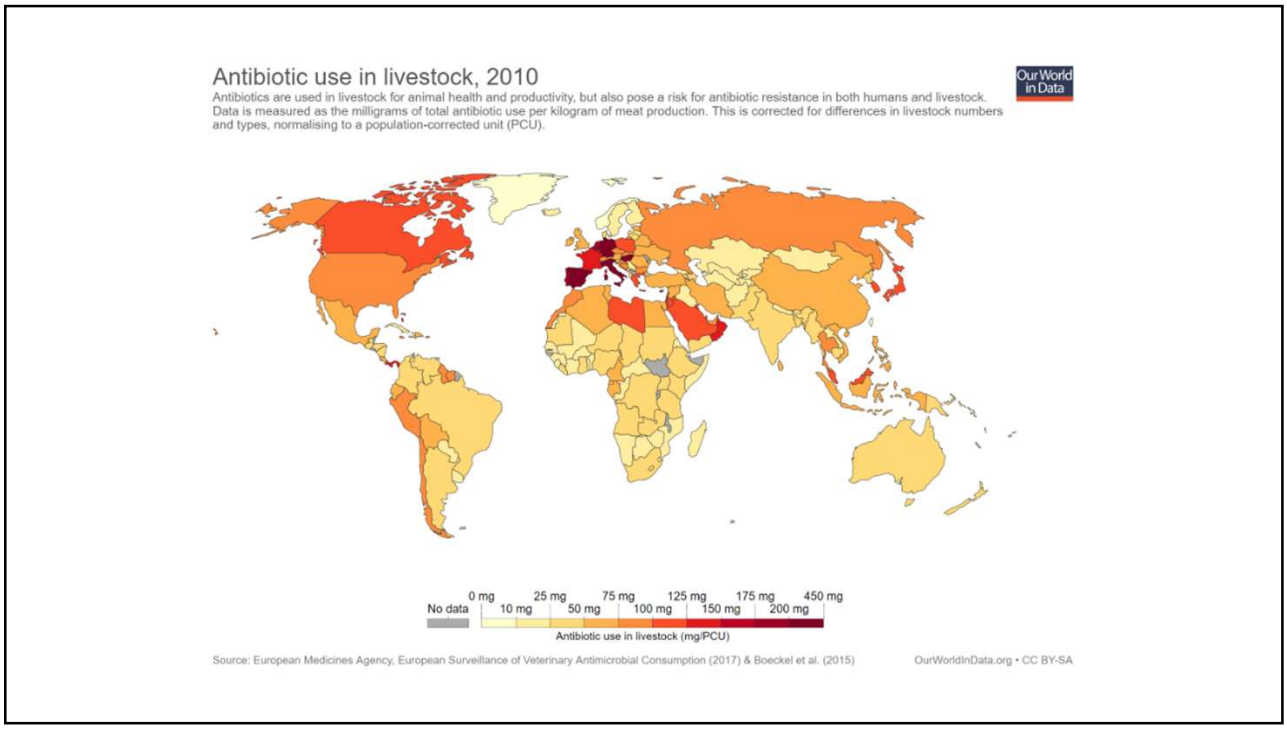

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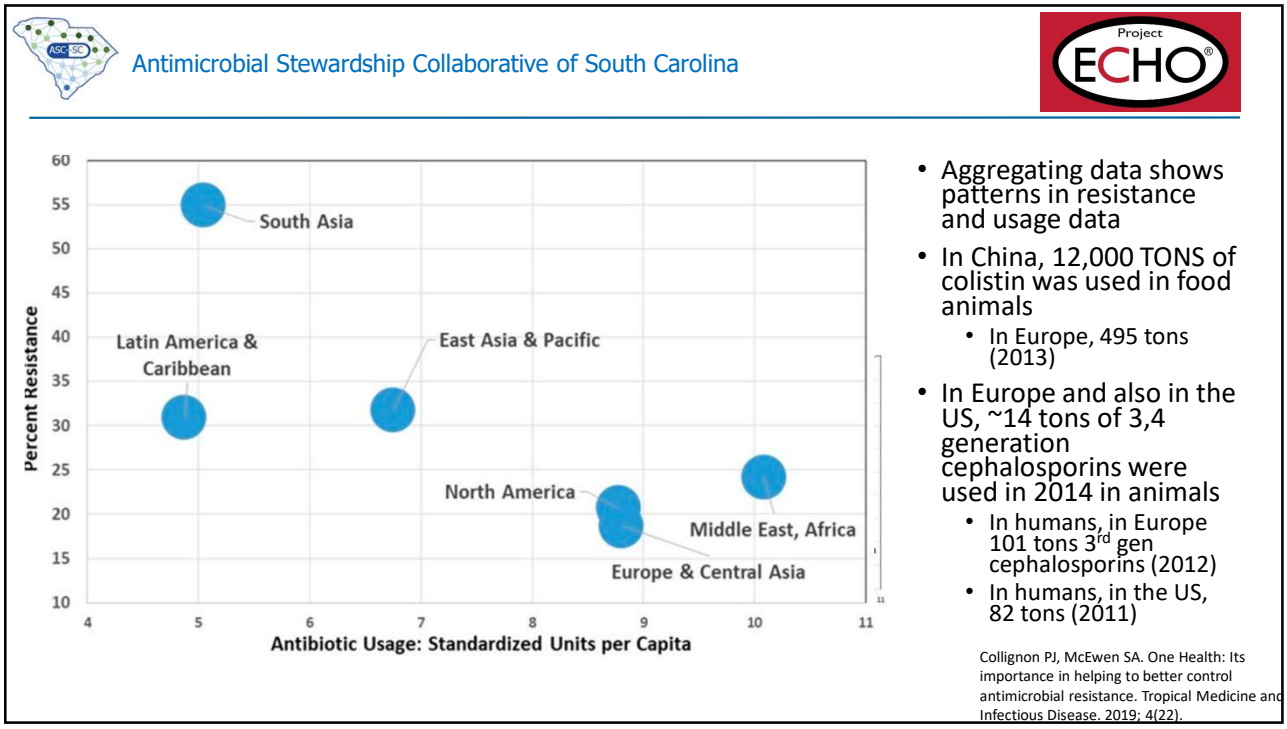

- Aggregating data shows patterns in resistance and usage data
- In China, 12,000 TONS of colistin was used in food animals
  - In Europe, 495 tons (2013)
- In Europe and also in the US, ~14 tons of 3,4 generation cephalosporins were used in 2014 in animals
  - In humans, in Europe 101 tons 3rd gen cephalosporins (2012)
  - In humans, in the US, 82 tons (2011)

Collignon PJ, McEwen SA. One Health: Its importance in helping to better control antimicrobial resistance. Tropical Medicine and Infectious Disease. 2019; 4(22).

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DRUG/DRUG CLASS	DRUG PRODUCT		
	Human	Veterinary	
		Food-producing Animals **	Companion Animals ***
Penicillins Natural Penicillins	Penicillin	Penicillin G Penicillin V	Penicillin G
