“bacteria are not simply foes to be vanquished, but a part of the natural world, capable of making deft adaptations to the drugs we use to fight them”

(Gordon 1998 from Rene Dubos)

Antimicrobial Use and Resistance in Agriculture

Sylvia Checkley, DVM PhD

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- Date: October 1, 2020

Presenter Disclosure

- I have no conflict of interest to declare.

Sylvia Checkley

Territorial Acknowledgement

I would like to take this opportunity to acknowledge the traditional territories of the people of the Treaty 7 region in Southern Alberta, which includes the Blackfoot Confederacy (comprising the Siksika, Piikani, and Kainai First Nations), as well as the Tsuut'ina First Nation, and the Stoney Nakoda (including the Chiniki, Bearspaw, and Wesley First Nations). The City of Calgary is also home to Métis Nation of Alberta, Region III.

Learning Objectives

- What is the precautionary principle?
- Explore antimicrobial use (AMU) as a key determinant of antimicrobial resistance (AMR)
- Explore multiple perspectives on AMU
- Understand difficulties with quantification of AMU
- Debate the contribution of AMU in animals to AMR in animals and humans

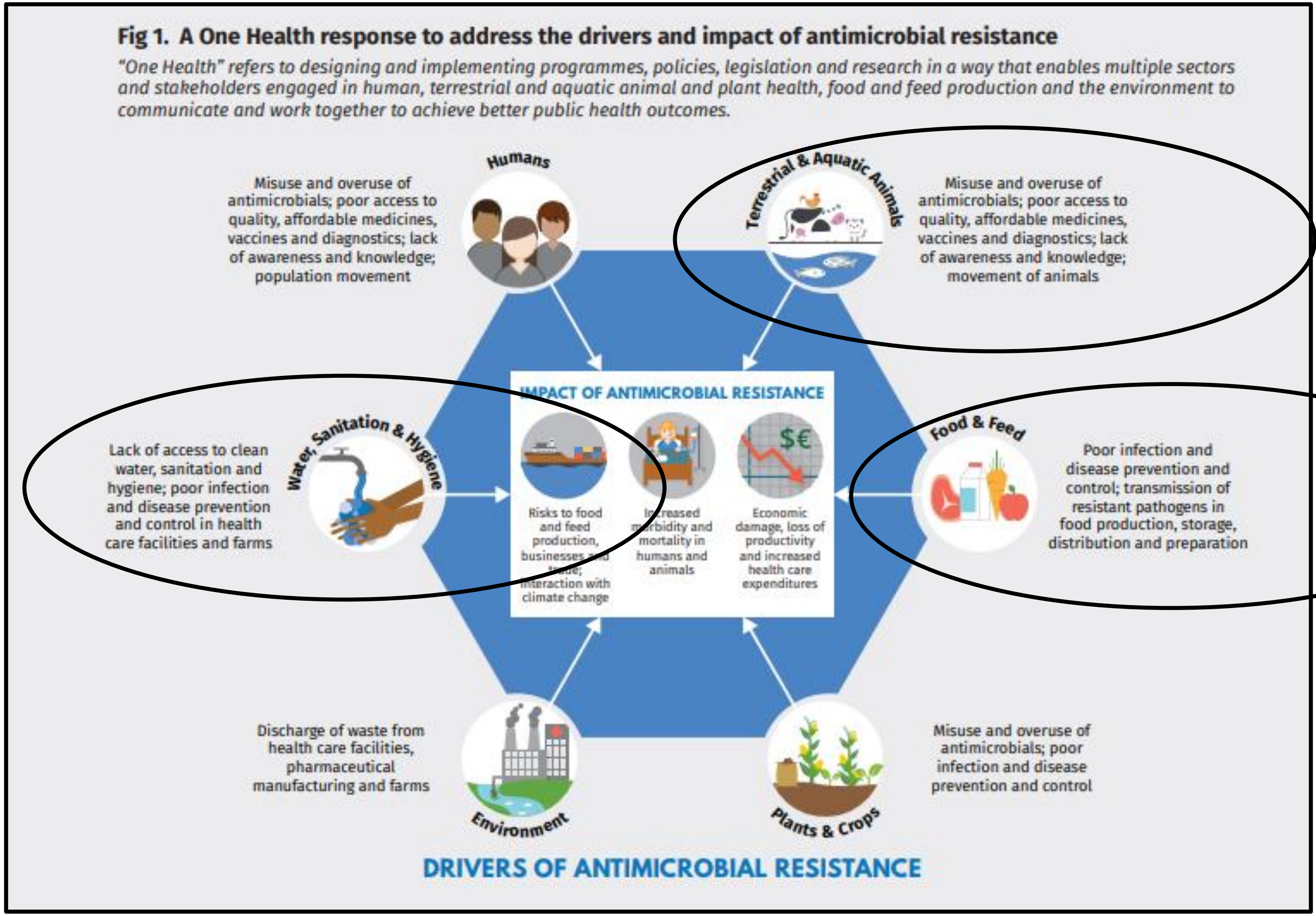
Sylvia Checkley

Lecture Overview

- During this lecture we will discuss AMU and AMR in the livestock sectors

This lecture contributes to the overall course learning objectives

- 1. Complex contributing factors to antimicrobial use and the emergence and spread of AMR
- 2. Practical approaches to limiting antimicrobial misuse in various contexts
- 3. The global interdependence of people, animals, and the environment (One Health)
- 4. The role of One Health in complex problems and AMR



https://www.who.int/antimicrobial-resistance/interagency-coordination-group/IACG_final_report_EN.pdf?ua=1

