



Good Practices in Antimicrobial Use (AMU) Surveillance – the Canadian Experience Implementing AMU Surveillance

APEC Workshop – Oct. 9, 2018
Santiago, Chile

PROTECTING AND EMPOWERING CANADIANS
TO IMPROVE THEIR HEALTH



Things to think about at the beginning...

Why do you want data about antimicrobial use?

Generally – it is all about comparisons...

- Is *antimicrobial consumption*/AMU increasing or decreasing?
- How do we compare to other areas?
- Is *antimicrobial consumption*/AMU different in different host species?
- What does *antimicrobial consumption*/AMU mean for resistance?

COMPARISONS CREATE DISCOMFORT!

- Are we sure?
- What are the implications of increasing precision/accuracy?

Setting your objectives – Language is important!

Surveillance ≠ Research

Types of surveillance

- Active – defined sample frame/protocol
- Passive – “take what you have in place”
- Enhanced passive - specific data collection in addition to passive data
- Continuous vs. periodic/episodic
- Comprehensive vs. sentinel/target site

What type of surveillance best meets your objectives?

Setting your objectives – Language is important!

Use ≠ Consumption

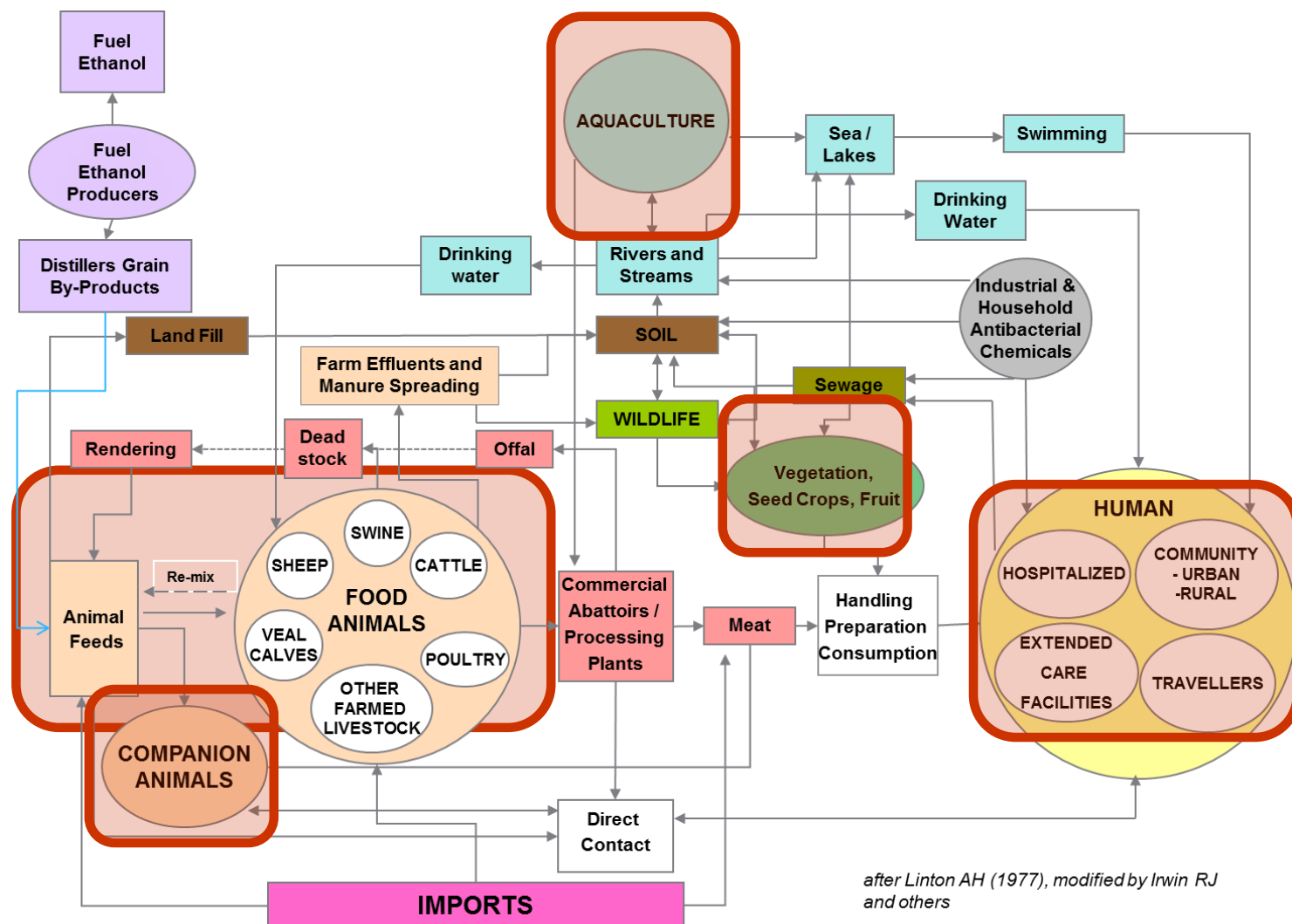
Use of antimicrobials – “The actual administration of antimicrobials to the animals or any process that suggests the antimicrobials have been or will be administered, for example prescribing or delivering antimicrobials to the farm(er).”

(AACTING Guidelines - http://www.aacting.org/swfiles/files/AACTING_Guidelines_V1.1_2018.03.23_39.pdf)

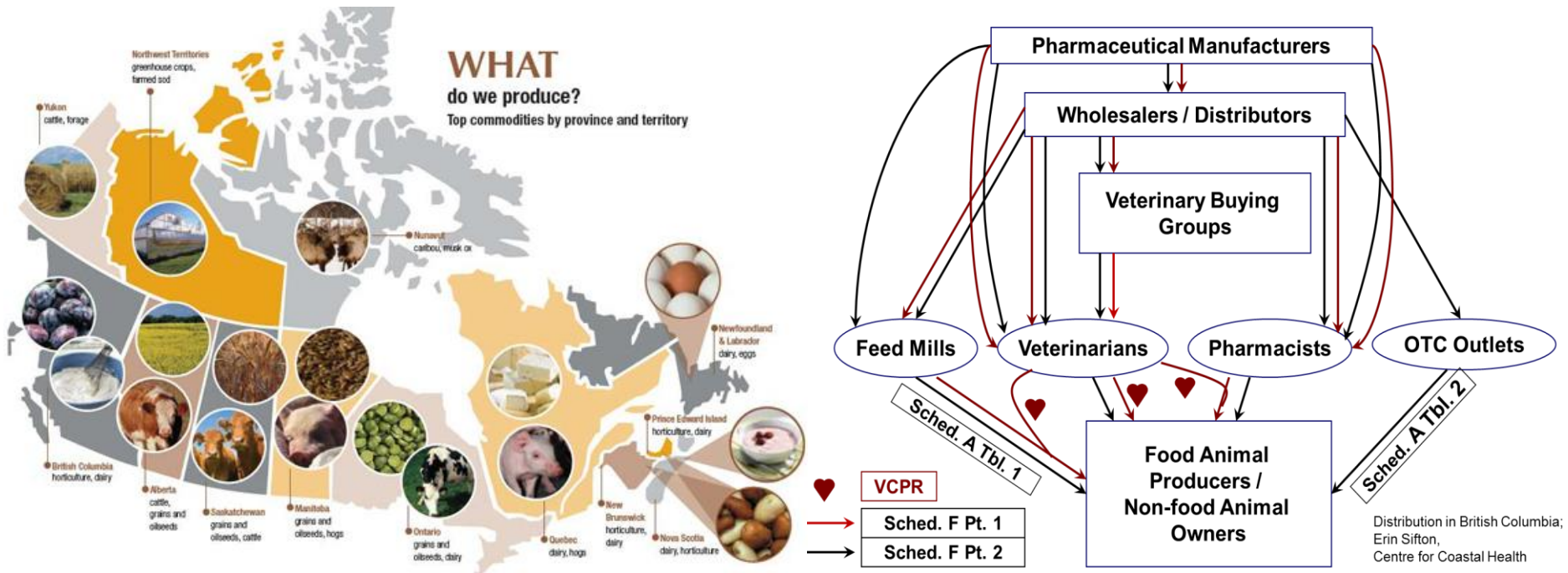
Antimicrobial consumption “statistics quantify the ecological selection pressure on microbial populations. Antimicrobial consumption often translates as sales of antimicrobial medicines. It permits benchmarking comparisons at global, country or healthcare facility level and evaluation of the impact of educational or regulatory interventions.”

(WHO - http://www.who.int/medicines/areas/rational_use/AMU_Surveillance/en/)

Setting your objectives - scope and system



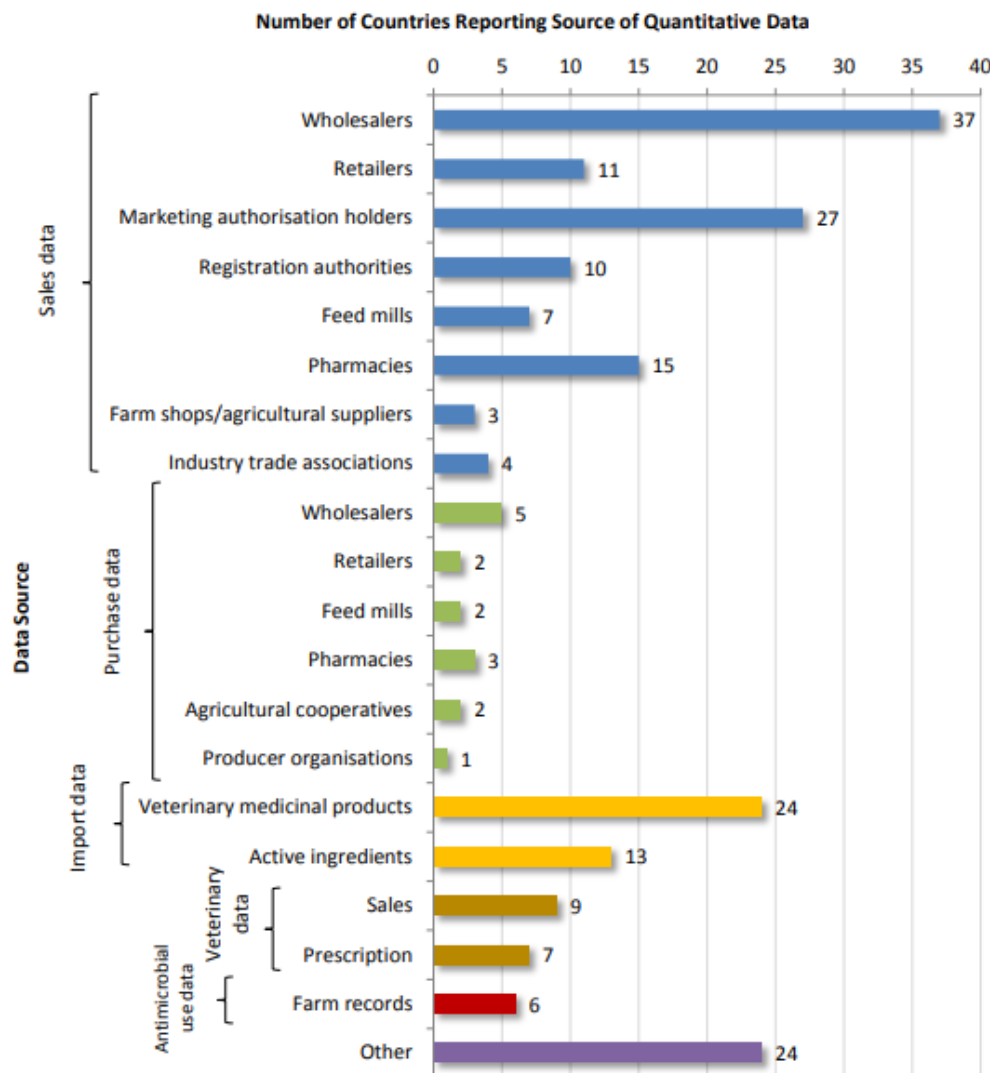
Details - where to collect information and from what?



Source: Agriculture and Agrifood Canada;
http://www4.agr.gc.ca/resources/prod/img/images/Map_Brochure_eng.jpg

Details - Types of data

Figure 7. Data Sources Selected by 107 Countries Reporting Quantitative Data from 2013-2016



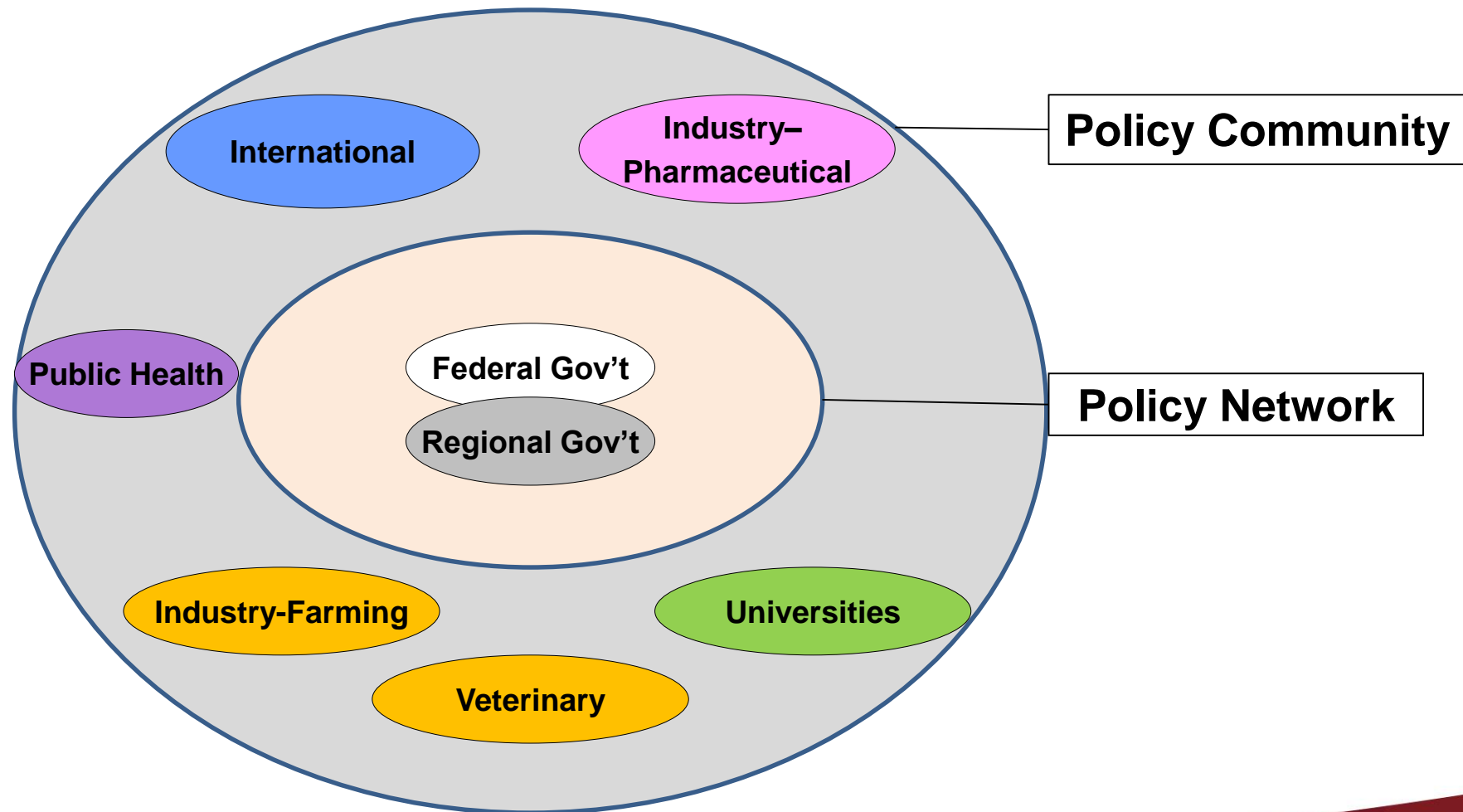
AACTING Guidelines (use):

http://www.aacting.org/swfiles/files/AACTING_Guidelines_V1.1_2018.03.23_39.pdf

- prescription records
- farm records
- veterinary practice records
- delivery notes and/or invoice

http://www.oie.int/fileadmin/Home/fr/Our_scientific_expertise/docs/pdf/AMR/Annual_Report_AMR_2.pdf

