Antimicrobial resistance and food safety:

a slumgullion stew of science, policy, and practice

NIFA-IFSN Webinar Series

April 20, 2017 15:00 EDT

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Slumgullion stew…

- *"a meat stew…"*[1]
- Best described as: an '*if it's*' *stew*
  - *"If it's in the refrigerator it goes into the mix"* [2]

slumgullion

noun slum·gul·lion \ˈsləm-ˌgəl-yən\ [1]

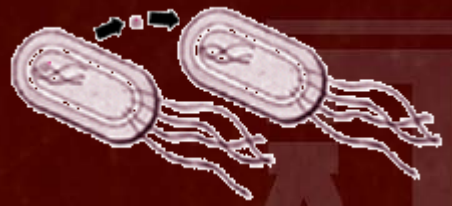
[1] Merriam-Webster's online dictionary
[2] Shared Tastes WordPress blog

Outline

- Contemporary 'science' of antimicrobial resistance
  - Overview of AMR at the interface of food production and public health
  - Introduction to several critical issues
    - ESBL and AmpC producing Enterobacteriaceae
    - Carbapenemase producing Enterobacteriaceae
    - Colistin resistance
- Issues impacting antimicrobial use policy: from farm to fork
  - The debate about agricultural uses of antibiotics and possible solutions
- Practice evidence: identifying and implementing best practices to reduce or mitigate AMR risks
  - Risk assessment and risk management

Mechanisms of Resistance

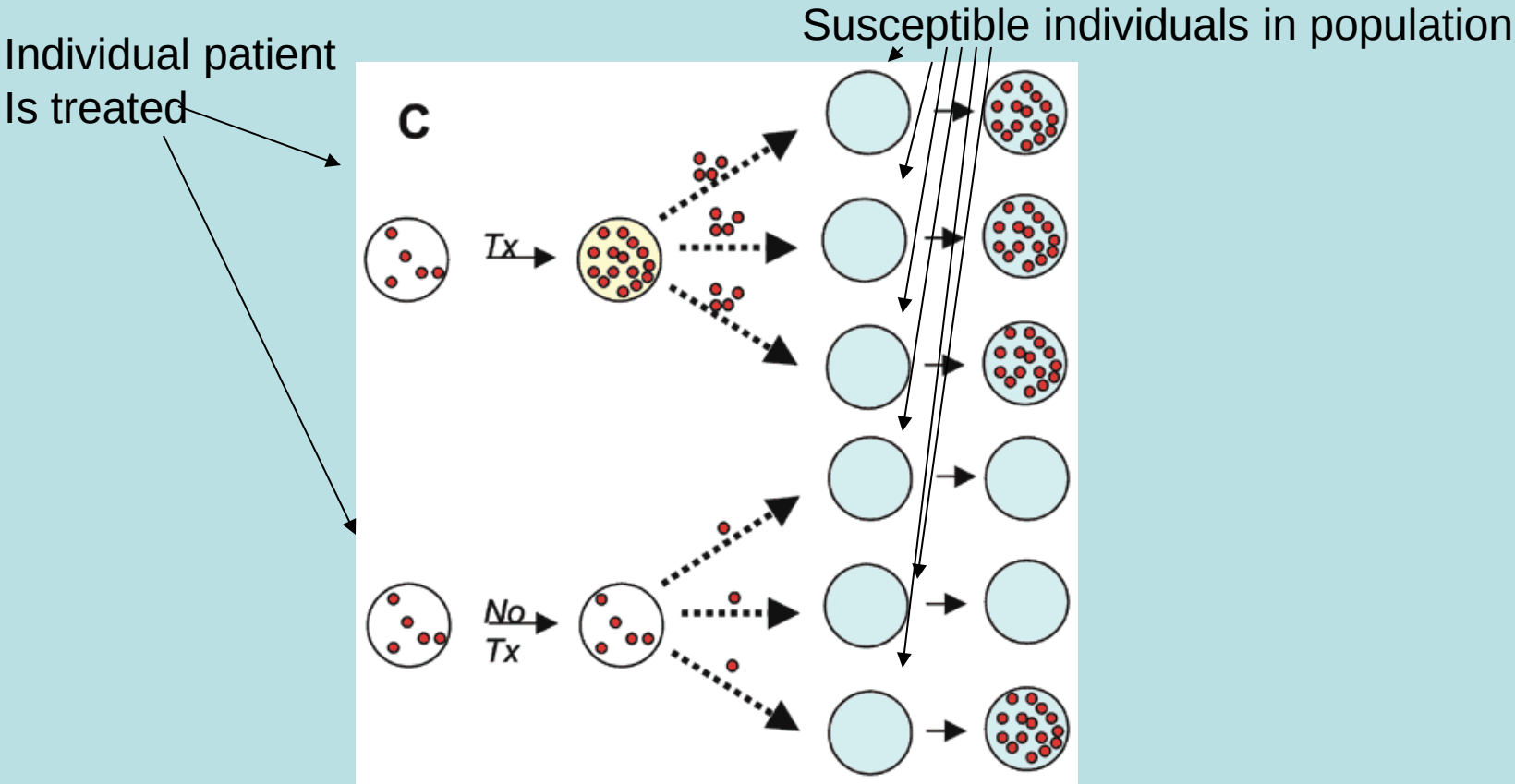
- **Random genetic mutations**
  - Strains propagate where fitness advantage exists for the mutation
- **Acquired resistance**
  - Horizontal gene transfer
- **Resistance genes code:**
  - **Efflux pumps** (rid the cell of the antimicrobial)
  - **Enzymes** that metabolize the antimicrobial
  - **Ribosomal protection**
  - **Physical-chemical features** that inhibit antimicrobial entry into the cell



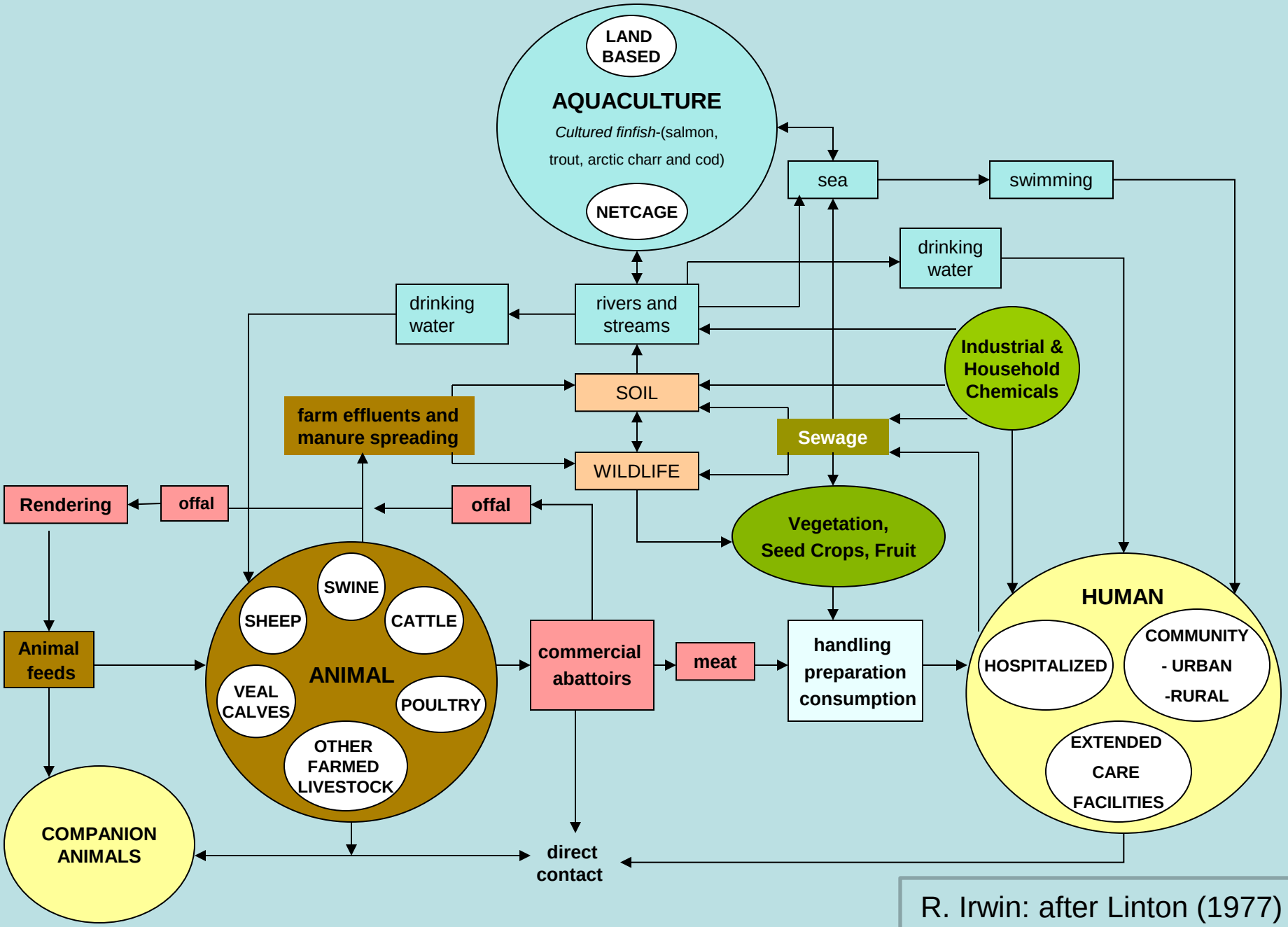
Graphics: FDA

How does antimicrobial selection pressure help to propagate and transmit AMR?

One example from: Lipsitch and Samore (2002)

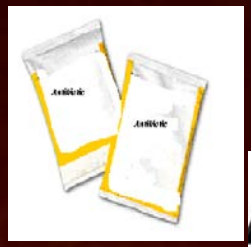


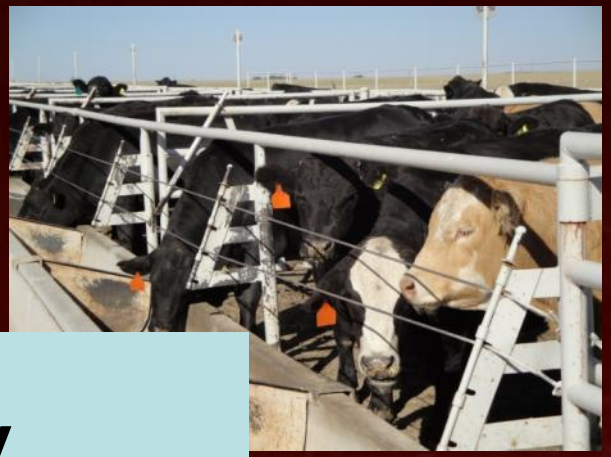
ECOLOGY OF ANTIMICROBIAL RESISTANCE



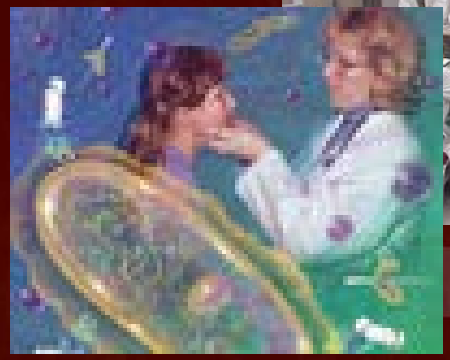
R. Irwin: after Linton (1977)

What do we know about the risks from agricultural use of antimicrobials?