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- Multiple intersecting drivers

Antimicrobial Use

- **1. Therapeutic**
  - Treat clinical disease
    - Informed by isolation of agent and antimicrobial sensitivity profile
- **2. Metaphylaxis**
  - Treatment of a group of animals considered high risk after diagnosis of disease within the group
    - e.g. Treatment of high risk feedlot cattle on arrival at the feedlot
- **3. Preventive/prophylaxis**
  - Treatment of high risk healthy animals to prevent disease from occurring
    - e.g. dry cow therapy
- 4. **Growth Promotion**
  - Longer term, subtherapeutic concentration

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OXFORD FEMS JOURNALS investing in science

Pathogens and Disease, 75, 2017, ftx083

doi: 10.1093/femspd/ftx083
Advance Access Publication Date: 20 July 2017
Minireview

MINIREVIEW

Do antimicrobial mass medications work? A systematic review and meta-analysis of randomised clinical trials investigating antimicrobial prop… or metaphylaxis against naturally occurring b… respiratory disease

Keith Edward Baptiste* and Niels Christian Kyvsgaard

Danish Medicines Agency, Axel Heides Gade 1, DK-2300 Copenhagen S, Denmark

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One sentence summary: A systematic review and meta-analysis of randomised clinical trials investigating antimicrobial proph… against naturally occurring bovine respiratory disease.

Editor: Edmundo Calva

ABSTRACT

Animal Health Research Reviews

cambridge.org/ahr

Systematic Review

Cite this article: O'Connor AM *et al* (2019). A systematic review and network meta-analysis of injectable antibiotic options for the control of bovine respiratory disease in the first 45 days post arrival at the feedlot. *Animal Health Research Reviews* **20**, 163–181. https://doi.org/10.1017/S1466252320000031

Received: 31 July 2019
Revised: 4 December 2019
Accepted: 15 December 2019

Key words:
Antibiotics; bovine; meta-analysis; respiratory disease; systematic review

A systematic review and network meta-analysis of injectable antibiotic options for the control of bovine respiratory disease in the first 45 days post arrival at the feedlot

A. M. O'Connor[1], D. Hu[2], S. C. Totton[3], N. Scott[1], C. B. Winder[4], B. Wang[5], C. Wang[1,2], J. Glanville[6], H. Wood[6], B. White[7], R. Larson[7], C. Waldner[8] and J. M. Sargeant[3]

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Abstract

We conducted a systematic review and network meta-analysis to determine the comparative

The Story of VRE in Europe

- Avoparcin is a glycopeptide antimicrobial that was used as a growth promotant in Europe
- Growth promotant – enhance growth rate and production performance with subtherapeutic doses
- Vancomycin resistant enterococci (VRE), *E. faecium*, was first isolated in France in 1986
- Avoparcin use thought to be associated with high-level of community-acquired VRE *(E. faecium)* in humans 1994/1995
  - Hospital-acquired VRE in NA
- Precautionary principle invoked – banning antimicrobials as growth promotants
- Avoparcin banned as growth promotant
  - EU 1995 - 1999

Nilsson (2012); Wegener et al. (1999)

The Story of VRE in Europe

- Large body of evidence to support the association between the presence of VRE and the use of avoparcin
  - Pigs: 8/10 herds using avoparcin had VRE isolated; 2/10 herds not using avoparcin had VRE isolated (p = 0.043, risk ratio [RR] 3.3; 95% confidence interval [CI]: 1.1, 10.0). (Denmark)
  - Country level
- Prevalence of VRE began to decrease immediately in poultry and after banning of tylosin in pigs in 1998
  - Poultry: VRE isolated from n flocks at slaughter decrease from 82% (1995) to 12% (1998) (x^2 = 68.3 on 5 df.; p <0.0001) (Denmark)
  - Pigs: clone with genes for glycopeptide and macrolide resistance the same plasmid
- Prevalence of VRE in humans (fecal carriage) and poultry meat decreased by1999
  - Poultry meat: proportion of VRE-positive samples decreased from 100% in 1994 to 25% in 1997 (Germany)
- Fecal samples from humans in the community:
  - Carrier rate decreased from 12% in 1994 to 3% in 1997
- Supported by molecular epidemiology