Who has data and who can contribute to reporting



CIPARS



Government
of Canada

Gouvernement
du Canada

2015

CANADIAN INTEGRATED PROGRAM FOR ANTIMICROBIAL RESISTANCE SURVEILLANCE (CIPARS)

ANNUAL REPORT



Canada

CANADIAN ANTIMICROBIAL RESISTANCE SURVEILLANCE SYSTEM 2017 REPORT



PROTECTING AND EMPOWERING CANADIANS TO IMPROVE THEIR HEALTH

Public Health
Agency of Canada

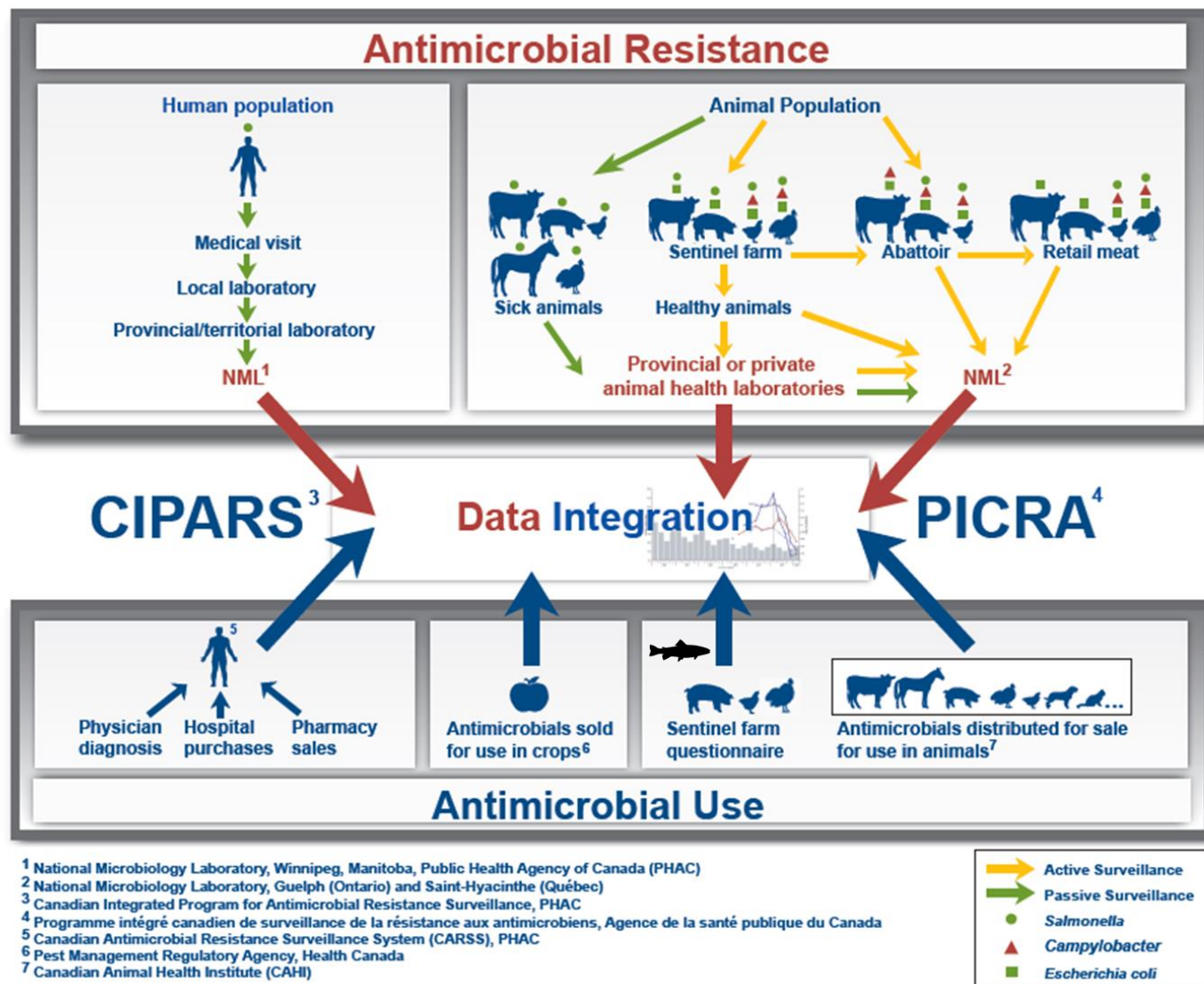
Agence de la santé
publique du Canada

Canada

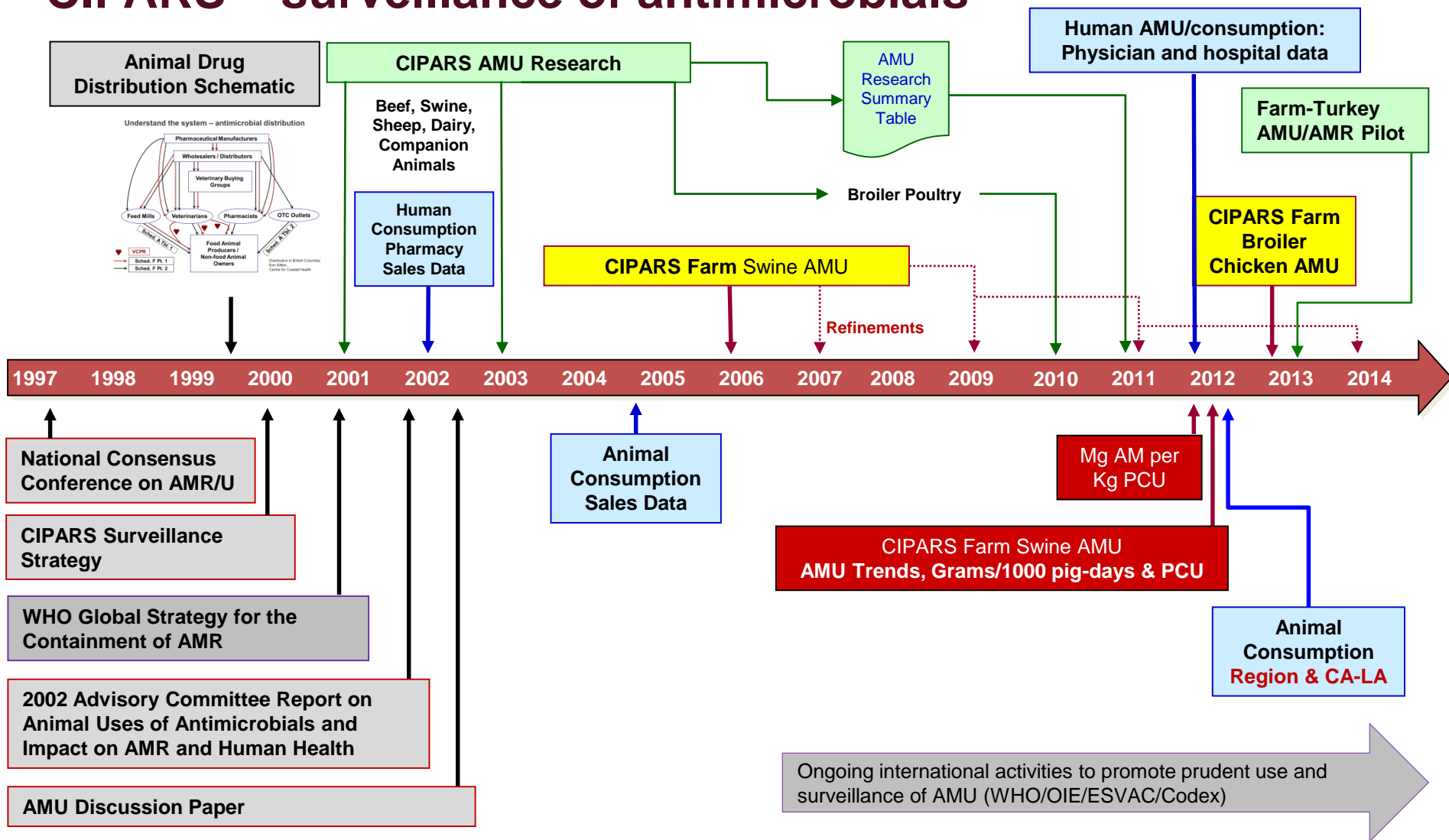
CIPARS Objectives

- Unified approach to monitor trends in antimicrobial resistance (AMR) & antimicrobial use (AMU) in humans & animals
- Allow accurate international comparisons with other countries that use similar surveillance systems
- Generate data and timely reports to facilitate the assessment of the public health impact of antimicrobials used in human & agricultural sectors

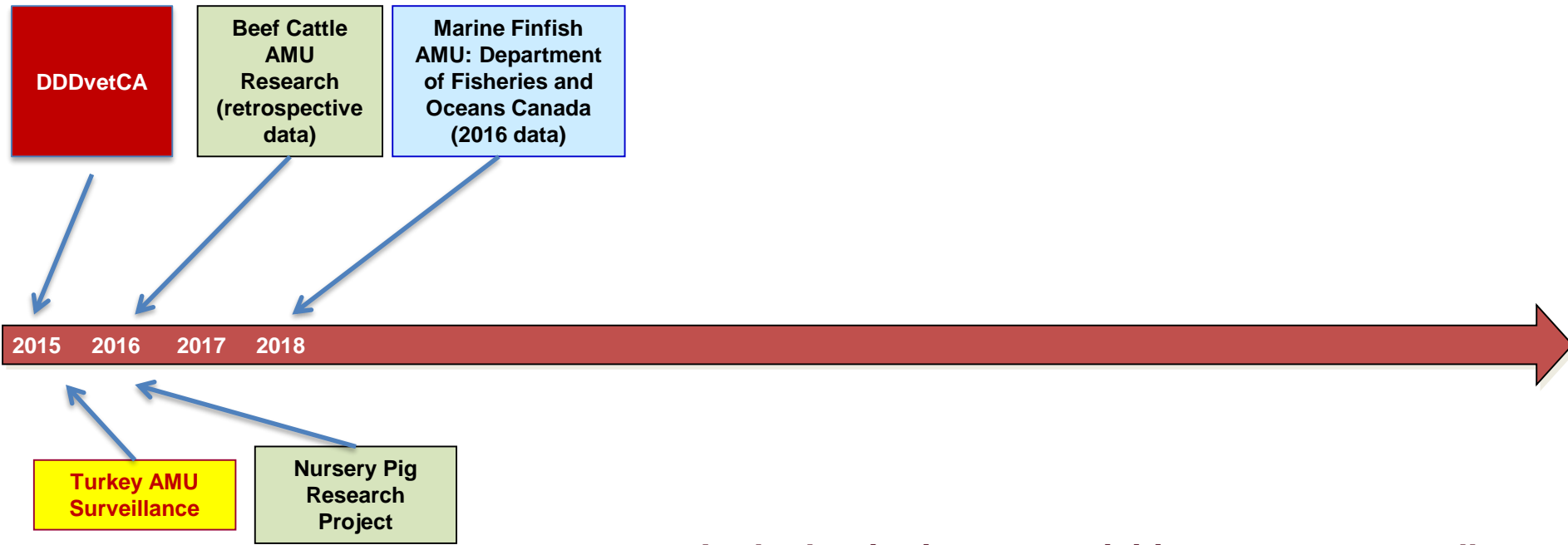
Partnership
and collaboration



CIPARS – surveillance of antimicrobials



CIPARS – surveillance of antimicrobials



- In the beginning our activities were very small.
- But we had a great plan(ner)!
- Critical to just start.