Penicillins Penicillinase-stable Penicillins	Dicloxacillin Naficillin Oxacillin	Naficillin Hetacillin	Dicloxacillin
Penicillins Carboxypenicillins	Carbenicillin **** Ticarcillin ****	NONE APPROVED	Ticarcillin
Penicillins Ureidopenicillins	Piperacillin	NONE APPROVED	NONE APPROVED
Penicillins Aminopenicillins	Amoxicillin Ampicillin	Ampicillin	Ampicillin Amoxicillin
β-lactam/β-lactamase Inhibitor Combinations	Amoxicillin-clavulanic acid Ampicillin-sulbactam Piperacillin-tazobactam Ceftolozane-tazobactam	NONE APPROVED	Amoxicillin-clavulanic acid
Cephalosporins 1st Generation	Cefazolin Cephalexin	Cephapirin	Cephalexin Cefadroxil
Cephalosporins 2nd Generation	Cefamandole Cefprozil Cefuroxime	NONE APPROVED	NONE APPROVED
Cephalosporins All other cephalosporins not considered 1st or 2nd generations	Cefixime Ceftibuten Cefpodoxime Cefotaxime Ceftazidime Ceftriaxone Cefepime Ceftaroline Cefiderocol	Ceftiofur	Ceftiofur Cefovecin Cefpodoxime