Nilsson (2012); Wegener et al. (1999)

Medically Important Antimicrobials

- Category I: Very High Importance

  e.g. 3rd and 4th generation cephalosporins, carbapenems, fluoroquinolones

- Category II: High importance

  e.g. macrolides, penicillins

- Category III: Medium Importance

  e.g. aminoglycosides, tetracyclines

- Category IV: Low Importance

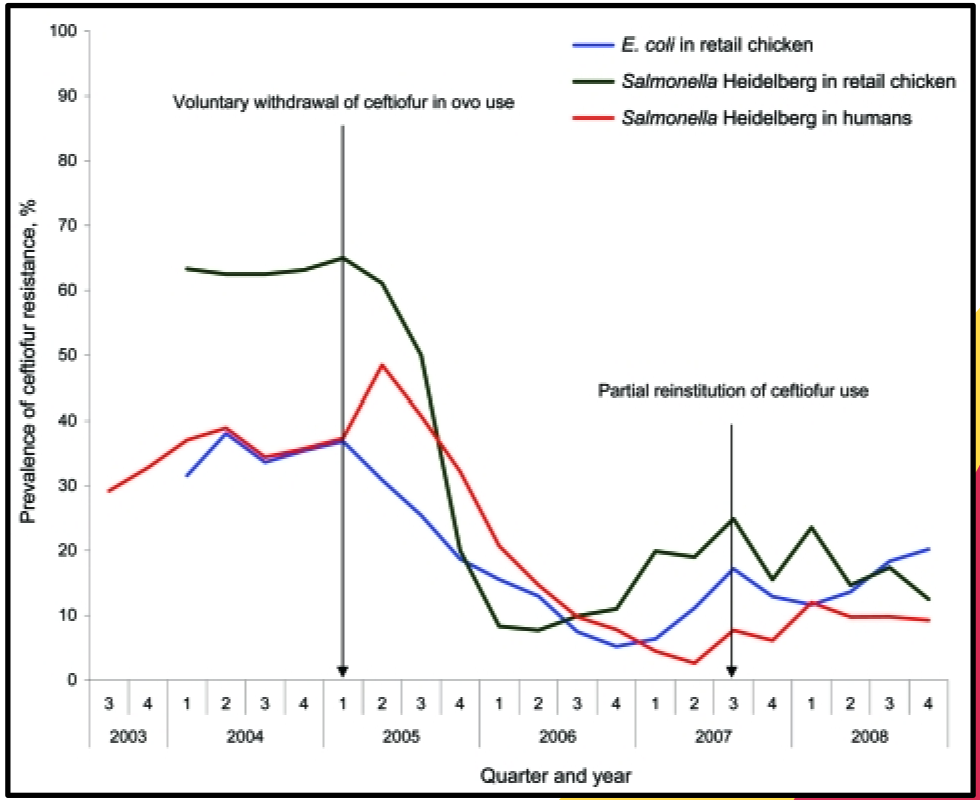
  e.g. Ionophores, chemical coccidiostats, flavophospholipids

Canadian Categorization is slightly different from WHO list of critically important antimicrobials

https://www.canada.ca/en/health-canada/services/drugs-health-products/veterinary-drugs/antimicrobial-resistance/categorization-antimicrobial-drugs-based-importance-human-medicine.html

Canada – AMR in poultry products

- CIPARS
- Correlation between) between ceftiofur-resistant *Salmonella* Heidelberg from retail chicken and ceftiofur-resistant *Salmonella* Heidelberg infections in humans
- May be related to ceftiofur use in hatcheries (QC)
- Ethical decision/policy making
  - Voluntary ban by poultry industry
  - Subsequent decision to discontinue all preventive use of Category 1 antimicrobials
- Fluoroquinolone resistance in *Campylobacter spp.*
- Quinolone resistance in *Salmonella* Enteritidis



Dutil et al, Used with permission

Systematic Review and Meta-Analysis

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Articles

Restricting the use of antibiotics in food-producing animals and its associations with antibiotic resistance in food-producing animals and human beings: a systematic review and meta-analysis

Karen L Tang, Niamh P Caffrey, Diego B Nóbrega, Susan C Cork, Paul E Ronksley, Herman W Barkema, Alicia J Polachek, Heather Ganshorn, Nishan Sharma, James D Kellner, William A Ghali

Summary

Background Antibiotic use in human medicine, veterinary medicine, and agriculture has been linked to the rise of antibiotic resistance globally. We did a systematic review and meta-analysis to summarise the effect that interventions to reduce antibiotic use in food-producing animals have on the presence of antibiotic-resistant bacteria in animals and in humans.