Data sources - antimicrobials intended for use in animals

- CIPARS farm questionnaire
 - Data voluntarily provided by participating producers and veterinarians
 - Broiler chickens, turkeys, grower-finisher pigs
 - Beef and dairy farm surveillance frameworks under development
- *Quantity of active ingredient distributed for use in animals since 2006*
 - *Data voluntarily provided by the Canadian Animal Health Institute (CAHI)*
 - *Stratified by province and type of animal (companion vs. production animal)*
- Marine Finfish data - Fisheries and Oceans Canada requires industry owners and operators to report on their use of drugs and pesticides, including antimicrobials under the authority of the Aquaculture Activities Regulations authorized under the Fisheries Act
 - Freshwater finfish data anticipated for 2017

Data sources - antimicrobials intended for use in people

- **Purchased from IQVIA – provided to CIPARS via CARSS**
 - Physician diagnosis and antimicrobial recommendations
 - *Hospital purchases*
 - *Pharmacy dispensations*
- *Additional data from Northern Communities included in pharmacy data*

Data sources - antimicrobials intended for use on crops

- **Provided by Health Canada's Pest Management Regulatory Agency**
 - *Annual Canadian sales data from all pesticide manufacturers*
 - *Fireblight on pome fruits (apples, pears, quince), caneberries and Saskatoon berries; blossom blast and bacterial canker on cherries; stem canker and bacterial spot on greenhouse and field fruiting vegetables (peppers, tomatoes, and eggplant); and walnut blight of walnuts.*

Continuing to evolve – *animal sales data*

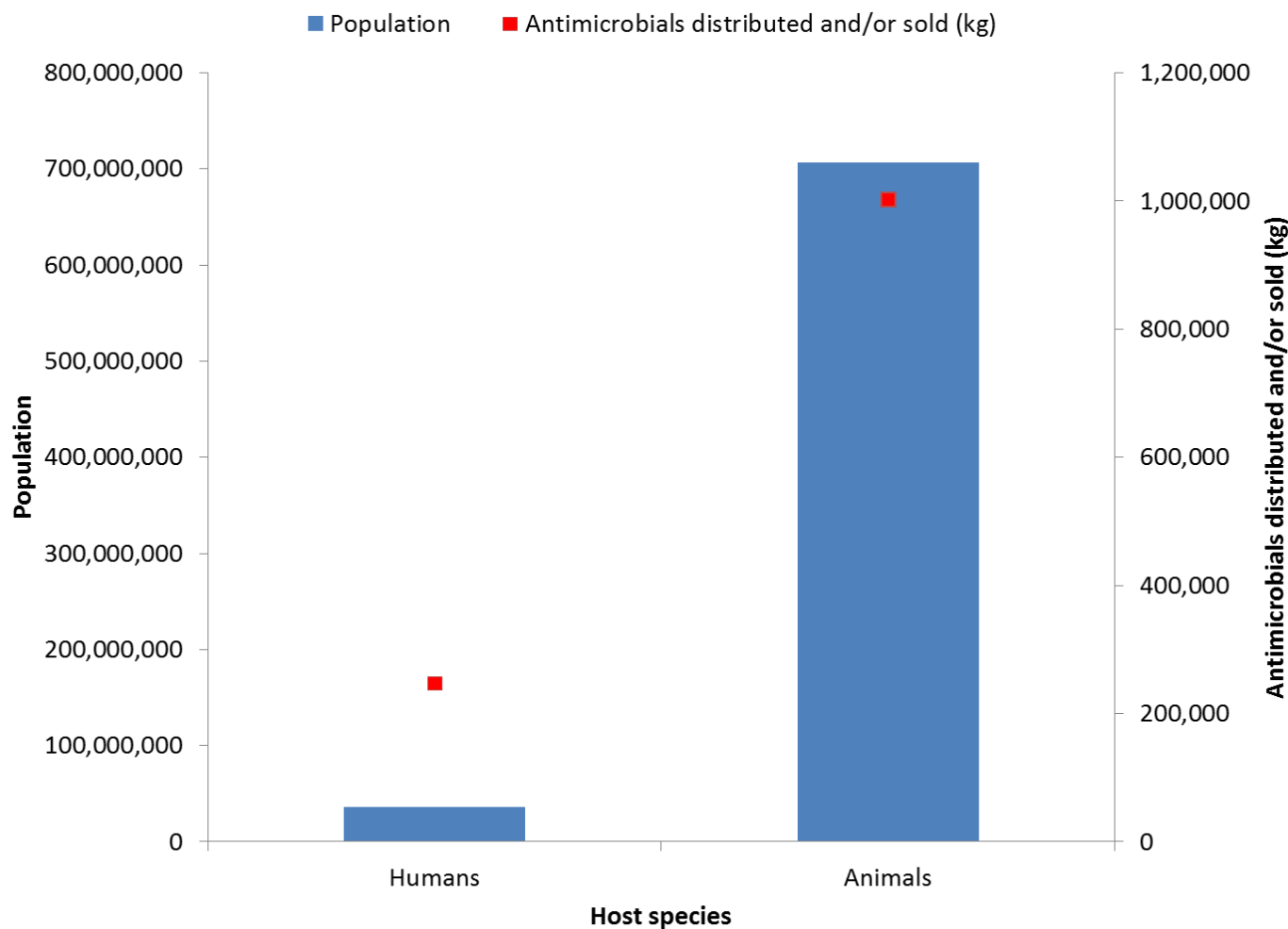
Current	2019 (for 2018 data)
Voluntary provision (Canadian Animal Health Institute)	Regulatory authority
90%-95% of animal health product market	All antimicrobials
Missing some imported products	Will capture data from importers
<ul style="list-style-type: none">• By animal type<ul style="list-style-type: none">• Production animal• Companion animal	<ul style="list-style-type: none">• By animal species (low/high estimates)<ul style="list-style-type: none">• Cattle (dairy, beef, veal)• Pigs• Chickens (broilers, layers)• Turkeys• Horses• Aquaculture (finfish, shellfish)• Small ruminants• Companion animals• Other

<https://www.canada.ca/en/public-health/services/antibiotic-antimicrobial-resistance/animals/veterinary-antimicrobial-sales-reporting.html>

Ok. Now we have data...

- This is not hard (mathematically).
- This is very meticulous work.
- This has fancy language.
- Technical details matter.
 - *Decisions about these can be complex*
 - *Not everyone needs to know the technical details!*
- This is not hard.

Yes, you need a denominator!



Animal distribution data does not include own use imports or active pharmaceutical ingredients used in compounding.

Data sources: CAHI, IQVIA via CARSS, Statistics Canada, Ag Canada, Equine Canada

Fancy language to remember

Animal Biomass = number of animals x how heavy they are

Technical Details

- What animal species to include?
- Inclusion of imported animals/exported animals?
- If average weight at treatment – *Population Correction Unit (PCU)*
 - 1 kg animal = 1 PCU

Defined Daily Dose Vet = “assumed average dose per kg animal per species per day”

(https://www.ema.europa.eu/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddveter-defined-course-dose-animals-dcdvet_en.pdf)

Technical Details

- Based on average or median of labelled doses
- Do these standards need to be country-specific?
- How often are standards reviewed?
- Are the standards weighted by the number of products with the same dose?
- What to do with long acting products?
- What to do with antimicrobials used in an extra-label manner?

Evolution of *antimicrobial consumption/use* reporting

Consumption: kg  mg/animal biomass

- Animal biomass based on average weight at treatment (PCU)
 - Criticisms: uncertainty and variability with this weight choice
 - Pros: if done 'right' the one weight reflects weight at exposure to the drug
- Animal biomass based on live animal weight at time of slaughter (e.g., OIE denominator)
 - Criticisms: we generally don't administer antimicrobials to animals at this weight (i.e., withdrawal periods)
 - Pros: this often is a 'known' weight

Use: if you have good quality farm level data – you can report in any metric!

- Mg/biomass
- DDDvet/1000 animal-days
 - Country-specific DDDvet standards take time to develop
 - Dependent on your objectives

CIPARS – how we measure *consumption*/AMU

Unit of Measurement	Indicator (=numerator/denominator)	Sales Data	Sentinel farm data
Count-based	<ul style="list-style-type: none"> • #farms/total sampled • #rations medicated/total #rations • days exposed • % herd exposed 	NA	✓ ✓ ✓ ✓
Weight-based	<ul style="list-style-type: none"> • mg/PCU 	√*	√
Dose-based	<ul style="list-style-type: none"> • nDDD_{vetCA}/PCU • nDDD_{vetCA}/1000 animal-days 	Coming...	√

Denominator: PCU=Population Correction Unit (1 PCU =1 kg animal)

Average weight at treatment (Canadian and ESVAC) – dual reporting

*Inclusion of beef cows

DDD_{vetCA}=defined daily dose for animals based on Canadian product labels

In summary

- What do you want to know?
 - What outputs/outcomes meet your objectives?
- Set objectives – design your surveillance to meet your objectives
- Surveillance ≠ research
- Just start. No matter how small. And have a great plan.
- Antimicrobial use/*consumption* surveillance – analysis is not hard, but it is meticulous
- Technical details and language matter – know who to deliver this info to

Next....
We answer questions.



AMU - When you only have the basic data. What is useful for?

APEC Workshop – Oct. 10, 2018
Santiago, Chile



Why do you want data about antimicrobial use?

Generally speaking – it is all about comparisons...these are often what your surveillance objectives are based on

- Is *antimicrobial consumption*/AMU different in different host species?
 - Regardless of objectives – be prepared for this
- Is *antimicrobial consumption*/AMU increasing or decreasing?
 - What practices are related to this? (stewardship)
- How do we compare to other areas?
- What does *antimicrobial consumption*/AMU mean for resistance?

COMPARISONS CREATE DISCOMFORT!

But can drive stewardship

Are we sure? What are the implications of increasing precision/accuracy?

OIE – Reporting Options

OIE Annual collection of data on antimicrobial agents intended for use in animals

- Baseline – quantitative data not available
 - Are antimicrobial agents used for growth promotion
 - Does legislation/regulations exist about this
 - What are the list of authorised products for growth promotion
- Reporting Option 1
 - Overall amount sold for use/used in animals by antimicrobial class
 - Possibility to separate by type of use (therapeutic/prevention vs. growth promotion)
- Reporting Option 2
 - Additionally can separate by animal groups
 - All food producing animals, companion animals and/or by terrestrial and aquatic animals
- Reporting Option 3
 - Additionally by route of administration

CIPARS – how we measure *consumption*/AMU

Unit of Measurement	Indicator (=numerator/denominator)	Sales Data	Sentinel farm data
Count-based	<ul style="list-style-type: none"> • #farms/total sampled • #rations medicated/total #rations • days exposed • % herd exposed 	NA	✓ ✓ ✓ ✓
Weight-based	<ul style="list-style-type: none"> • mg/PCU 	✓*	✓
Dose-based	<ul style="list-style-type: none"> • $nDDD_{\text{vetCA}}/\text{PCU}$ • $nDDD_{\text{vetCA}}/1000 \text{ animal-days}$ 	Coming...	✓

Denominator: PCU=Population Correction Unit

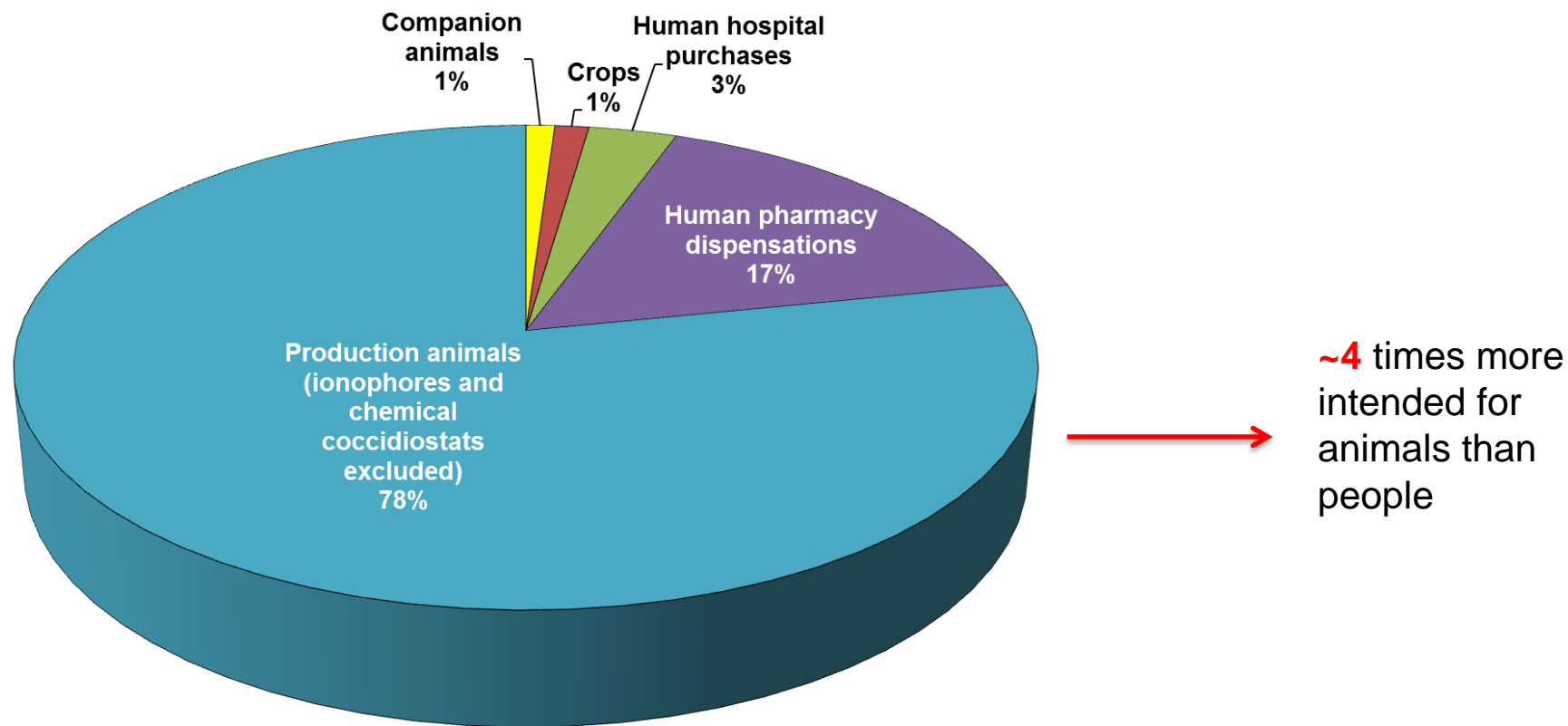
Average weight at treatment (Canadian and ESVAC) – dual reporting

*Inclusion of beef cows

DDD_{vetCA} =defined daily dose for animals based on Canadian product labels

Is consumption/AMU different in different host species?

Metric: kg

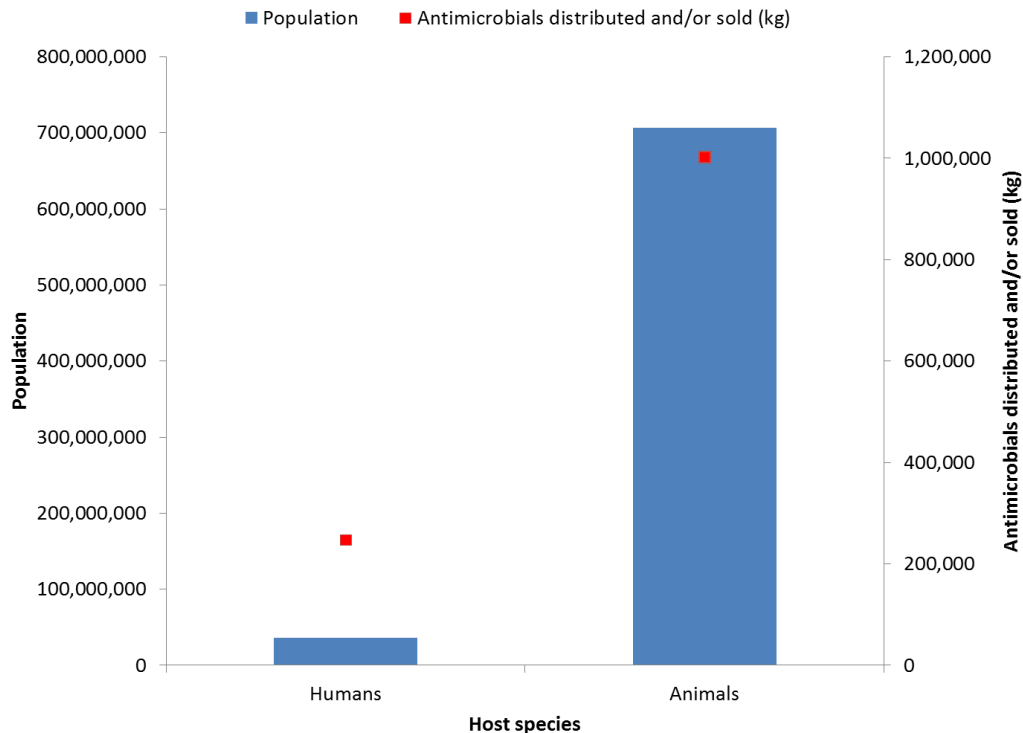


Data sources: CAHI, IQVIA via CARSS, Health Canada

Animal distribution data currently does not account for quantities imported for own use or as active pharmaceutical ingredients for further compounding; hence are underestimates of total quantities used.