DRUG/DRUG CLASS	DRUG PRODUCT		
	Human	Veterinary	
		Food-producing Animals **	Companion Animals ***
Aminoglycosides	Amikacin Gentamicin Tobramycin Kanamycin Streptomycin Neomycin Plazomicin	Neomycin Streptomycin Apramycin Gentamicin	Amikacin Gentamicin Kanamycin Neomycin
Antimycobacterials	Isoniazid Pyrazinamide Ethambutol Bedaquiline	NONE APPROVED	NONE APPROVED
Carbapenems	Imipenem Meropenem Ertapenem	NONE APPROVED	NONE APPROVED
Cephamycins	Cefotetan Cefoxitin	NONE APPROVED	NONE APPROVED
Quinolones	Ciprofloxacin Ofloxacin Levofloxacin Moxifloxacin Delafloxacin	Enrofloxacin Danofloxacin	Difloxacin Enrofloxacin Marbofloxacin Orbifloxacin Pradofloxacin
Fosfomycins	Fosfomycin	NONE APPROVED	NONE APPROVED
Glycopeptides	Vancomycin	NONE APPROVED	NONE APPROVED
Lincosamides	Clindamycin Lincomycin	Lincomycin Pirlimycin	Clindamycin Lincomycin
Lipoglycopeptides	Telavancin Dalbavancin Oritavancin	NONE APPROVED	NONE APPROVED
Lipopeptides	Daptomycin	NONE APPROVED	NONE APPROVED
Macrolides	Erythromycin Azithromycin Clarithromycin Fidaxomycin	Tilmicosin Tulathromycin Tylosin Tylvalosin Oleandomycin	Erythromycin
Methenamine	Methenamine	NONE APPROVED	Methenamine
Monobactams	Aztreonam	NONE APPROVED	NONE APPROVED
Nitrofurans	Nitrofurantoin	NONE APPROVED	Nitrofurazone
Nitroimidazoles	Metronidazole Tinidazole Secnidazole	NONE APPROVED	NONE APPROVED
Oxazolidones	Linezolid Tedizolid	NONE APPROVED	NONE APPROVED

www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance

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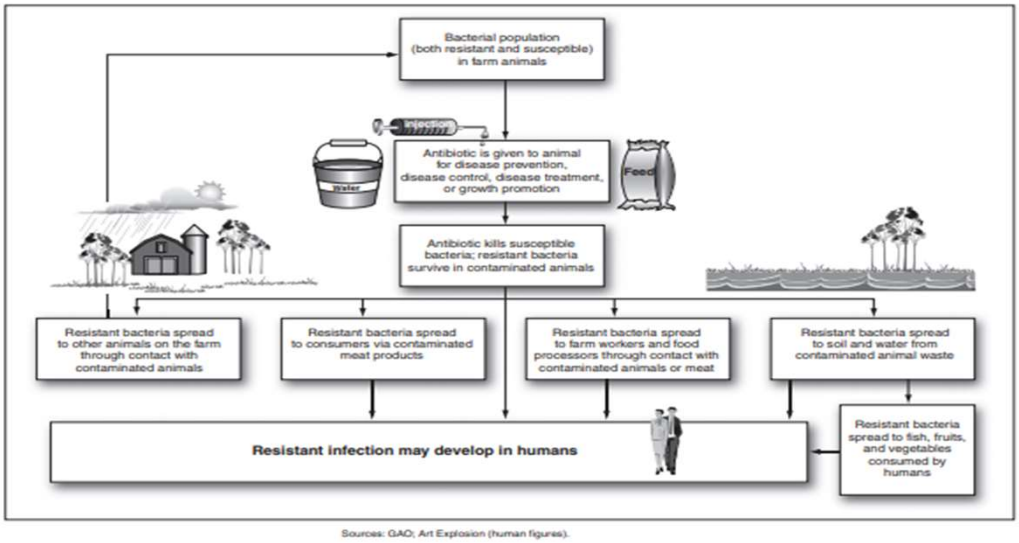
Figure 1: Potential Pathways for Spread of Antibiotic-Resistant Bacteria from Animals to Humans



Sources: GAO; Art Explosion (human figures).

