Government of Canada Gouvernement du Canada

2012

CANADIAN INTEGRATED PROGRAM FOR ANTIMICROBIAL RESISTANCE SURVEILLANCE (CIPARS) ANNUAL REPORT

CHAPTER 4

INTEGRATED FINDINGS AND DISCUSSION

Canada

TO PROMOTE AND PROTECT THE HEALTH OF CANADIANS THROUGH LEADERSHIP, PARTNERSHIP, INNOVATION AND ACTION IN PUBLIC HEALTH.

—Public Health Agency of Canada

Également disponible en français sous le titre :

Rapport annuel du Programme intégré canadien de surveillance de la résistance aux antimicrobiens (PICRA) de 2012, Chapitre 4 — Intégration des résultats et discussion

To obtain additional information, please contact:

Public Health Agency of Canada
Address Locator 0900C2
Ottawa, ON K1A 0K9
Tel.: 613-957-2991
Toll free: 1-866-225-0709
Fax: 613-941-5366
TTY: 1-800-465-7735
E-mail: publications@hc-sc.gc.ca

This publication can be made available in alternative formats upon request.

Publication date: December, 2015

Cat.: HP2-4E-PDF

ISSN: 1925-9859

Pub.: 150095

Suggested Citation

Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) 2012 Annual Report, Chapter 4—Integrated Findings and Discussion. Public Health Agency of Canada, Guelph, Ontario, 2015.

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CONTRIBUTORS

PROGRAM COORDINATORS

Rita Finley[1], Rebecca Irwin[2], and Michael Mulvey[3]

SURVEILLANCE COMPONENT LEADS

Surveillance of Human Clinical Isolates

Rita Finley and Michael Mulvey

Retail Meat Surveillance

Brent Avery

Abattoir Surveillance

Anne Deckert

Farm Surveillance

Agnes Agunos, Anne Deckert, Sheryl Gow, and David Léger

Surveillance of Animal Clinical Isolates

Brent Avery and Jane Parmley

DATA MANAGEMENT, ANALYSIS, AND REPORTING LEADS

Brent Avery, Antoinette Ludwig, and Jane Parmley

LABORATORY COMPONENT LEADS

Laboratory for Foodborne Zoonoses, Guelph

Linda Cole (*Salmonella* Typing)

Andrea Desruisseau and Chad Gill (Antimicrobial Susceptibility Testing)

Laboratory for Foodborne Zoonoses, Saint-Hyacinthe

Danielle Daignault and Manon Caron (Antimicrobial Susceptibility Testing)

National Microbiology Laboratory, Winnipeg

Helen Tabor (*Salmonella* Serotyping)

Rafiq Ahmed (*Salmonella* Phage Typing)

Michael Mulvey (Antimicrobial Susceptibility Testing)

AUTHORS/ANALYSTS

Brent Avery, Anne Deckert, Carolee Carson, Rita Finley, Shiona Glass-Kaastra, David Léger, Sheryl Gow, and Jane Parmley

REVIEWERS

Internal

Anne Deckert, Rita Finley, Shiona Glass-Kaastra, and Virginia Young

External

Xian-Zhi Li[4] and Marie Louie[5]

REPORT PRODUCTION

Michelle Tessier and Virginia Young

A complete listing of contributors can be found in Chapter 2—Antimicrobial Resistance and Chapter 3—Antimicrobial Use In Animals of the CIPARS 2012 Annual Report.

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[1] Centre for Food-borne, Environmental and Zoonotic Infectious Diseases, Public Health Agency of Canada (PHAC)

