Global Overview on Antibiotic Use Policies in Veterinary Medicine

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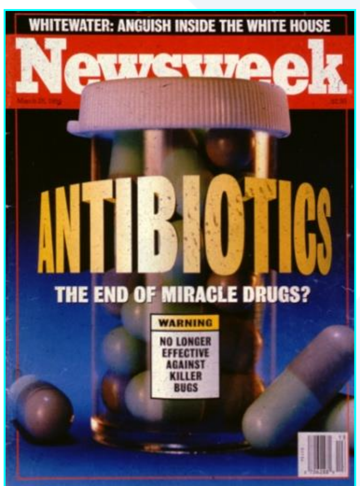
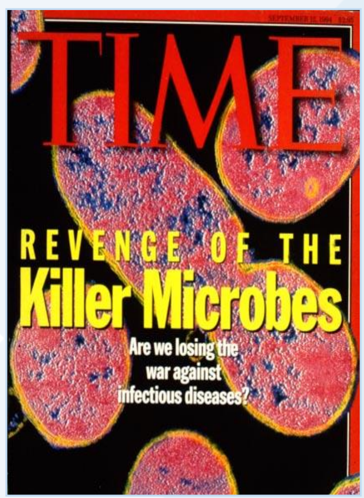
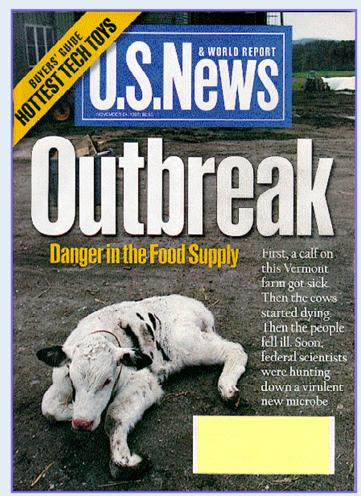
Resistance & Food Safety

There are public concerns that people may acquire foodborne illnesses that cannot be appropriately treated with antibiotics as a result of antibiotic-resistant bacteria that are derived from food animals that have been treated with antibiotics







Veterinarian’s Oath

(Approved by HOD, 1954; Revision approved by HOD, 1969; Revision approved by the Executive Board 1999, 2010, 2011)

Being admitted to the profession of veterinary medicine, I solemnly swear to use my scientific knowledge and skills for the benefit of society through the protection of animal health and welfare, the prevention and relief of animal suffering, the conservation of animal resources, the promotion of public health, and the advancement of medical knowledge.

I will practice my profession conscientiously, with dignity, and in keeping with the principles of veterinary medical ethics.

I accept as a lifelong obligation the continual improvement of my professional knowledge and competence.

https://www.avma.org/KB/Policies/Pages/veterinarians-oath.aspx

Contents

Europe
Where have we been?

Responsible Use vs. Precautionary Principle

The Danish Experiment

1995	National ban on avoparcin
1998	National ban on virginiamycin
1999	Voluntary agreement to discontinue antibiotic growth promoter (AGP's) for finishing swine
2000	Voluntary ban of AGP in piglets

AGP misconception: feed efficiency and reduced rates of infection

Has the Danish Experiment Been Beneficial?

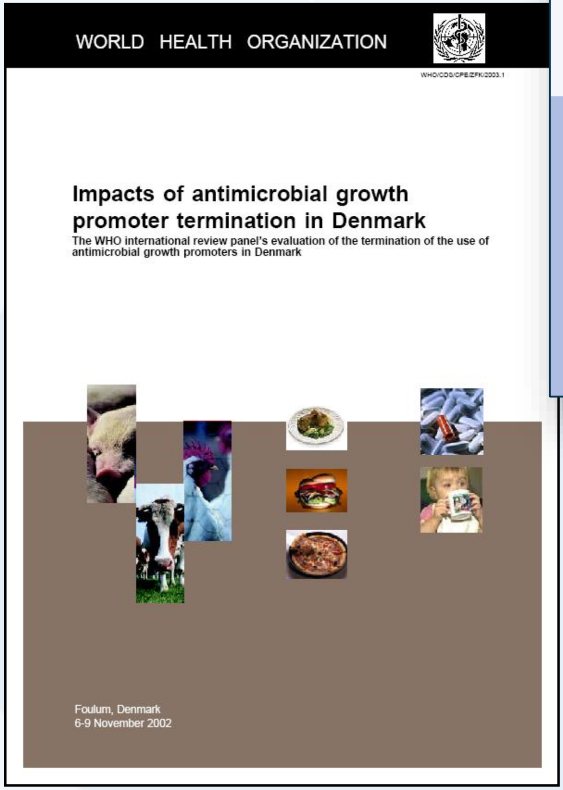
1. Decrease antibiotic use?

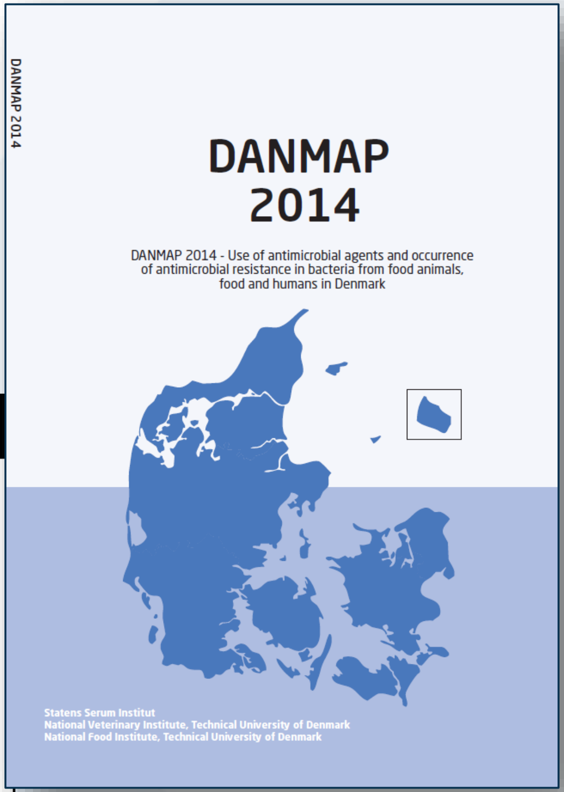
2. Public Health Benefit?

   Reduced illness

   Reduced resistance in human isolates

3. Animal Health?



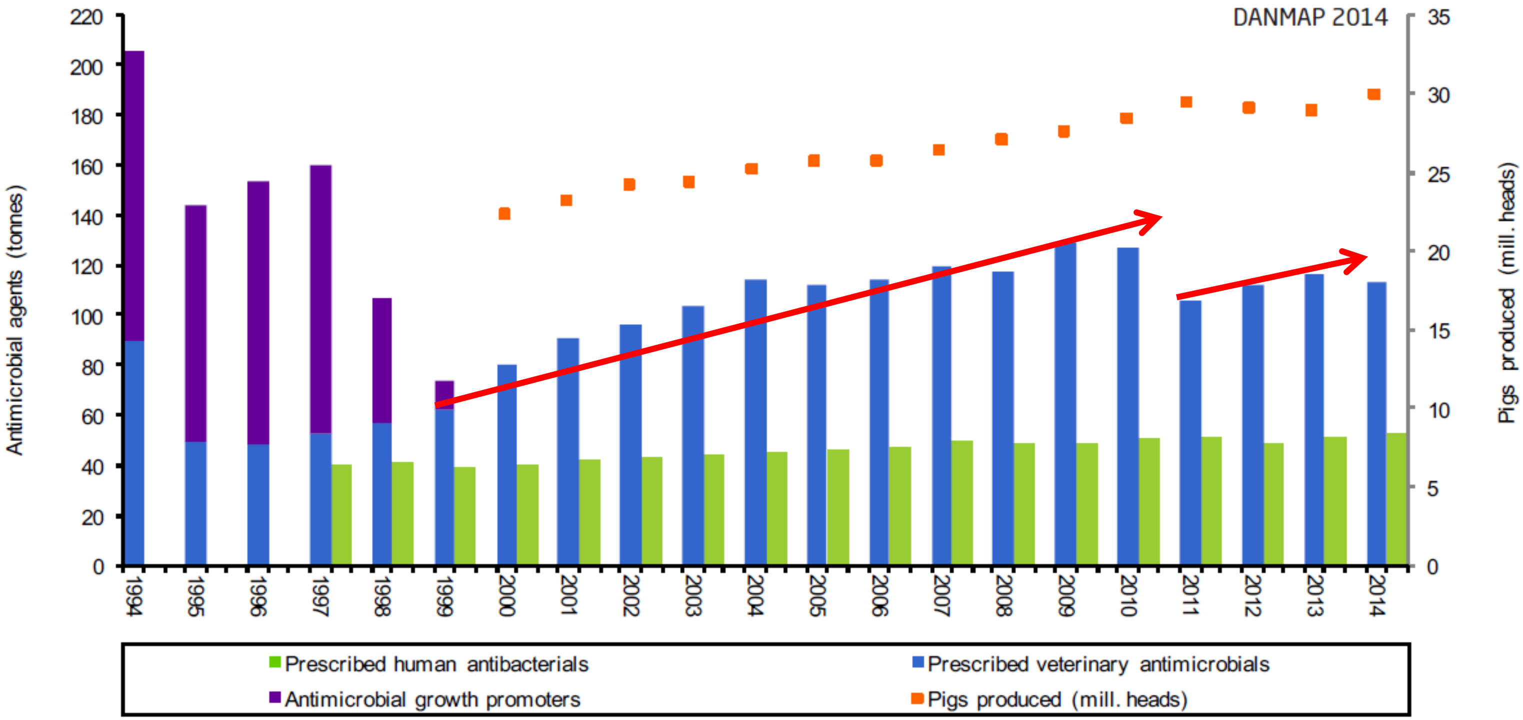


Card System

Denmark – GP v. Rx

Taxes

Figure 4.1. Prescribed antimicrobial agents for humans, and for animals compared with the number of pigs produced, Denmark



