CIPARS – The Canadian Integrated Program for Antimicrobial Resistance Surveillance

Highlights from 2016
Agenda and Presentation Outline

• Welcome and technical information
• Meeting objective
• Program overview
• CIPARS 2016 integrated results
• Comments, questions and answers
Conducting this teleconference/webinar

- **Presentation**
  - See CAHSS website: https://www.cahss.ca/about/

- **Survey/Poll**
  - Caller demographics and specific input
  - WebEx-based

- **Questions and comments**
  - Participants will be able to pose questions in 2 ways:
    - By posting in the WebEx “chat” window throughout the presentation
    - Verbally over the phone at the end of the presentation

- **Data presented are from the 2016 CIPARS Annual Report and select CIPARS-associated research projects**

*The purpose of this meeting is to foster exchange of information between collaborators, stakeholders and CIPARS*
PROGRAM OVERVIEW
2016 Integrated Results

• Integrated antimicrobial use data (Carolee Carson)
• Integrated antimicrobial resistance data (Brent Avery)
  – Resistance to >5 antimicrobial classes (i.e., highly drug resistant)
  – Ciprofloxacin resistance in Campylobacter
• Integrated antimicrobial use and resistance data (Jane Parmley)
  – Ceftriaxone resistance in Salmonella and E. coli
  – Emerging gentamicin resistance
• Animal health – contextual data (Anne Deckert)

• Other topics not presented today in detail:
  – International antimicrobial use comparison
  – Carbapenemase-producing Enterobacteriaceae
  – Colistin resistance
  – Fluoroquinolone resistance in Salmonella and E. coli
INTEGRATED ANTIMICROBIAL USE DATA
Why we use different antimicrobial use metrics

• **# farms** – tells us how extensive across Canada the use practice is
• **% animals exposed** – tells us how intensively a drug may be used on farm
• **Kg** – tells us raw selection pressure
  – BUT 1 kg antimicrobial A ≠ 1 kg antimicrobial B
    • More kg might be needed on a daily basis of A than B
• **DDDvet** – tells us how many standard doses were given
  – Helps us to better understand trends and exposure

• Denominator – critical context for trends, regional comparisons, inter-sectoral comparisons
  – We have more of some animals than others and animal species are not the same size – how much antimicrobials are administered per kg of ‘animal’
    • PCU
  – Sample data (animals not studied for 1 year)
    • Sample data need a denominator that accounts for time the animals were studied (in addition to the number of animals)
      per 1000 animal-days
Integrated AMU

Data on antimicrobials intended for use in/on:

- People
- Production animals
- Companion Animals
- Grower-finisher pigs
- Broiler chickens
- Turkeys
- Crops

Inter-sectoral comparisons (quantities, trends, antimicrobial classes, reasons for use)

Intra-sectoral comparisons (different metrics)

**New!** Separation of ionophores and chemical coccidiostats for reporting data on antimicrobials intended for use in animals
What removal of ionophores and chemical coccidiostats looks like: grower-finisher pigs

Total antimicrobial use quantity per kg pig (Mg/PCU)

G-F Pigs - Feed AMU (mg/PCU), including ionophores

G-F Pigs - Feed AMU (mg/PCU), excluding ionophores
What removal of ionophores and chemical coccidiostats looks like: broiler chickens

Total antimicrobial use quantity per kg chicken (Mg/PCU)

Broiler Chicken - All AMU (mg/PCU), including ionophores and chemical coccidiostats

Broiler Chicken - All AMU (mg/PCU), excluding ionophores and chemical coccidiostats
What removal of ionophores and chemical coccidiostats looks like: turkeys

Total antimicrobial use quantity per kg turkey (Mg/PCU)

Turkey - All AMU (mg/PCU), including ionophores, chemical coccidiostats and arsenicals

Turkey - All AMU (mg/PCU), excluding ionophores, chemical coccidiostats and arsenicals
Need to consider the size of the population to understand the quantities of antimicrobials

~ 1.5 times more antimicrobials were distributed for use in animals than humans on a per kg host basis.