[2] Laboratory for Foodborne Zoonoses, PHAC

[3] National Microbiology Laboratory, PHAC

[4] Health Canada, Veterinary Drugs Directorate

[5] Provincial Laboratory for Public Health, Alberta

PREAMBLE

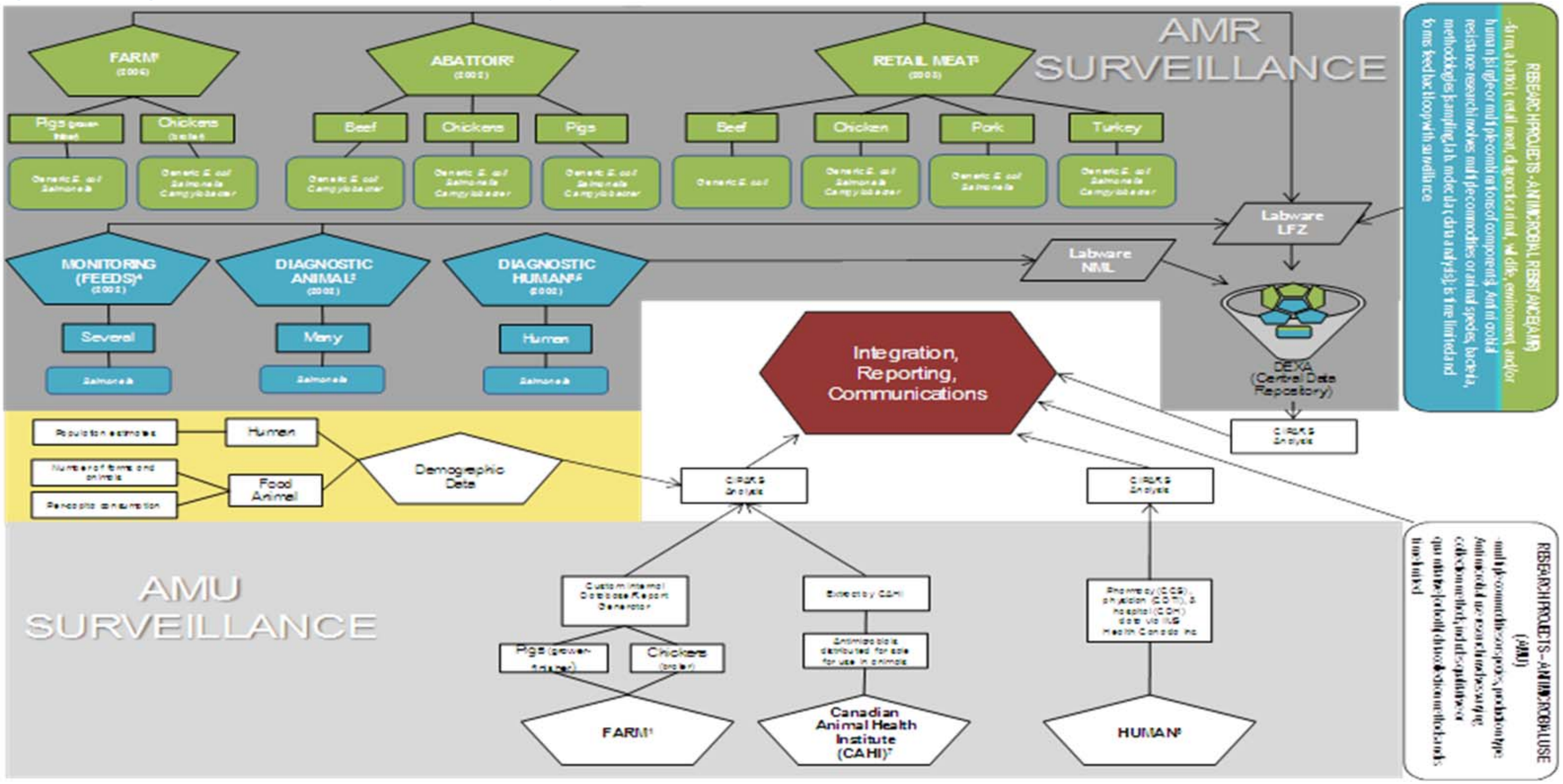
ABOUT CIPARS

The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS), created in 2002, is a national program dedicated to the collection, integration, analysis, and communication of trends in antimicrobial use (AMU) and resistance (AMR) in selected bacteria from humans, animals, and animal-derived food sources across Canada. This information supports (i) the creation of evidence-based policies for AMU in hospitals, communities, and food-animal production with the aim of prolonging the effectiveness of these drugs and (ii) the identification of appropriate measures to contain the emergence and spread of resistant bacteria among animals, food, and people.

During 2012, CIPARS held discussions on alternative methods of analyzing and presenting the surveillance data to adjust for different data closure dates, and to maximize the integration of existing data. The Annual Report will now be released in a Chapter format to improve the timeliness of data publication. The new Annual Report will consist of 4 chapters: Chapter 1—Design and Methods, Chapter 2—Antimicrobial Resistance, Chapter 3—Antimicrobial Use In Animals, and Chapter 4—Integrated Findings and Discussion. Chapter 1 includes detailed information on the design and methods used by CIPARS to obtain and analyze the AMR and AMU data, including 2 summary tables describing changes that have been implemented since the beginning of the program. Chapters 2 and 3 present results for AMR and AMU, respectively, with each chapter including a section on the top key findings. Chapter 4 brings together some of the results across surveillance components, over time, across regions, and across host/bacterial species.

SUMMARY OF CIPARS SAMPLES AND DATA FLOW

Figure 1. Diagram of CIPARS surveillance components



🟩 = Active surveillance; primary data, primarily for prevalence estimation 🟦 = Passive surveillance ; secondary data, primarily for AMR detection

LFZ: Laboratory for Foodborne Zoonoses NML: National Microbiology Laboratory

1-7=CIPARS project leads: 1(pigs)-David Léger (david.leger@phac-aspc.gc.ca) and Sheryl Gow (sheryl.gow@phac-aspc.gc.ca); 1(chicken)-Agnes Agunos (agnes.agunos@phac-aspc.gc.ca); 2-Anne Deckert (anne.deckert@phac-aspc.gc.ca); 3-Brent Avery (brent.avery@phac-aspc.gc.ca); 4-Jane Parmley (jane.parmley@phac-aspc.gc.ca); 5-Rita Finley (rita.finley@phac-aspc.gc.ca); 6-Michael Mulvey (michael.mulvey@phac-aspc.gc.ca); 7-Carolee Carson (carolee.carson@phac-aspc.gc.ca)

CIPARS Coordinators: Rebecca Irwin (rebecca.irwin@phac.gc.ca); Michael Mulvey (michael.mulvey@phac-aspc.gc.ca); Rita Finley (rita.finley@phac-aspc.gc.ca)

HOW TO READ THIS CHAPTER

INTEGRATION OF ANTIMICROBIAL RESISTANCE DATA

In order to identify the key integrated findings arising from the 2012 CIPARS surveillance year, the CIPARS analysis team closely examined all of the data coming out of all the individual components of CIPARS together. Select findings included in this chapter involve "common themes" that span multiple components and species (including humans). For example, this might include similar trends in resistance for a given *Salmonella* serovar across components (agri-food and human). Alternatively, results might also reflect similar trends across components in terms of bacterial prevalence, yet very different rates of antimicrobial resistance.