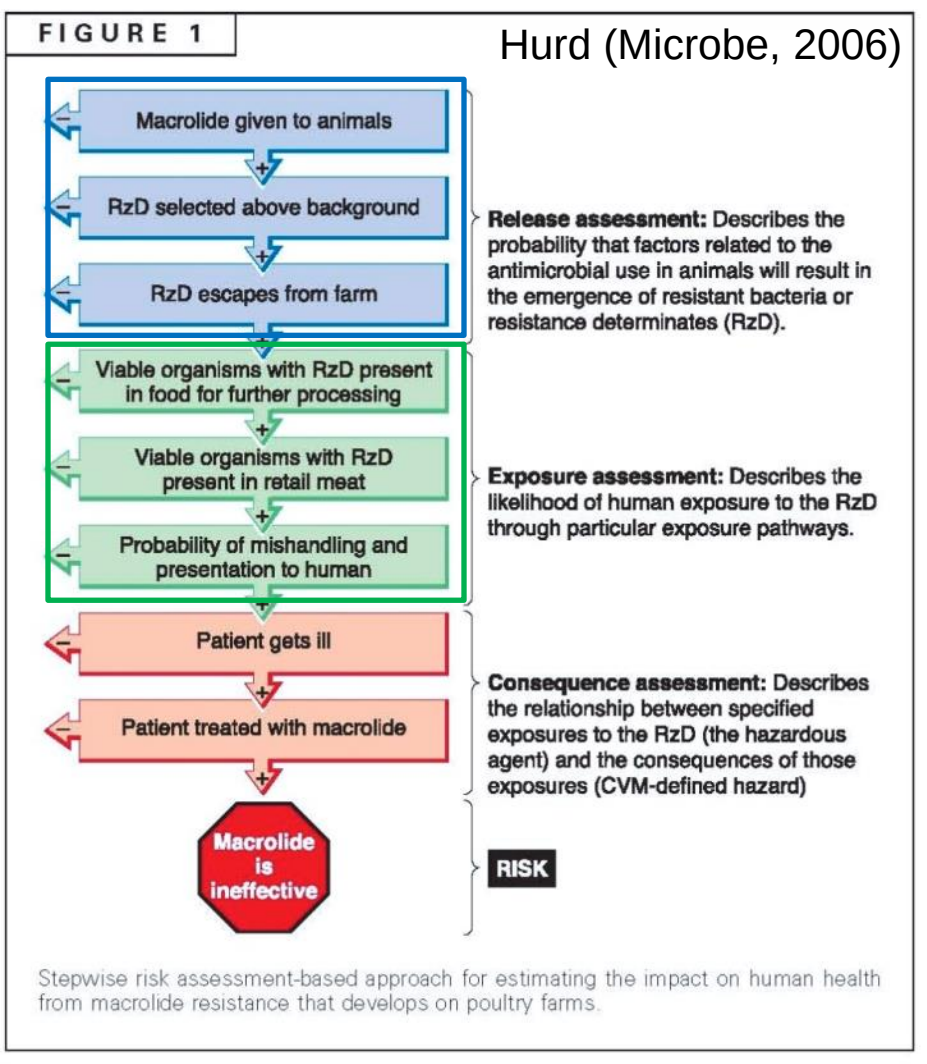




Surprisingly little…

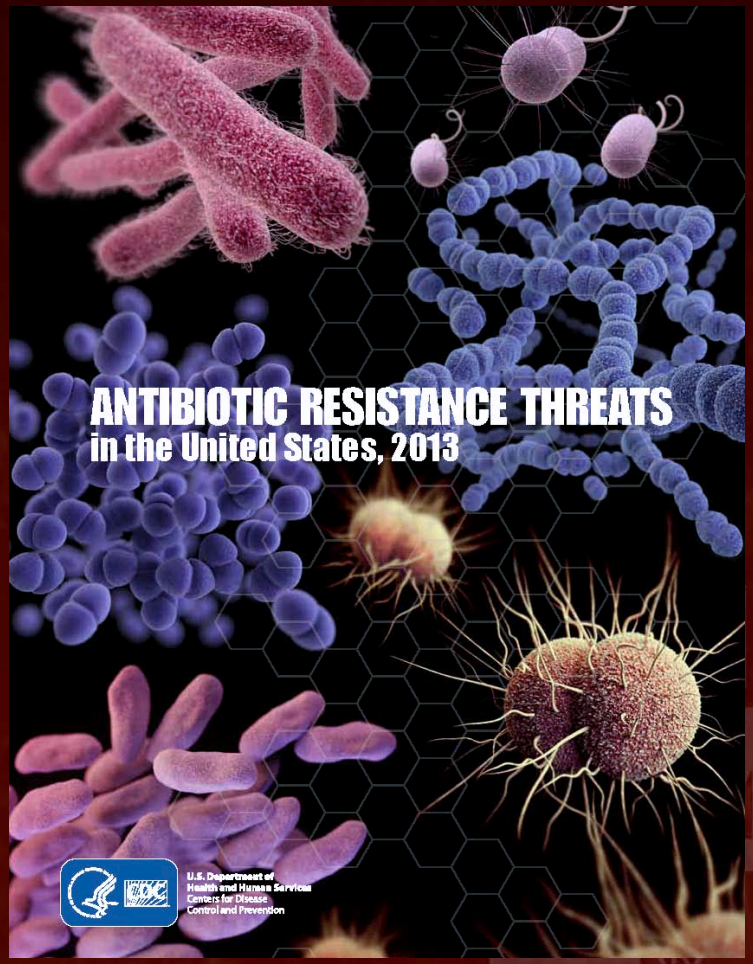


One risk assessment framework

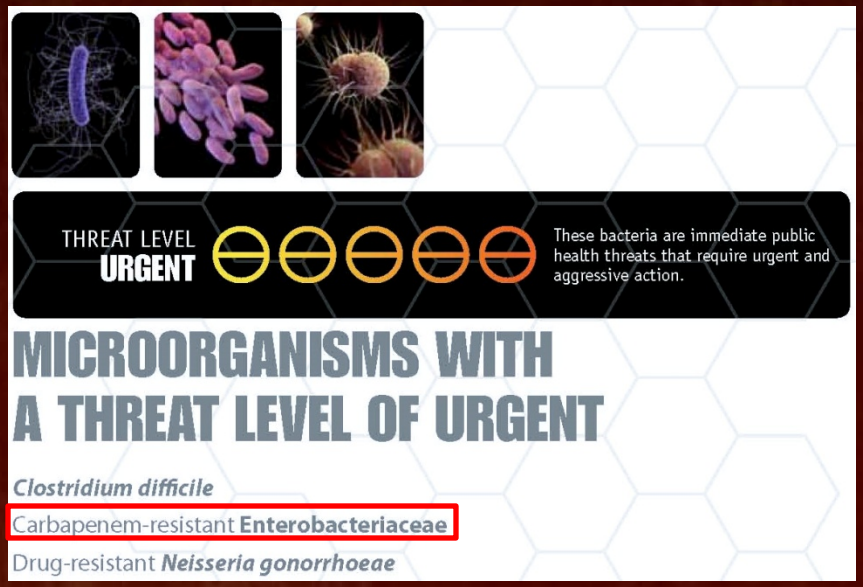


CDC threat report

- September, 2013
- Three threat levels
  - Urgent
  - Serious
  - Concerning



Introduction - Urgent threat



- Of concern to U.S. food production
  - *Carbapenem-resistant Enterobacteriaceae (CREs)

*Direct selection by carbapenems does not occur in US agriculture

Notes from the field…

Notes from the Field: Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing Klebsiella pneumoniae — Washoe County, Nevada, 2016 | MMWR

MENU CDC A-Z SEARCH

CDC > MMWR

Notes from the Field: Pan-Resistant New Delhi Metallo-Beta-Lactamase-Producing *Klebsiella pneumoniae* — Washoe County, Nevada, 2016

Weekly / January 13, 2017 / 66(1);33

Format: Select one

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View suggested citation

1818
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Mendeley (17)

On August 25, 2016, the Washoe County Health District in Reno, Nevada, was notified of a patient at an acute care hospital with carbapenem-resistant Enterobacteriaceae (CRE) that was resistant to all available antimicrobial drugs. The specific CRE, *Klebsiella pneumoniae*, was isolated from a wound specimen collected on August 19, 2016. After CRE was identified, the patient was placed in a single room under contact precautions. The patient had a history of recent hospitalization outside the United States. Therefore, based on CDC guidance (*1*), the isolate was sent to CDC for testing to determine the mechanism of antimicrobial resistance, which confirmed the presence of New Delhi metallo-beta-lactamase (NDM).

The patient was a female Washoe County resident in her 70s who arrived in the United States in early August 2016 after an extended visit to India. She was admitted to the acute care hospital on August 18 with a primary diagnosis of systemic inflammatory response syndrome, likely resulting from an infected right hip seroma. The patient developed septic shock and died in early September. During the 2 years preceding this U.S. hospitalization, the patient had multiple hospitalizations in India related to a right femur fracture and subsequent osteomyelitis of the right femur and hip; the most recent hospitalization in India had been in June 2016.

Rare Superbug Gene Discovered on U.S. Pig Farm - NBC News

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HEALTH DEC 6 2016, 8:46 AM ET

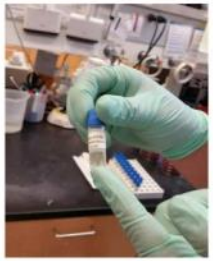
Rare Superbug Gene Discovered on U.S. Pig Farm

by MAGGIE FOX

SHARE

Researchers have found a rare and frightening superbug gene on a U.S. pig farm and say their discovery suggests raw meat could carry the dangerous germs into the human population.

No pigs scheduled for slaughter carried the mutant gene, the researchers stressed, and they haven't found any threat to people yet. And none of the pigs were sick. But the mutant should not have been on the farm at all and they have no idea how it got there.

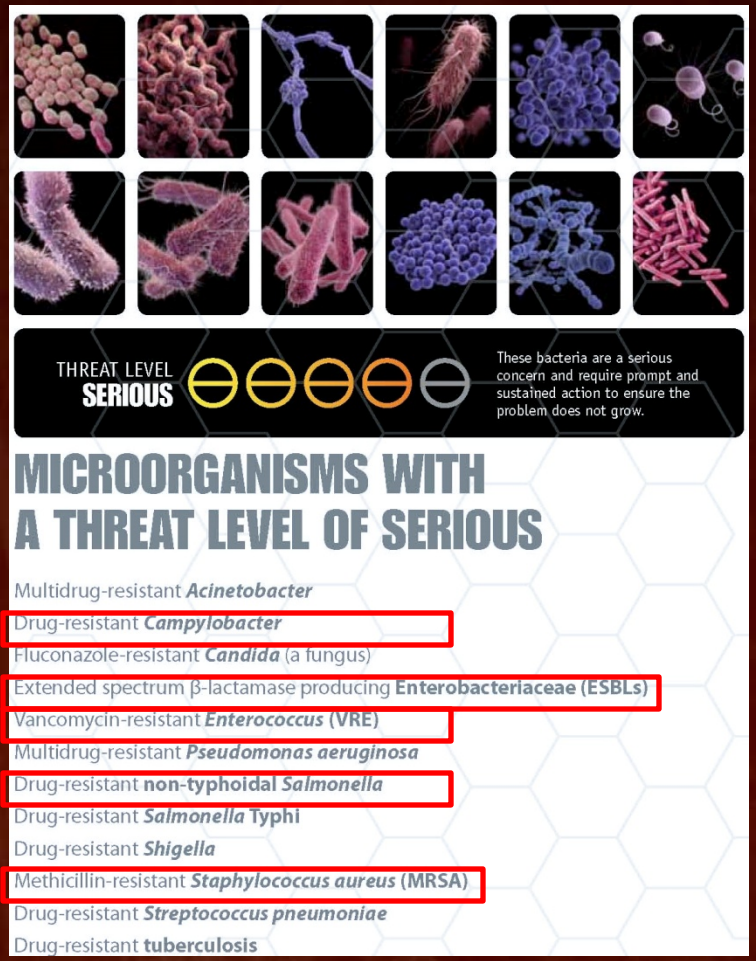


A researcher at Walter Reed Army Institute for Research holds a sample being tested for superbugs. | Maggie Fox, NBC News / NBC News

"It is an extremely rare gene. How it got on this farm, we don't know," said Thomas Wittum, chair of the veterinary medicine team at The Ohio State University, who led the study team.