(European standard weights of animals)

Animal distribution data does not include own use imports or active pharmaceutical ingredients used in compounding.
The predominant sector to which antimicrobials are sold/distributed (kg) is production animals.

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.
The relative proportions of antimicrobial classes differ between animals and people (kg)

Values do not include antimicrobials imported under the “own use” provision or imported as active pharmaceutical ingredients used in compounding.
The relative proportions of antimicrobial classes differ between animal species (mg/PCU)
Quantities distributed for sale have declined – in what sector(s) is this occurring?

Values do not include antimicrobials imported under the 'own use' provision or imported as active pharmaceutical ingredients used in compounding.
The mg/PCU is lowest in 2016 and varies across species

**BROILERS AND TURKEYS**

**GROWER-FINISHER PIGS**

Data sources: CIPARS Farm

Number of flocks, year, and species

Broilers - all routes
Pigs - feed only
However when adjusting for the average daily dose, this changes (nDDDvetCA/PCU)

**BROILERS AND TURKEYS**

- Fluoroquinolones
- Third generation cephalosporins
- Aminoglycosides
- Lincosamides-aminocyclitol
- Macrolides
- Penicillins
- Streptogramins
- Trimethoprim and sulfonamides
- Bacitracins
- Tetracyclines
- Orthomycins

**GROWER-FINISHER PIGS**

- Tetracyclines
- Sulfonamides
- Pleuromutilins
- Bacitracins
- Aminoglycosides
- Streptogramins
- Penicillins
- Macrolides
- Lincosamides

Data sources: CIPARS Farm

Broilers - all routes
Pigs - feed only
Trends in AMU metric - broiler chicken - different

These 2 metrics show similar trend; appear to correlate better

↓ overall
Top 3: Bacitracins, Trimet.-sulfa, and streptogramin

↑ overall
Top 3: Bacitracins, streptogramin and orthosomycin

Data sources: CIPARS Farm
Choice of metric affects interpretation – G-F pigs

These 2 metrics show similar trend; appear to correlate better

mg/PCU\(^1\)

n\(\text{DDD}_{\text{vet CA}}/\text{PCU}\)

n\(\text{DDD}_{\text{vet CA}}/1,000\) PD

↓ Overall: 35% change, Top 3: TET, TYL & LIN

↓ Overall: 29% change, Top 3: TYL, LIN & TET

\(^1\)ESVAC recommended for farm-level data collection. \(^2\) Denominator to better describe sample survey (e.g., CIPARS farm program framework)
The frequency of AMU in feed changes over time and by class.

**Grow-finisher pigs**

Significant decrease in Tylosin use frequency 2009-2016

**Broiler chickens**

Significant increase in Avilamycin use frequency 2013-2016

The frequency of AMU in water has not changed over time and is uncommon in both pigs and chickens.
The frequency of AMU by injection changes over time

**Grow-finisher pigs**

Significant increase in Florfenicol use frequency 2009-2016

**Broiler chickens**

Increase in % of flocks that do not use any antimicrobial use 2013-2016

Data sources: CIPARS Farm
Quantities have declined in grower-finisher pigs and broiler chickens in 2016 (mg/PCU); particularly for growth promotion.

Data sources: CIPARS Farm
Reasons for Use-Humans

- Brendan Dougherty PhD Student
- **Objective**
  - To gain a better understanding of antibiotic prescribing practices for bacterial enteric infections using FNC data
    - *Campylobacter, Salmonella, VTEC, Shigella and Yersinia*
- **Results** – for lab confirmed cases these are the % receiving antimicrobials:

<table>
<thead>
<tr>
<th>Bacterial Species</th>
<th>% Receiving Antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Campylobacter</td>
<td>51%</td>
</tr>
<tr>
<td>Salmonella</td>
<td>45%</td>
</tr>
<tr>
<td>VTEC</td>
<td>28%</td>
</tr>
<tr>
<td>Shigella</td>
<td>58%</td>
</tr>
<tr>
<td>Yersinia</td>
<td>44%</td>
</tr>
</tbody>
</table>
AMU Summary