Salmonella is the only bacteria for which data are available across all components; as such, several of the integrated AMR findings presented in this chapter are about select *Salmonella* serovars. In addition, we have carefully reviewed the data about other potential human enteric pathogens. In 2012, findings about ciprofloxacin resistance in *Campylobacter* are presented despite having no data about resistance in *Campylobacter* isolates from human cases. Finally, we have reported on isolates that exhibit concerning multiclass resistance profiles.

The main focus of the AMR integration is on antimicrobials of very high importance to human medicine (Category I) and other clinically important antimicrobials. All of the data presented and summarized in this chapter have been reported previously in the CIPARS 2012 Annual Report, Chapter 2—Antimicrobial Resistance, Chapter 3—Antimicrobial Use In Animals, and in the Public Health Agency of Canada's Human Antimicrobial Drug Use Report 2012/2013[6].

INTEGRATION OF ANTIMICROBIAL USE DATA

In working with Canadian and international stakeholders, CIPARS has made significant strides in collecting and reporting antimicrobial use in both the human and the agri-food sectors.

Human AMU information represents total antimicrobials dispensed through community pharmacies as well as total antimicrobials purchased by hospitals. In addition, information is also available to describe the indication/diagnoses for which an antimicrobial was recommended by office-based physicians. These data are purchased from IMS Health Inc. and detailed information is presented as part of the PHAC's Human Antimicrobial Drug Use Report[6].

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[6] Public Health Agency of Canada, 2014. Human antimicrobial drug use report 2012/2013. Available at: www.phac-aspc.gc.ca/publicat/hamdur-rumamh/2012-2013/index-eng.php. Accessed January 2015.

Animal antimicrobial use information is provided by the Canadian Animal Health Institute (CAHI) and consists of antimicrobial quantities distributed for sale. These data do not account for antimicrobials imported under the own-use provisions or as active pharmaceutical ingredients (used for compounding), as these measures are currently unknown. It should be noted that distribution data do not represent actual antimicrobial use in a given year; they reflect the volume of antimicrobials distributed by manufacturers. Furthermore, caution must be applied to avoid using national distribution (CAHI) data to infer any species-specific antimicrobial use practices; some antimicrobials are not used in some animal species, yet intensively used in others. Information on antimicrobial use in grower-finisher pigs (closest growth phase to the consumer; approximately 2 to 6 months of age) is collected from swine sentinel farms as part of the CIPARS *Farm Surveillance* component. This data source provides commodity-specific information including the reasons for antimicrobial use in this phase of swine production.

More information regarding the collection of sentinel farm and CAHI data can be found in the 2012 CIPARS Annual Report, Chapter 1—Materials and Methods[7].

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[7] Public Health Agency of Canada, 2014. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) - Annual Report 2012. Available at: www.publications.gc.ca/pub?id=472507&sl=0. Accessed January 2015.

SUMMARY—INTEGRATED FINDINGS

Common threads, or stories, surface through analysis of CIPARS data. These findings may traverse host species (human, chicken, pigs, beef cattle, and turkey), the components (human, farm, abattoir, retail meat, and clinical animals), AMR and AMU, or a combination of these. This chapter aims to identify the most relevant of these findings and present data from multiple CIPARS sources together in an integrated manner.

SALMONELLA ENTERITIDIS; HUMAN INCIDENCE AND AGRI-FOOD RECOVERY

- *Salmonella* Enteritidis was the most common *Salmonella* serovar identified from human *Salmonella* infections and isolated from retail chicken meat, thus fresh chicken could be an important source of *S*. Enteritidis in people.
- No AMR was detected in *S*. Enteritidis from farm, abattoir, and retail samples for any animal species tested.
- Resistant *S*. Enteritidis from ill people does not appear to be coming from the major Canadian agri-food commodities sampled in this program (cattle, chickens, and pigs).

SALMONELLA HEIDELBERG AND RESISTANCE TO THIRD-GENERATION CEPHALOSPORINS

- *Salmonella* Heidelberg was isolated at higher levels from ill people and routine chicken samples from Eastern Canada compared to Western Canada.
- Similar to previous years, high resistance to third-generation cephalosporins (drugs of very high importance to human medicine) was found in *S*. Heidelberg from ill people and chicken meat.

CAMPYLOBACTER JEJUNI ISOLATION AND RESISTANCE TO CIPROFLOXACIN

- High recovery rates of *Campylobacter jejuni* from retail chicken suggest that human cases may be related to domestically produced chicken products. Potential links between people and chicken meat may be further clarified with the addition of AMR data for human *Campylobacter* infections.
- The pattern of ciprofloxacin (a drug of very high importance to human medicine) resistant *Campylobacter* in retail chicken continues to change over time and across regions.

MULTICLASS RESISTANCE IN *SALMONELLA* ACROSS COMMODITIES

- Some human and agri-food isolates were found with resistance to 5 or more antimicrobial classes.
- Not all resistance trends for human salmonellosis appear to be linked to the major agri-food commodities (cattle, pigs, and chickens).