Is consumption/AMU different in different host species?

Metric: mg/PCU



~ 1.5 times more antimicrobials were distributed for use in animals than humans (per kg host)

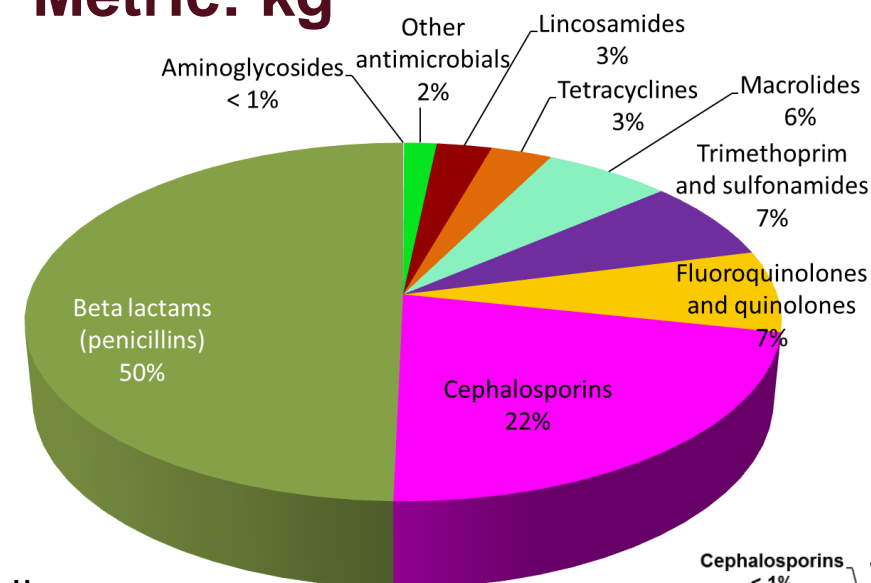
(European standard weights of animals)

Data sources: CAHI, IQVIA via CARSS, Statistics Canada, Ag Canada, Equine Canada

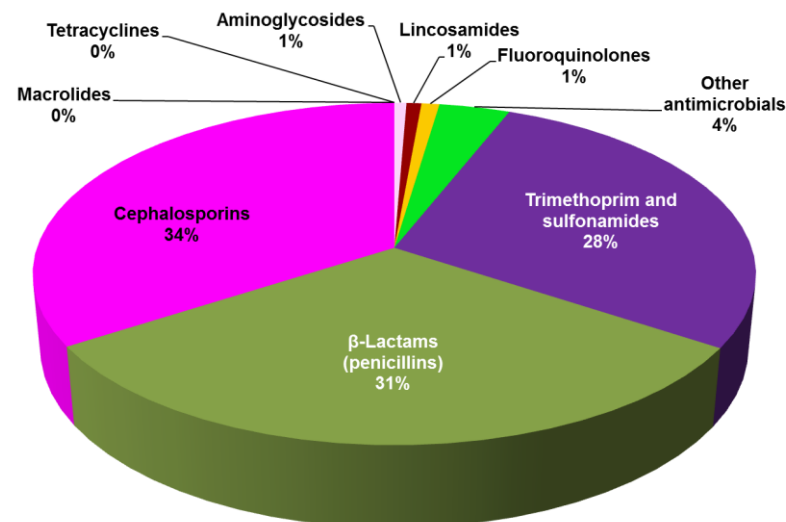
Animal distribution data does not include own use imports or active pharmaceutical ingredients used in compounding.

Is consumption/AMU different in different host species?

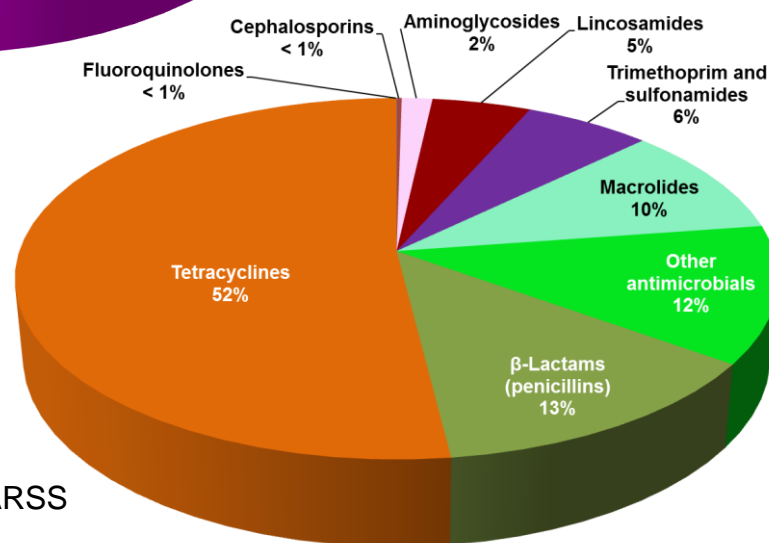
Metric: kg



Humans



Companion animals



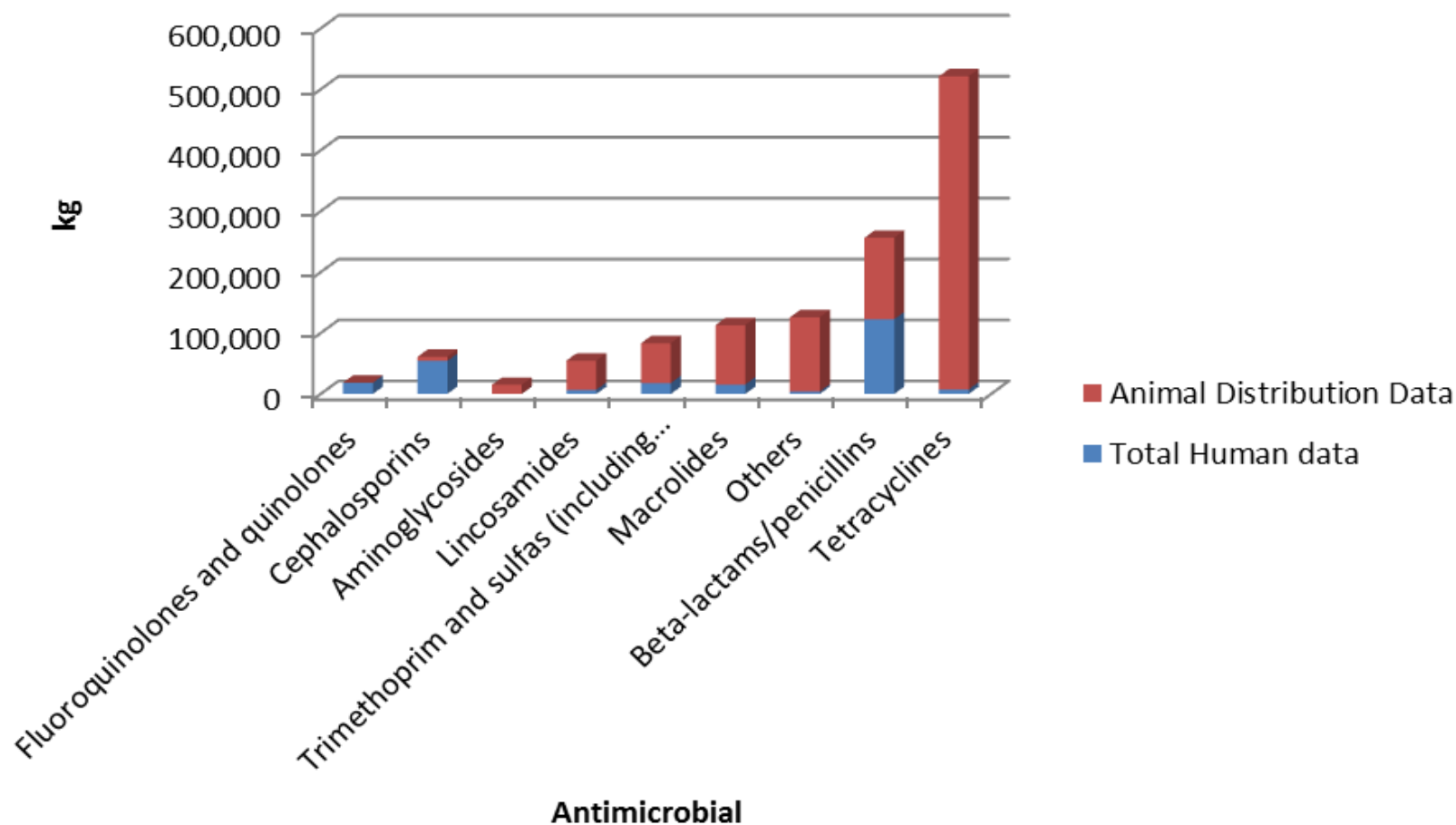
Production animals

Values do not include antimicrobials imported under the “own use” provision or imported as active pharmaceutical ingredients used in compounding.

Data sources: CAHI, IQVIA via CARSS

Is consumption/AMU different in different host species?

Metric: kg

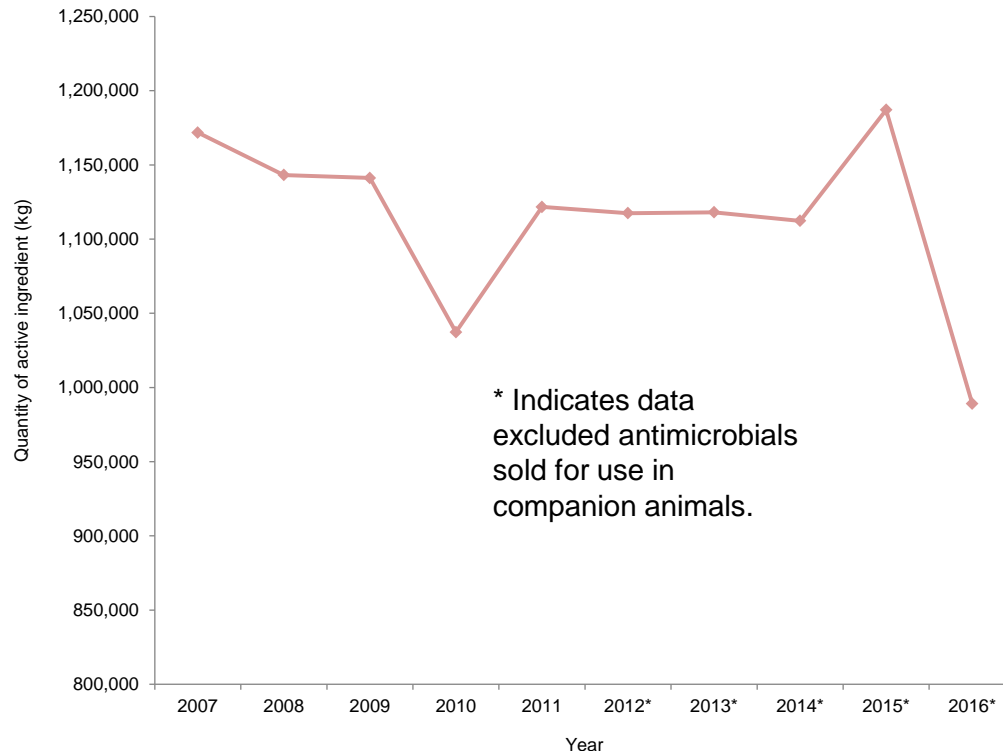


Data sources: CAHI, IQVIA via CARSS

Is consumption/AMU increasing or decreasing? Animal Metric - kg

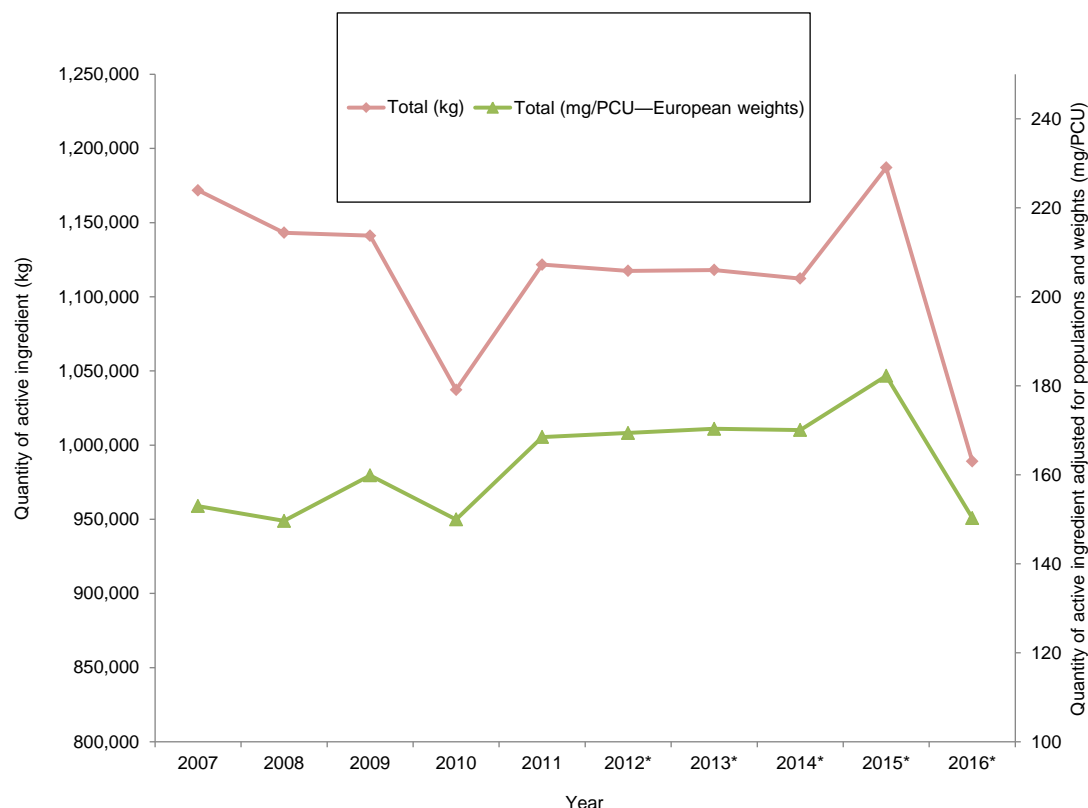
Percentage change (kg)