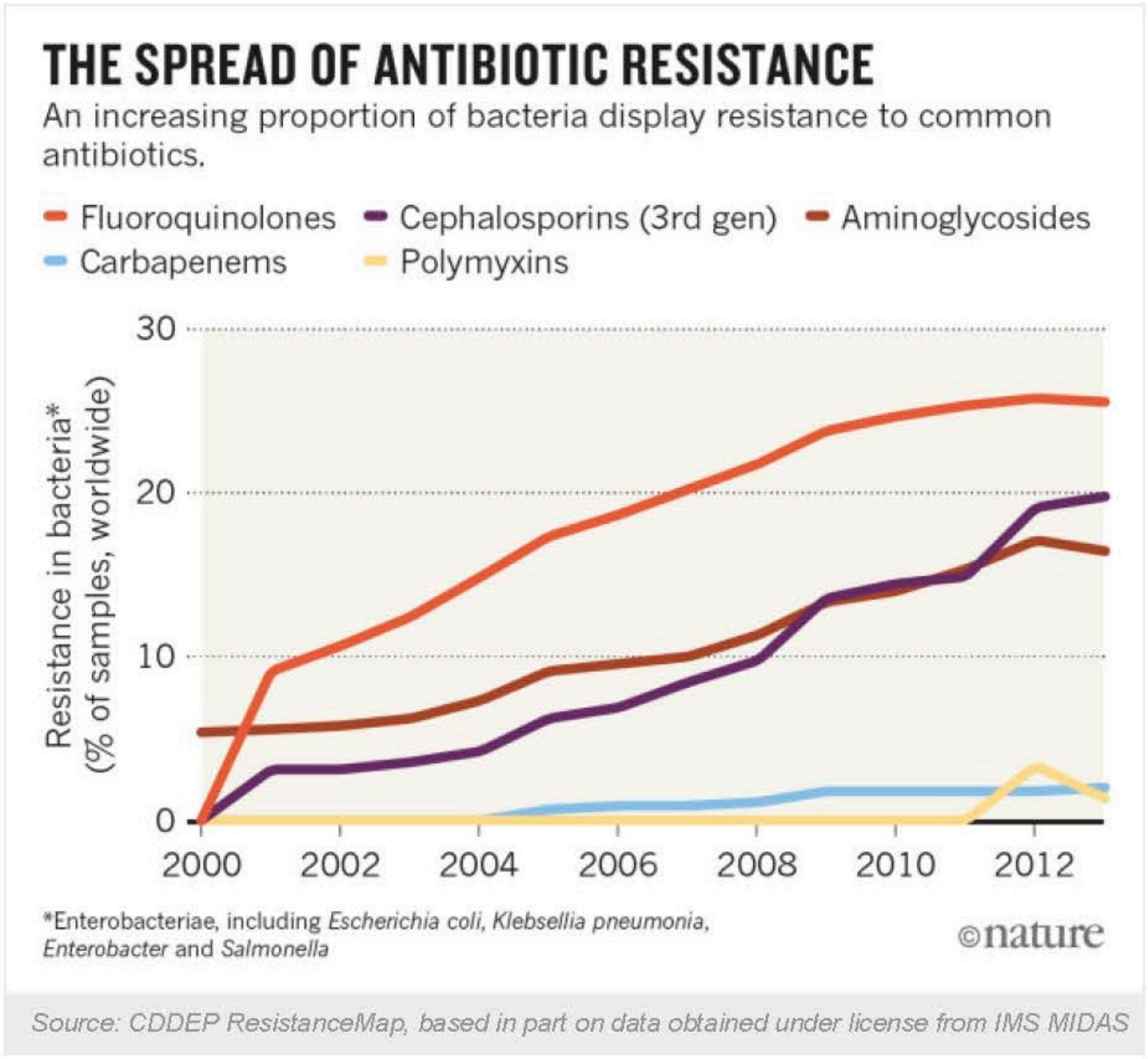
The gene is called bla IMP-27 and it gives bacteria the ability to resist the effects of a class of antibiotics called carbapenems.

Introduction – Serious threat

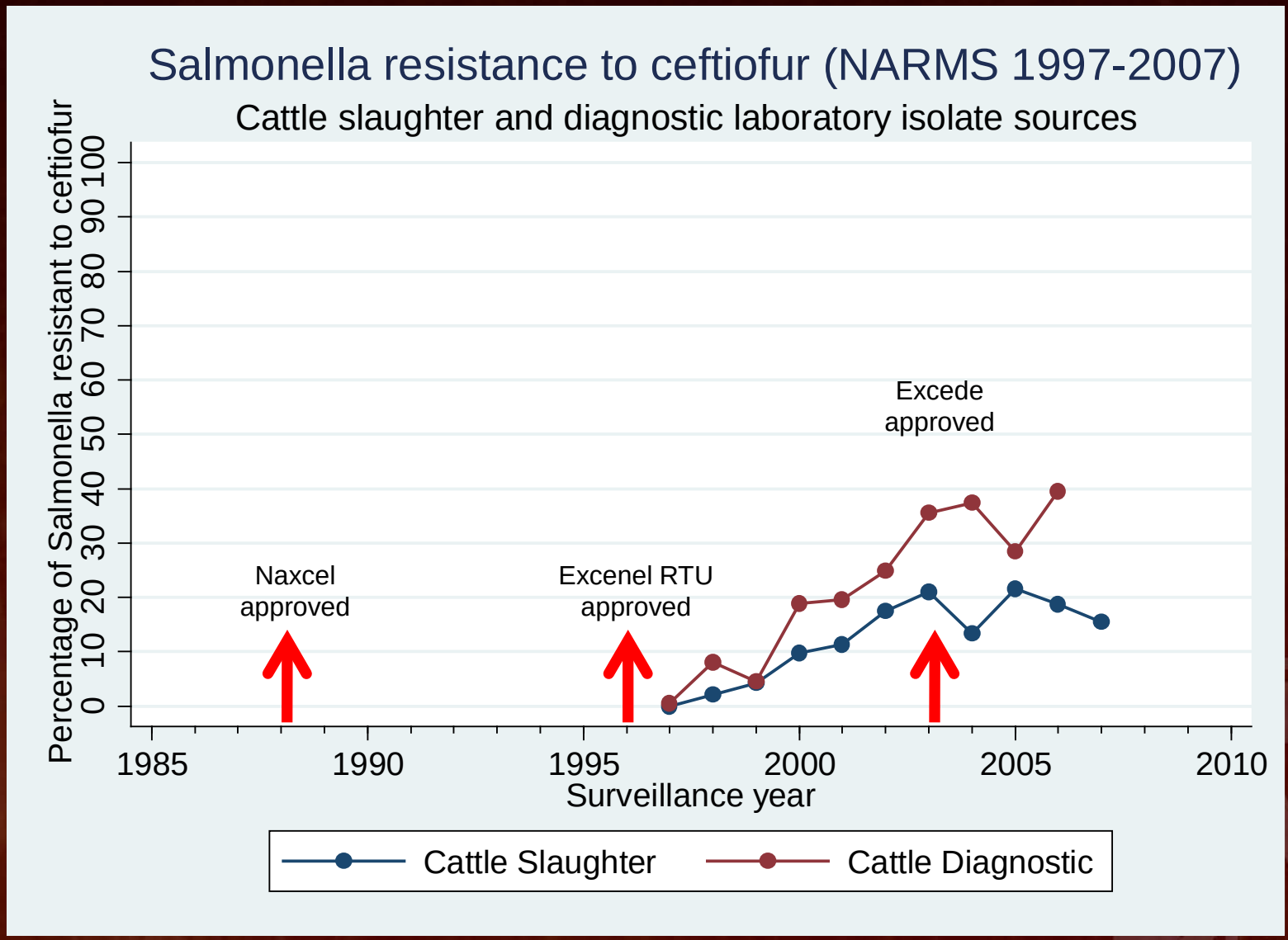


- Of concern to U.S. food production
  - *Drug-resistant *Campylobacter*
  - *Drug-resistant non-typhoidal *Salmonella*
  - *Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
    - 3rd and 4th generation cephem resistance
  - *Methicillin-resistant *Staphylococcus aureus*
  - Vancomycin-resistant *Enterococcus* spp.

*Commonly found in U.S. animal agriculture



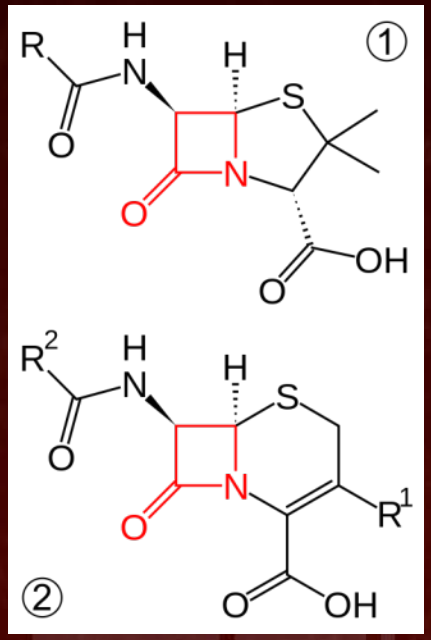
Nature: after CDDEP

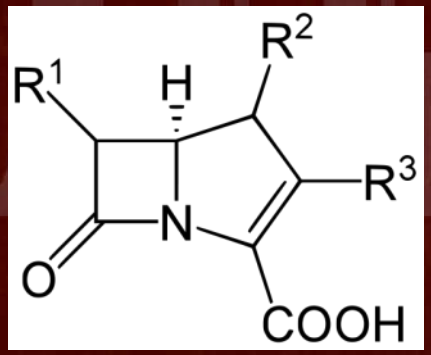


Data source: www.ars.usda.gov

Extended spectrum beta-lactams

- Beta-lactams
  - **Penicillin (1)**
  - **Ampicillin, amoxicillin**
  - **Cephalosporins (2)**
    - 1st generation (cefalotin,…)
    - 2nd generation (cefoxitin,…)
    - 3rd generation (ceftriaxone,…)
    - 4th generation (cefepime,…)
  - **Carbapenems**
    - Imipenem, ertapenem, meropenem