Sources: Human therapeutics: The Danish Medicines Agency. Veterinary consumption: Until 2001, data are based on reports from the pharmaceutical industry of total annual sales from the Federation of Danish pig producers and slaughterhouses (1994-1995) and Danish Medicines Agency and Danish Plant Directorate (1996-2000). Data from 2001-2014 originate from VetStat.

DANMAP 2014 | 29

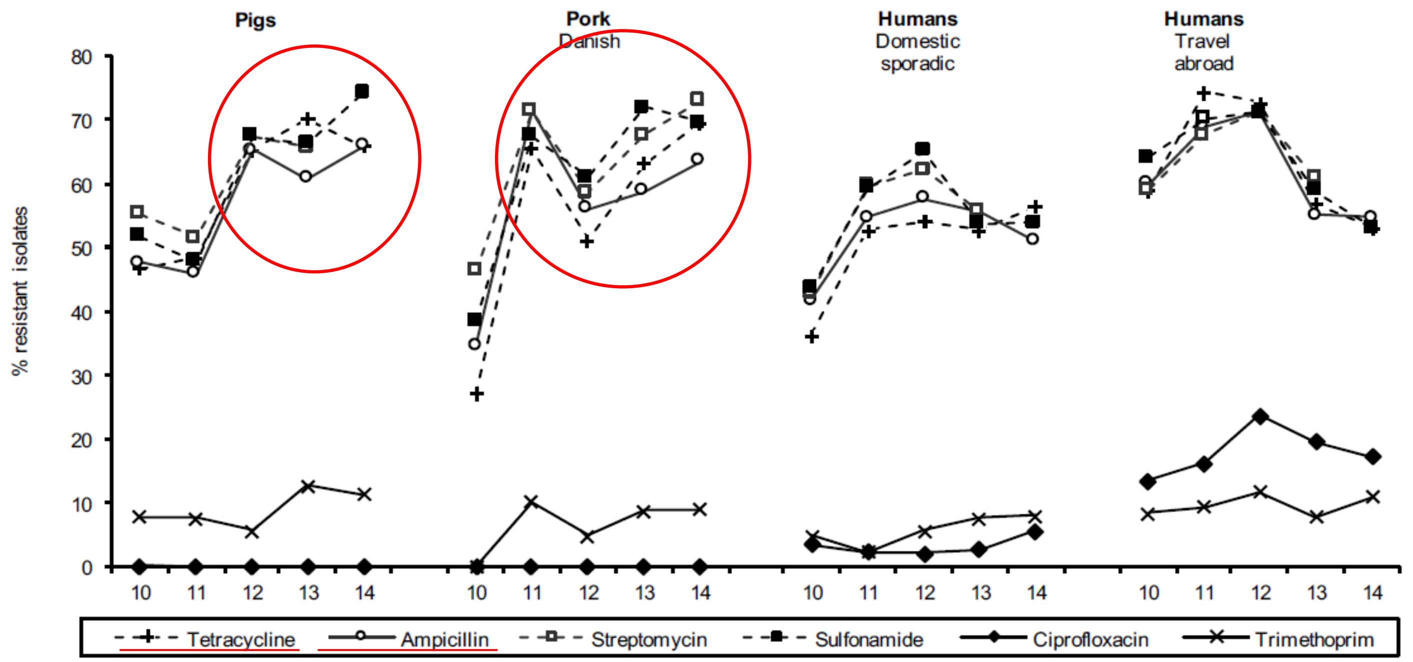
Increased NE poultry / dysentery in swine, consequently cost of production and food price increase

Has the Danish Experiment Benefited Public Health? – Not yet

- Reduced human food borne illness?
  - Salmonella → Decreasing, but still high prevalence
  - Campylobacter → Decreasing, but still high prevalence
- Reduced resistance in human pathogens?
  - NO, increased in Salmonella
  - NO, remains low in Campylobacter
  - VRE, steady over time in hospital patients

Resistance among *Salmonella typhimurium* in pigs and humans

Figure 6.2. Resistance (%) in *Salmonella* Typhimurium in[(a)] pigs, pork and human cases[(b)], Denmark DANMAP 2014



Note: The number of isolates varies between years (pigs: n = 144-434, Danish pork: n = 26-70, domestic sporadic human cases: n = 106-227 and travel related human cases: n = 51-95).

a) Include isolates verified as monophasic variants of S. Typhimurium with antigenic formulas S. 4,[5],12:i:-

b) An isolate is categorised as 'domestic sporadic' if the patient did not travel outside Denmark one week prior to the onset of disease and was not reported as being part of an outbreak.

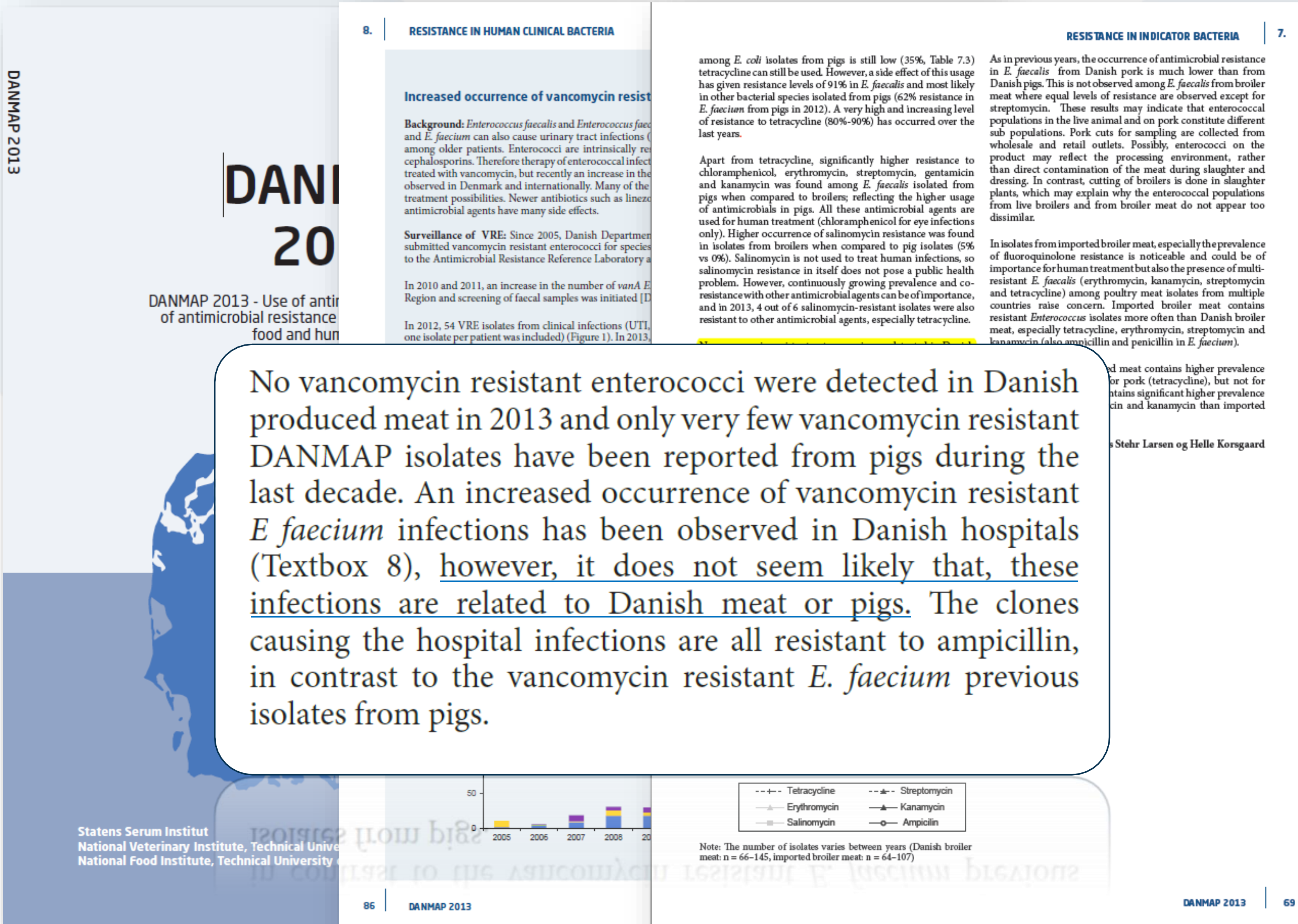
DANMAP 2014

Reverse seen in USA as they still have AGPs

Did the Danish Experiment work?