Methods On July 14, 2016, we searched electronic databases (Agricola, AGRIS, BIOSIS Previews, CAB Abstracts,

Lancet Planet Health 2017; 1: e316–27

Published Online November 6, 2017 http://dx.doi.org/10.1016/S2542-5196(17)30141-9

Antimicrobial Use in Canada

Canadian Integrated Program for Antimicrobial Resistance surveillance (CIPARS)

John Campbell

Antimicrobial Use Metrics

- Sales Value
- Drug mass in kg
  - Adjusted by biomass - standardization
- # of animals treated
- Treatment rate
- Animal defined daily dose (ADDD)
  - ADDD / 1000 animals – standardized

Benedict et al, 2012

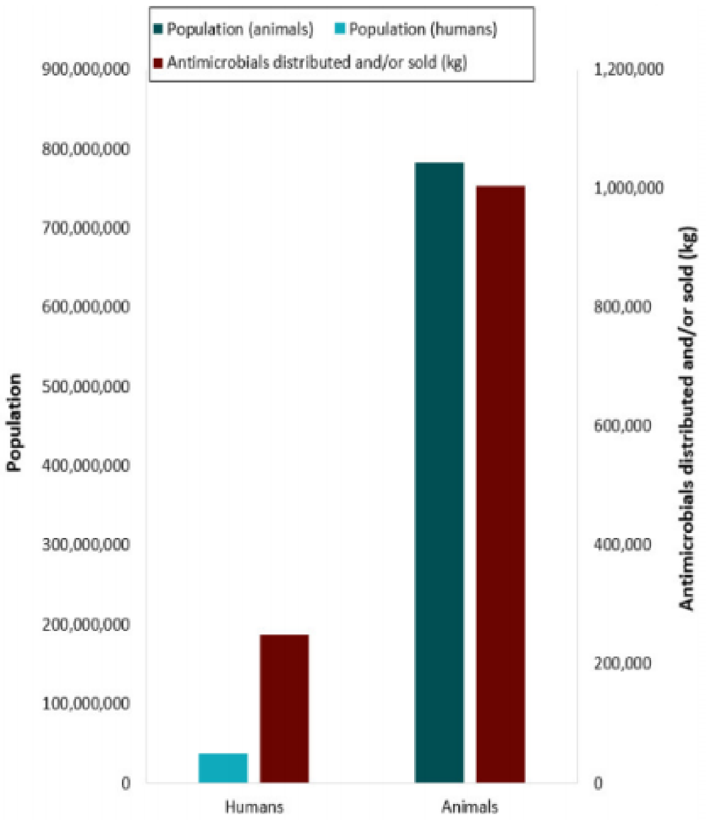
COMPARING HUMANS, ANIMALS, AND CROPS

5%

INCREASE IN TOTAL QUANTITY OF ANTIMICROBIALS (ADJUSTED BY BIOMASS) DISTRIBUTED FOR USE IN PRODUCTION ANIMALS SINCE 2017 AS A RESULT OF INCREASED SALES OF TETRACYCLINE.

~1.4x

MORE ANTIMICROBIALS WERE DISTRIBUTED FOR USE IN ANIMALS THAN HUMANS AFTER ADJUSTING FOR UNDERLYING BIOMASS IN 2018.



21x

MORE ANIMALS THAN PEOPLE IN CANADA IN 2018.

Note: This is an underestimation, as fish are not included in the animal estimate.

PUBLIC HEALTH AGENCY OF CANADA > 14

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CIPARS (2019), used with permission

Integrated AMU Data

Of the antimicrobials distributed or sold* in 2018:

78% were intended for **production animals**

21% were intended for **humans**

1% were intended for **companion animals**

<1% were intended for **crops**

*Animal distribution data currently do not account for quantities imported as active pharmaceutical ingredients intended for further compounding; hence, these are underestimates of total quantities used.

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CIPARS (2019), used with permission

Integrated AMU Data

For both humans and animals, the β-lactams (penicillins) were one of the main antimicrobial classes distributed/sold on a per kg of antimicrobial basis.

Similar antimicrobials were licensed for use in humans and animals; however, some antimicrobial classes were sold or distributed more for use in humans than animals and vice-versa.

The relative quantity of cephalosporins and fluoroquinolones intended for use in people is higher compared to animals (~7x and 25x higher for people, respectively).

Tetracyclines are used predominantly in production animals.

Humans

Antimicrobial class	%
B-lactams (penicillins)	52%
Cephalosporins	18%
Trimethoprim and sulfonamides	7%
Fluoroquinolones and quinolones	6%
Macrolides	5%

Production Animals

Antimicrobial class	%
Tetracyclines	57%
Other antimicrobials	12%
B-lactams (penicillins)	11%
Macrolides	9%
Trimethoprim and sulfonamides	5%

Companion Animals

Antimicrobial class	%
Cephalosporins	35%
B-lactams (penicillins)	33%
Trimethoprim and sulfonamides	27%
Lincosamides	2%
Fluoroquinolones	1%

Notes:

1. Cephalosporins are β-lactam antimicrobials, but we are displaying them separately for visualization purposes.

2. The percentages are based on total kilograms of active ingredients intended for use in that host species.

3. Other antimicrobials for animals: avilamycin, bacitracins, bambermycin, chloramphenicol, chlorhexidine gluconate, florfenicol, fusidic acid, novobiocin, polymixin B, tiamulin, and virginiamycin.