Extended Spectrum Beta-lactamases (ESBLs)

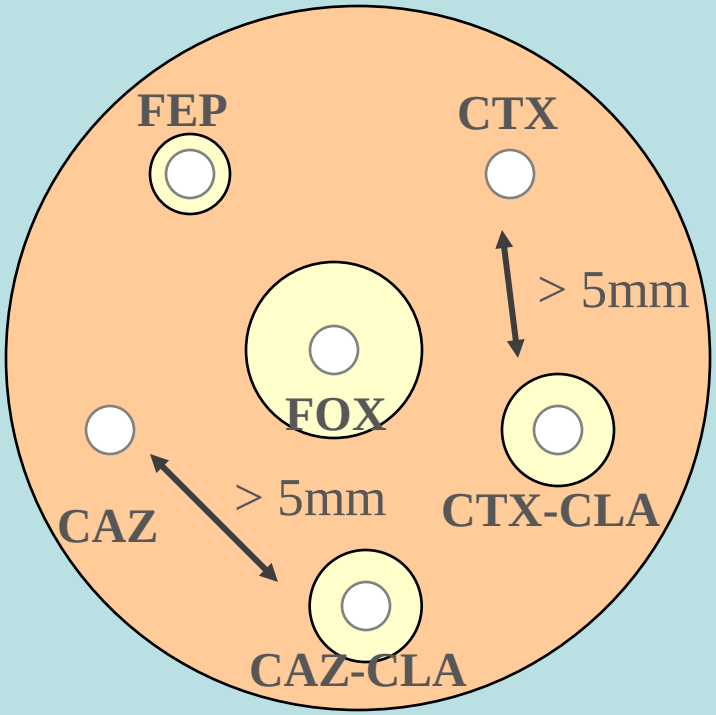
- Beta-lactamases
  - **Penicillin**
  - **Ampicillin, amoxicillin**
    - (*TEM-1*, *SHV-1*)
  - **Cephalosporins**
    - 1st generation (cefalotin) (*TEM*, *SHV-1*)
    - 2nd generation (cefoxitin) (*CMY-2*)
    - 3rd generation (ceftriaxone) (*CMY-2, CTX-M, SHV-2*)
    - 4th generation (cefepime) (*CTX-M*)
  - **Carbapenems**
    - Imepenem, ertapenem, meropenem (*KPC, NDM, OXA-48, IMP*)

Extended Spectrum Beta-lactamases (ESBLs)

- The abbreviations or acronyms that make up the beta-lactamase (*bla*$_{(subscript)}$) name are generally logical, in some cases historically informative, and occasionally amusing.
  - The CTX-M family of genes (active on cefotaxime, first isolated at Munich) family has multiple subtypes designated starting at CTX-M-1,
  - The SHV family refers to the sulfhydryl reagent variable,
  - The TEM was named after the patient from whom the bacterial isolate was discovered (Temoneira), and
  - The CMY family indicates it is active on cephamycins.

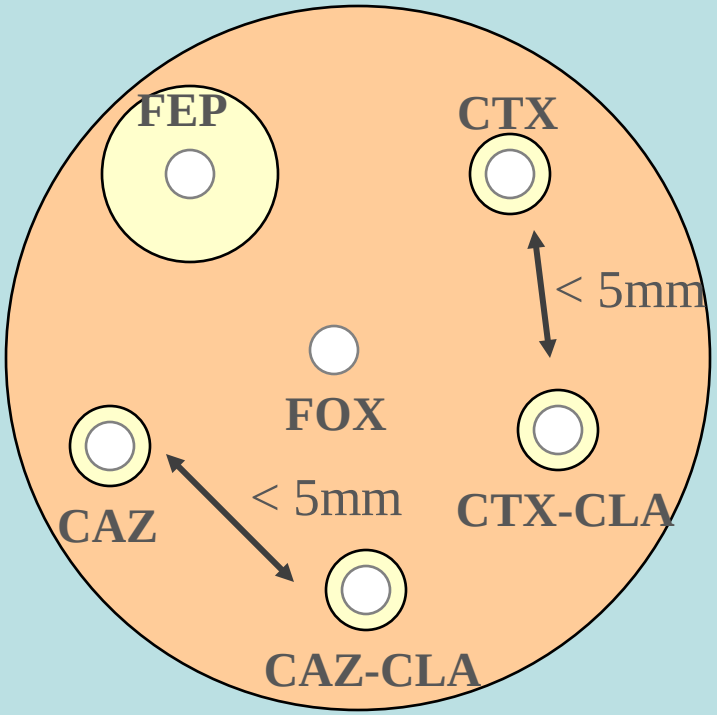
ESBL/AmpC β-lactamase disk diffusion test
(CTX = cefotaxime, CAZ = ceftazidime, CLA = clavulanic acid, FOX = cefoxitin, FEP = cefepime)

ESBL



Synergy!

AmpC



No synergy!

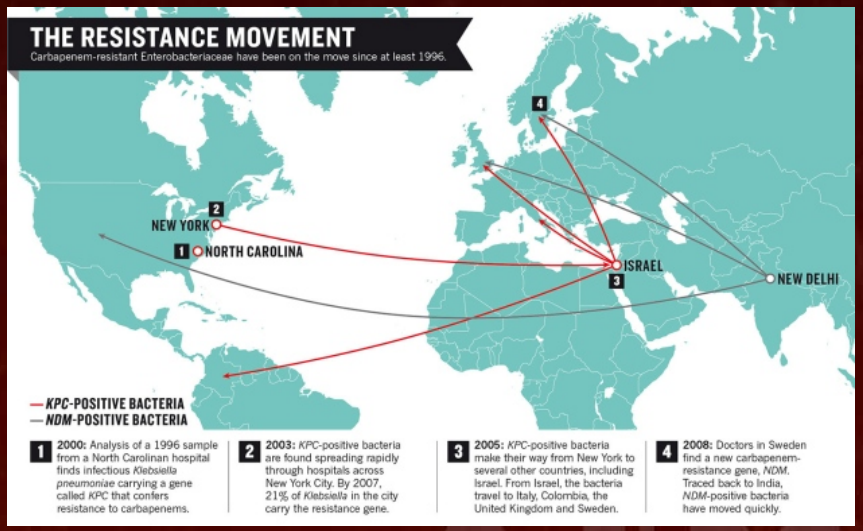
Courtesy: Rene Hendriksen, DTU

ESBLs versus AmpC in food animal species and food products

- Europe
  - ESBLs, particularly CTX-M
  - Poultry in Netherlands
- USA (and Canada)
  - AmpC, particularly CMY-2
  - Cattle and poultry in USA and Canada

Carbapenems

- Carbapenems
  - Imipenem, ertapenem, meropenem
  - No agricultural direct selection
  - Lots of background noise
  - KPC and NDM have been found in food animals overseas
- CREs
  - KPC***
  - NDM***
  - VIM
  - OXA-48
  - IMP



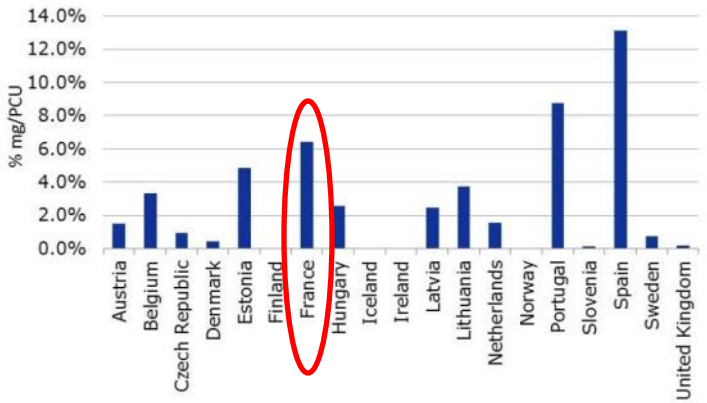
Maryn McKenna, Nature, July 24, 2013

Colistin

- Very old drug (Polymixin E)
  - Polymixin class
  - Effective against coliforms
- Nephrotoxic so rarely used in humans until recently
- Highly variable use in agriculture around the world
- So far as we know…
  - Lots in China, S and SE Asia, S America and Europe
  - Very little to no use in US and Canada

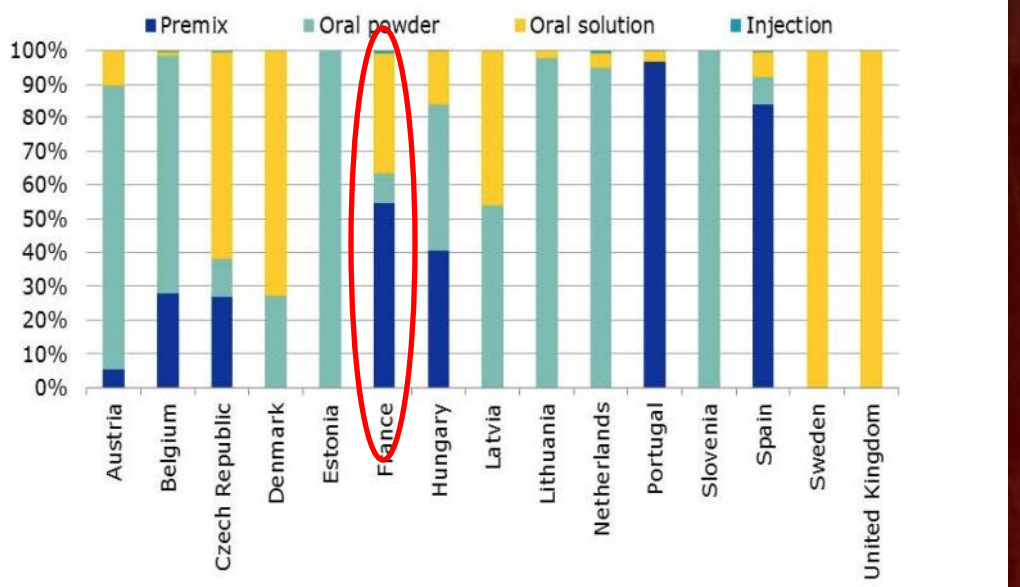
Colistin use in Europe

Figure 3 Percentage of sales for food producing animals (including horses), in mg per population correction unit (mg/PCU), of polymyxins, by country, for 2010 (ESVAC, 2012). No sales reported in Finland, Iceland, Ireland or Norway.



Use of colistin in food-producing animals in the European Union: development of resistance and impact on human and animal health
EMA/755938/2012 Page 8/25

Figure 4 Distribution of sales by pharmaceutical form for polymyxins, in tonnes of active ingredient, by country, for 2010 (ESVAC, 2012). No sales reported in Finland, Iceland, Ireland or Norway. Negligible amounts sold as bolus, oral pastes, intramammary and intrauterine preparations.



US NADA label

000017

FIRST GUARD™
(Colistimethate Sodium)
Sterile Powder

1. **Date:** June 1996

2. **Name of Applicant:** ALPHARMA INC.