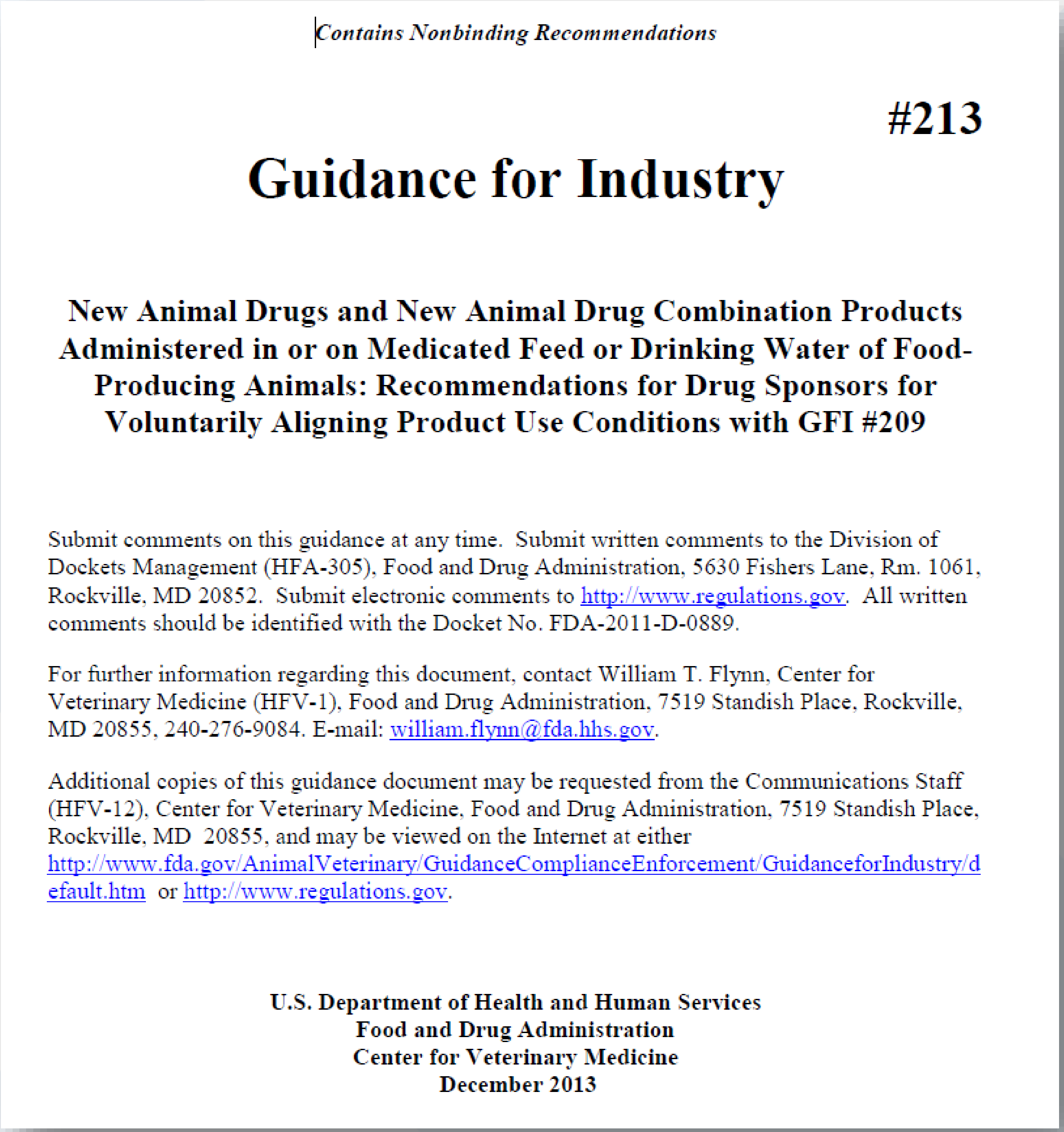
Summary of the Danish Experiment

- Decrease antibiotic use? – Depends…
  - Danish therapeutic antibiotic use is on the rise
  - Unintended consequence - increase treatment antibiotic use, including human use antibiotics
- Public Health Benefit? – None shown yet
  - No decrease in *Salmonella* illness
  - Increased resistance in *Salmonella* Typhimurium
- Antibiotics are still a necessary tool used in raising pigs!



No vancomycin resistant enterococci were detected in Danish produced meat in 2013 and only very few vancomycin resistant DANMAP isolates have been reported from pigs during the last decade. An increased occurrence of vancomycin resistant *E faecium* infections has been observed in Danish hospitals (Textbox 8), however, it does not seem likely that, these infections are related to Danish meat or pigs. The clones causing the hospital infections are all resistant to ampicillin, in contrast to the vancomycin resistant *E. faecium* previous isolates from pigs.

USA
Where Are They Going?



Contains Nonbinding Recommendations

#213

Guidance for Industry

New Animal Drugs and New Animal Drug Combination Products Administered in or on Medicated Feed or Drinking Water of Food-Producing Animals: Recommendations for Drug Sponsors for Voluntarily Aligning Product Use Conditions with GFI #209

Submit comments on this guidance at any time. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.regulations.gov. All written comments should be identified with the Docket No. FDA-2011-D-0889.

For further information regarding this document, contact William T. Flynn, Center for Veterinary Medicine (HFV-1), Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, 240-276-9084. E-mail: william.flynn@fda.hhs.gov.

Additional copies of this guidance document may be requested from the Communications Staff (HFV-12), Center for Veterinary Medicine, Food and Drug Administration, 7519 Standish Place, Rockville, MD 20855, and may be viewed on the Internet at either http://www.fda.gov/AnimalVeterinary/GuidanceComplianceEnforcement/GuidanceforIndustry/default.htm or http://www.regulations.gov.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Veterinary Medicine
December 2013

Decade plus after EU AGP decision FDA decision on AGP (Precautionary P vs. Science)

WHO Critical Antibiotics List

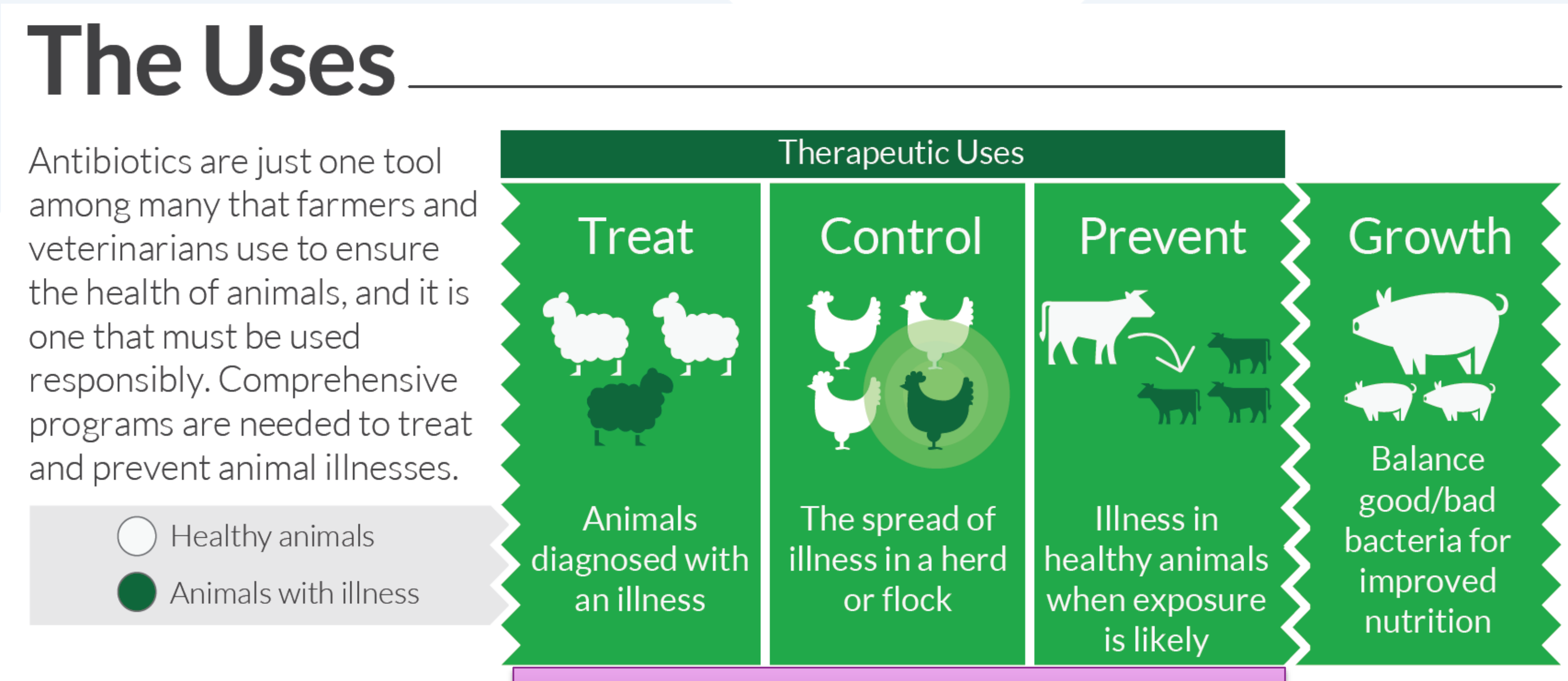
WHO listing (1st and 3rd revision, 2005 & 2012) of critically important antimicrobials for human medicine