- 25% decline since 2006
- 17% decline since 2015



Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada

Is consumption/AMU increasing or decreasing? Animal Metric – mg/PCU_{EU}



Percentage change (kg)

- 25% decline since 2006
- 17% decline since 2015

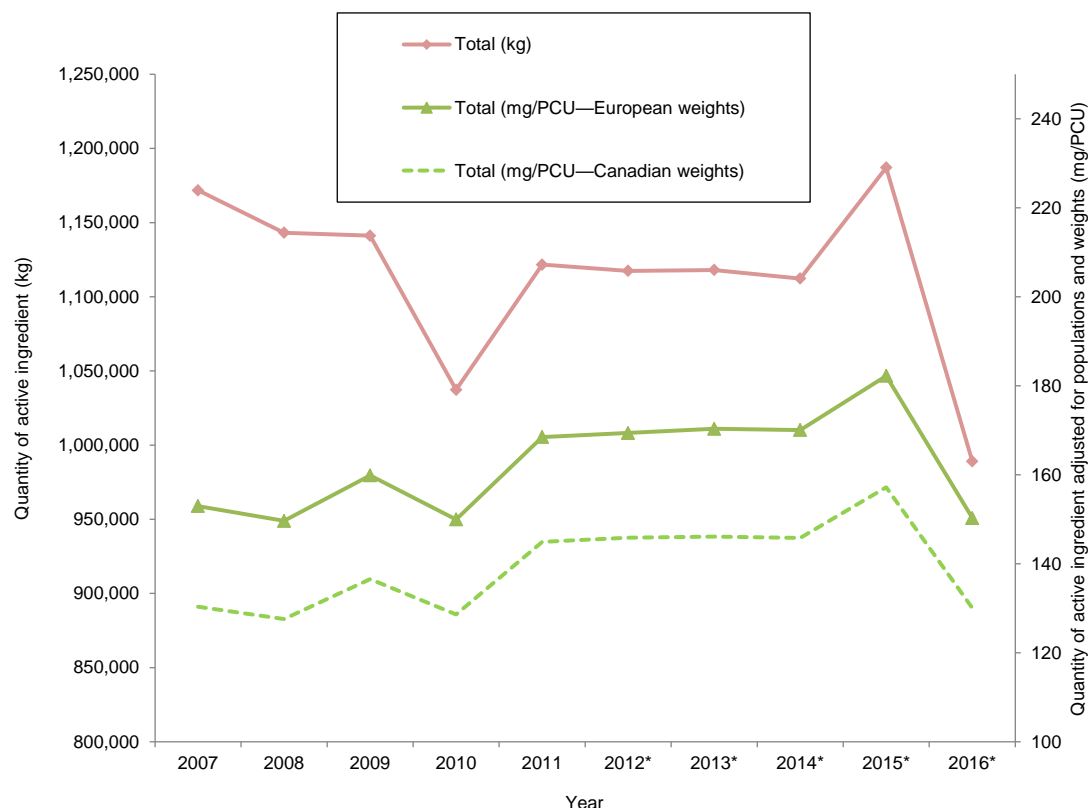
Percentage change (mg/PCU_{EU})

- 11% decline since 2006
- 18% decline since 2015

But ... some Canadian production classes are heavier than their European counterparts...

Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada

Is consumption/AMU increasing or decreasing? Animal Metric – mg/PCU_{CA}



Percentage change (kg)

- 25% decline since 2006
- 17% decline since 2015

Percentage change (mg/PCU_{EU})

- 11% decline since 2006
- 18% decline since 2015

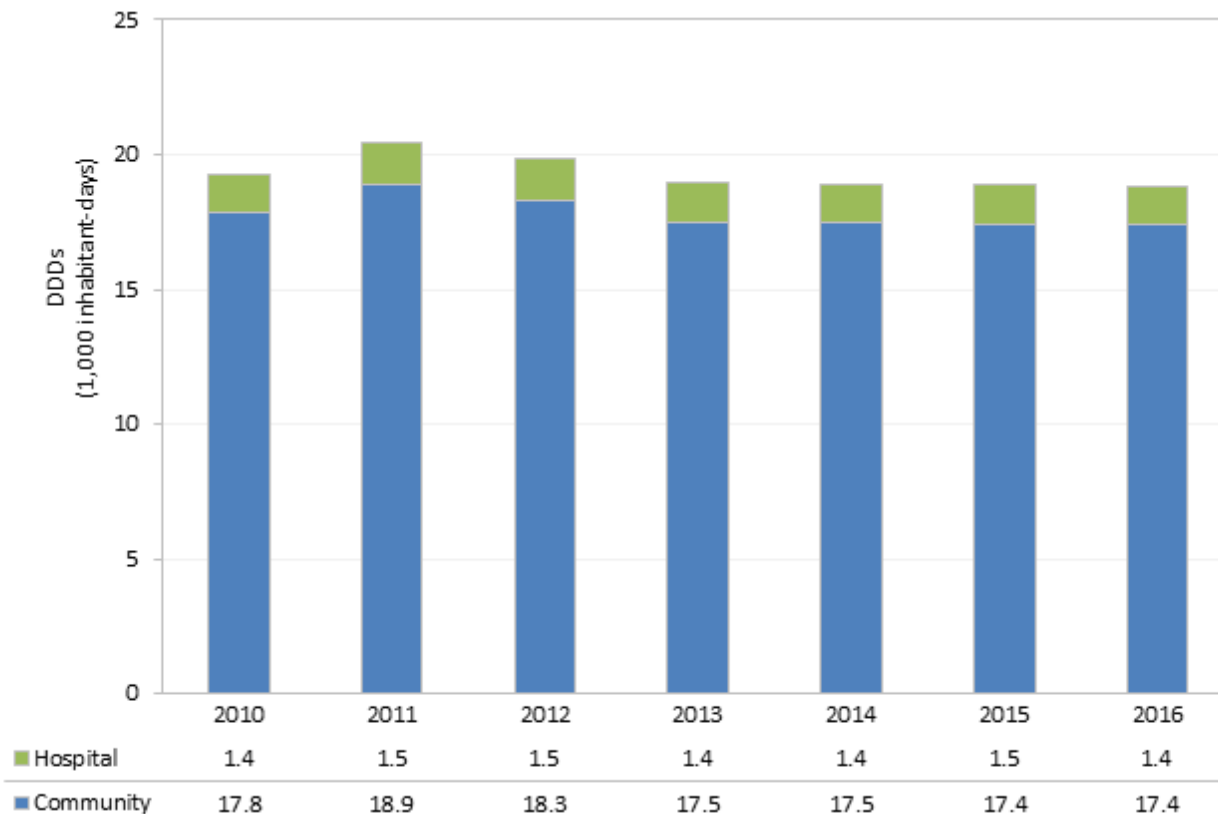
Percentage change (mg/PCU_{CA})

- 10% decline since 2006
- 17% decline since 2015

Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. Data sources: Canadian Animal Health Institute, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada

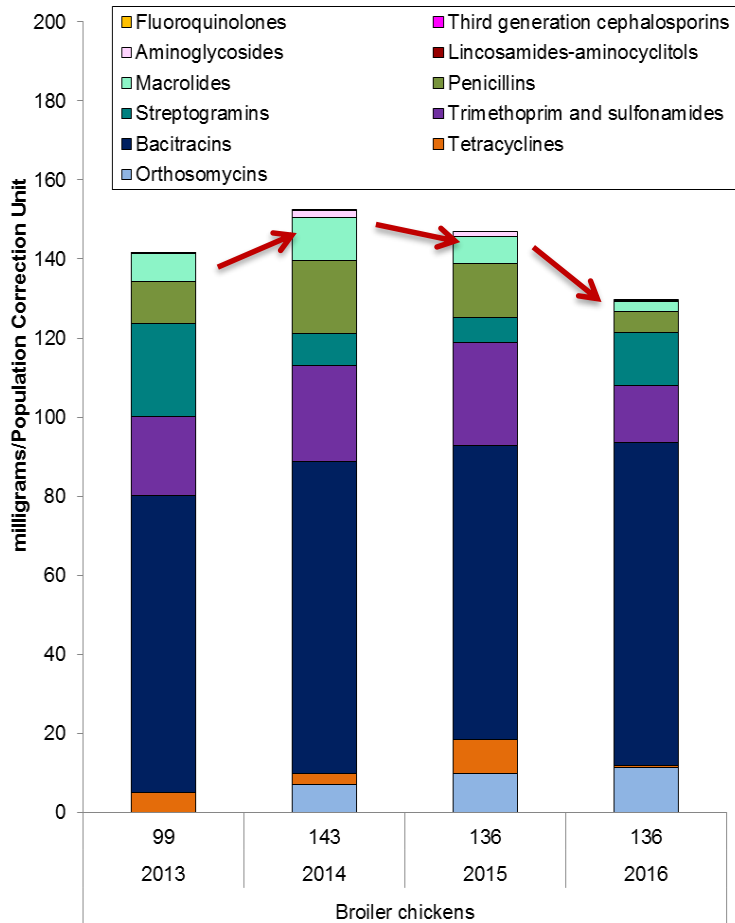
Did the different animal weights make a difference?

Is consumption/AMU increasing or decreasing? Human Metric: DDD/1000 inhabitant-days



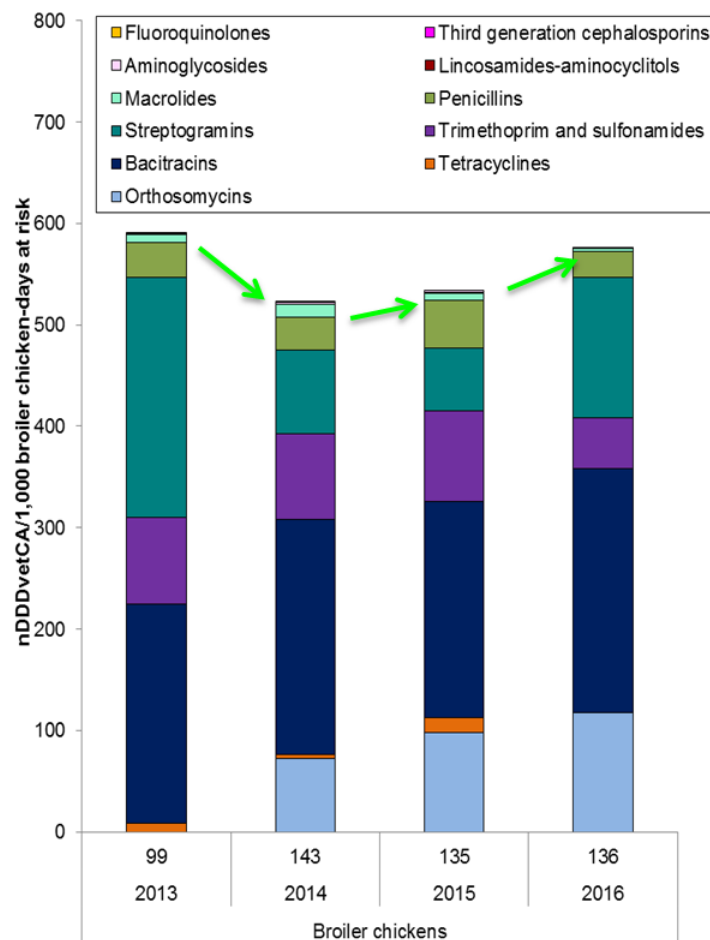
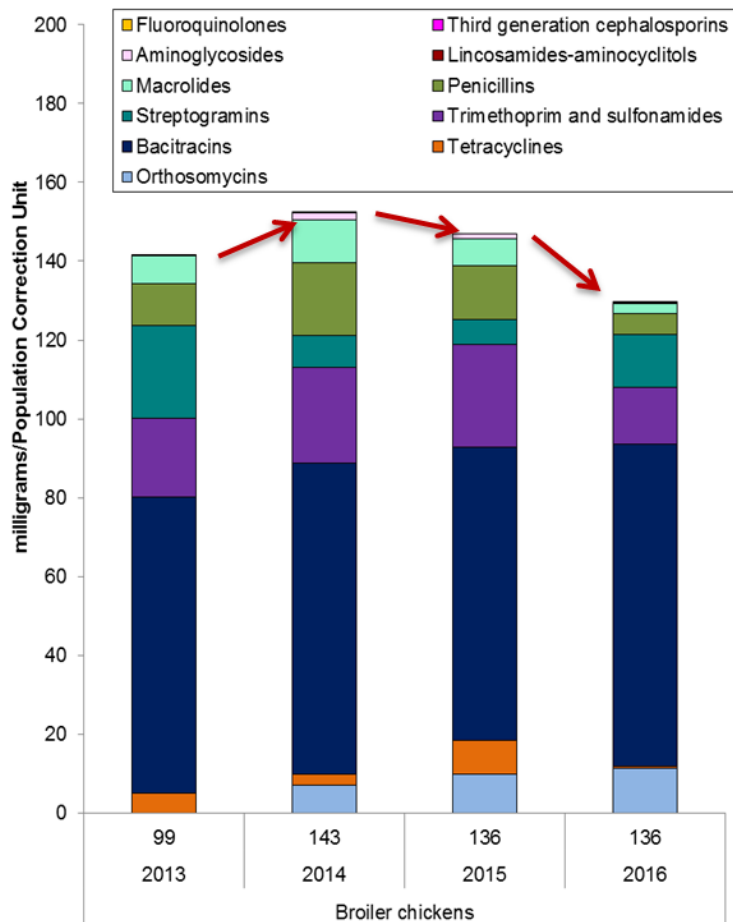
IQVIA data – CARSS. <https://www.canada.ca/en/public-health/services/publications/drugs-health-products/canadian-antimicrobial-resistance-surveillance-system-2017-report-executive-summary.html>