3. **Address:** One Executive Drive
Fort Lee, NJ 07024

4. **Description of Proposed Action**

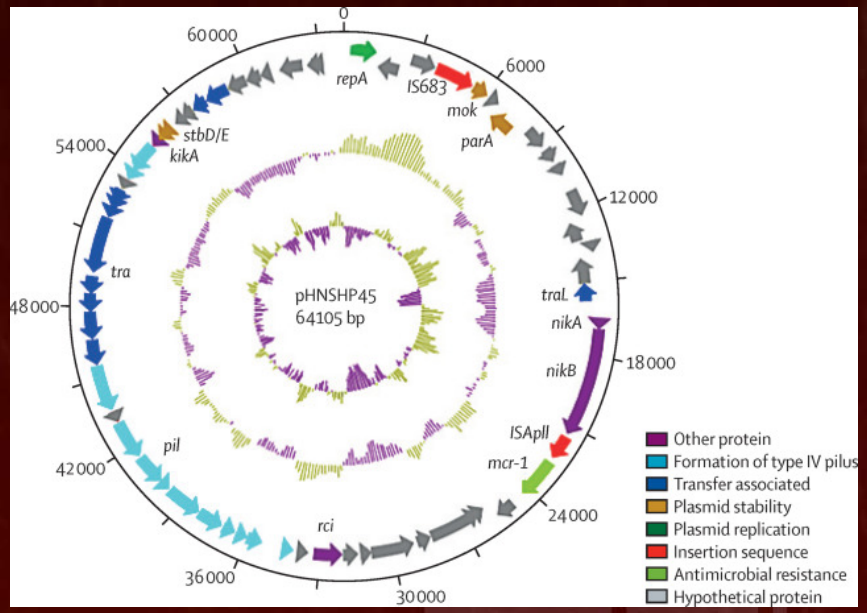
4.1 Request Approval

This environmental assessment is submitted to the new animal drug application (NADA) for the sterile powder First Guard™ (Colistimethate Sodium) for the treatment of colibacillosis in day-old chicks to prevent mortality in young chickens infected with *Escherichia coli* (early chick mortality).

The ultimate purpose is to increase the availability of poultry for human consumption. Economic benefits are to reduce the cost of poultry production, thereby reducing the cost of poultry products to the consumer.

February 2016: Lancet Infectious Diseases

We observed *mcr-1* carriage in *E. coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection.



The plasmid carrying *mcr-1* was mobilised to an *E. coli* recipient at a frequency of 10^{-1} to 10^{-3} cells per recipient cell by conjugation, and maintained in *K pneumoniae* and *Pseudomonas aeruginosa*.

Liu et al 2016 (online November 2015)

France as one example

Table 1. Isolate information for colistin-resistant isolates selected for whole genome sequencing. Sample ID, serotype, sample origin information (year of collection, sample type, and French department [Dept.]), phenotypic antimicrobial susceptibility data, Genbank accession number, and plasmid replicon harboring *mcr-1* for each isolate

Sample ID	Serotype	Year	Sample Type	Dept.	AMP	AMC	CAZ	CHL	CEF	CIP	CST	CTX	GEN	KAN	NAL	OFX	STR	SSS	SXT	TET	Accession Number	Replicon harboring *mcr-1*
2013LSAL02374	Derby	2013	chipolata sausage	62				■			■						■	■	■	■	LNCZ00000000	IncP
12CEB4337SAL	Paratyphi B	2012	ready-to-cook guinea fowl pie	56				■		■	■		■				■	■	■	■	LKJK00000000	IncX4
12CEB2196SAL	Paratyphi B	2012	chicken breast with skin	85				■		■	■		■		■		■	■	■	■	LKJJ00000000	IncX4
2013LSAL04524	I 4,[5],12:i:-	2013	boot swabs from broiler farm	01	■			■			■		■				■	■	■	■	LKJD00000000	IncP

Black blocks represent resistance; AMP, ampicillin; AMC, amoxicillin-clavulanic acid; CHL, chloramphenicol; CAZ, ceftazidime; CEF, cefalotine; CIP, ciprofloxacin; CST, colistin (highlighted in gray); CTX, cefotaxime; GEN, gentamicin; KAN, kanamycin; NAL, nalidixic acid; OFX, ofloxacine; STR, streptomycin; SSS, sulfonamides; SXT, trimethoprim-sulfamethoxazole; TET, tetracycline N/A; no information available

- EU surveillance directive
  - 5.9% prevalence in turkey *E. coli*
- High levels of colistin use in animal agriculture

Webb et al, Lancet Inf Dis 2016

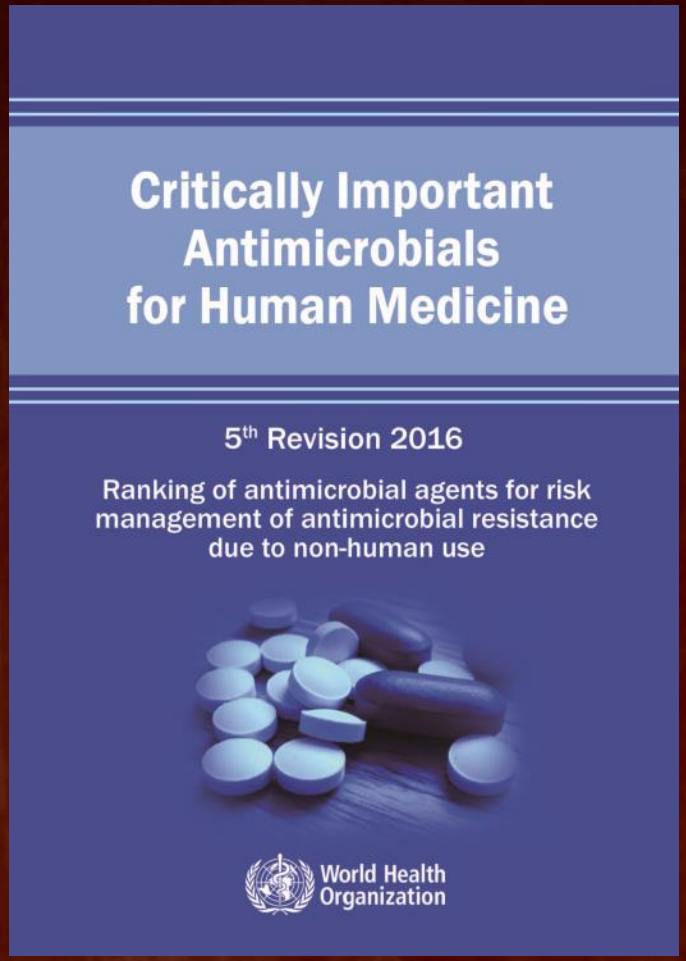
Year	Animals	*E. coli* strains tested for MIC N	*E. coli* strains resistant to colistin N	Proportion of *mcr-1* positive (n) among colistin-resistant *E. coli* strains (N) n/N	Prevalence of *mcr-1* positive *E. coli* strains % (95%CI)
2014	Turkeys	239	14	14/14	5.9 (2.9–8.8)
	Broilers	227	4	4/4	1.8 (0.1–3.5)
2013	Pigs	196	1	1/1	0.5 (0.0–1.5)
	Broiler	193	3	3/3	1.6 (0.0–3.3)
2012	Pigs	194	0	N.a.	N.a.
	Broiler	201	0	N.a.	N.a.
2011	Pigs	200	1	1/1	0.5 (0.0–1.5)
2007	Turkeys	ND[a]	ND[a]	0/246[a]	0 (0.0–1.2)
Total	All	1,450	23	N.a.[a]	N.a.[a]

CI: confidence interval; MIC: minimum inhibitory concentration; N.a.: not applicable; ND: not determined.

[a] As susceptibility to colistin was not tested in 2007, each isolate obtained in that year was tested for the presence of *mcr-1*.

Perrin-Guyomard Eurosurveillance 2016

Just published April 14, 2017



8. Highest Priority Critically Important Antimicrobials

These are the classes of drugs that met all three priorities (P1, P2, and P3): quinolones, third- and fourth- and fifth-generation cephalosporins, macrolides and ketolides, glycopeptides and polymyxins.

Quinolones are known to select for quinolone-resistant *Salmonella* and *E. coli* in animals. At the same time, quinolones are one of few available therapies for serious *Salmonella* and *E. coli* infections. Given the high incidence of human disease due to *Salmonella* and *E. coli*, the absolute number of serious cases is substantial.

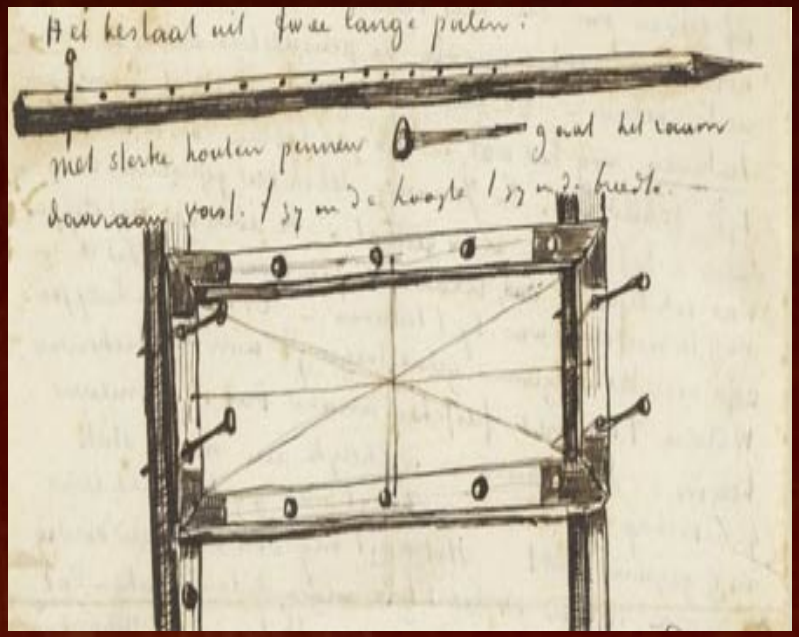
Cephalosporins (3rd and higher generation) are known to select for cephalosporin-resistant *Salmonella* and *E. coli* in animals. At the same time, third- and higher generation cephalosporins are one of few available therapies for serious *Salmonella* and *E. coli* infections in humans, particularly in children. Given the high incidence of human disease due to *Salmonella* and *E. coli*, the absolute number of serious cases is substantial.

Macrolides and ketolides are known to select for macrolide-resistant *Campylobacter* spp. in animals, especially *Campylobacter jejuni* in poultry. At the same time, macrolides are one of few available therapies for serious *Campylobacter* infections, particularly in children, for whom quinolones are not recommended for treatment. Given the high incidence of human disease due to *Campylobacter* spp., especially *Campylobacter jejuni*, the absolute number of serious cases is substantial.

Glycopeptides are known to select for glycopeptide-resistant *Enterococcus* spp. in food animals (e.g. when avoparcin was used as a growth promoter, vancomycin-resistant enterococci (VRE) developed in food animals and were transmitted to people). At the same time, glycopeptides are one of the few available therapies for serious enterococcal infections. Given the high number of cases, the previously documented occurrence of transmission of VRE to people from food animals, and the very serious consequences of treatment failures in such cases, glycopeptides are classified as being of the highest priority.

Polymyxins (e.g. colistin) are known to select for plasmid mediated polymyxin-resistant *E. coli* in food animals. At the same time, intravenous polymyxins are one of few available therapies for serious *Enterobactericeae* and *Pseudomonas aeruginosa* multi-resistant infections in people in healthcare settings in many countries, especially in seriously ill patients in critical care. Given the high incidence of human disease due to *Enterobactericiae*, the absolute number of serious cases where colistin is needed can be considered substantial.