Critically Important	Highly Important	Important	Unclassified
Aminoglycosides	Amdinopenicillins	Aminocyclitols	Ionophores
Carbapenems and other penems	Amphenicols	Cyclic polypeptides	Orthosomycins
Cephalosporins (3rd and 4th generation)*	Cephalosporins (1st and 2nd generation)	Nitrofurantoins	Bambermycins
Cyclic esters	Licomsamides	Nitroimidazoles	Carbadox
Fluro and other quinolones*	Penicillins (anti-staphylococcal)		
Glycopeptides*	pleuromutilins		
Glycylcylines	Riminofenazines		
Lipopeptides	Steroid antibacterials		
Macrolides and ketolides*	Streptogramins		
Monobactams	Sulfonamides		
Oxazolidinones	Sulfones		
Penicillins (natural aminopenicillins and antipseudomonal)	Tertacyclines		
Polymyxins			
Rifamycins			
Tuberculosis and other mycobacterial drugs			

*The top 4 critically important antimicrobials are prioritized on: (1) high absolute number of people affected by disease for which the antimicrobial is the sole or one of few alternatives to treat serious human disease, and (2) high frequency of use of the antimicrobial for any indication in human medicine, since usage may favour selection of resistance. In addition, a focusing criterion for the above classifications is that there is a greater degree of confidence that there are nonhuman sources that result in transmission of bacteria or their resistance genes to humans (WHO 2005 & 2012)

Adopted from: Michael P. Doyle, Guy H. Loneragan, H. Morgan Scott, and Randall S. Singer. 2013. Antimicrobial Resistance: Challenges and Perspectives. Comprehensive Reviews in Food Science and Food Safety. 12: 234-248

Use of The Three Categories of Antibiotics



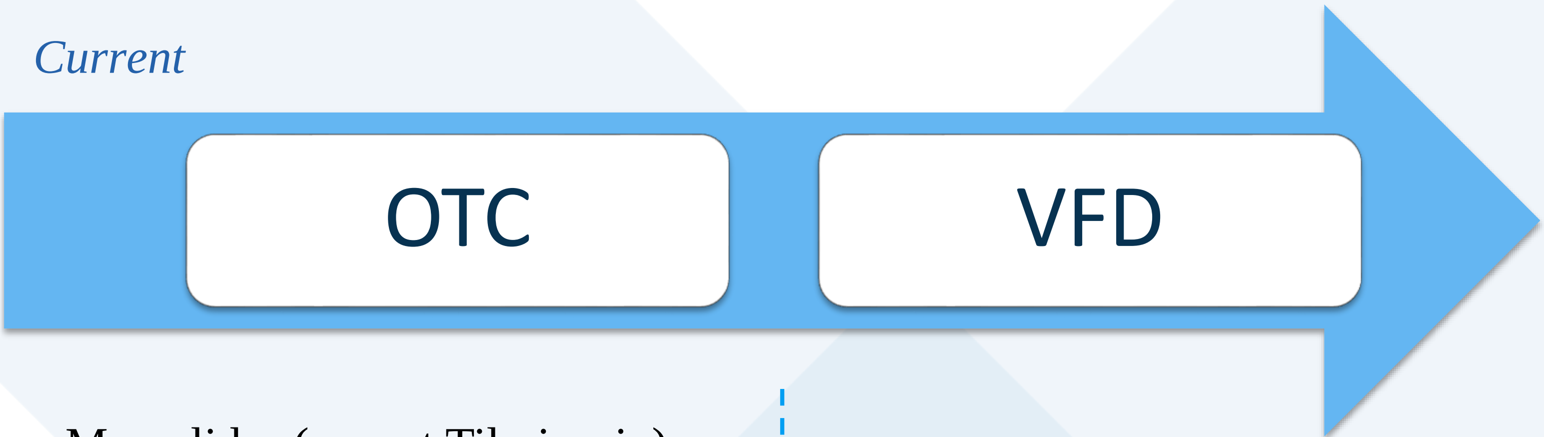
Shared Classes of Antibiotics

Animal Only Classes of Antibiotics

Marketing Status Transition

Therapeutic and/or Performance Indications

Current



Macrolides (except Tilmicosin)
Penicillin
Tetracycline
Streptogramins
Aminoglycosides
Lincosamides
Sulfonamides
Other veterinary use only agents (e.g. Ionophores)

Macrolide (Tilmicosin)
Phenicol (Florfenicol)

Marketing Status Transition

Therapeutic Indications VFD
Performance Indications and/or Therapeutic Indications OTC

After

OTC	VFD
Avilamycin (AGP)	Macrolides
Ionophores	Penicillin
Bacitracin	Avilamycin (Therapeutic)
Bambermycin	Tetracycline
Carbadox (MA Removable Recommended)	Streptogramins
Other veterinary use only agents	Aminoglycosides
	Lincosamides
	Sulfonamides
	Phenicol

Food Brands
Where Do They Want To Go?

Statement on Antibiotic Use

SHARE

Antimicrobial use in food animals is an issue that impacts people and animals. Global organizations like McDonald's Corporation need to pay attention to it. We have maintained a global policy on antibiotic use in food animals since 2003. In March 2015, McDonald's released our Global Vision for Antimicrobial Stewardship in Food Animals, which strives to preserve antimicrobial effectiveness in the future through ethical practices today. It builds on our 2003 policy and provides guidance to our suppliers in parts of the world where the industry does not yet have systems in place that would allow them to verify compliance throughout the supply chain.

In the US, we agree antibiotics have important benefits, but we believe that a few sensible changes can both maintain their most important benefits while helping to reduce their use overall. We are committing to use chicken that is not raised with antibiotics important to human medicine. McDonald's has been working closely with farmers for years to reduce the use of antibiotics in our supply, thus we are able to commit today to stop using antibiotics important to human medicine in chicken production for McDonald's USA by March 2017.

http://news.mcdonalds.com/Corporate/Media-Statements/Response-to-The-Use-of-Antibiotics-in-Chicken

2003

RELEASED JUNE 2003 (2015 GLOBAL VISION FOR ANTIMICROBIAL STEWARDSHIP IN FOOD ANIMALS AVAILABLE HERE)

McDonald's Global Policy on Antibiotic[1] Use in Food Animals[2]

Introduction

McDonald's recognizes that the use of antibiotics in food animals is under active review by scientists and regulators around the world, and we support these transparent, science-based processes. We also recognize the importance of combating antibiotic resistance, and believe that voluntary, market-based actions can complement ongoing activities to address the issue of antibiotic resistance. McDonald's policy represents one such complementary step and provides the foundation for further work on the sustainable use of antibiotics. McDonald's policy was formed with input from a variety of experts, including physicians, suppliers, animal welfare scientists, retail representatives, and environmental experts. We know that scientific understanding of antibiotic resistance continues to grow, and we will update our policy as necessary to remain consistent with available scientific information.

Executive Summary

- All uses of antibiotics in food animal production should follow the Guiding Principles for Sustainable Use. Sustained reductions in the total use of antibiotics belonging to classes of compounds currently approved for use in human medicine are encouraged and will be considered a favorable factor in supply decisions.
- The use of those antibiotics belonging to classes of compounds currently approved in one or more countries worldwide for use in human medicine is prohibited when used solely for growth promotion purposes[3].
- McDonald's Antibiotics Use Policy applies to all global suppliers where McDonald's has a "direct relationship" in the meat purchasing supply chain process. For suppliers with whom McDonald's does not have a "direct relationship", compliance with this policy will be a favorable factor in supply decisions.
- McDonald's Antibiotics Use Policy will be enforced through supplier certification and assurance programs or regular audits. This policy is to be phased in by the end of 2004.