Is *consumption/AMU* increasing or decreasing? Animal Metric – mg/PCU



Data source:
CIPARS

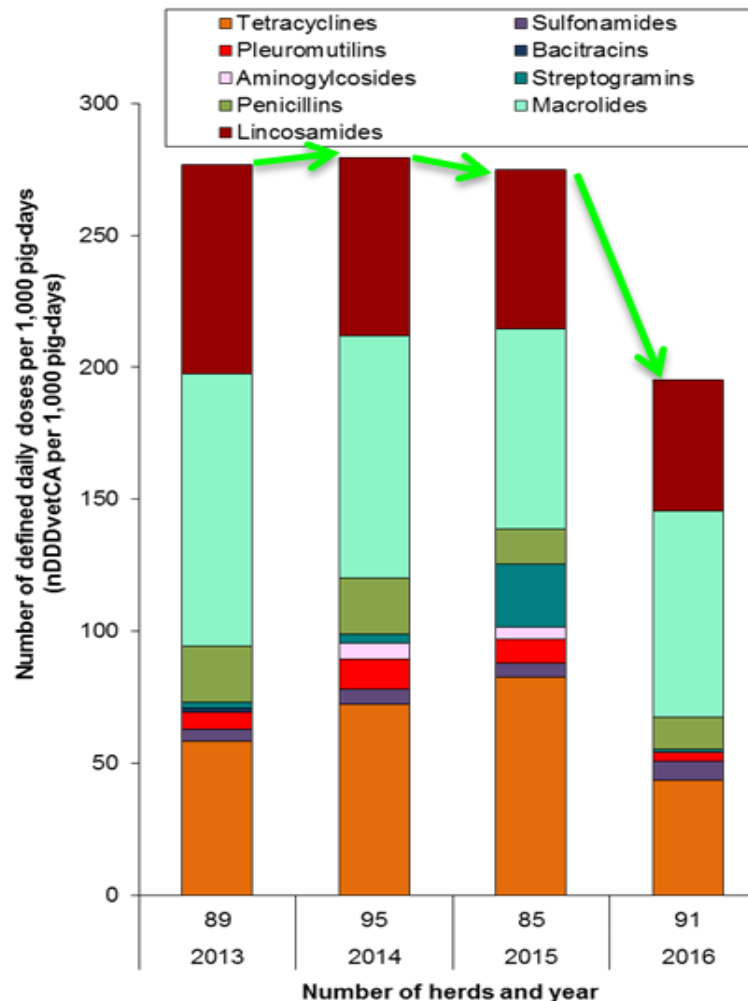
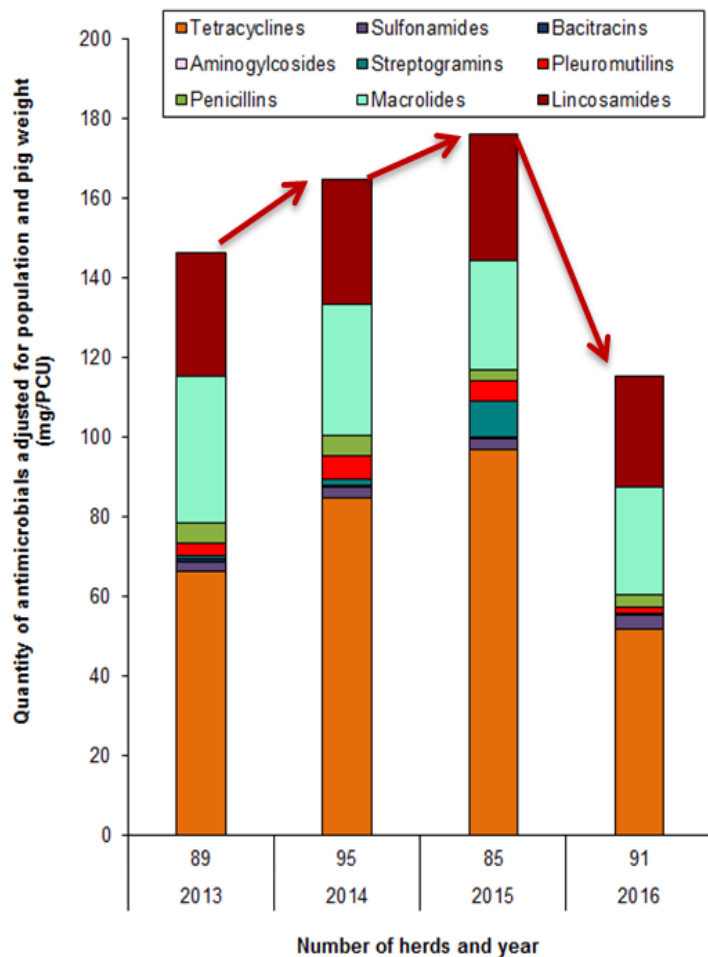
Is *consumption/AMU* increasing or decreasing? Animal Metric – mg/PCU and DDDvetCA/1000 animal-days



Data source:
CIPARS

Did AMU
decline?

Is *consumption/AMU* increasing or decreasing? Animal Metric – mg/PCU and DDDvetCA/1000 animal-days



Data source:
CIPARS

Did AMU
decline?

Future considerations – DDDvet and DDDvetCA



23 June 2015
EMA/710019/2014
Veterinary Medicines Division

Principles on assignment of defined daily dose for animals (DDDvet) and defined course dose for animals (DCDvet)

Draft agreed by European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) drafting group	9 March 2015
Start of public consultation	12 March 2015
End of consultation (deadline for comments)	12 May 2015
Revision agreed by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) drafting group	8 June 2015

https://www.ema.europa.eu/documents/scientific-guideline/principles-assignment-defined-daily-dose-animals-dddvet-defined-course-dose-animals-dcdvet_en.pdf

Developing Canadian Defined Daily Doses for Animals: A Metric to Quantify Antimicrobial Use

Angelina L. Bosman^{1,2}, Daleen Loest¹, David F. Léger¹, Agnes Agunos¹, Lucie Collineau³, Carolee A. Carson^{1}

¹Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada, Guelph, ON, Canada. ²Population Medicine, University of Guelph, Guelph, ON, Canada. ³Public Health Risk Sciences Division, National Microbiology Laboratory, Public Health Agency of Canada, Guelph, ON, Canada

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Email: bosmana@uoguelph.ca

Keywords: antimicrobial use; defined daily dose; veterinary; Canada; surveillance; food animals; metrics

Abstract (350 words)

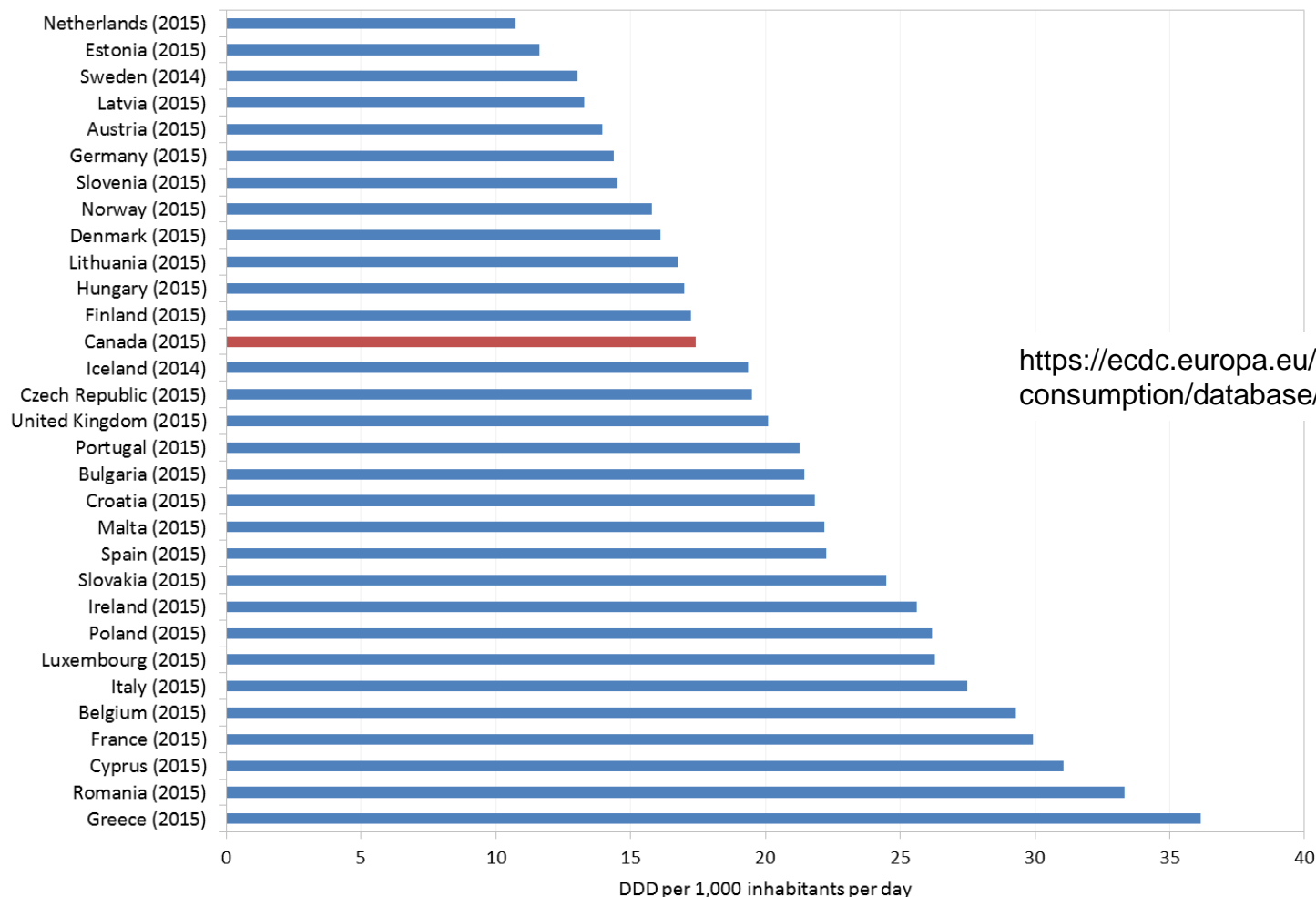
Background: Antimicrobial use surveillance data need to be analyzed and reported in a reliable and harmonized way. In veterinary medicine, one approach is to use defined daily doses for animals (DDDvet), which are technical standards used to adjust the kilograms of active antimicrobial ingredients by the amount administered daily per kg of animal. Recently, the European Medicines Agency published principles for assigning these standard values based on European antimicrobial product labels. For measuring antimicrobial use within Canada, DDDvets reflective of Canadian veterinary antimicrobial use were needed (DDDvetCA).

Objectives: To describe the development of DDDvetCA standards for pigs, broiler chickens and turkeys for authorized and compounded antimicrobial active ingredients used in Canada, including those used in an extra-label manner; and to compare the DDDvetCAs with the DDDvetEMA, where possible.

Paper coming...

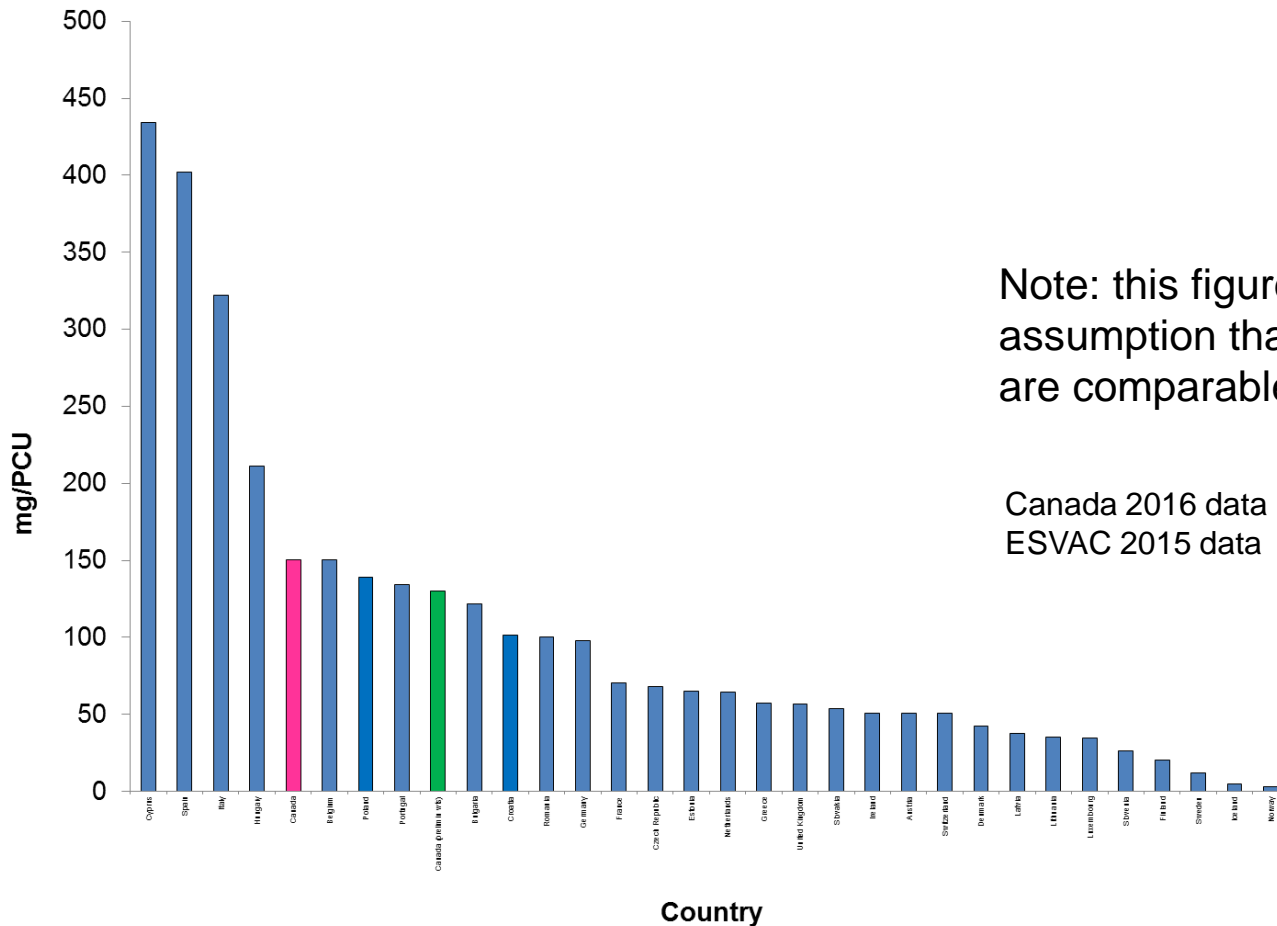
How do we compare to other areas? Human

Metric: DDD/1000 inhabitant-days



<https://ecdc.europa.eu/en/antimicrobial-consumption/database/country-overview>

How do we compare to other areas? Animal Metric: mg/PCU



Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding. Data sources: Canadian Animal Health Institute, ESVAC, Statistics Canada, Agriculture and Agri-food Canada, Equine Canada

Did the different animal weights make a difference?

Summary

- First think about what you are trying to do with your surveillance data
- Simple metrics are very powerful
- “Perfect is the enemy of good” (Voltaire). (better data comes with a cost)
- There are some sticky and important technical decisions
 - Which weight in the denominator
 - Which animal populations to include
 - Which standard dose?