Report no. GAO 11-801 (2011)

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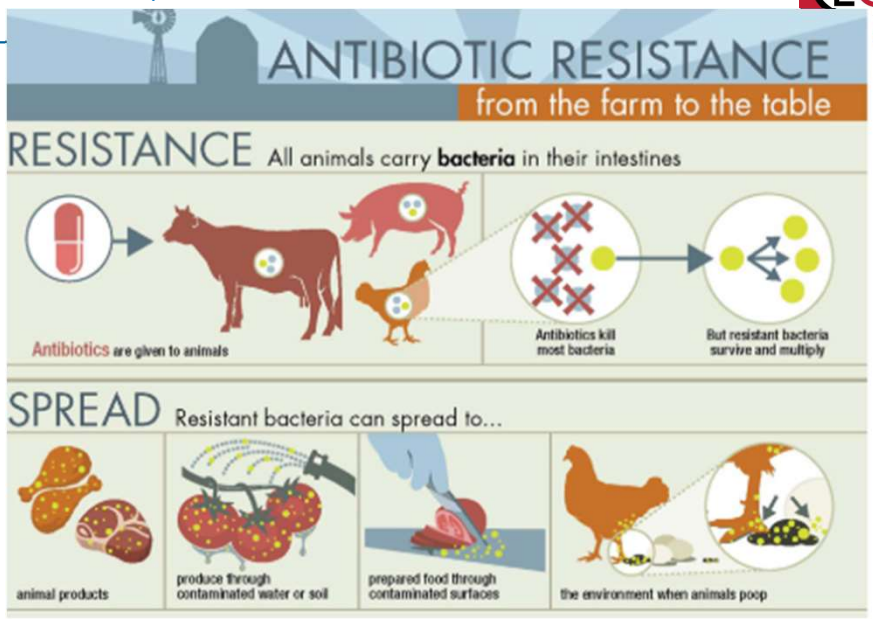

CDC.

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One Health

- 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.
  - Human expanding into new geographic areas, which may put them in contact with wild/domestic animals
  - Climate change and change in land use (deforestation, intensive farming practices) disrupt environmental conditions→can provide new opportunities for diseases to pass to animals (and vice versa!)
  - International travel moving people, animals, and animal products allows diseases to travel across borders

https://www.cdc.gov/onehealth/basics/index.html

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Common One Health issues

- Zoonotic diseases
- Antimicrobial resistance
- Food safety
- Food security
- Vector-borne diseases
- Environmental contamination

- Emphasis on collaboration across sectors: human health, animal health, environmental & agricultural experts, law enforcement, policymakers

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Livestock-associated MRSA colonisation and infection among livestock workers and veterinarians

- 3490 studies, 14 038 participants eligible for the meta-analysis.
- The pooled OR Livestock Associated (LA)-MRSA among livestock workers and veterinarians is 9.80 (95% CI 6.89 to 13.95; p=0.000)
  - OR for swine workers was highest at 15.41 (95% CI 9.24 to 25.69), followed by cattle workers (11.62), veterinarians (7.63), horse workers (7.45), livestock workers (5.86), poultry workers (5.70), and industrial slaughterhouse workers (4.69).
- Livestock workers, particularly swine farmers, are at significantly higher risk for LA-MRSA colonisation and subsequent infection. These results support the need for preventive practices to reduce LA-MRSA risk among those who handle and treat livestock.

Chen C, Wu F. *Occupational and Environmental Medicine.* Online First: 23 October 2020. doi: 10.1136/oemed-2020-106418

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Antimicrobial resistance in the sewers

- investigated if effluent from a large Swedish hospital, as well as influent and effluent from the connected municipal wastewater treatment plant select for antibiotic resistant Escherichia coli in three controlled experimental setups.
- Exposure of sterile-filtered hospital effluent to a planktonic mix of 149 different E. coli wastewater isolates showed a **strong selection of multi-resistant strains**.
- An analysis of commonly used antibiotics and non-antibiotic pharmaceuticals in combination with growth and resistance pattern of individual E. coli isolates suggested a possible contribution of ciprofloxacin and β-lactams to the selection by hospital effluent.
- Such effects may be more pronounced in countries with higher antibiotic use than Sweden.
- Despite the limited antibiotic use in Sweden, the hospital effluent strongly and consistently selected for multi-resistance, indicating widespread risks. Hence, there is an urgent need for further evaluation of risks for resistance selection in hospital sewers, as well as for strategies to remove selective agents and resistant bacteria.