Rationale

McDonald's is committed to a global policy on the sustainable use of antibiotics because:

1. Antibiotics are important for maintaining health and welfare and reducing morbidity and mortality of food animals.
2. Antibiotic use contributes to the selection of antibiotic resistance in disease causing bacteria.
3. Antibiotic-resistant bacterial pathogens are a risk to human and animal health because they compromise the effectiveness of antibiotics used in human and veterinary medicine.
4. All users of antibiotics, including those who supervise use in animals and those who supervise use in humans, must work to sustain the long-term efficacy of antibiotics for human and veterinary medicine.

[1] The term antibiotic is used in this policy to refer to both antibiotics (as defined in the Definitions section below) and synthetic agents that have an antibiotic effect (commonly referred to as antimicrobials). This policy allows the use of ionophores and other anticoccidials for the treatment and prevention (as defined by this policy) of coccidiosis. The use of anticoccidials from classes of drugs not approved for use in human medicine is permitted for other purposes as approved by applicable regulatory authorities. Use of these compounds is not linked to the development of resistance in bacteria that cause disease in humans.
[2] The term food animal is used in this policy to refer to all species of farmed animals including cultivated fish and shellfish.
[3] When drug combinations are used, this policy applies to every antibiotic in the combination.

2015

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.

Our vison for antimicrobial stewardship is *"Preserving antimicrobial effectiveness in the future through ethical practices today"*.

To achieve this vision, the guiding principles for judicious use of antimicrobials should be understood, implemented and verified on all farm operations raising food animals (see Appendix I). Second, meaningful veterinary oversight is imperative when antimicrobial use is required to maintain the health and welfare of animals. Third, we support the World Health Organization's (WHO) characterization of critically, highly and important antimicrobials in human medicine (see Appendix II). We acknowledge antimicrobials differ in terms of their importance in both human and animal health care, and those differences were considered. Four criteria have been outlined to guide our work and will serve as goals for our supply chain:

I. Prohibit the use of antimicrobials in food animals that are by WHO definition "critically important" to human medicine, and not presently approved for veterinary use.
II. Classes of antimicrobials that are currently approved as dual use (for use in both human and veterinary medicine) for <u>treatment or prevention</u> of animal disease can only be used in conjunction with a veterinary-developed animal health care program.
III. Prohibit the use of any medically important antimicrobials for growth promotion in food animals, as defined by WHO.
IV. Utilize animal production practices that reduce, and where possible eliminate, the need for antimicrobial therapies and adopt existing best practices and/or new practices that would result in subsequent reductions of antimicrobial use. Successful strategies will be shared broadly.

McDonald's recognizes the importance of decisions made by beef, pork, poultry, dairy and egg producers in managing the animals entrusted to their care. We are familiar with the extensive educational support and producer collaboration that has been developed and implemented in many areas of the world, and where industry trade groups have localized quality assurance programs that focus on continuous improvement through education and collaboration. We strongly support the implementation of all education, training and outreach programs and seek the development of verification programs for judicious antimicrobial use in all species to achieve our vison for antimicrobial stewardship.

McDonald's has prioritized the following initial areas of focus:

1. Establish principles and criteria for antimicrobial use
2. Develop field projects, as needed, to serve as Centers of Innovation (i.e. demonstration farms) for each species in an effort to demonstrate the benefits of judicious antimicrobial use
3. Develop methods to verify judicious antimicrobial use and establish goals for measuring progress.

* Food animal(s) are defined in this document as beef, pork, poultry, dairy and eggs. See Appendix III.

McDonald's Corporation – Vision for Antimicrobial Stewardship in Food Animals
March 2015

http://www.aboutmcdonalds.com/content/dam/AboutMcDonalds/Sustainability/Antimicrobial_Stewardship_Vision.pdf

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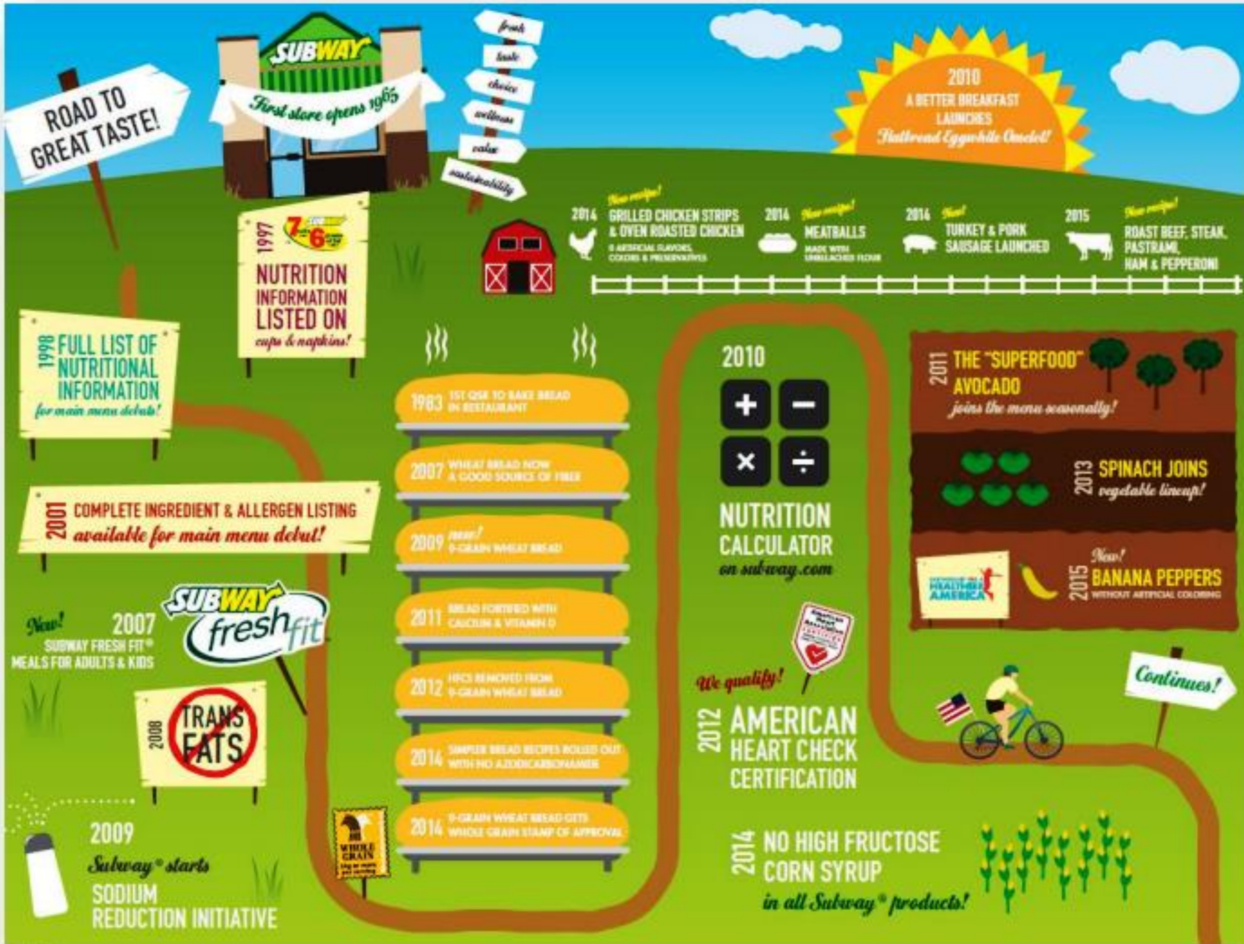


Oct. 20, 2015

SUBWAY® Restaurants Elevates Current Antibiotic-Free Policy U.S. Restaurants Will Only Serve Animal Proteins That Have Never Been Treated With Antibiotics

Kellie For Ag

Subway, I'm Choosing to Care for My Animals

www.kellieforag.com

BEEF

Subway, I'm Choosing to Care for My Animals.

Subway Updates Statement on Antibiotic Use in Livestock

Posted on October 23, 2015 by Ryan Goodman in antibiotics, Food // 3 Comments

31 9 Rate This

Earlier this week, Subway restaurants announced changes to their policies regarding antibiotics use in livestock, stating they would begin sourcing only protein products from livestock never receiving antibiotics. The tone in which this news was released did not sit well with livestock farmers and ranchers across the country. Frustrating the situation even more was the censoring of comments in disagreement with the announcement on Subway's Facebook page and lack of response from the company itself.

SUBWAY eat fresh.™

Subway relents on antibiotics decision

Story Comments Print Font Size:

Posted: Wednesday, November 4, 2015 10:45 am | *Updated: 10:49 am, Wed Nov 4, 2015.*

Hub Opinion

0 Share

A rose to ... Subway, which listened to the complaints of livestock industry advocates and decided to temper its decision to serve only meat from animals that were never given antibiotics. Subway's anti-antibiotic marketing idea hit a brick wall in rural Nebraska, where livestock producers rely on antibiotics to help sick animals.