• Overall, based on the majority of antimicrobial use metrics, use is lower in 2016 than 2015
• Though in broiler chickens, the number of doses per kg chicken or per bird may have increased
  – Need to look at things more than one way
• Each species has a different spectrum of drugs that are used
• AMU in turkeys, reported for the 1st time, was generally lower regardless of the metrics used
• In animals, from the species we survey at the farm, using medically important antimicrobials for growth promotion has declined
• In humans, antimicrobials are used to treat infections that come through the food-chain
INTEGRATED ANTIMICROBIAL RESISTANCE DATA
Increasing numbers of highly drug resistant *Salmonella* isolates from humans and animals, 2007-2016

Data sources: CIPARS
CIPARS also monitors for isolates of highly resistant (i.e., resistant to > 5 antimicrobial classes) *E. coli* from animals and food only.
Increasing numbers of highly-drug-resistant *Salmonella* and *E. coli*

- Bacteria resistant to more than 5 antimicrobial classes
- Since 2011, a small but increasing number of highly-resistant isolates have been recovered
  - Most from clinically sick cattle; and most of these are *S. Dublin* (106/161; 66%) and *S. Typhimurium* (42/161; 26%).
- The number of highly-resistant *Salmonella* isolates from humans has also increased
  - Four human isolates have shown resistance to all 7 antimicrobial classes tested:
- The numbers of highly resistant *E. coli* from animals and meat were much lower relative to those seen in *Salmonella* in recent years
- Evidence that overall, highly-resistant isolates may becoming more frequent in humans and animals in Canada and is a trend that will continue to be monitored
Ciprofloxacin resistance in *Campylobacter*

Data sources: CIPARS/FoodNet Canada

*For BC: Data from Antimicrobial Resistance Trends in the Province of British Columbia—2014 Report. BCCDC

**In the Prairie region, human data presented do not represent a full year (n = 29 total)
Ciprofloxacin resistance in *Campylobacter*

- **Human:**
  - Very limited data available; **new**! in 2016 some data from FoodNet Canada

- **Retail chicken meat:**
  - Resistance remains highest in British Columbia despite a small decrease in 2016 relative to 2015

- **Abattoir:**
  - Chicken – Resistance decreased slightly in 2016 but remains elevated relative to historical levels and remains highest in British Columbia
  - Cattle – *Resistance increased to 14% in 2016 from 11% in 2015 & 5% in 2014*
  - Pigs - *Slight increase in resistance overall (all C. coli) in 2016; highest levels in Québec*

- **Farm (Chicken):**
  - Chicken - Resistance highest in British Columbia (similar levels to 2015), up in the Prairies and no resistance observed in Ontario or Québec in 2016
  - Turkey - 40/171 (23%) of all 2016 isolates were resistant and most of these *(n=37)* were from British Columbia
INTEGRATED ANTIMICROBIAL USE AND RESISTANCE DATA
Ceftriaxone resistance in non-typhoidal *Salmonella* & *E. coli*

- In mid-2014, the poultry industry implemented a national ban on the use of Category I antimicrobials for disease prevention purposes.
- Consistent with the timing of this ban, reported ceftiofur use in broiler chickens continued to decrease and dropped to 0% among participating flocks in 2015 and remained at 0% in 2016.
- Over the same time period, CIPARS observed a concurrent decline in ceftriaxone resistance in *Salmonella* from multiple surveillance components (humans, chickens and chicken meat) and similar trends were observed in *E. coli*.
- Most ceftriaxone resistance in humans has been observed in *S. Heidelberg*.
  - In 2016, ceftriaxone resistance in *S. Heidelberg* isolates from humans dropped significantly to 16% vs 27% in 2015 (p=0.001).
Reduction in reported use of ceftiofur on farm and changing resistance to ceftriaxone in *Salmonella* from humans and chicken

Data sources: CIPARS

2014 formal elimination of preventive ceftiofur use. No antimicrobial use data collection prior to 2013.
Declining resistance to ceftriaxone in *E. coli* from chicken and reported decrease in use of ceftiofur

Data sources: CIPARS

2014 formal elimination of preventive ceftiofur use. No antimicrobial use data collection prior to 2013
Conclusions

• The industry-led initiative to eliminate use of ceftiofur, and all other Category I antimicrobials, in poultry for disease prevention is appearing to have the desired effect

• CIPARS data show a reduction in reported use of ceftiofur in broiler chickens (measured as % farms) as well as reduced resistance in both *E. coli* and *Salmonella* from chickens and chicken meat

• CIPARS will continue to assess this trend in coming years and the impact of this important intervention on resistance in *Salmonella* from humans will also continue to be monitored

• This is a good news story but…. has this change led to other issues?