Nadine Kraupner, Marion Hutinel, Kilian Schumacher, Declan A. Gray, Maja Genheden, Jerker Fick, Carl-Fredrik Flach, D.G. Joakim Larsson. Evidence for selection of multi-resistant E. coli by hospital effluent. Environment International, 2021 (151):106436.

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Resistance

- 2016 study in Europe: resistance was found in 1.9% *E. coli* found in broilers, 6.1% of turkeys
- mcr-1 (colistin plasmid) found in *E. coli* from meat from China
  - Subsequently been demonstrated in the environment, from offal
  - Mcr-2 recently found in pigs in Belgium
- Organisms with resistance likely due to overuse in agriculture: *Salmonella, Campylobacter jejuni, E. coli* (ESBL)
  - MRSA seen in animals and previously was relatively rare

Collignon PJ, McEwen SA. One Health: Its importance in helping to better control antimicrobial resistance. Tropical Medicine and Infectious Disease. 2019; 4(22).

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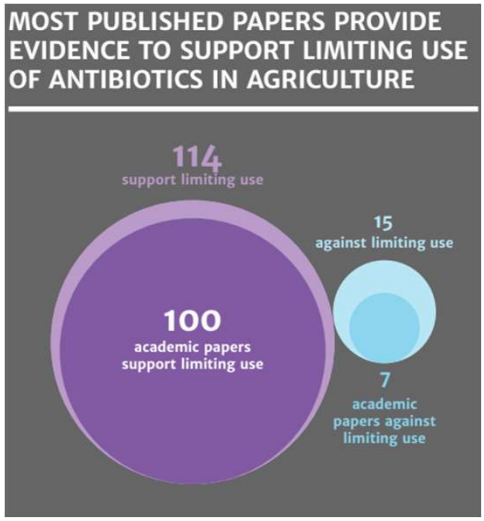
So… what can we do?

> *Without good surveillance, we cannot effectively counter the threat that antimicrobial resistance poses to health systems and people all over the world. It is also vital that countries work together to make sure old and new technologies are rolled out in a way that supports better global "One Health" AMR surveillance including animals and the environment.*
>
> Yasuhisa Shiozaki, Minister of Health, Labour and Welfare for Japan



O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations. Review on Antimicrobial Resistance 2016; CC BY 4.0.

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USDA and FDA

- HHS->FDA
  - Allows for antibiotic use for disease treatment, disease control, disease prevention, or growth promotion
  - 2003: Animal Drug Use Feed Amendments: collect/publish data from pharmaceutical companies on antibiotics sold for use in food animals
    - Flaw: Published in aggregate
    - 33% decrease
- USDA
  - Collects information regarding antibiotic use and resistance in food animals
- Together, ensure the safety of the food supply

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Preservation of antibiotics for medical treatment

- PAMTA (HR 1150), introduced 1999
- Preventing Antibiotic Resistance Act (S1256)
- Phase out medically important antibiotics
- 1999 and reintroduced every year since…never passed
- 450 public health, medical organization support this legislature

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Concept Paper: Potential Approach for Ranking of Antimicrobial Drugs According to Their Importance in Human Medicine: A Risk Management Tool for Antimicrobial New Animal Drugs

- New proposal before the FDA
- *In October 2003, ….Since then, GFI #152 has supported FDA's efforts to assess the safety of antimicrobial new animal drugs intended for use in food-producing animals by providing a recommended risk assessment methodology for evaluating and mitigating antimicrobial resistance concerns.*
- Revising the list of "medically important" drugs

https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance

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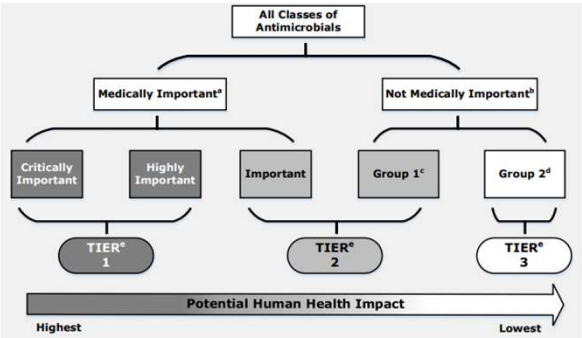
Figure 1: Characterization of potential human health impact based on medical importance antimicrobial drug designation



[a] Medically Important: Antimicrobial drugs that meet the criteria (as defined in this concept paper) for a ***critically important***, ***highly important***, or ***important antimicrobial drug.***

[b] Not Medically Important: Antimicrobial drugs that do not meet the criteria (as defined in this concept paper) for a ***critically important, highly important, or important*** antimicrobial drug.