Subway altered its strategy, in response to farmers and ranchers who educated the sandwich giant about the usefulness of antibiotics in caring for cattle, swine and poultry. Somehow, Subway was led to believe livestock producers use antibiotics only as growth enhancers.

Subway Announces That a Bullet Is Their Treatment Of Choice For Sick Animals...

****AUTHORS NOTE: Due to the huge response to this blog post and my responsibilities on the farm, I am unable to respond to each comment made by readers. I am reading the comments, and I plan to post a new blog responding to questions brought up in the comment section within the next few days. Thank you for reading, and thank you for caring. It renews my faith in our country that 400,000 of you all care enough about your food to read a farmer's thoughts.**

Tuesd
2016 i
source
spoke
from a

Karl Jacobson
@Sodbusterk
Follow

So it's ok for humans to take antibiotics to combat sickness, but not animals???? #subway??

RETWEETS 18 LIKES 30

Andrew Dalgarno
@Andrew_Dalgarno
Follow

Hey @SUBWAY , don't you give antibiotics to your kids when the doctor prescribes them? Why shouldn't farmers do the same with sick animals?

RETWEETS 114 LIKES 158

As such, SUBWAY said it is asking its suppliers to do the following (**Oct. 23, 2015)**:

- Adopt, implement and comply with the U.S. Food and Drug Administration's ("FDA's") guidance for industry 209 and 213, which requires that medically important antibiotics not be used for growth promotion. Visit the FDA site to learn more

- Assure that all antibiotics use is overseen, pre-approved and authorized by a licensed veterinarian before they are administered to any animal

- Keep accurate and complete records to track use of all antibiotics

- Adhere at all times to all legal requirements governing antibiotic withdrawal times. This assures that antibiotics have been eliminated from the animals' systems at the time of slaughter

- Actively encourage, support and participate in research efforts focused on improving animal health while reducing antibiotics use

Implementing Responsible Use

Where Should We Go?

Global AMR Action Plans

Options for action
8 March 2012

*"In terms of new replacement antibiotics, the pipeline is virtually dry. But much can be done. This includes prescribing antibiotics appropriately and only when needed, following treatment correctly, **restricting the use of antibiotics in food production to therapeutic purposes** and tackling the problem of substandard and counterfeit medicines."*

The May 2015 World Health Assembly adopted a global action plan on antimicrobial resistance, which outlines five objectives:

- To improve awareness and understanding of antimicrobial resistance through effective communication, education and training

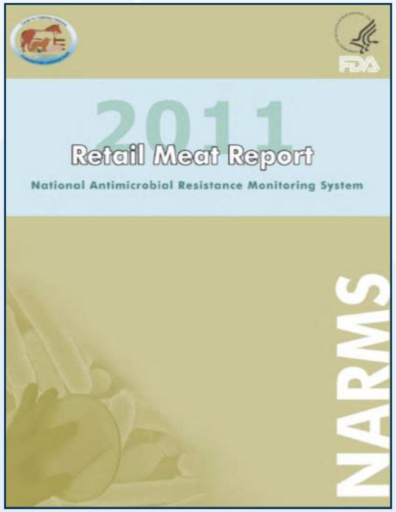
- To strengthen the knowledge and evidence base through surveillance and research

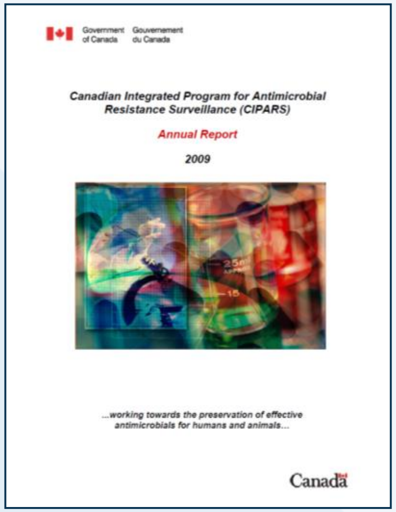
- To reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures

- To optimize the use of antimicrobial medicines in human and animal health;

- To develop the economic case for sustainable investment that takes account of the needs of all countries and to increase investment in new medicines, diagnostic tools, vaccines and other interventions.

Antibiotic Resistance Monitoring





All great programs however these are not harmonised and comparing data is difficult

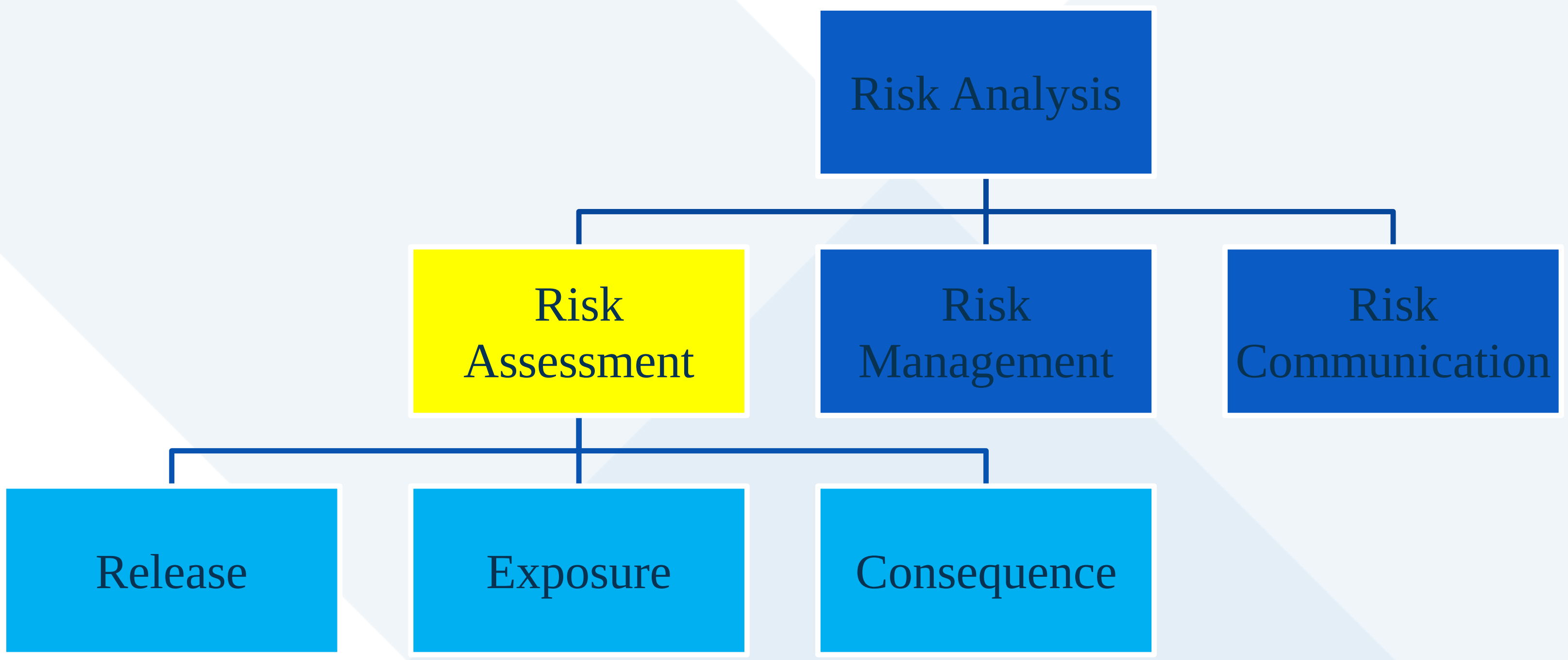
MIC µg/mL		Host and Country of Origin: Cattle					Cattle
Data	Conc	Dk	F	G	H	P	Total
%	>256		11.1				3.6
	256		22.2	100			14.3
	128		22.2				7.1
	64		11.1			33.3	7.1
	32						
	16				12.5		3.6
	8	50			50		25
	4	50	33.3		37.5	33.3	35.7
	2					33.3	3.6
	≤1						
n	>256		1				1
	256		2	2			4
	128		2				2
	64		1			1	2
	32						
	16				1		1
	8	3			4		7
	4	3	3		3	1	10
	2					1	1
	≤1						
Total n		6	9	2	8	3	28
MIC50		*	*	*	*	*	8
MIC90		*	*	*	*	*	256
n Resistant Isolates		0	6	2	0	1	9
% Resistance		0	66.7	100	0	33.3	32.1