Policy: perspectives and values



Shared perspectives

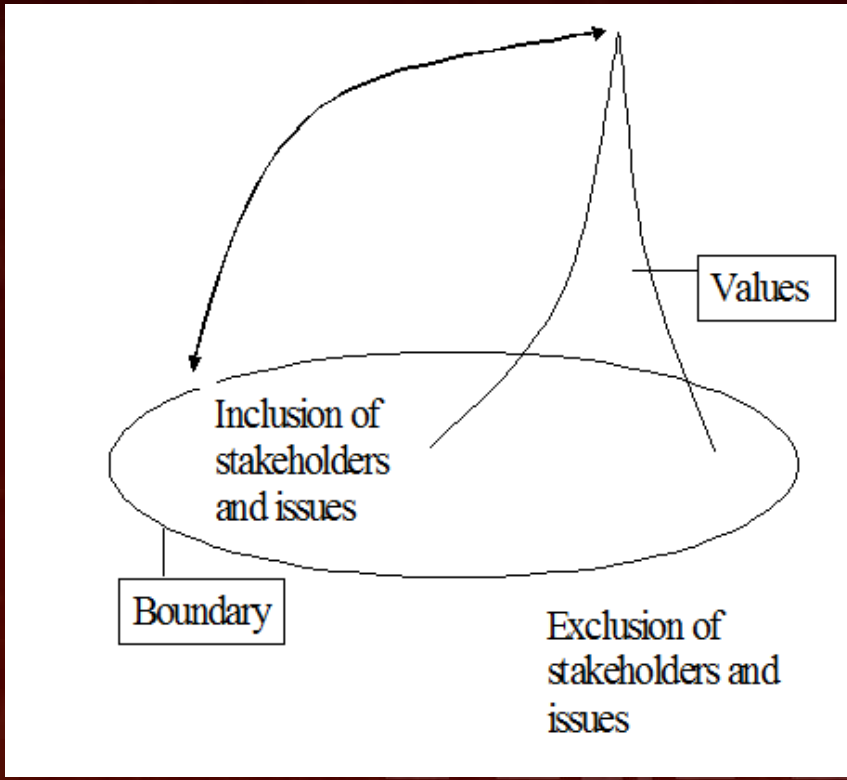
- Antimicrobials enhance the health and well-being of humans and animals
- There is overuse/misuse of antimicrobials in both human and animal settings
- Protecting the efficacy of antimicrobials for future generations is a good thing to do

One person's perspective

- Human medicine takes precedence over veterinary medicine and animal agriculture
- Precautionary principle should prevail
- Increasing order of defensible use: growth promotion, prophylaxis, control, treatment
- Drugs deemed critically important to human medicine should not be used at all in animal agriculture

Systemic Intervention - Values

- *"Purposeful action by an agent to create change (in relation to reflection upon boundaries)"…* (Midgley 2006)

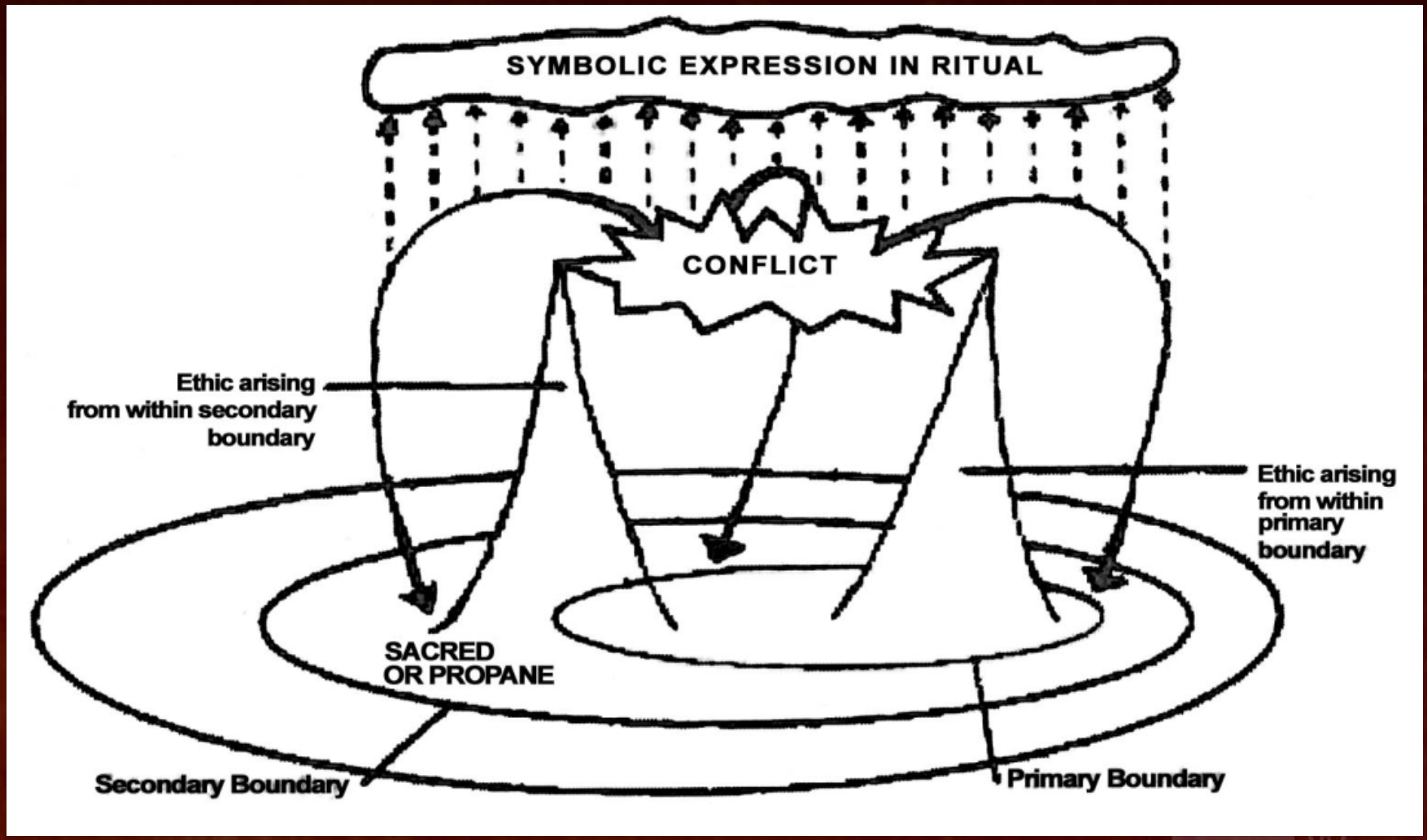


(after Cabrera 2008, and modified by Midgley)

Another person's perspective

- Antimicrobial therapy should be viewed as a last resort
  - A systemic 'failure' of sorts
- Prevention and control of disease in food animals improves both animal and human health
- Antimicrobials help improve food security in a world with growing needs

Systemic Intervention - Values

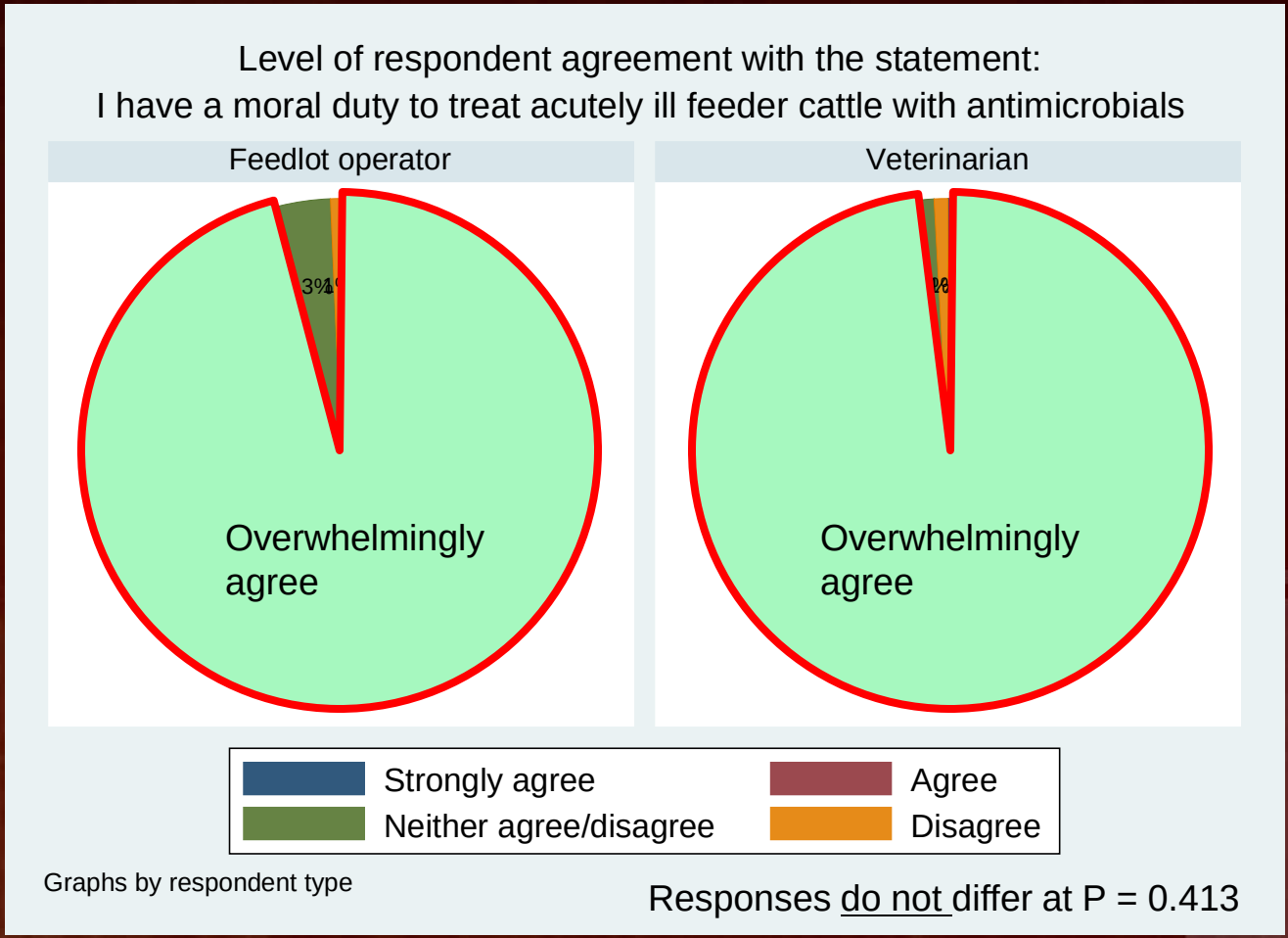


(after Cabrera 2008, and modified by Midgley)