4. Other antimicrobials for humans: bacitracin, chloramphenicol, colistimethate, colistin, daptomycin, fidaxomicin, fosfomycin, fusidic acid, linezolid, methenamine hippurate, methenamine mandelate, metronidazole, nitrofurantoin, polymyxin B, quinupristin/dalfopristin, vancomycin.

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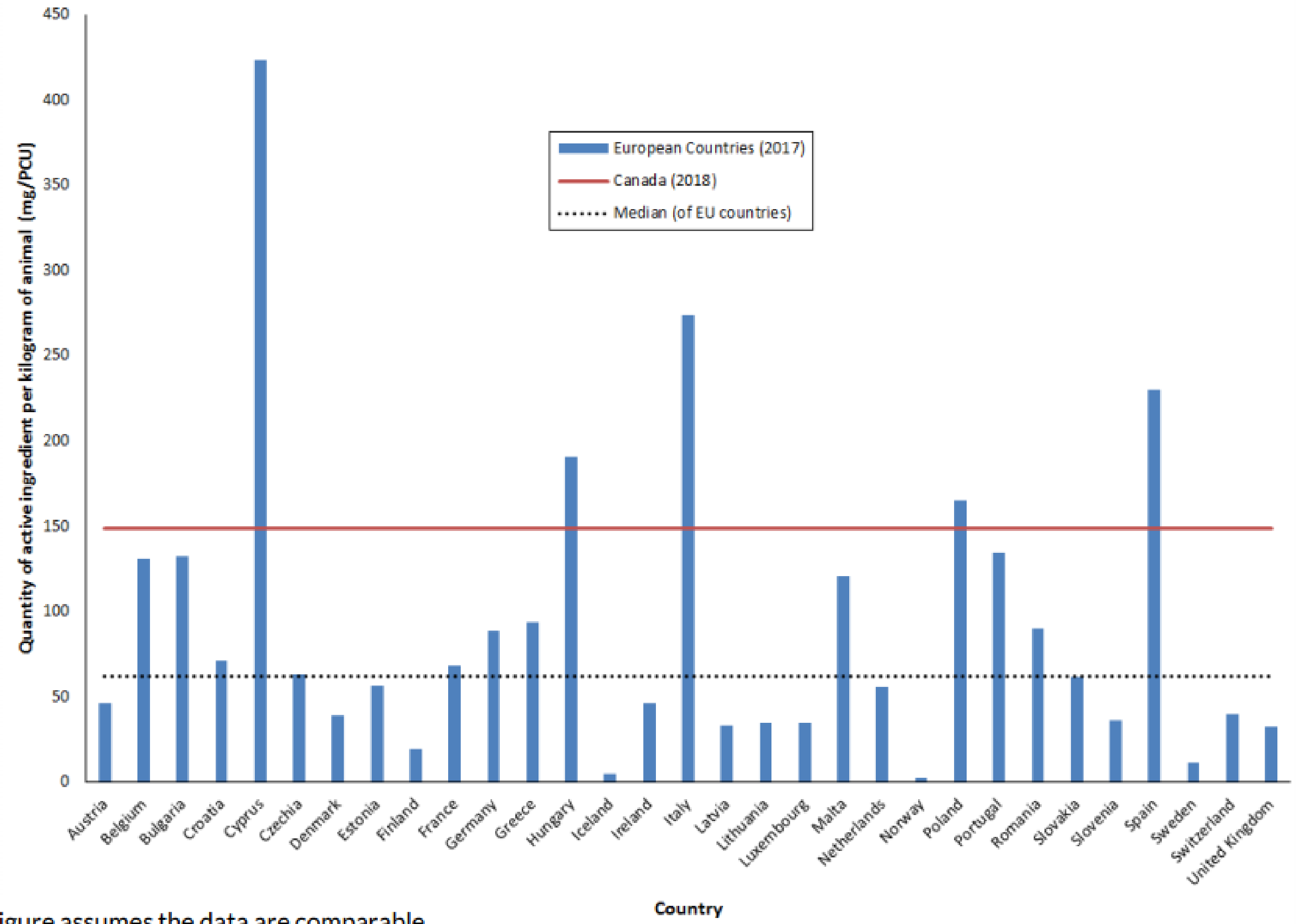
Canada is the 6th highest country (in comparison to Europe) for quantities of antimicrobials sold (mg/PCU).



Note: This figure assumes the data are comparable.