KILOGRAMS OF ANTIMICROBIALS USED PER KILOGRAM OF WEIGHT IN HUMANS AND ANIMALS

- The quantity of antimicrobials distributed and/or sold for use in animals was 1.4 times (based on European standard weights at treatment) greater than the quantity distributed to people in 2012.

SECTORS USING ANTIMICROBIALS IN CANADA

- Among antimicrobials distributed for use in Canada (excluding ionophores, chemical coccidiostats, and arsenicals), 80% were intented for use in production animals (food animals and horses).
- 74% of human antimicrobial use occurred in community settings, 26% of use was in hospitals.
- Less than 1% of animal antimicrobial use was for companion animals.

USE BY ANTIMICROBIAL CLASS DIFFERS IN HUMANS AND ANIMALS

- Although the same antimicrobial classes are used in humans and animals, some classes are used at much greater volumes in human medicine than veterinary medicine, and vice versa.

INDICATIONS FOR USE AMONG HUMANS AND ANIMALS

- Most use among humans was for respiratory and urinary tract infections, while most use in pigs was to treat and/or prevent respiratory disease.
- Most use of antimicrobials of high importance to human medicine reported in swine was to treat and/or prevent respiratory disease.

INTEGRATED ANTIMICROBIAL RESISTANCE FINDINGS AND DISCUSSION

SALMONELLA ENTERITIDIS: HUMAN INCIDENCE AND AGRI-FOOD RECOVERY

In 2012, *Salmonella* Enteritidis was the most common serovar causing salmonellosis in people in Canada (n=2,117; 30% of all *Salmonella* cases)[8]. It was the most frequent serovar in all provinces and represented between 24% (282/1,190) of all *Salmonella* isolates (Québec) and 48% (73/151) (Nova Scotia). However, resistance among human *S.* Enteritidis isolates is relatively low; in 2012, 16% (191/1,179) of all *S*. Enteritidis isolates from humans submitted to CIPARS demonstrated resistance to one or more antimicrobial classes tested. The most common resistance pattern observed was to nalidixic acid, a quinolone antimicrobial (12%, 145/1,179). Resistance to nalidixic acid can be an indicator of resistance to fluoroquinolones, which are antimicrobials of very high importance to human medicine (Category I). The most common Category I resistance observed in *S*. Enteritidis was to ciprofloxacin (1%, 10/1,179), a fluoroquinolone antimicrobial.

In contrast with the human data, *Salmonella* Enteritidis was not the most common serovar observed in the animal and agri-food data in 2012. When isolated, this serovar was more frequently associated with chickens and chicken meat than any other animal species or meat type; 1% (7/684) of abattoir chicken samples and 5% (37/818) of retail chicken samples yielded *S*. Enteritidis isolates.

Important regional differences were observed in the recovery of this serovar from retail chicken. In Western Canada (British Columbia and Saskatchewan), *S*. Enteritidis was the most common serovar recovered from retail chicken meat; 11% (18/166) of samples from British Columbia and 10% (14/140) from Saskatchewan resulted in positive cultures for *S.* Enteritidis. In Ontario and Québec, *S*. Enteritidis was rarely detected; just 1% (3/232) of retail chicken samples purchased in Ontario were contaminated with *S*. Enteritidis and no *S*. Enteritidis isolates were recovered from samples purchased in Québec.

Although isolation of *S.* Enteritidis from retail turkey samples was low, it also varied by region. In British Columbia and Ontario, *S.* Enteritidis was recovered in 5% (7/153) and 2% (5/223) of retail turkey samples, respectively. No isolates of *S*. Enteritidis were recovered from retail turkey purchased in any other province sampled.

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[8] Public Health Agency of Canada, 2014. National Enteric Surveillance Program, 2012. Available at: www.publications.gc.ca/collections/collection_2014/aspc-phac/HP37-15-2012-eng.pdf. Accessed January 2015.

Unlike *S*. Enteritidis isolates recovered from humans, no isolates from routine retail or abattoir surveillance demonstrated resistance to any of the antimicrobials tested. However, an *S*. Enteritidis isolate from a chicken nugget purchased in Saskatchewas as part of a targeted retail project was resistant to 4 classes of antimicrobials (β-lactams, folate pathway inhibitors, aminoglycosides, and tetracyclines); more specifically, ampicillin, streptomycin, sulfisoxazole, and tetracycline. As well, 80% (4/5) of clinical isolates from cattle demonstrated resistance to 3 Category I antimicrobials tested (amoxicillin-clavulanic acid, ceftriaxone, and ceftiofur). However, no quinolone resistance was observed in any *S*. Enteritidis isolates recovered from any agri-food sources.

Figure 2 displays human *S.* Enteritidis incidence as well as the proportion of samples that yielded an *S*. Enteritidis isolate (recovery) from retail chicken by province. The apparent correlation between human incidence and recovery from retail chicken is stronger in Western Canada than in other regions, suggesting that regional differences in exposure affect the incidence of human *S*. Enteritidis. It should be noted that human incidence rates presented in Figure 2 include travel related cases. In Canada, approximately 30% of all *Salmonella* human cases are travel acquired[9]. Therefore, these rates include cases for which a Canadian exposure may not have been the cause of infection.