Zoonoses and Public Health

REVIEW ARTICLE

Guidance on the Selection of Appropriate Indicators for Quantification of Antimicrobial Usage in Humans and Animals

L. Collineau^{1,2}, C. Belloc², K. D. C. Stärk¹, A. Hémonic³, M. Postma⁴, J. Dewulf⁴ and C. Chauvin⁵

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² BIOEPAR, INRA, Oniris, Nantes, France

³ IRP – French Pork and Pig Institute, Le Rheu, France

⁴ Department of Reproduction, Obstetrics and Herd Health, Veterinary Epidemiology Unit, Faculty of Veterinary Medicine, Ghent University, Ghent, Belgium

⁵ Anses – French Agency for Food, Environmental and Occupational Health and Safety, Ploufragan, France

Impacts

- Various indicators are available to quantify antimicrobial usage from sales, deliveries or reimbursement data in human and veterinary medicine; results can differ substantially depending on the method used.
- To select the most appropriate indicators of antimicrobial usage, the study objective must first be determined; if the overall aim is to compare antimicrobial usage between populations, standardized parameters should be used, whereas the quantification of exposure to antimicrobials should rely on actual parameters.
- Major gaps such as the absence of a gold standard for evaluating indicators and the lack of a scientific basis to assess antimicrobial selection pressure hamper the identification of the most suitable indicator for a given study objective.

“overall aim is to compare antimicrobial usage between populations, standardized parameters should be used, whereas the quantification of exposure to antimicrobials should rely on actual parameters”

In other words: if you want to look deep at AMU and relationship AMR, the metrics need to be tailored to the population under study. If you want to compare, metrics need to be stable and standard.

The BIG questions:
What does *antimicrobial consumption*/
AMU mean for: Resistance?

Or stewardship?



AMU and AMR monitoring programs; how they feed each other

Integrated Surveillance

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TO IMPROVE THEIR HEALTH

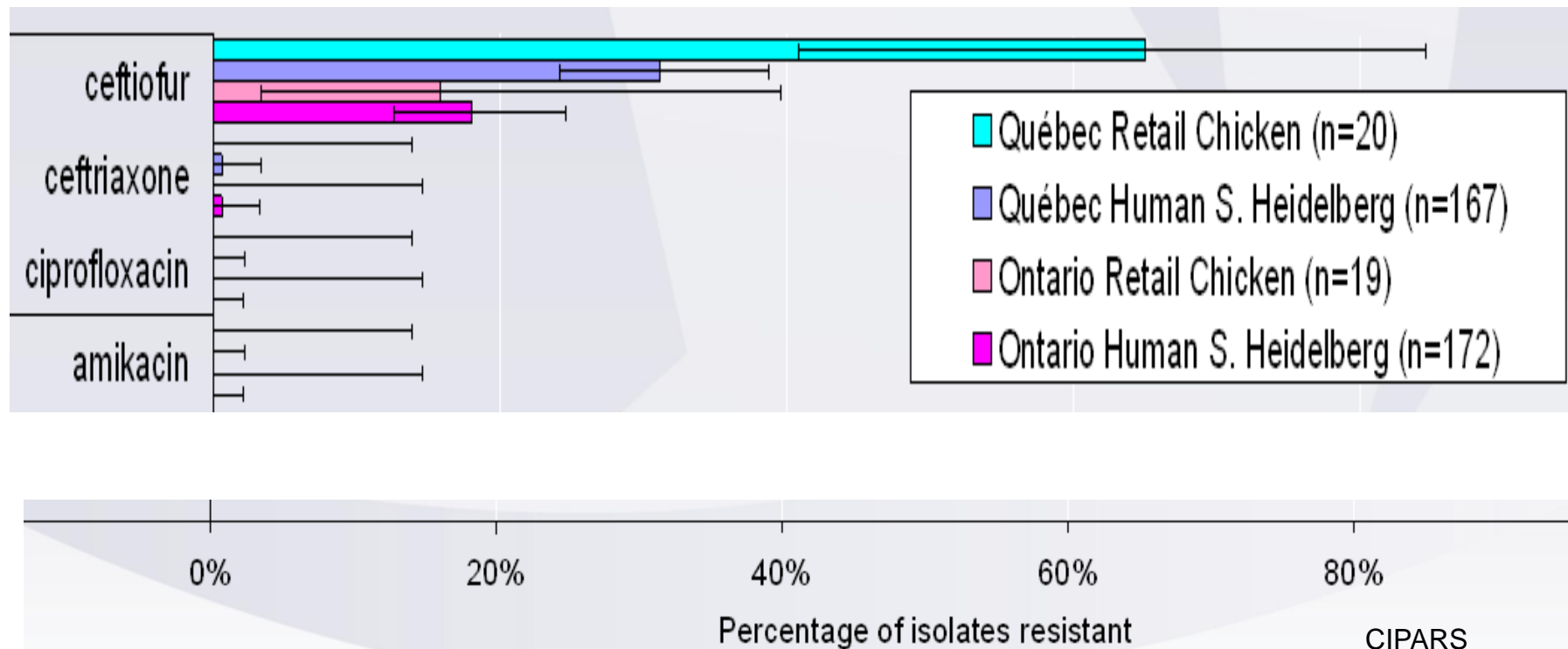


Surveillance information is compelling

Harmonization enables **comparisons & integration**

So you have this surveillance data

Ceftiofur resistance in *Salmonella* Heidelberg in 2003



What might be the first questions you ask or get asked?

COMPARISONS CREATE DISCOMFORT!
But can be a great motivator for change.

Context

Ceftiofur

- 3rd generation cephalosporin – class considered critical in human medicine
- Can be used in many animal species, but NOT licensed for chicken in Canada
- Used extra-label for the control of *E. coli* omphalitis

Salmonella Heidelberg

- Frequent: Top 3 serovars in humans in Canada since 1995
- Invasive: Can cause septicemia, myocarditis, extra-intestinal infections, & death
- Treatment concern: Resistance to ceftiofur = resistance to ceftriaxone; a drug of choice for treatment of pregnant women & children

Questions?

Is this happening in other animal species?

Is this happening in other strains of *Salmonella*

Is this happening in other bacterial species?

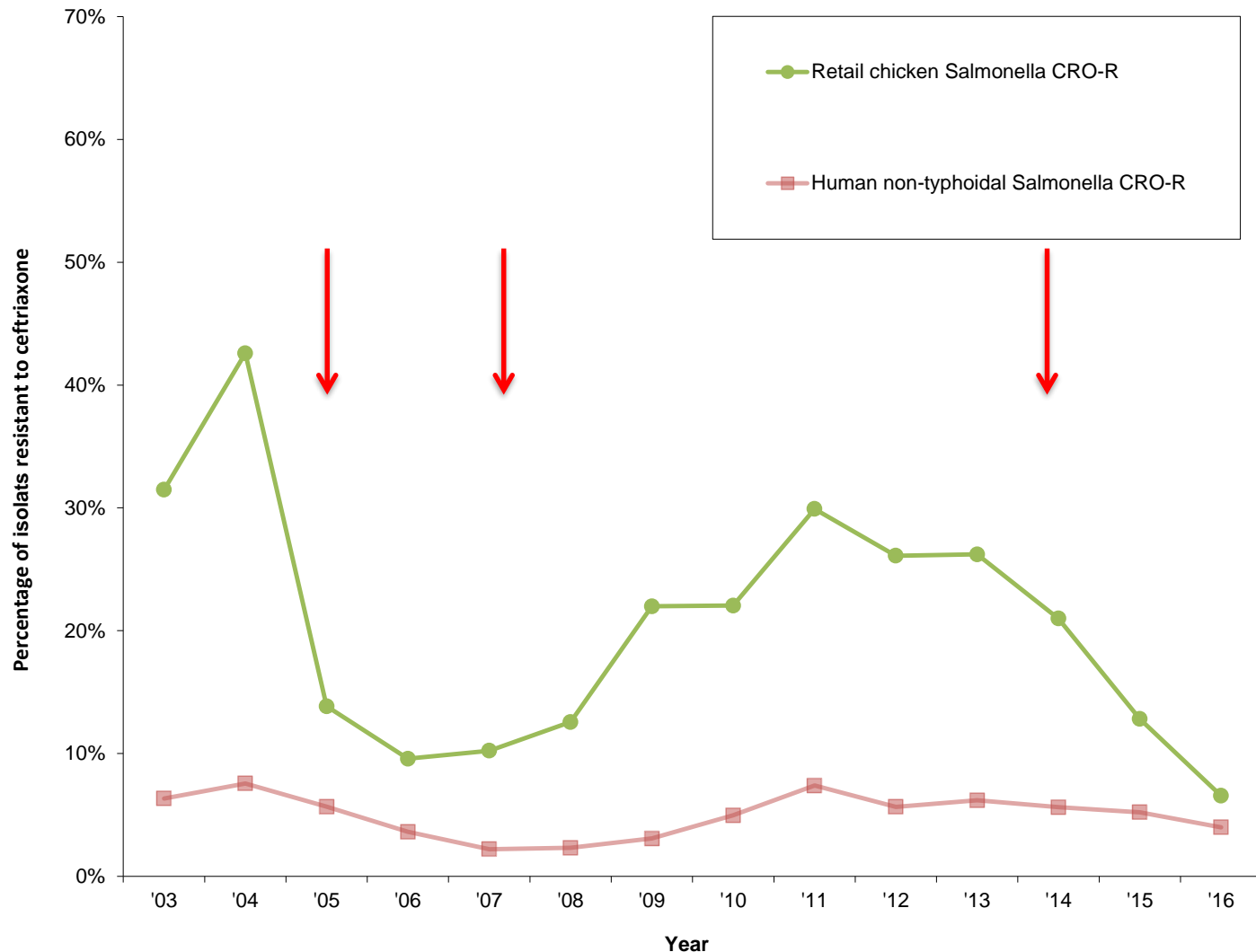
Or is this just a clone of *Salmonella* that is spreading?

Is this happening in other regions?

What is happening at other stages in the food chain (i.e., farm, slaughter)

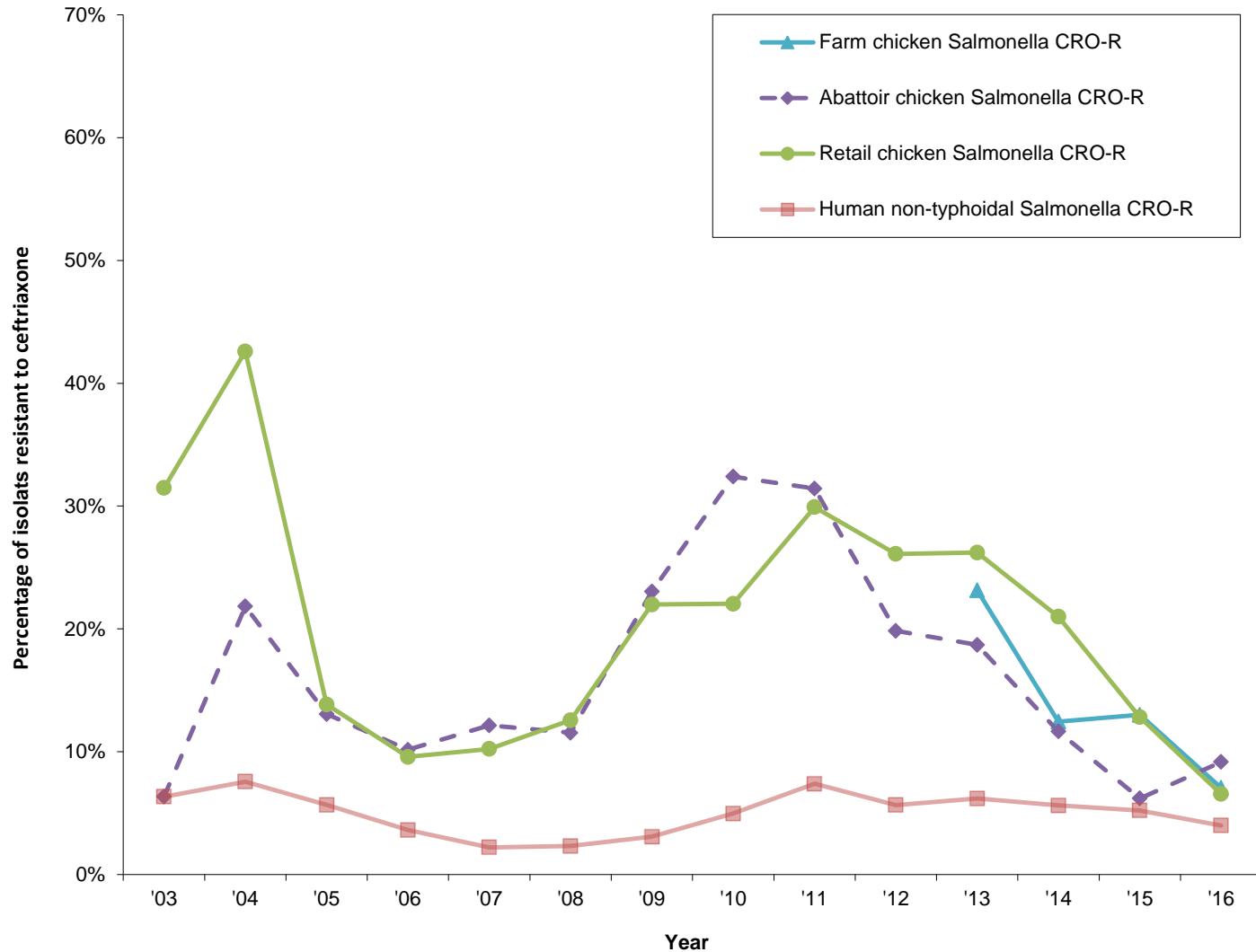
What is happening with antimicrobial use?