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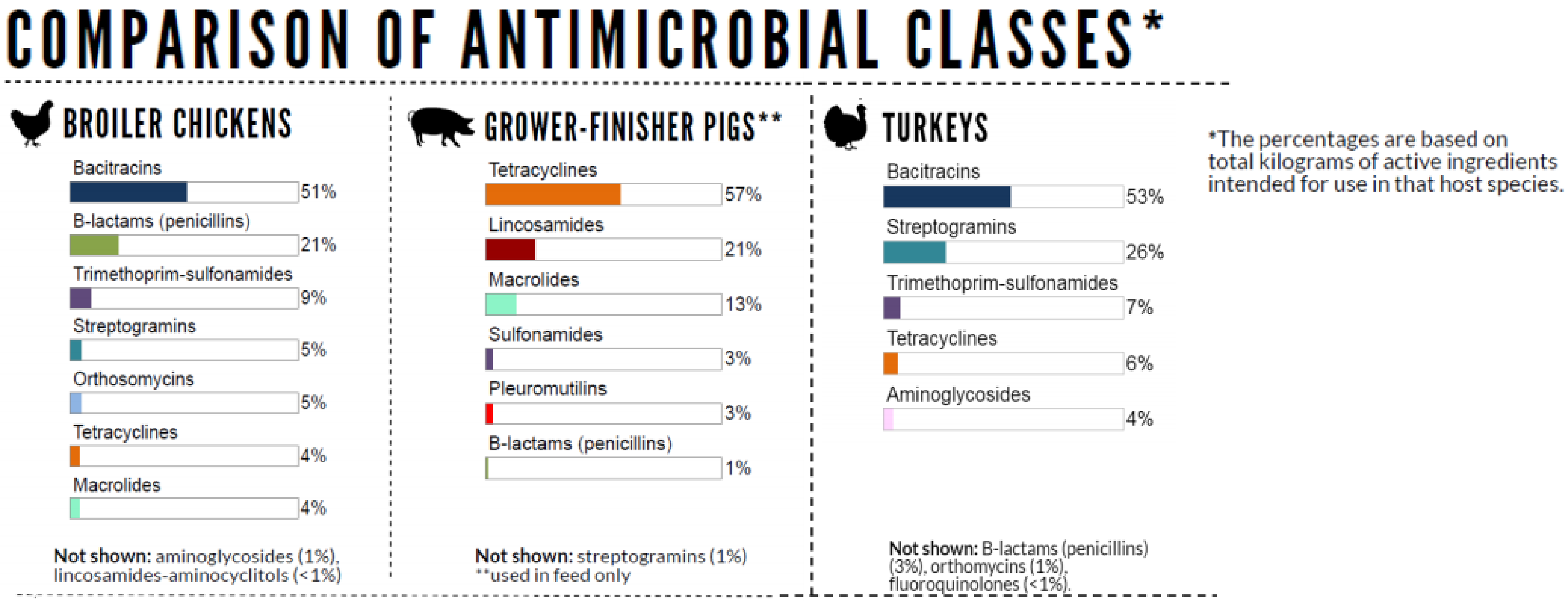
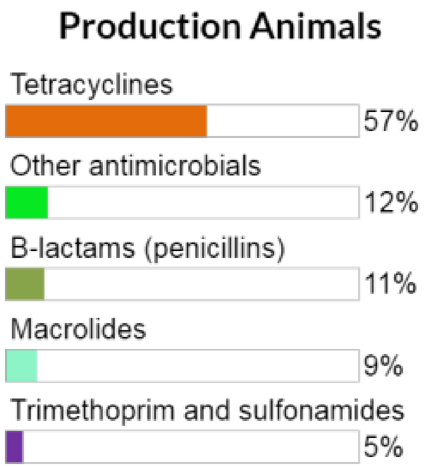
CIPARS (2019), used with permission

Integrated AMU Data





There are important differences in the types and relative quantities of antimicrobials reported for use between food animal species, which is why we need ongoing surveillance across the food animal species.