[c] Group 1: Antimicrobial drugs that are not considered ***medically important*** because such drugs do not meet the current criteria to be ranked as ***medically important*** and the drug is 1) a drug that is approved for human use or 2) a new drug class with limited history and experience of use in animals.

[d] Group 2: Antimicrobial drugs that are not considered ***medically important*** because such drugs do not meet the current criteria to be ranked as ***medically important*** and such drugs have an extensive history and experience of use in animals.

[e] Tier: Grouping of antimicrobial drugs that considers qualitatively, the potential human health impact if resistance to the antimicrobial drug emerges (Tier 1, highest impact; Tier 2, medium or intermediate impact; Tier 3, lowest impact).

https://www.fda.gov/animal-vete health/antimicrobial-resistance

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Table 1: Ranking of Antimicrobial Drugs According to their Therapeutic Use in Human Medicine [11]

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Penicillins Natural Penicillins	H		X		Preferred therapy for syphilis.
Penicillins Penicillinase-stable Penicillins	H		X		One of available therapies for serious infections due to methicillin-susceptible ***Staphylococcus aureus.***
Penicillins Carboxypenicillins	H		X		One of available therapies for serious infections due to gram-negative bacteria including ***Pseudomonas aeruginosa.***
Penicillins Ureidopenicillins	H		X		One of available therapies for serious infections due to gram-negative bacteria including ***Pseudomonas aeruginosa.***
Penicillins Aminopenicillins	C	X			One of limited available therapies for serious infections due to ***Listeria monocytogenes*** in adults and children, and Group B ***Streptococcus*** in neonates.
β-lactam/β-lactamase Inhibitor Combinations	C	X			One of limited available therapies for serious infections due to beta lactamase producing gram-negative bacteria.
Cephalosporins 1st Generation	H		X		Used to treat non-serious infections for which drugs from more than a few antimicrobial classes are available. One exception is cefazolin which is considered highly important as it is used for the treatment of serious infections due to methicillin-susceptible ***Staphylococcus aureus.***
	I			X	
Cephalosporins 2nd Generation	H		X		One of available therapies for serious infections due to ***S. aureus, Haemophilus influenzae, Escherichia coli.***
Cephalosporins All other cephalosporins not considered 1st or 2nd generations	C	X			One of limited available therapies for serious infections due to gram-negative and gram-positive bacteria (certain drugs), including ***Neisseria spp.***, ***P. aeruginosa***, ***S. aureus, Streptococcus pneumoniae***, and complicated ***Salmonella*** infections.
Aminoglycosides	C	X			One of limited available therapies for serious infections caused by gram-negative bacteria, including those due to multidrug resistant isolates, ***Y. pestis and Francisella tularensis***; one of limited available inhaled therapies for cystic fibrosis.
Antimycobacterials (drugs solely used to treat tuberculosis or other mycobacterial diseases)	C	X			One of limited available therapies for treatment of tuberculosis or other mycobacterial diseases.

https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance

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Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Carbapenems	C	X			One of limited available therapies for serious infections due to gram-negative bacteria, including those due to extended spectrum beta lactamase producing organisms.
Cephamycins	H		X		One of available therapies for pelvic inflammatory disease in the inpatient setting.
Quinolones	C	X			One of limited available therapies for serious infections due to gram-negative bacteria including diarrheal pathogens, ***Yersinia pestis*** and prophylaxis against inhalational anthrax.
Fosfomycin	C	X			One of limited available therapies for some serious infections due to resistant gram-negative bacteria.
Glycopeptides	C	X			One of limited available therapies for serious infections due to methicillin-resistant ***S. aureus*** (MRSA); oral vancomycin is one of the few available therapies for infections due to ***C. difficile.***
Lincosamides	H		X		One of available therapies for of serious infections due to Group A streptococci and ***Staphylococcus aureus.***
Lipoglycopeptides	H		X		One of available therapies for serious infections due to MRSA.
Lipopeptides	C	X			One of limited available therapies for serious infections due to MRSA and some vancomycin-resistant enterococci (VRE).