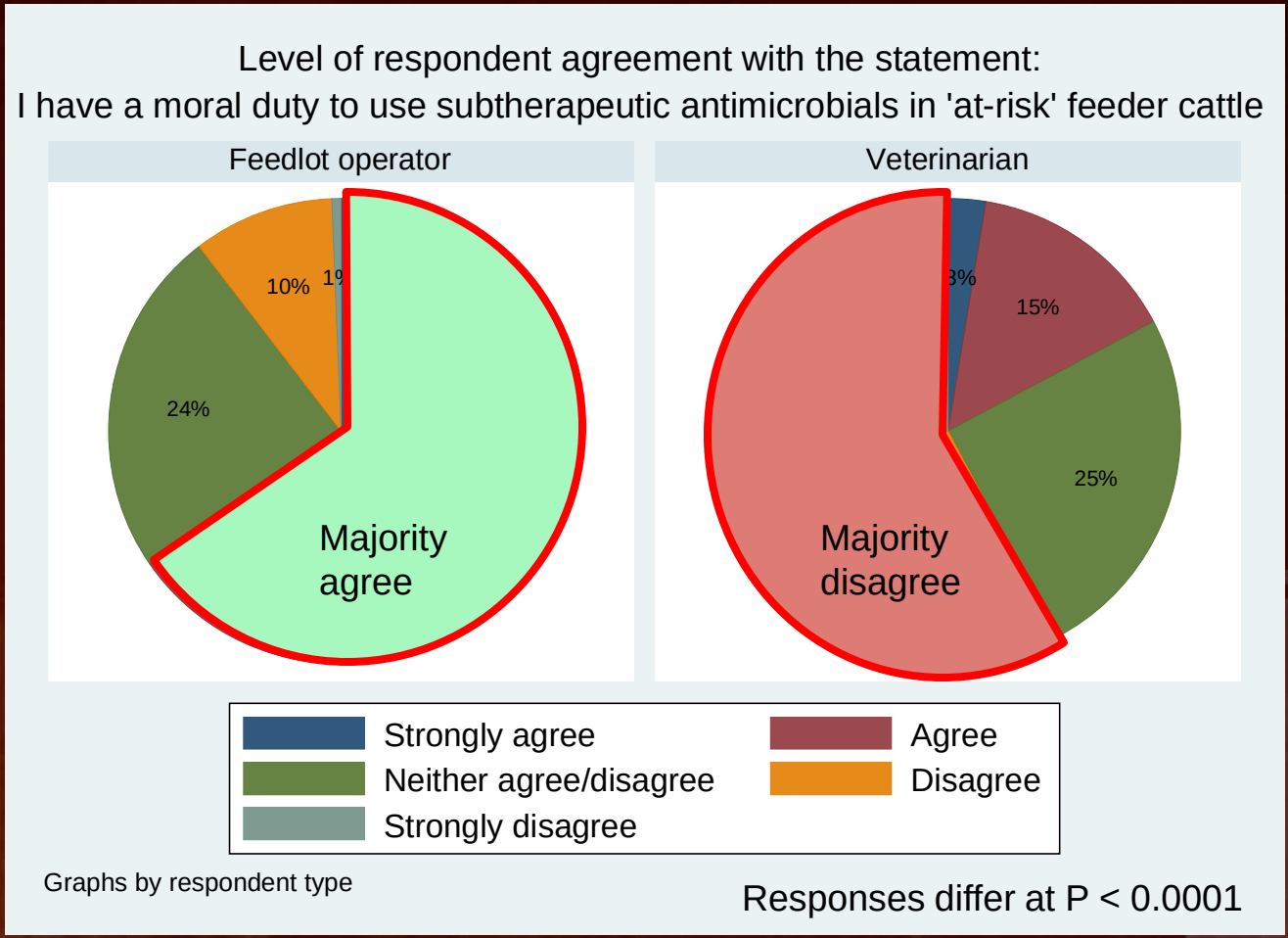
The ‘economies’ of antibiotic use

- Monetary economics
  - Cost/benefit
  - ‘Behavioral control’
- Political economy
  - Regulations, patent law
- Moral economy
  - Attitudes, beliefs, moral and social norms, trust, intentions, behavioral constraints

I have a moral duty to use antimicrobials as therapy



I have a moral duty to use antimicrobials as non-therapy



The future: where do we go from here?

"To preserve the effectiveness [of antibiotics], we simply must use them as judiciously as possible"

Dr. Joshua Sharfstein, then US FDA deputy commissioner, in June of 2010 suggesting that antibiotics should only be used to protect the health of an animal and not to help it grow faster or more efficiently

"Preserving antimicrobial effectiveness in the future through ethical practices today"

McDonald's Global Vision for Antimicrobial Stewardship in Food Animals*

"Preserving antimicrobial effectiveness in the future through ethical practices today"

As the body of scientific evidence grows, and scientific consensus emerges, we recognize the importance of continuing to evolve our position on antimicrobial use. In 2014, McDonald's assembled a team of experts from around the world to study, debate and comment on antimicrobial use in food animals. These experts represented veterinarians, physicians, academicians, clinical pharmacologists, epidemiologists, ethicists, animal health and welfare experts and other food animal production experts, and developed recommendations for antimicrobial stewardship in food animals, building on McDonald's 2003 global policy on antibiotic use in food animals.

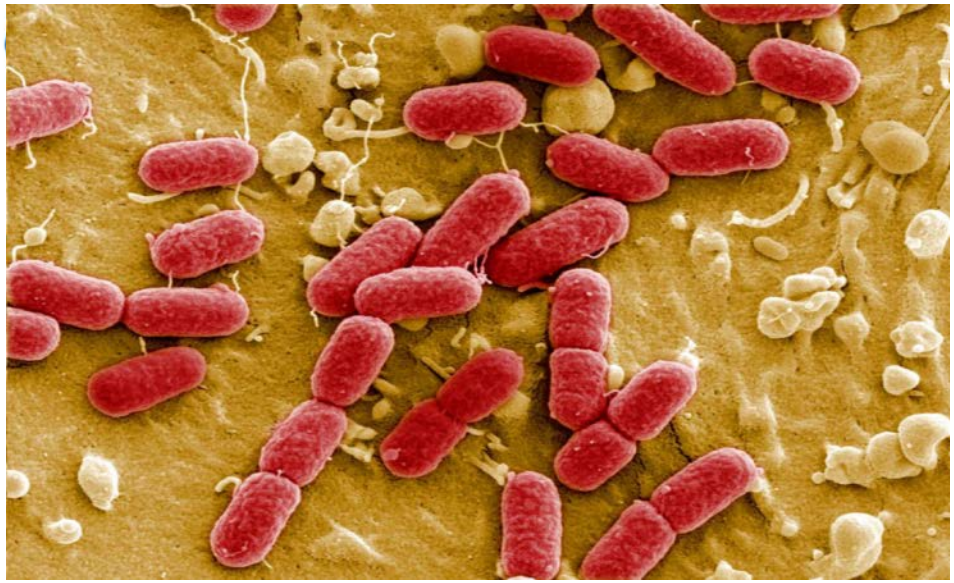
We anticipate the body of knowledge on antimicrobial use in food animals and its impact on antimicrobial resistance in animal and human populations will continue to evolve. As a global enterprise conducting business in more than 100 countries, we also understand the complexities of different global industry structures, government bodies and regulations, and regulatory oversight where we conduct business, making it difficult to implement a single approach that has the same impact globally. It is our intent to work with governments, non-government organizations (NGOs), veterinary and university extension networks, industry leaders and retailers in roundtables to gain alignment and identify paths forward.

News › Science

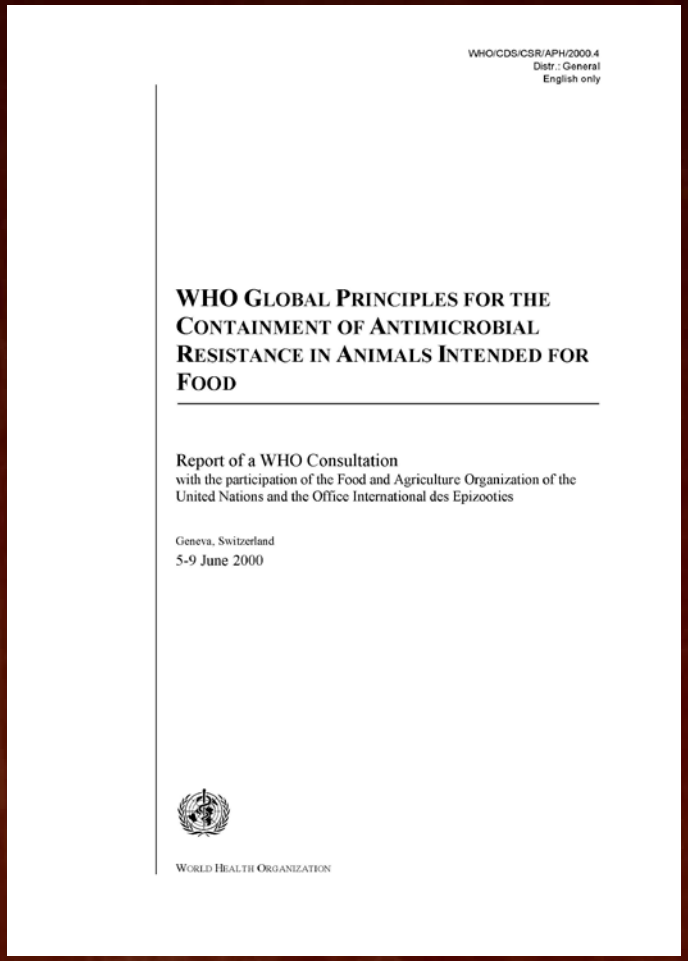
Antibiotics: World leaders sign groundbreaking UN declaration to tackle 'biggest global health threat'

If antibiotics lose their effectiveness then key medical procedures – including gut surgery, caesarean sections, joint replacements and chemotherapy – could become too dangerous to perform

Adam Withnall | @adamwithnall | Wednesday 21 September 2016 | 17 comments



Practice evidence: the role of informed policy



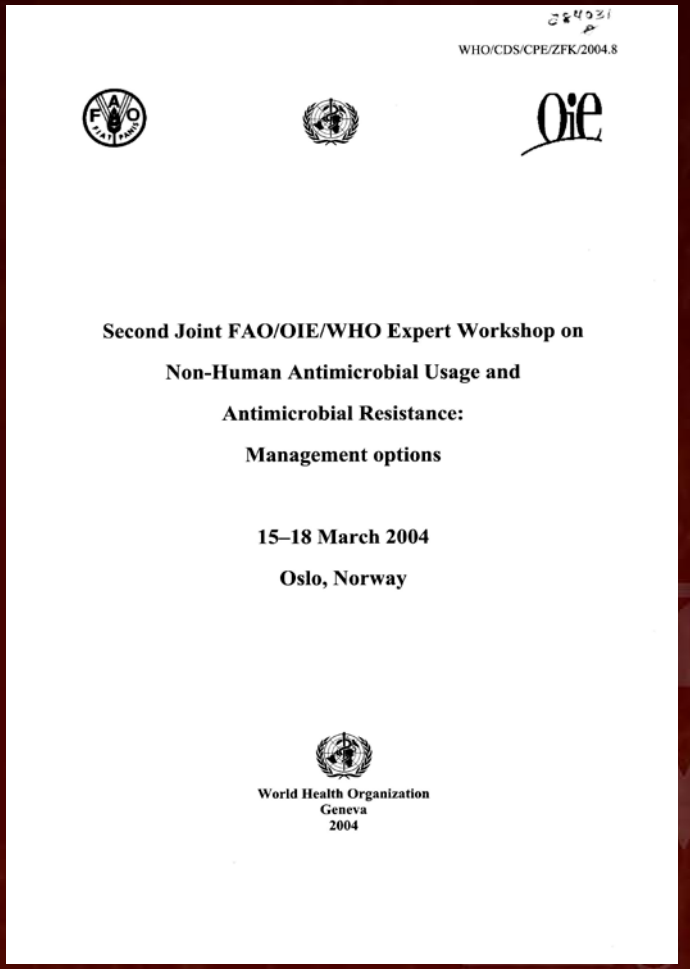
WHO/CDS/CSR/APH/2000.4
Distr.: General
English only