Despite similar patterns in incidence and recovery of *S*. Enteritidis overall, resistant *S*. Enteritidis isolates infecting people may not be originating from the major agricultural food-producing animals and food commodities produced in Canada and sampled through CIPARS. Retail chicken, however, may still be an important exposure source for people infected with susceptible *S*. Enteritidis in Canada.

Key message: Resistant S. Enteritidis isolates infecting people may not be originating from the major agricultural food-producing animals and food commodities produced in Canada and sampled through CIPARS. Retail chicken, however, may still be an important exposure source for people of susceptible S. Enteritidis in Canada.

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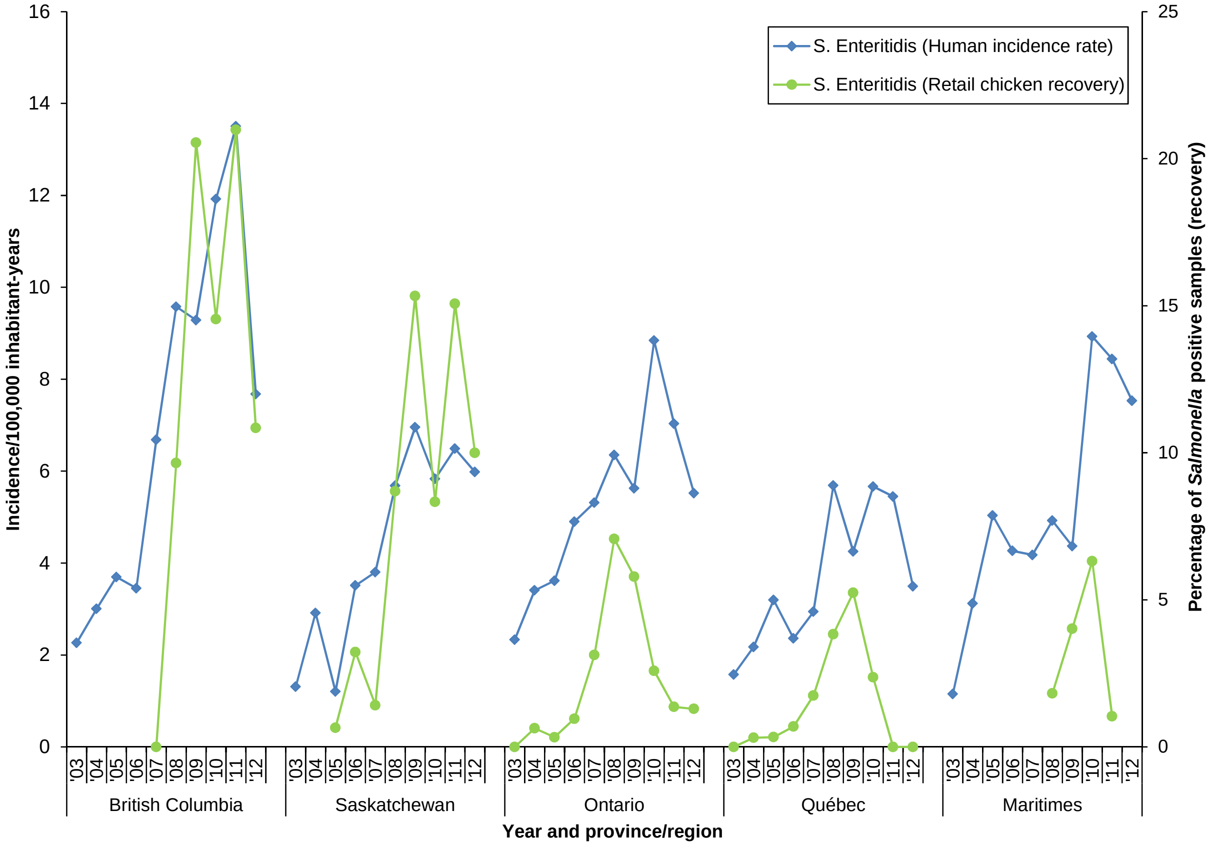
[9] Public Health Agency of Canada, 2014. FoodNet Canada 2012 Report. Available at: www.publications.gc.ca/collections/collection_2014/aspc-phac/HP37-17-1-2012-eng.pdf. Accessed January 2015.

Figure 2. Incidence of human *Salmonella* Enteritidis and proportion of retail chicken positive for *Salmonella* Enteritidis



The Maritimes region includes New Brunswick, Nova Scotia, and Prince Edward Island.
Due to unforeseen and lengthy delays in retail sampling in the Maritimes in 2012, data are not presented for this year in the interest of precision.

SALMONELLA HEIDELBERG AND RESISTANCE TO THIRD-GENERATION CEPHALOSPORINS

After *S*. Enteritidis, *S*. Heidelberg was the next most common *Salmonella* serovar identified from humans *Salmonella* infections submitted for susceptibility testing in 2012, representing 13% (555/4,129) of all human *Salmonella* isolates. The proportion of human *Salmonella* cases represented by *S*. Heidelberg was 21% in both Québec (128/595) and the Atlantic provinces (New Brunswick, Nova Scotia, Prince Edward Island, and Newfoundland and Labrador; 89/418). In Western Canada and in Ontario, *S.* Heidelberg made up a smaller proportion of human *Salmonella* cases ranging from 9% in both British Columbia (39/438) and Alberta (37/421) to 14% (222/1,547) in Ontario. *Salmonella* Heidelberg is usually more invasive than other common non-typhoidal *Salmonella* serovars that infect people and can cause bloodstream, heart muscle, and other infections outside of the gastrointestinal tract and is therefore an important serovar to monitor.