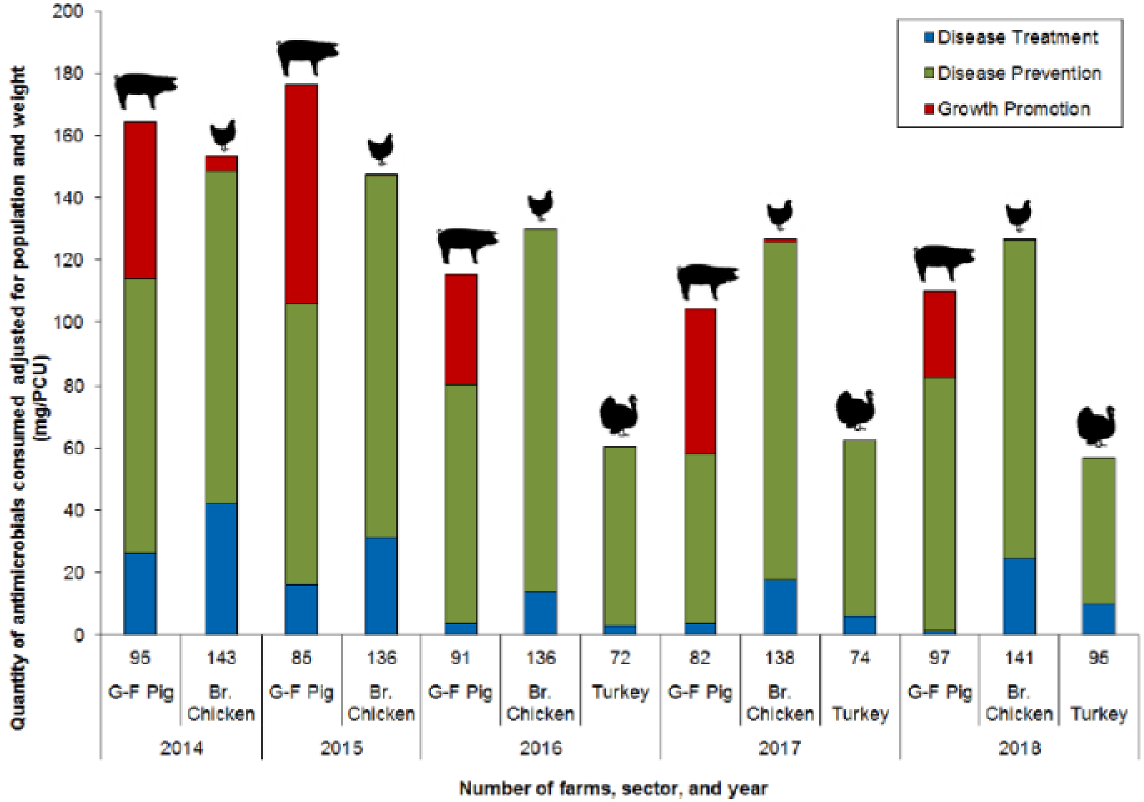
CIPARS (2019), used with permission

Integrated AMU Data

REASONS FOR ANTIMICROBIAL USE

- In broiler chickens (Br. Chicken), turkeys, and grower-finisher pigs (G-F Pig), the predominant reason for reported administering antimicrobials was for **disease prevention**.
- In grower-finisher pigs, there continues to be reported use of antimicrobials for growth promotion.

Quantity of antimicrobials used (mg/PCU) by reason for use; CIPARS Farm 2014 to 2018.



Note: Swine data are for antimicrobial use in feed only; chicken and turkey data include all routes of administration.

Antimicrobial Use and Resistance

Kimera *et al. Antimicrobial Resistance and Infection Control* (2020) 9:37
https://doi.org/10.1186/s13756-020-0697-x

Antimicrobial Resistance and Infection Control

REVIEW — Open Access

Antimicrobial use and resistance in food-producing animals and the environment: an African perspective

Zuhura I. Kimera[1,2*], Stephen E. Mshana[3], Mark M. Rweyemamu[4], Leonard E. G. Mboera[4] and Mecky I. N. Matee[1,4]

Abstract

Background: The overuse of antimicrobials in food animals and the subsequent contamination of the environment have been associated with development and spread of antimicrobial resistance. This review presents information

frontiers in Veterinary Science

ORIGINAL RESEARCH
published: 26 February 2020
doi: 10.3389/fvets.2020.00055

Antimicrobial Use in Extensive Smallholder Livestock Farming Systems in Ethiopia: Knowledge, Attitudes, and Practices of Livestock Keepers

Biruk Alemu Gemeda[1*], Kebede Amenu[2], Ulf Magnusson[3], Ian Dohoo[4], Gunilla Ström Hallenberg[3], Gezahegn Alemayehu[1], Hiwot Desta[1] and Barbara Wieland[1]

- Systematic review
- Conclusions
  - High levels of AMU and AMR
  - high prevalence of resistance
  - Weak regulations and surveillance

- KAP Research
- Conclusions
  - Variable AMU
  - Good practices associated with education
  - Need for education interventions

Pre-Reading 1

Global resistance to antimicrobials and their sustainable use in agriculture (Lhermie et al, 2019)

- Emphasizes transdisciplinarity
  - Economics, behaviour, ethics, culture
- Determine optimal AMU
  - Social-ecological systems (SES) framework
    - Public Health-Economic-Environmental-Social-Political model
  - Systems dynamics modelling
    - Assessments of associations and indicators
  - Multi-criteria decision analysis
    - Tradeoffs between animal and human welfare