MIC µg/mL		Host and Country of Origin: Pig						Pig
Data	Conc	B	Dk	F	G	H	Esp	Total
%	>256	3		2.4	15	5	1.3	4.5
	256	4	24.2	7.1	30	10	11.3	13
	128	3		31	8.3	15	8.8	9.6
	64	11	6.1	14.3	6.7	12.5	10	10.1
	32	1			6.7	7.5	2.5	2.8
	16	3	3	2.4	1.7	2.5	11.3	4.5
	8	21	9.1	23.8	8.3	22.5	26.3	19.4
	4	54	54.6	14.3	23.3	25	26.3	34.6
	2		3	4.8			1.3	1.1
	≤1						1.3	0.3
n	>256	3		1	9	2	1	16
	256	4	8	3	18	4	9	46
	128	3		13	5	6	7	34
	64	11	2	6	4	5	8	36
	32	1			4	3	2	10
	16	3	1	1	1	1	9	16
	8	21	3	10	5	9	21	69
	4	54	18	6	14	10	21	123
	2		1	2			1	4
	≤1						1	1
Total n		100	33	42	60	40	80	355
MIC50		4	4	64	128	16	8	8
MIC90		64	256	128	>256	256	256	256
n Resistant Isolates		21	10	23	36	17	25	132
% Resistance		21	30.3	54.8	60	42.5	31.3	37.2

MIC µg/mL		Host and Country of Origin: Chicken					Chicken
Data	Conc	F	G	H	Esp	UK	Total
%	>256		2.3				0.6
	256	5.9	7			6.7	3.2
	128	11.8	4.7				2.6
	64		7	3	6.7		3.8
	32	5.9	20.9	18.2	6.7		14.7
	16		2.3	19.7		6.7	9.6
	8	41.2	23.3	43.9	66.7	33.3	39.1
	4	17.7	30.2	12.1	13.3	53.3	21.8
	2	17.7	2.3	3			3.8
	≤1				6.7		0.6
n	>256		1				1
	256	1	3			1	5
	128	2	2				4
	64		3	2	1		6
	32	1	9	12	1		23
	16		1	13		1	15
	8	7	10	29	10	5	61
	4	3	13	8	2	8	34
	2	3	1	2			6
	≤1				1		1
Total n		17	43	66	15	15	156
MIC50		8	8	8	8	4	8
MIC90		128	128	32	32	16	64
n Resistant Isolates		3	9	2	1	1	16
% Resistance		17.7	20.9	3	6.7	6.7	10.3

*less than 10 isolates so MIC_{50} and MIC_{90} not calculated

Risk Analysis Components



The 3-step RA Process

- An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance in food animals during treatment
  - Release

- A person must ingest meat from a treated animal that is contaminated with those same antibiotic-resistant foodborne bacteria
  - Exposure

- The person that ingests these bacteria must become sick with a bacterial infection that cannot be appropriately treated with antibiotics as a result of those animal-derived antibiotic-resistant bacteria
  - Consequence

Ionophore Risk

The use of ionophores in food animals does not create a risk to human health because none of the risk criteria are met.

- An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance…
- A person must ingest meat from a treated animal that is contaminated…
- The person that ingests these bacteria must become sick with a bacterial infection…

Orthosomycin Risk

The use of orthosomycins in food animals does not create a risk to human health because the third risk criteria is not met.

- ✓ An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance…
- ✓ A person must ingest meat from a treated animal that is contaminated…
- ✘ The person that ingests these bacteria must become sick with a bacterial infection…

No Risk vs. Low Risk: Macrolides

The use of macrolides in food animals could potentially compromise human health risk; all of the risk criteria are met

- ✓ An antibiotic must select for foodborne bacteria that acquire antibiotic-resistance…
- ✓ A person must ingest meat from a treated animal that is contaminated…
- ✓ The person that ingests these bacteria must become sick with a bacterial infection…

Full Risk Assessment would be needed!

Journal of Food Protection, Vol. 67, No. 5, 2004, Pages 980–992

Public Health Consequences of Macrolide Use in Food Animals: A Deterministic Risk Assessment†

H. SCOTT HURD,[1]* STEPHANIE DOORES,[2] DERMOT HAYES,[3] ALAN MATHEW,[4] JOHN MAURER,[5] PETER SILLEY,[6] RANDALL S. SINGER,[7] AND RONALD N. JONES[8]

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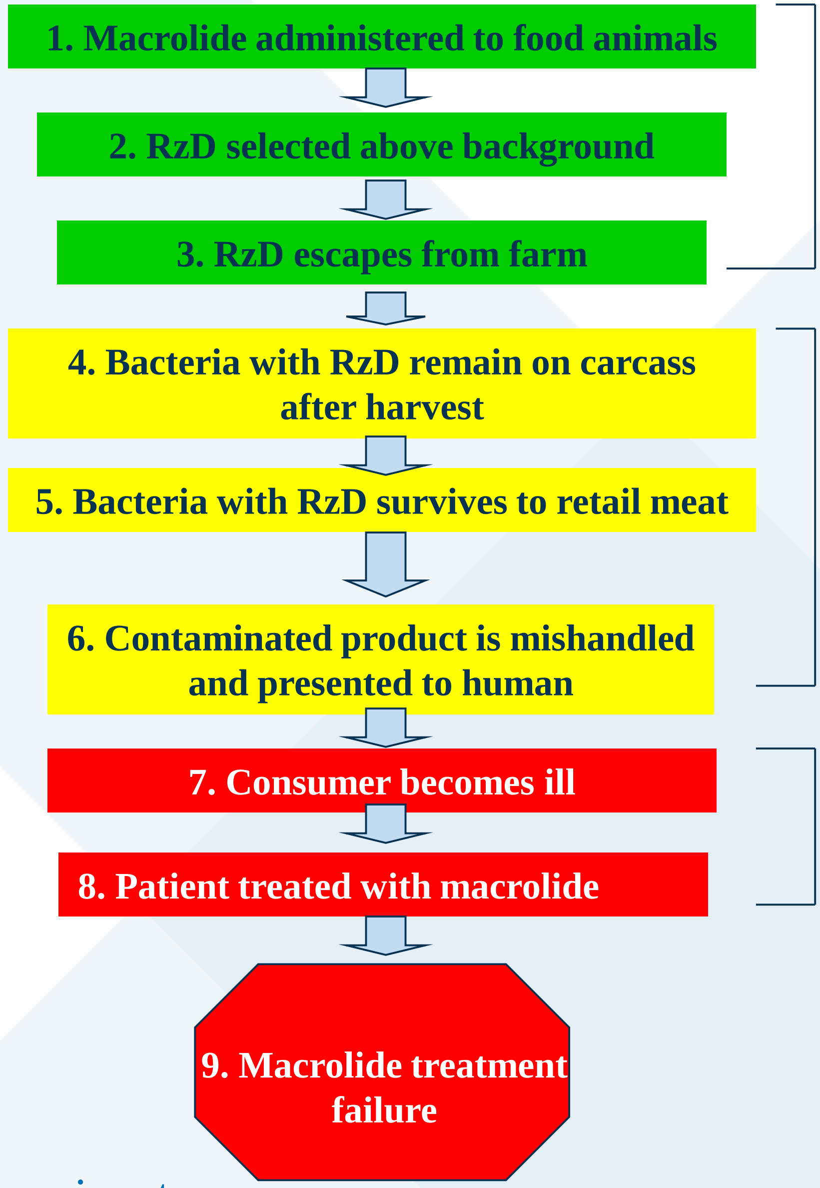
MS 03-374: Received 21 August 2003/Accepted 4 January 2004

J. Food Protection, May 2004

www.ifss.iastate.edu/macrolide

Pathway of events leading to the risk of foodborne human illness with resistant organism due to antibiotic treatment of food animals



Release Assessment: Describes the probability that factors related to the antimicrobial use in animals will result in the emergence of resistant bacteria or resistance determinates (RzD).

Exposure Assessment: Describes the likelihood of human exposure to the RzD through particular exposure pathways.

Consequence Assessment: Describes the relationship between specified exposures to the RzD (the hazardous agent) and the consequences of those exposures.