Drug/Drug Class	Ranking[1]	Ranking Criterion[2]			Comments[3]
		1	2	3	
Macrolides	C	X			One of limited available therapies for serious infections due to ***Clostridioides difficile*** (fidaxomicin), ***Campylobacter jejuni.*** One of limited available therapies as part of a combination regimen for nontuberculous mycobacteria, and infections due to ***Helicobacter pylori.***
Methenamine	I			X	Drugs from more than a few antimicrobial classes are available.
Monobactams	C	X			One of limited available therapies for serious infections due to gram-negative bacteria including those due to metallo-beta lactamase producing isolates; one of limited available inhaled therapies for cystic fibrosis.
Nitrofurans	H		X		One of limited available therapies for uncomplicated urinary tract infections.
Nitroimidazoles	H		X		One of available therapies for serious infections due to ***C. difficile*** and other anaerobic infections.
Oxazolidinones	C	X			One of limited available therapies for serious infections due to MRSA and VRE.
Phenicols	H		X		One of available therapies for serious infections due to ***Rickettsiae***, ***Salmonella*** spp. when other agents are contraindicated or ineffective.
Pleuromutilins	H		X		One of available therapies for of infections due to ***S. pneumoniae***, ***H. influenzae***, ***M. pneumoniae*** (including macrolide-resistant strains).

https://www.fda.gov/animal-veterinary/safety-health/antimicrobial-resistance

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Guidance for Industry #213

- 2013: FDA policy prohibiting the use of medically important antibiotics for "production purposes" (promote growth, feed efficiency)
- Fully implemented by January 2017
- Any addition of antibiotics to feed/water requires the oversight of a veterinarian
  - Veterinary Feed Directive (2015): outlines the conditions under which veterinarians can authorize antibiotic use in animal feed and the accompanying responsibilities veterinarians must assume

https://www.pewtrusts.org/-/media/assets/2018/02/arp_antibiotics_and_animal_agriculture_a_primer.pdf

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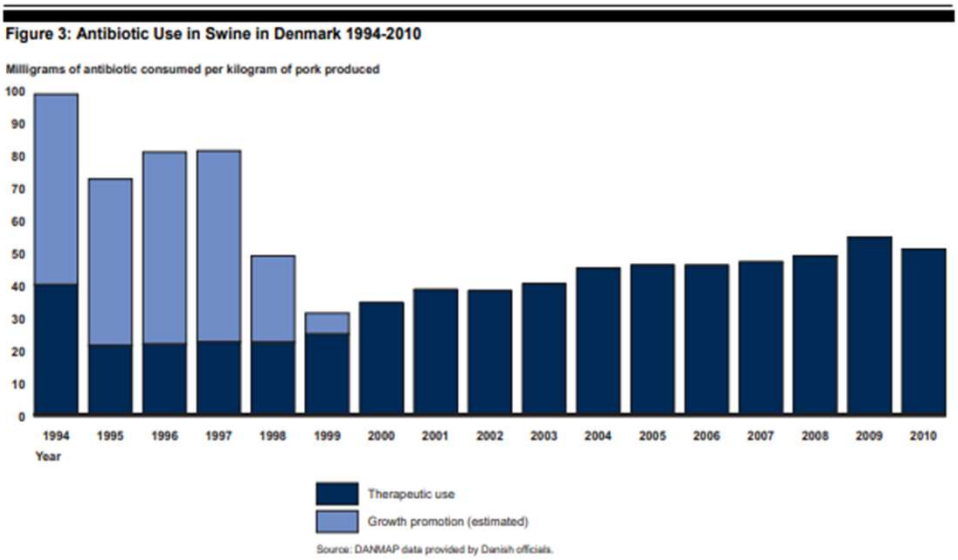

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Questions?