Pre-Reading 2

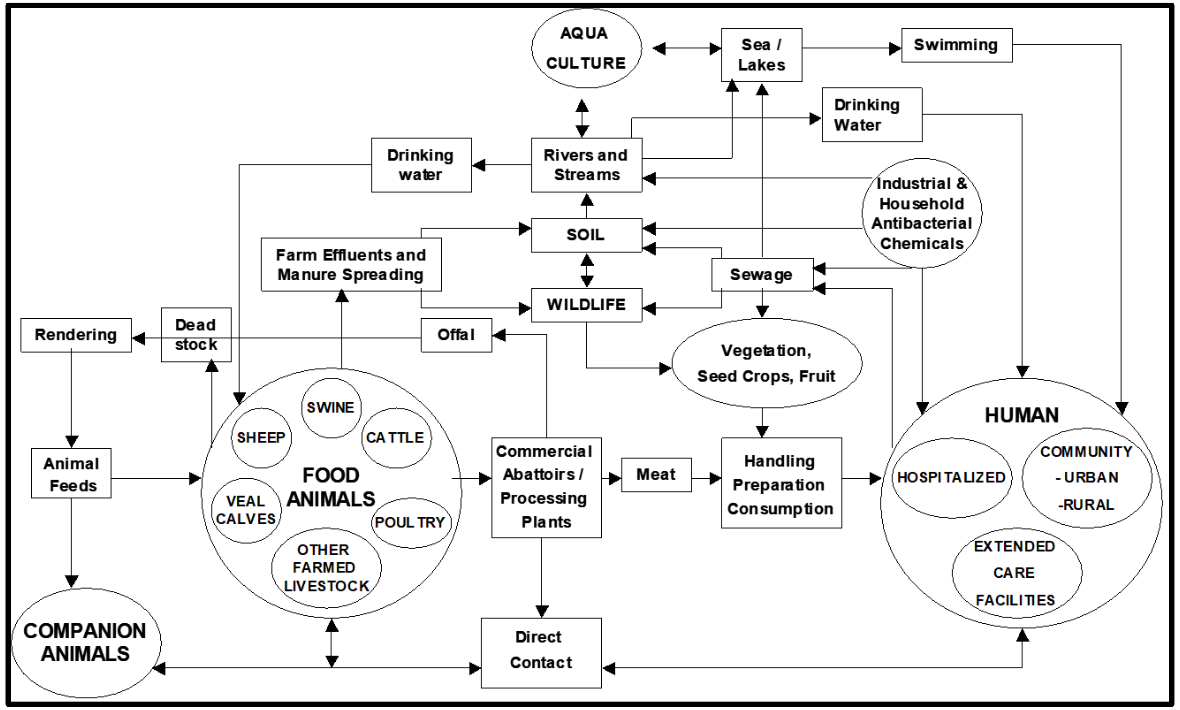
Exploring Perspectives on AMU…
(Coyne et al 2019)

- 3 overarching themes affecting AMU practices
  - Farming systems
  - Farm management strategies
  - Farm-level economics
- Complex
- Profitability and disease burden were major drivers for AMU
- Guidance on routine preventive measures and disease prevention would allow more informed decision making

AMR as a One Health Issue

Camila de Queiroz

Complex issue of Antimicrobial Use and Resistance need a One Health Approach



Based on Linton Vet Rec 1977, 100:354
Updated by VDD 2002 (used with permission)

One Health Definition

“a transdisciplinary approach to address issues that emanate from the intersection of animals, humans, and their environment”

http://www.phac-aspc.gc.ca/owoh-umus/index-eng.php

One Health Further Definition

Addresses:

- Systems and disease
- Environmental complexity
- Agricultural sustainability
- Concepts and knowledge transfer

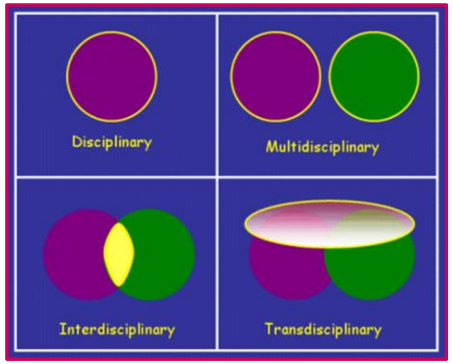


Image Copyright Unknown

Methodological Pillars:

- Systems thinking
- Transdisciplinarity
- Community participation
- Gender and social equity
- Sustainability
- Knowledge to Action (i.e. contributes to policy development)

As stakeholders, we all “own” a piece of the issue

- Acknowledge contributions from different sectors
- Understand effects of increasing AMR in humans, animals and the environment
- Develop policies, procedures, and protocols to reduce or eliminate our contribution to the problem

Summary

- The precautionary principle has guided some AMU decision making
- AMU is a key determinant of antimicrobial resistance
- Multiple perspectives exist on AMU in animals
- Comparisons and quantification of AMU between sectors/countries is not straightforward
- The contribution of AMU in animals to AMR in humans is less clear

Additional Resources

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Discussion and Question(s)

- Can we substantially reduce AMU in animals?
- What do we need to do to move forward and 'solve' this problem?

John Campbell

Thank You!

- Please feel free to contact me with any questions
- Sylvia Checkley - slcheckl@ucalgary.ca