RzD: Resistance determinant

Table 1. Assessment of the Adverse Human Health Impact Attributable to the Use of Macrolides in Food Animals, key parameters and results

Components / Binomial events	Poultry CAMPY	Poultry ENT	Swine CAMPY	Swine ENT	Beef Cattle CAMPY	Beef Cattle ENT
RELEASE						
1. Animals exposed to T-T (million)[a]	652.1	652.1	49.0	49.0	16.1	16.1
2. RzD develops in exposed animals (Pr%) function of [b]:	1	70	2	86	1	89
- Bacteria presence in animals (%)	50	100	80	100	50	100
- Susceptible bacteria in population (%)	90	70	95	86	99	89
- Resistance in human isolates (%)	3	100	3	100	3	100
3. RzD escapes from the farm (Pr%) [c]	100	100	100	100	100	100
EXPOSURE						
4. Bacteria with RzD remain on carcass after slaughter (Pr%) [d]	88	100	32	31	4	8
EXPOSURE and CONSEQUENCE						
5.-7.Contaminated carcass leads to human illness (ratio method) [e]	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}	8.6×10^{-6}
CONSEQUENCE						
8. Cases of diarrhea treated with a macrolide (Pr%) [f]	3	10^{-6}	3	10^{-6}	3	10^{-6}
9. Treatment fails if RzD infection is treated with a macrolide (Pr%) [g]	50	100	50	100	50	100
RISK Adverse health events in US due to treatment of RzD caused foodborne infection with macrolide (annual Pr) [h]	<1 in 14 million	<1 in 3 billion	<1 in 53 million	<1 in 21 billion	<1 in 236 million	<1 in 29 billion

a. Based on industry usage surveys (treatment, control, prevention, performance)

Risk Comparison of Macrolide Antibiotics (Tylosin & Tilmicosin)

Risk (High to Low)	Yearly Probability
Being the victim of a violent crime	1 in 200
Dying from heart disease	1 in 384
Dying from cancer	1 in 514
Dying from a stroke	1 in 1,750
Being murdered	1 in 18,000
Dying from choking	1 in 200,000
Acquiring a food-borne infection from fruit or vegetables	1 in 375,000
Being struck by lightning	1 in 550,000
Being attacked by a shark	1 in 700,000
Acquiring a food-borne infection from beef	1 in 900,000
Dying from a bee sting	1 in 6 million
→ Acquiring resistant *Campylobacter* from macrolide-treated poultry which results in treatment failure	<1 in 14 million
Dying from a dog bite	1 in 18 million
→ Acquiring resistant *Campylobacter* from macrolide-treated swine which results in treatment failure	<1 in 53 million
Odds of winning the Powerball® lottery	1 in 120 million
Dying from *Salmonella* poisoning from an egg shell	<1 in 142 million
→ Acquiring resistant *Campylobacter* from macrolide-treated beef which results in treatment failure	<1 in 236 million
→ Acquiring resistant *E. faecium* from macrolide-treated poultry which results in treatment failure	<1 in 3 billion
→ Acquiring resistant *E. faecium* from macrolide-treated swine which results in treatment failure	<1 in 21 billion
→ Acquiring resistant *E. faecium* from macrolide-treated beef which results in treatment failure	<1 in 29 billion

Definition: Treatment failure is defined as longer duration of symptoms such as diarrhea; progression to more severe disease; or in the worst-case scenario, mortality.

Colistin - Reactions from the EU

Transferable Colistin Resistance – *mcr*1

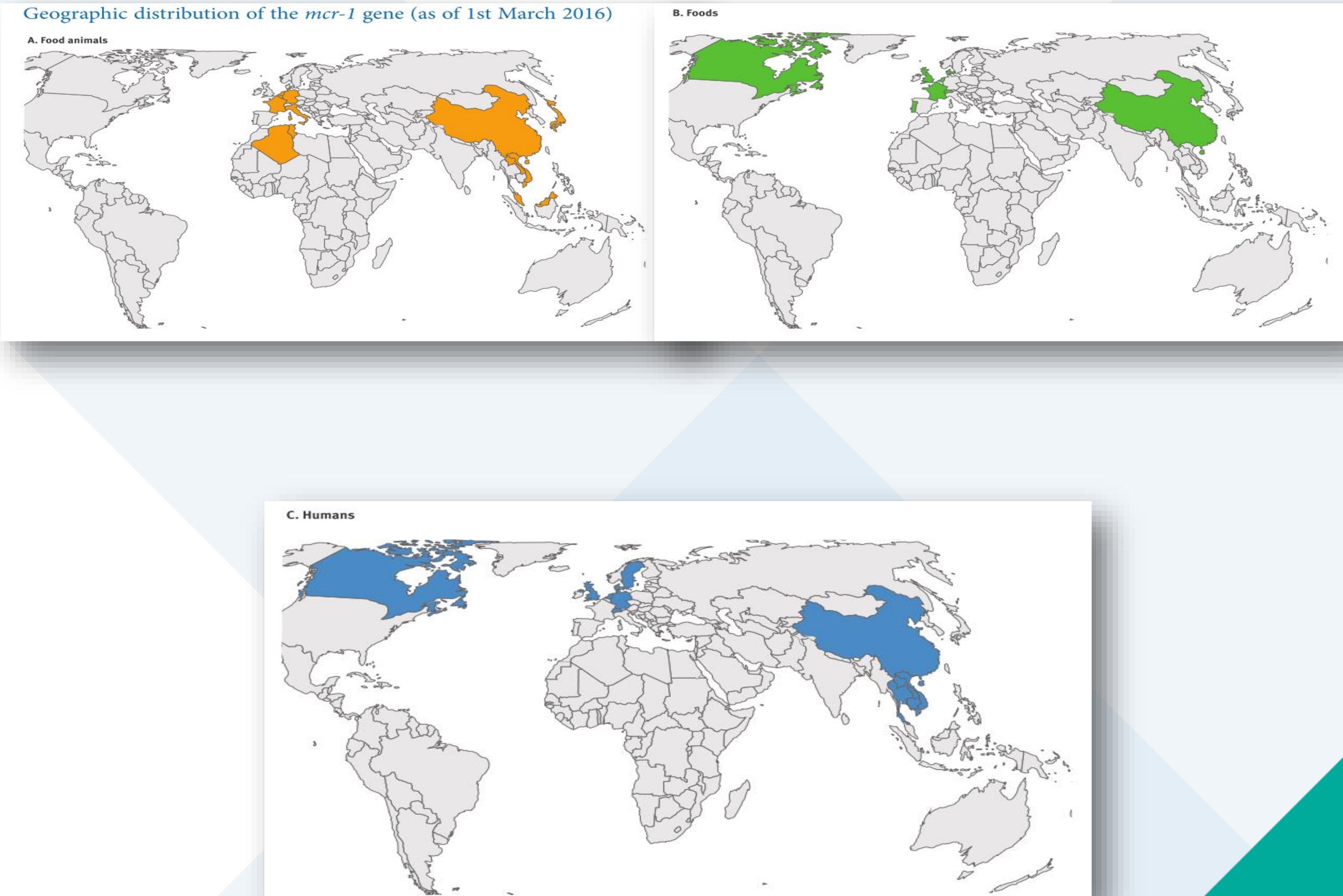
Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

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

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 coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Lancet Infect Dis 2015
Published Online
November 18, 2015
http://dx.doi.org/10.1016/S1473-3099(15)00424-7
See Online/Articles
http://dx.doi.org/10.1016/


Geographic distribution of the *mcr-1* gene (as of 1st March 2016)
A. Food animals
B. Foods
C. Humans

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

22 April 2016
EMA/CVMP/249719/2016
Press Office

Press release

food-producing species. The matter was referred to the Committee by the European Commission under Article 35 of Directive 2001/82/EC, due to concerns related to antimicrobial resistance and the need to ensure responsible use of the substance in protecting animal health and limiting the possibility of future risk to public health. The Committee adopted by consensus an opinion concluding that the benefit-risk balance for the products concerned is negative as no benefit could be demonstrated of using colistin combination products over monotherapy and no feasible risk mitigation measures could be identified to address the potential risk to human health. The CVMP recommended the withdrawal of the marketing authorisations for all veterinary medicinal products containing colistin in combination with other antimicrobial substances to be administered orally to food producing species.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

27 July 2016
EMA/CVMP/CHMP/231573/2016
Committee for Medicinal Products for Veterinary use (CVMP)
Committee for Medicinal Products for Human Use (CHMP)

Updated advice on the use of colistin products in animals within the European Union: development of resistance and possible impact on human and animal health

Agreed by the Antimicrobial Advice ad hoc Expert Group (AMEG)	2 May 2016
Adopted by the CVMP for release for consultation	19 May 2016
Adopted by the CHMP for release for consultation	23 May 2016
Start of public consultation	26 May 2016
End of consultation (deadline for comments)	26 June 2016
Agreed by the Antimicrobial Advice ad hoc Expert Group (AMEG)	1 July 2016
Adopted by the CVMP	12 July 2016
Adopted by the CHMP	22 July 2016

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An agency of the European Union

Risk management measures

In its updated advice, AMEG recommends that Member States should reduce the use of colistin to a maximum level of 5 mg colistin/PCU (population correction unit) and consider setting stricter national targets, ideally lower than 5 mg/PCU of colistin, e.g. below 1 mg/PCU as a desirable level. The AMEG emphasises that reduction of colistin use should not be compensated for by increasing the use of other types of antimicrobials. Instead, the use of this antibiotic should be reduced through other measures such as improved farming conditions, biosecurity in between production cycles, and vaccination.

In addition, colistin should be reclassified and added to Category 2 of the AMEG classification system, which includes medicines reserved for treating infections in animals for which no effective alternative treatments exist. This category includes certain classes of antimicrobials listed by the World Health Organization (WHO) as critically important to human health. Because of the risk posed to public health by their veterinary use, these medicines are subject to specific restrictions.

“Responsible use does not simply equate to using fewer antimicrobials.

Use the right drug in the right amount by the right route for the right period of time”

Jackie Atkinson, Director of Authorisations
Veterinary Medicines Directorate
United Kingdom
January 21, 2012

Questions? …Let’s Talk!