Because of the same mechanism of resistance, if a bacterium is resistant to ceftiofur, it is almost always resistant to ceftriaxone and all other third-generation cephalosporins. Therefore, resistance in the following discussion pertains to third-generation cephalosporin resistance. Twenty-seven percent (150/555) of human *S.* Heidelberg isolates were resistant to third-generation cephalosporins in 2012; this was significantly lower than the 33% (125/377) observed in 2011. Although *S*. Heidelberg was less frequently recovered from people in Western Canada, the proportion of isolates resistant was higher in this region. Combined, 51% (59/116) of *S*. Heidelberg isolates from the 4 Western provinces demonstrated resistance, compared to 21% (91/439) in Ontario, Québec and the Atlantic provinces.

Along with *S*. Kentucky, *S*. Heidelberg was the most common serovar recovered from farm, abattoir, and retail meat surveillance components in 2012. Chicken sources accounted for the majority (81%, 123/152) of *S.* Heidelberg isolates, and of these, 76% (94/123) were from retail chicken meat specifically. In 2012, recovery of *S*. Heidelberg from retail chicken meat samples was less common in Western Canada than in Central Canada; recovery in both British Columbia and Saskatchewan was 4% (7/166 and 5/140, respectively), compared to 18% (42/232) in Ontario and 14% (40/280) in Québec.

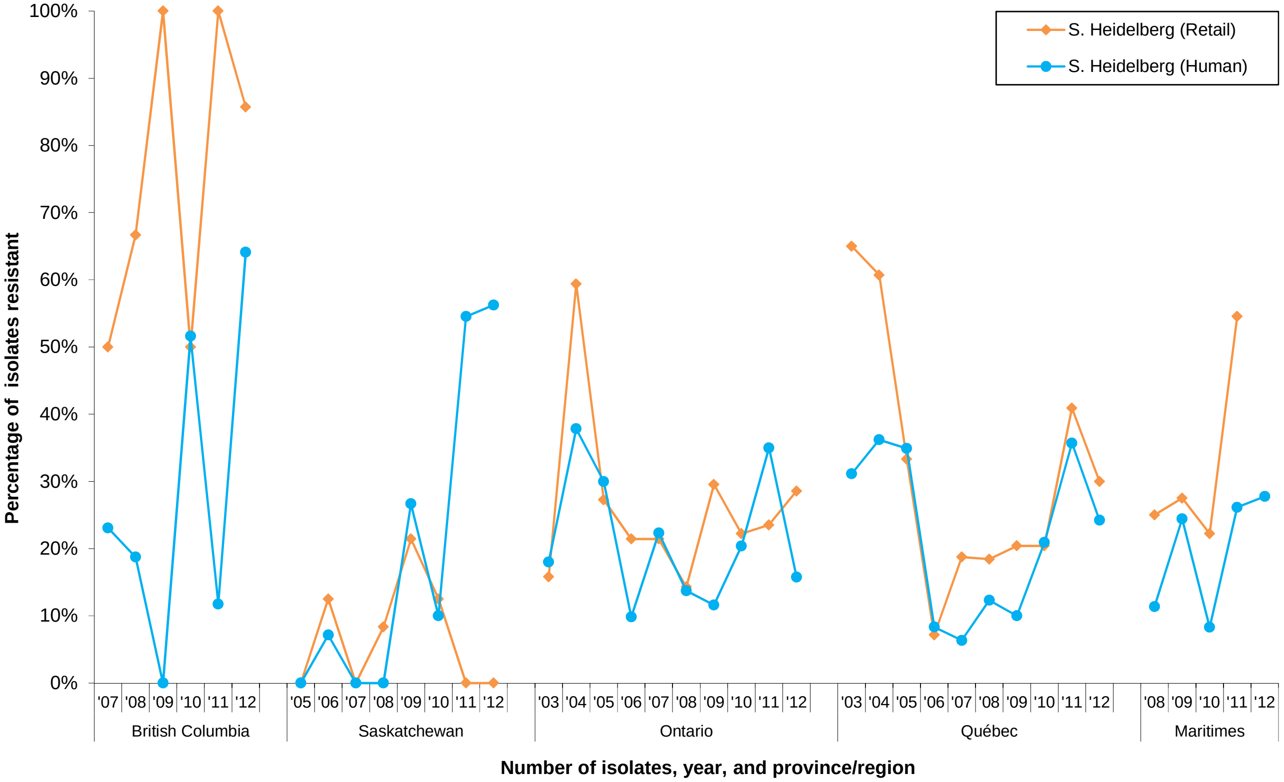
Similar to the human data, resistance to third-generation cephalosporins was commonly observed in *S*. Heidelberg isolates from agri-food sources in 2012. Among isolates from retail chicken meat, 32% (30/94) were resistant. However, resistance varied regionally; in Ontario and Québec, respectively, 29% (12/42) and 30% (12/40) of isolates were resistant. In British Columbia, 86% (6/7) of isolates were resistant and no resistance was observed among isolates from Saskatchewan (0/5) (Figure 3). In addition to retail chicken, although the numbers were small, *S.* Heidelberg isolates from retail turkey and chicken nuggets (targeted retail project) also displayed resistance. Overall, 39% (11/28) of isolates from retail turkey were resistant in 2012; 67% (2/3) from British Columbia, 0% (0/7) from Saskatchewan, 21% (3/14) from Ontario, and 67% (6/9) of isolates from Québec. In retail, 48% (22/46) of the isolates from chicken nuggets were resistant and included 17% (2/12) from British Columbia, 60% (3/5) from Saskatchewan, 55% (6/11) from Ontario, and 61% (11/18) from Québec.