Ceftriaxone resistance in non-typhoidal *Salmonella* & *E. coli*
Increasing gentamicin resistance

- In 2016, an increase in gentamicin resistance was observed in multiple CIPARS surveillance components, including human *Salmonella* isolates, for the second straight year
  - In humans, we mostly see this in *S. Heidelberg* and *Salmonella* 4, 5, 12: i:-
- Although there is minor variation, much of the increase in resistance in poultry is in *E. coli* – hence the focus of the slides that follow is on *E. coli* and chickens
Increasing gentamicin resistance in retail chicken and turkey

- *E. coli* from chicken - gentamicin resistance increasing in all regions sampled
- *E. coli* from ground turkey - gentamicin resistance increasing in all regions sampled except Ontario

Data sources: CIPARS
Increasing gentamicin resistance in abattoir chicken

- *E. coli* from chicken - increasing trend in gentamicin resistance sustained since 2015; highest in Québec in 2016
- *Salmonella* from chicken - gentamicin resistance also increasing

Data sources: CIPARS
Increasing gentamicin resistance on farm

- **Chicken:**
  - *E. coli* from chicken (pre-harvest) - slight increase in gentamicin resistance overall (19% in 2015 to 21% in 2016) but varies by region (increase in Ontario, decrease in British Columbia & Québec)

- **Turkey:**
  - First year data presented for turkey at the farm level
  - Gentamicin resistance in *Salmonella* from turkey was common in 2016 (32%), especially in Ontario (44%)

- **Swine:**
  - Gentamicin resistance in *Salmonella* from pigs increased in Québec in 2016 (only province where gentamicin resistance was observed)
AMU and Gentamicin resistance

• Chicken:
  – No reported gentamicin use in Québec in 2016
  – Use of **lincomycin-spectinomycin** (frequency) was highest in Québec
    • Highest levels of gentamicin resistance in *E. coli* from multiple surveillance components in Québec
    • co-selection between the use of lincomycin-spectinomycin and gentamicin resistance has now been documented (Veterinary Microbiology 203 (2017) 149–157)
  – Decreased **gentamicin** use (frequency) in British Columbia in 2016 but still represents the most reported gentamicin use (hatchery level)

• Turkey:
  – Gentamicin used extensively in turkey poults (hatchery): 81% of the 73 flocks (similar levels in all three provinces) reported use of gentamicin.
  – No reported lincomycin-spectinomycin use in turkeys

Data sources: CIPARS
Gentamicin and lincomycin-spectinomycin use - hatcheries

Use in 2016:
- Gentamicin:
  - 3 hatcheries (1 each ON, BC, SK)
  - 4 flocks (1 ON, 2 BC, 1 SK)
- Lincomycin-spectinomycin:
  - 6 hatcheries (1 AB, 2 BC, 3 QC)
  - 27 flocks (1 AB, 2 BC, 2 ON, 22 QC)

Data sources: CIPARS
Moving from ceftriaxone resistance to gentamicin resistance and into the future….

Data sources: CIPARS

Graph showing the percentage of flocks reporting use of ceftiofur and the percentage of isolates resistant to ceftriaxone from '03 to '16.
Moving from ceftriaxone resistance to gentamicin resistance and into the future.

Data sources: CIPARS
Moving from ceftriaxone resistance to gentamicin resistance and into the future....

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Moving from ceftriaxone resistance to gentamicin resistance and into the future….

Data sources: CIPARS
Moving from ceftriaxone resistance to gentamicin resistance and into the future....