Integrated surveillance - AMU and AMR (*Salmonella*)



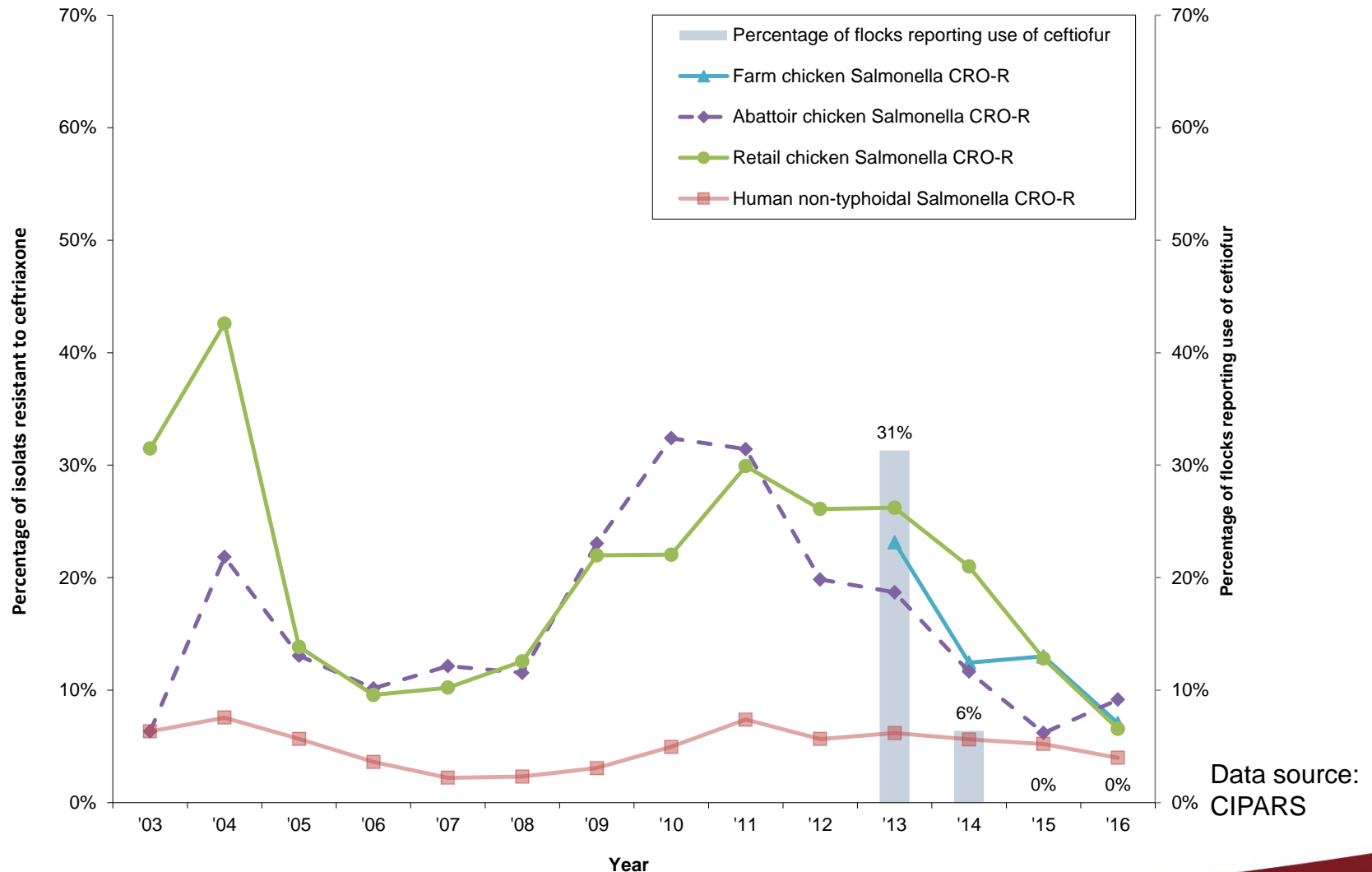
Data source:
CIPARS

Integrated surveillance - AMU and AMR (*Salmonella*)



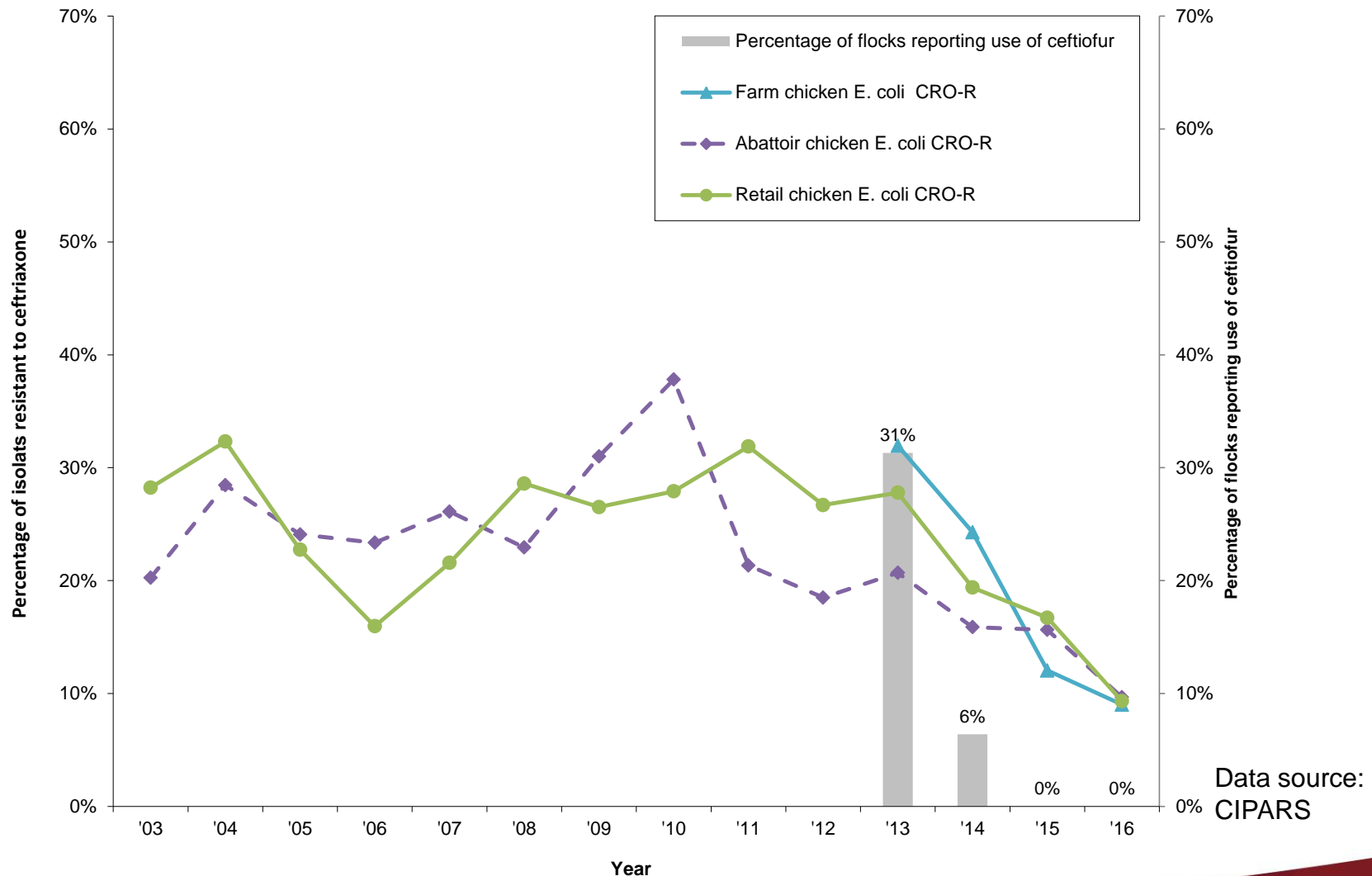
Data source:
CIPARS

Integrated surveillance - AMU and AMR (*Salmonella*)



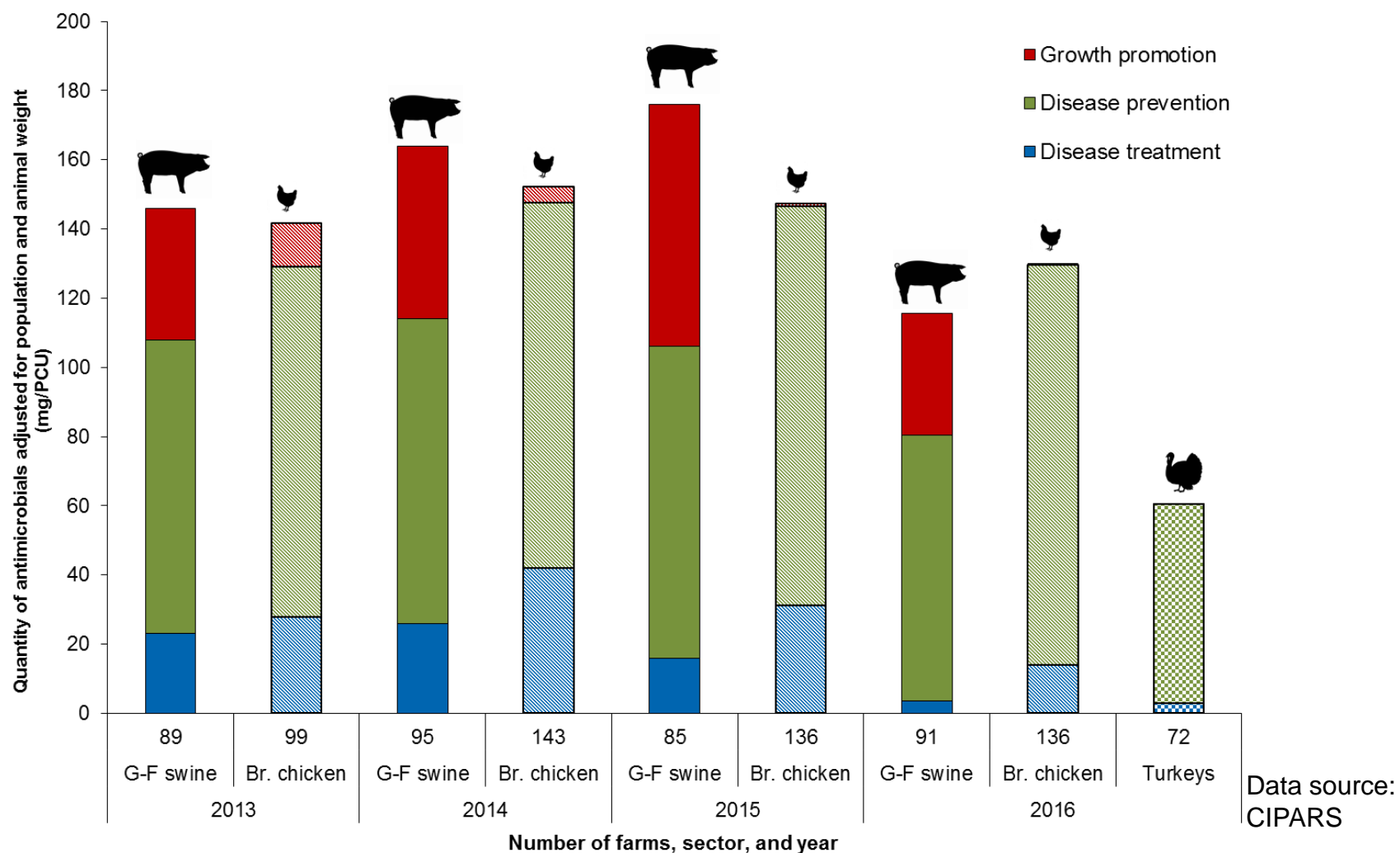
Frequency-based indicator – can show effect of intervention and easy to communicate

Integrated surveillance - AMU and AMR (*E. coli*)

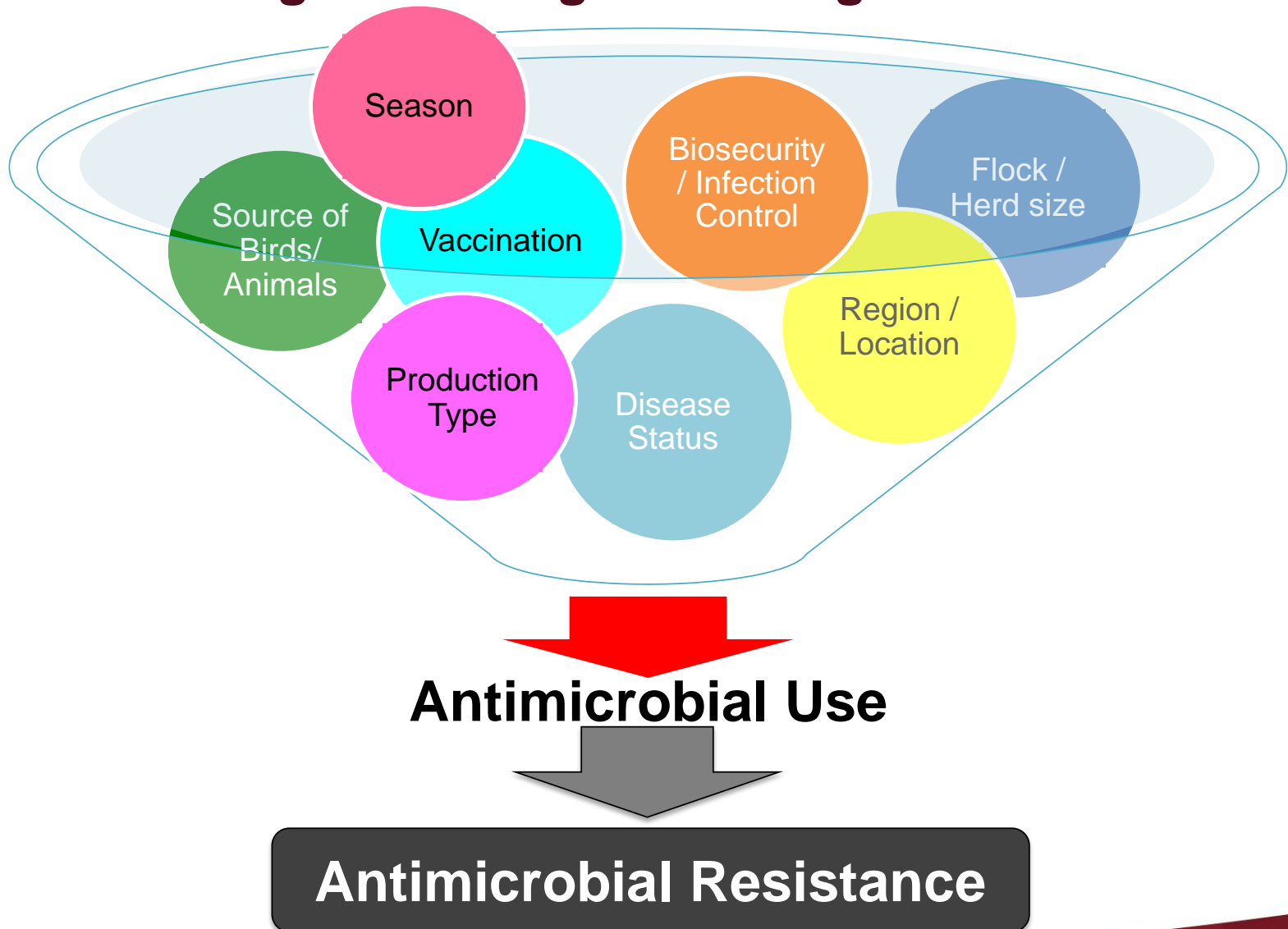


**When you have use and resistance data –
what next?**

How are drugs being used? Reasons for use (animals)



What can change how drugs are being used?



Conclusions

- Need to be clear on what it is you want to do
- More than one indicator is necessary to answer all the things we want to do with AMU data
- What level of 'correct' is good enough to suit the need?
- Comparisons can drive change
- Simple ways of communicating about comparisons and data can drive change
- The industry-led initiative to eliminate use of ceftiofur in poultry for disease prevention is appearing to have the desired effect
- Surveillance needs to be designed well to meet objectives and answer questions