Regardless of the source of *S*. Heidelberg (human or agri-food), resistance to third-generation cephalosporins remained high in 2012 (Figure 3). Ceftriaxone is used in people to treat a variety of infectious diseases and is one of the drugs of choice for treating patients hospitalized with severe salmonellosis or other foodborne bacterial infections. In contrast, ceftiofur is only used in animals and is used to treat and prevent a variety of infectious animal diseases. Although not labelled for use in chickens or turkeys in Canada, ceftiofur is used to control *Escherichia coli* omphalitis in broiler chicks.

In Québec, the proportion of human and retail *S*. Heidelberg isolates resistant to ceftiofur display a marked temporal relationship (Figure 3). Interestingly, this was not evident or as pronounced for other provinces. Although, the reason(s) for this difference are not clear, this may be a result of the phage types which are most prevalent in different regions. Among human infections, resistance to ceftiofur is driven mainly by the presence/absence of phage type (PT) 29; as PT 29 decreases, resistance to third-generation cephalosporins decreases, and vice versa. Therefore, the proportion of resistant isolates may differ dramatically among regions based upon the most prevalent phage types causing human infection and present in retail chicken.

Key Message: Salmonella Heidelberg is more commonly observed in people and chicken meat in Ontario, Québec, and the Atlantic provinces. Although much less common in Western Canada, a higher percentage of the isolates demonstrate concerning resistance to third-generation cephalosporins.

Figure 3. Proportion of human and retail *Salmonella* Heidelberg isolates resistant to third-generation cephalosporins



Province/region	British Columbia					
Year	'07	'08	'09	'10	'11	'12
Number of retail isolates	4	3	6	4	6	7
Number of human isolates	13	16	17	31	17	39
Percentage of isolates resistant						
S. Heidelberg (Retail)	50%	67%	100%	50%	100%	86%
S. Heidelberg (Human)	23%	19%	0%	52%	12%	64%

Province/region	Saskatchewan							
Year	'05	'06	'07	'08	'09	'10	'11	'12
Number of retail isolates	5	8	9	12	14	8	0	5
Number of human isolates	15	14	11	7	15	10	11	16
Percentage of isolates resistant								
S. Heidelberg (Retail)	0%	13%	0%	8%	21%	13%	NA	0%
S. Heidelberg (Human)	0%	7%	0%	0%	27%	10%	55%	56%

Province/region	Ontario									
Year	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12
Number of retail isolates	19	32	11	14	42	21	44	18	34	42
Number of human isolates	172	185	140	122	94	102	112	157	140	222
Percentage of isolates resistant										
S. Heidelberg (Retail)	16%	59%	27%	21%	21%	14%	30%	22%	24%	29%
S. Heidelberg (Human)	18%	38%	30%	10%	22%	14%	12%	20%	35%	16%

Province/region	Québec									
Year	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12
Number of retail isolates	20	28	12	14	32	38	49	49	22	40
Number of human isolates	167	116	106	96	63	65	100	129	84	128
Percentage of isolates resistant										
S. Heidelberg (Retail)	65%	61%	33%	7%	19%	18%	20%	20%	41%	30%
S. Heidelberg (Human)	31%	36%	35%	8%	6%	12%	10%	21%	36%	24%

Province/region	Maritimes				
Year	'08	'09	'10	'11	'12
Number of retail isolates	4	40	27	11	0
Number of human isolates	44	45	48	65	72
Percentage of isolates resistant					
S. Heidelberg (Retail)	25%	28%	22%	55%	NA
S. Heidelberg (Human)	11%	24%	8%	26%	28%

NA=Not available.

The Maritimes region includes New Brunswick, Nova Scotia, and Prince Edward Island.

Due to unforeseen and lengthy delays in retail sampling in the Maritimes in 2012, data are not presented for this year in the interest of precision.

CAMPYLOBACTER JEJUNI AND RESISTANCE TO CIPROFLOXACIN

Campylobacter is the second most common bacterial cause of gastrointestinal disease in people in Canada; it is estimated that there are 145,000 domestically-acquired cases annually[10]. In 2012, 1,994 laboratory confirmed human *Campylobacter* infections were reported to the National Enteric Surveillance Program (NESP)[11]. Unlike *Salmonella* cases, *Campylobacter* cases are not routinely reported to reference laboratories and therefore the numbers are greatly under-represented in NESP. Most human infections with *Campylobacter* are believed to be sporadic and rarely associated with an outbreak. Diarrhea, fever, and abdominal pain are common symptoms associated with acute *Campylobacter* infection. *Campylobacter* infections have also been associated with long term sequelae such as Guillian-Barré syndrome, an auto-immune condition that affects the peripheral nervous system. Most people with *Campylobacter* are infected with *C. jejuni*. At this time, CIPARS has no data about resistance in human *Campylobacter* infections.