Data sources: CIPARS

- Percentage of flocks reporting use of ceftiofur
- Percentage of flocks reporting use of gentamicin
- Percentage of flocks reporting use of lincomycin-spectinomycin
- Farm chicken E. coli CRO-R
- Farm chicken E. coli GEN-R

Year

- '12
- '13
- '14
- '15
- '16

Percentage of isolates resistant to ceftriaxone

Percentage of flocks reporting use of ceftiofur
Moving from ceftriaxone resistance to gentamicin resistance and into the future….

Data sources: CIPARS
Moving from ceftriaxone resistance to gentamicin resistance and into the future...

Data sources: CIPARS
Moving from ceftriaxone resistance to gentamicin resistance and into the future....

Data sources: CIPARS

- Percentage of flocks reporting use of ceftiofur
- Percentage of flocks reporting use of gentamicin
- Percentage of flocks reporting use of lincomycin-spectinomycin
- Retail chicken E. coli CRO-R

Year
- '12: 31%
- '13: 3%
- '14: 6%
- '15: 10%
- '16: 3%

Percentage of isolates resistant to ceftriaxone

Year
- '12: 24%
- '13: 24%
- '14: 24%
- '15: 30%
- '16: 20%

Percentage of flocks reporting use of ceftiofur
Moving from ceftriaxone resistance to gentamicin resistance and into the future....

Data sources: CIPARS
Emerging gentamicin resistance in chicken *E. coli* and changing use of gentamicin/lincomycin-spectinomycin

Data sources: CIPARS
Integration of the ceftriaxone resistance and gentamicin resistance stories

So we have:

a) Previous and continued finding of no reported ceftiofur use (broilers) and seemingly correlated decrease in ceftriaxone resistance from multiple components (including Salmonella in humans) and among Salmonella and E. coli (animal/food)

b) New finding of an increase in gentamicin resistance in E. coli from multiple components and Salmonella, primarily in humans

Is this potential cause and effect?

- There was a stop in preventive use of a Category I drug
- Subsequent reduction in ceftriaxone resistance
- Hypothesis - potential AMU change? i.e. Cat. 2 instead of Cat. 1
- Increase in gentamicin resistance - What is the public health implication?
- Soon – a stop in preventive use of Category II (and III) drugs
- What next?
Farm Contextual Data Collected

- Season
- Source of Birds/Animals
- Vaccination
- Production Type
- Disease Status
- Biosecurity / Infection Control
- Region / Location
- Flock / Herd size

Antimicrobial Use

Antimicrobial Resistance
Further analysis with contextual data

Antimicrobial use in Finisher pigs

Sow herd positive for Mycoplasma

Nursery pigs vaccinated for Lawsonia

Number of Diseases on Farm

Finisher pigs positive for PRRS

Region

Shower-in

Logistic Regression Model: Preliminary Results
AMU and AMR in Canada

• Since 2011, the number of isolates resistant to more than 5 antimicrobial classes has been increasing generally

• Fluoroquinolone-resistance in *Campylobacter* shows changing regional patterns in chicken but there are limited data available about resistance in human clinical isolates

• A change in use policy in poultry appears to be having the desired goal of reducing use of antimicrobials of very high importance
  
  – However, this may be associated with changes in use and leading to increases in resistance to other categories of antimicrobials?
  
  – What does the future hold?
ACKNOWLEDGEMENTS

We would like to thank all those who contribute to CIPARS:

- Human (AMR)
  - Provincial Public Health Laboratories
- Farm (AMR and AMU):
  - The veterinarians, producers and commodity groups who participate in the farm program, Alberta Agriculture and Saskatchewan Agriculture, Ontario Ministry of Agriculture, Food and Rural Affairs, and Canadian Poultry Research Council
- Abattoir:
  - The CFIA, abattoir operators, samplers and personnel
- Retail:
  - All the participating health units and institutions, particularly the University of Prince Edward Island
- Clinical Animal Isolates:
  - Provincial Animal Health Laboratories
- Antimicrobial Use - distribution in animals:
  - Canadian Animal Health Institute, Impact Vet
- Antimicrobial Use - distribution in humans:
  - Centre for Communicable Diseases and Infection Control
- Antimicrobials Sold as Pesticides for use in Crops
  - Health Canada
QUESTIONS?