- Key references:
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- Levy S. Reduced antibiotic use in livestock: how Denmark tackled resistance. *Environ Health Perspect*. 2014;122(6):A160–A165. doi:10.1289/ehp.122-A160
- US Government Accountability Office. "Antibiotic resistance: Agencies have made limited progress addressing antibiotic use in animals." *Report no. GAO-11-801* (2011). Available: https://www.gao.gov/assets/330/323090.pdf
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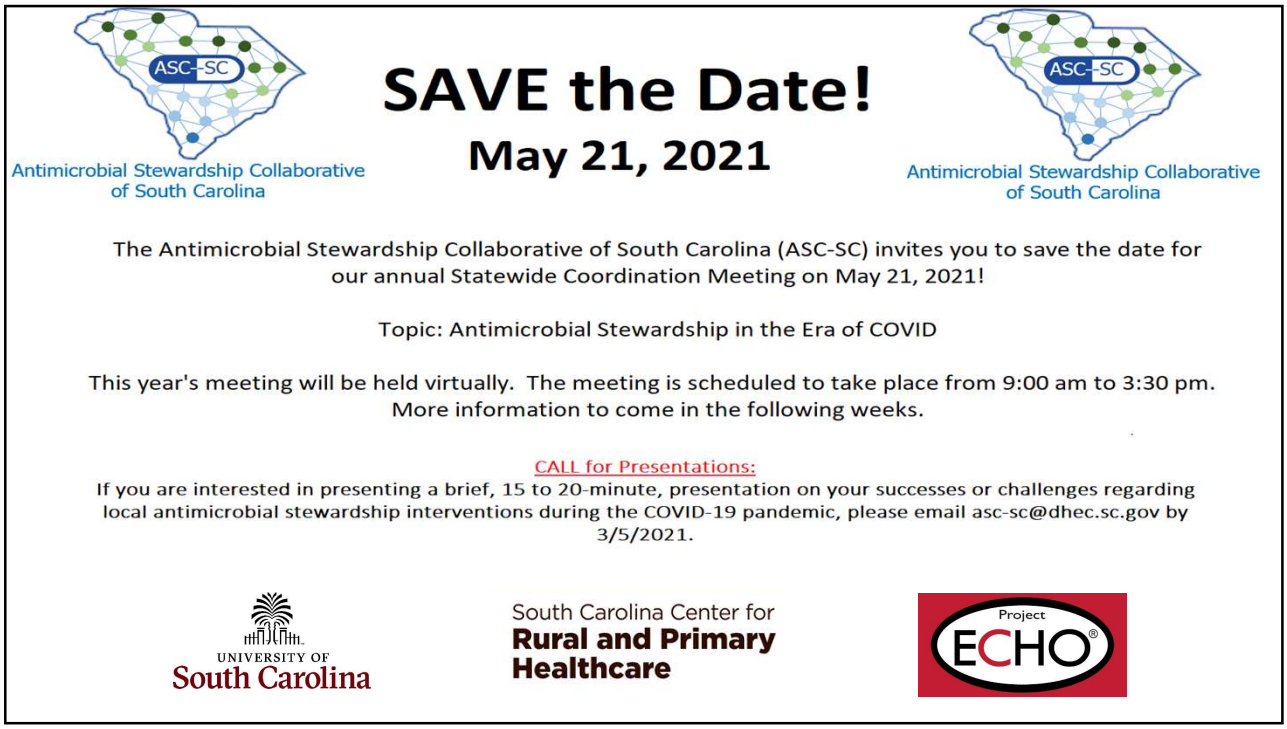
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SAVE the Date!
May 21, 2021
ASC-SC
Antimicrobial Stewardship Collaborative of South Carolina
The Antimicrobial Stewardship Collaborative of South Carolina (ASC-SC) invites you to save the date for our annual Statewide Coordination Meeting on May 21, 2021!
Topic: Antimicrobial Stewardship in the Era of COVID
This year's meeting will be held virtually. The meeting is scheduled to take place from 9:00 am to 3:30 pm. More information to come in the following weeks.
CALL for Presentations:
If you are interested in presenting a brief, 15 to 20-minute, presentation on your successes or challenges regarding local antimicrobial stewardship interventions during the COVID-19 pandemic, please email asc-sc@dhec.sc.gov by 3/5/2021.
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