WHO GLOBAL PRINCIPLES FOR THE CONTAINMENT OF ANTIMICROBIAL RESISTANCE IN ANIMALS INTENDED FOR FOOD

Report of a WHO Consultation
with the participation of the Food and Agriculture Organization of the United Nations and the Office International des Epizooties

Geneva, Switzerland
5-9 June 2000

WORLD HEALTH ORGANIZATION



WHO/CDS/CPE/ZFK/2004.8

Second Joint FAO/OIE/WHO Expert Workshop on Non-Human Antimicrobial Usage and Antimicrobial Resistance: Management options

15–18 March 2004

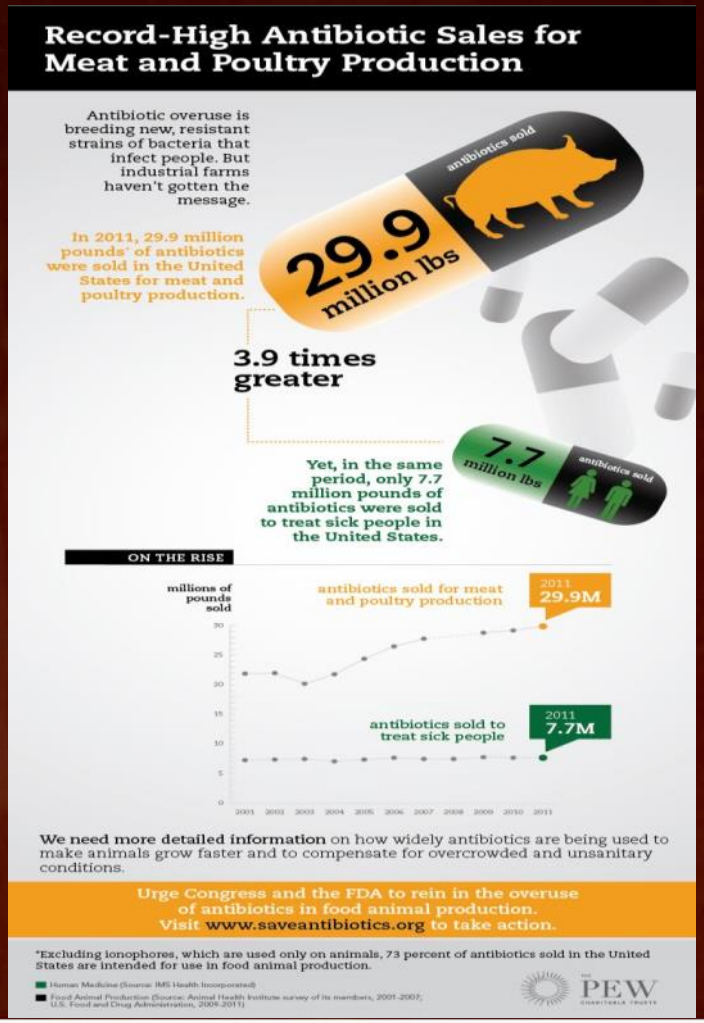
Oslo, Norway

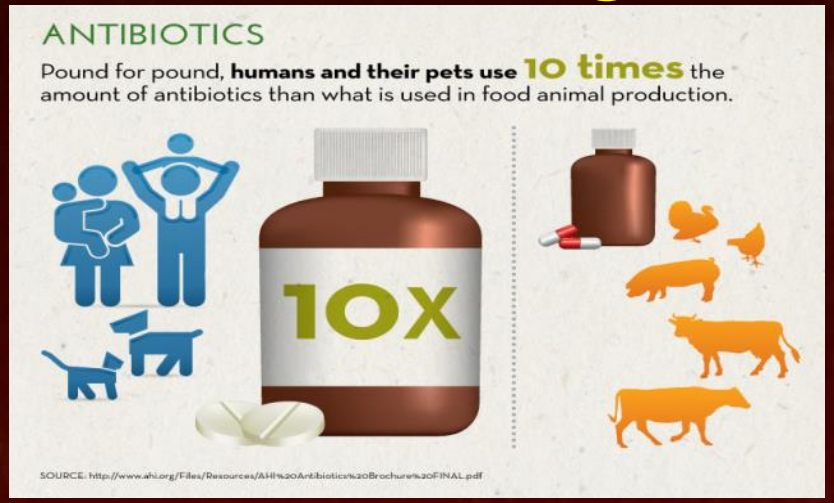
World Health Organization
Geneva
2004

WHO (2000) Global Principles on Containment of AMR

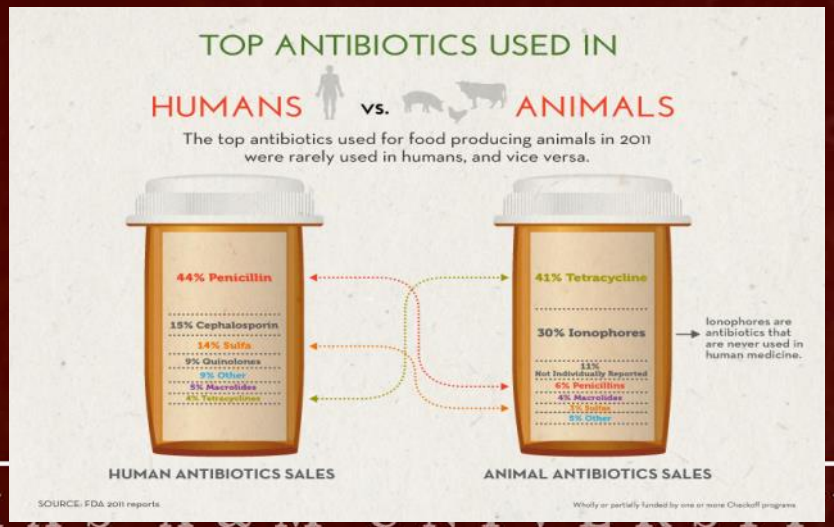
- “The[se] strengthen and endorse earlier WHO recommendations such as the need to terminate the use of antimicrobial growth promoters pending comprehensive human health safety evaluations, and the need to establish surveillance systems on antimicrobial consumption”.

Antibiotic usage data?
It depends who is counting





www.fooddialogues.com



www.pewhealth.org

FAO/OIE/WHO Expert (2004) Workshop: Management Options

The workshop process has resulted in suggestions for a way forward in this area, for Codex, as well as for FAO, WHO and OIE. Among the important conclusions were the following:

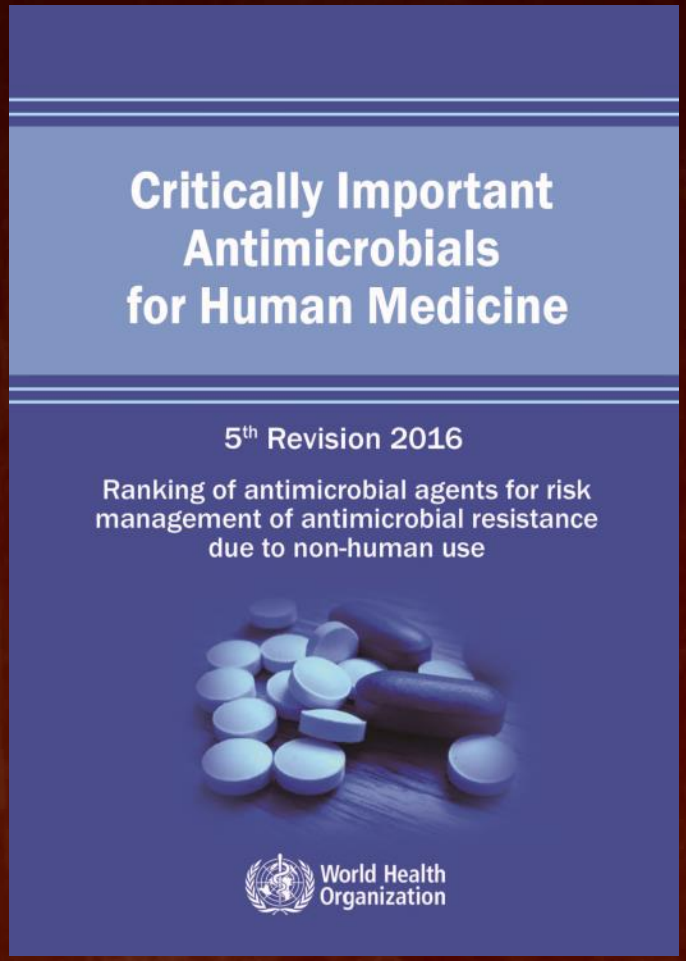
- The risks associated with non-human antimicrobial use and antimicrobial resistance should be part of the human safety assessment. The concept of "thresholds of resistance" should be pursued as a tool for risk management. A range of risk management actions should be triggered if these thresholds are exceeded.
- The concept of "critically important" classes of antimicrobials for humans should be developed by WHO with a view to enabling specific resistance-preventive actions for these antimicrobials in the context of non-human use. A similar list of "critically important" classes of antimicrobials for animals should be pursued by OIE.

Criticality – what it is, and why it's important

History of the lists of criticality

- U.S. regulatory actions
  - FDA late 1990s with fluoroquinolones and glycopeptides banning extra-label uses
  - Again in 2012 with cephalosporins
- Historical succession of mandates and recommendations culminating in 2005-2017 lists from WHO and OIE
- Updates and revisions
  - Ongoing revisions with WHO and OIE (and FDA GFI #152 Appendix A?)

WHO List of Critically Important Antimicrobials



- When a new class of [human] drug comes on the market, it should be considered critically important from the outset unless strong evidence suggests otherwise

- Existing drugs such as carbapenems, linezolid, tigecycline, and daptomycin, which are not currently used in food production, should likewise not be used in the future in animals, plants, or in aquaculture

Practice evidence in U.S. food production

- Good news!
  - No CRE or colistin (mcr-1) resistance reported as of yet in US pigs or pork products
  - No direct selection pressure for CRE and no labeled direct selection pressures for mcr-1
  - ESBL are infrequently reported, 3GC resistance dominated instead by CMY-2
  - Extra-label uses of cephalosporins generally prohibited since 2012

Practice evidence in U.S. food production

- Bad news?
  - We are seeing increased 3GC and FQ resistance over past few years
    - Wider variety of genes (e.g., CTX-M-27,-1, -55, -32 and qnrB)
  - We now have documented plasmid-borne CRE in food animals in USA
  - Multi-drug resistance (MDR) means co-selection (as opposed to direct selection) can threaten expansion of genes through use of tetracyclines and other classes

The way forward?

- Less use is better; however, zero is not an option
  - Less use will slow the rise in antimicrobial resistance; however, it will not eliminate it
  - Zero use is unacceptable: animal health and well-being are important shared values in our society
  - Defining ‘judicious use’ (or, what is not…) and developing and promoting stewardship suited to modern production agriculture are key

Thank you and acknowledgements!

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https://www.ncbi.nlm.nih.gov/myncbi/1fG-3OnckMRkE/cv/151725/

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