Although *Campylobacter* frequently colonizes animal hosts, it rarely causes disease and is mostly considered a commensal organism in animals (part of the natural bacterial flora). *Campylobacter* is particularly common in cattle and pigs, but can also be found in chickens. In 2012, 92% (152/166) of cattle caecal samples collected at slaughter tested positive for *Campylobacter*, 73% (111/152) of these were *C. jejuni*. Similarly in pigs, *Campylobacter* was recovered from 78% (289/360) of pigs at slaughter. In contrast with *Campylobacter* isolated from humans and cattle, all pig isolates in 2012 were *C. coli*. Recovery of *Campylobacter* from chicken is less common than cattle or pigs; 23% (155/685) of chickens at slaughter tested positive for *Campylobacter* in 2012 and 94% (145/155) of these were *C. jejuni*.

Retail pork and beef samples are not cultured for *Campylobacter* through CIPARS due to low recovery rates found in past sampling. However, *Campylobacter* is recovered from retail chicken and turkey meat. From retail chicken in 2012, 35% (280/806) of samples tested positive and 90% (253/280) of these were *C. jejuni*. Recovery from chicken samples varied by region: from 28% (78/274) in Québec to 44% (73/166) in British Columbia. *Campylobacter* was also recovered from retail turkey in 2012; 10% (74/750) of samples were positive of which 78% (58/74) were *C. jejuni*. Retail turkey recovery also varied by region, and ranged from 5% (6/128) in Saskatchewan to 22% (33/153) in British Columbia.

Among the *Campylobacter* isolates from abattoir in 2012, ciprofloxacin resistance was observed in 6% (8/152) of isolates from cattle caecal contents, 7% (11/155) of chicken isolates, and 10% (28/287) of pig isolates. The higher level of resistance in isolates from pigs may be attributed to the species of *Campylobacter* recovered; higher levels of resistance have been documented in

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[10] Thomas et al, 2013. Estimates of the burden of foodborne illness in Canada for 30 specified pathogens and unspecified agents, circa 2006. *Foodborne Pathog Dis*. 2013; 10(7): 639–648.

[11] Public Health Agency of Canada. 2014. National Enteric Surveillance Program (NESP), Annual Summary 2012. Available at: www.publications.gc.ca/site/eng/465160/publication.html. Accessed July 2014.

C. coli as compared with *C. jejuni*[12]. Overall, 8% (24/288) of retail chicken isolates and 11% (8/74) of retail turkey isolates demonstrated resistance to ciprofloxacin. However, important and changing regional differences in the level of resistance were observed in 2012 (Figure 4).

Resistance to ciprofloxacin among retail chicken varied among regions in 2012, and has been changing over time within regions. In retail chicken purchased in British Columbia, the proportion of ciprofloxacin-resistant *Campylobacter* have been on the decline, and this decline continued in 2012, dropping to 8% (6/73) from 13% (9/71) in 2011 and a high of 29% (22/77) in 2009. In Saskatchewan, the proportion of resistant *Campylobacter* isolates was 5% (2/40) in 2012; this was not different from the level of resistance observed in 2011. The province with the highest proportion of ciprofloxacin-resistant *Campylobacter* isolates from retail chicken in 2012 was Ontario; 16% (14/88) of isolates were resistant. This is the highest level of ciprofloxacin resistance observed to date in the province. Two ciprofloxacin-resistant isolates (3% of 79 isolates) were detected in Québec in 2012.

The pattern of ciprofloxacin resistant *Campylobacter* in retail turkey observed in 2012 was more similar to the pattern observed in retail chicken in 2010. A higher proportion of isolates from Western Canada demonstrated resistance: in British Columbia in 2012, 21% (7/33) of *Campylobacter* isolates from retail turkey were resistant as were 17% (1/6) of isolates from Saskatchewan. No ciprofloxacin resistance was observed in *Campylobacter* isolates from retail turkey purchased in Ontario or Québec.

Although no resistance data are available for human *Campylobacter* isolates at this time, subtyping results from CIPARS abattoir sampling (and past retail pork) suggest that pigs are not a source of human *C. jejuni* infections, as only *C. coli* have been isolated from pigs at slaughter. Similarly, although *C. jejuni* is commonly recovered from cattle at slaughter, it is very rarely detected in retail beef suggesting that cattle are not a major source of human *C. jejuni* infections arising from the foodchain. Due to high rates of *C. jejuni* isolation from retail chicken, these products are more likely to be associated with human illness.

Ciprofloxacin is a fluoroquinolone antimicrobial commonly used in human medicine to treat respiratory, urinary, gastrointestinal, skin, and bone/joint infections; it is considered to be of very high importance to human medicine (Category I). Ciprofloxacin is not used in livestock medicine but other fluoroquinolones (e.g. enrofloxacin) are approved as injectable solutions for treating respiratory disease in pigs and cattle. No fluoroquinolones are labelled for use in chickens and turkeys in Canada, despite resistance seen in isolates from chicken and turkey meat products. Resistance to ciprofloxacin in *Campylobacter* is of concern because infection with resistant bacteria has been associated with more severe illness in people[13].

The pattern of ciprofloxacin resistance in retail chicken differs across the country, and continues to change over time. In 2013, CIPARS will have antimicrobial use information for broiler flocks in the major chicken producing provinces which will provide an additional layer of

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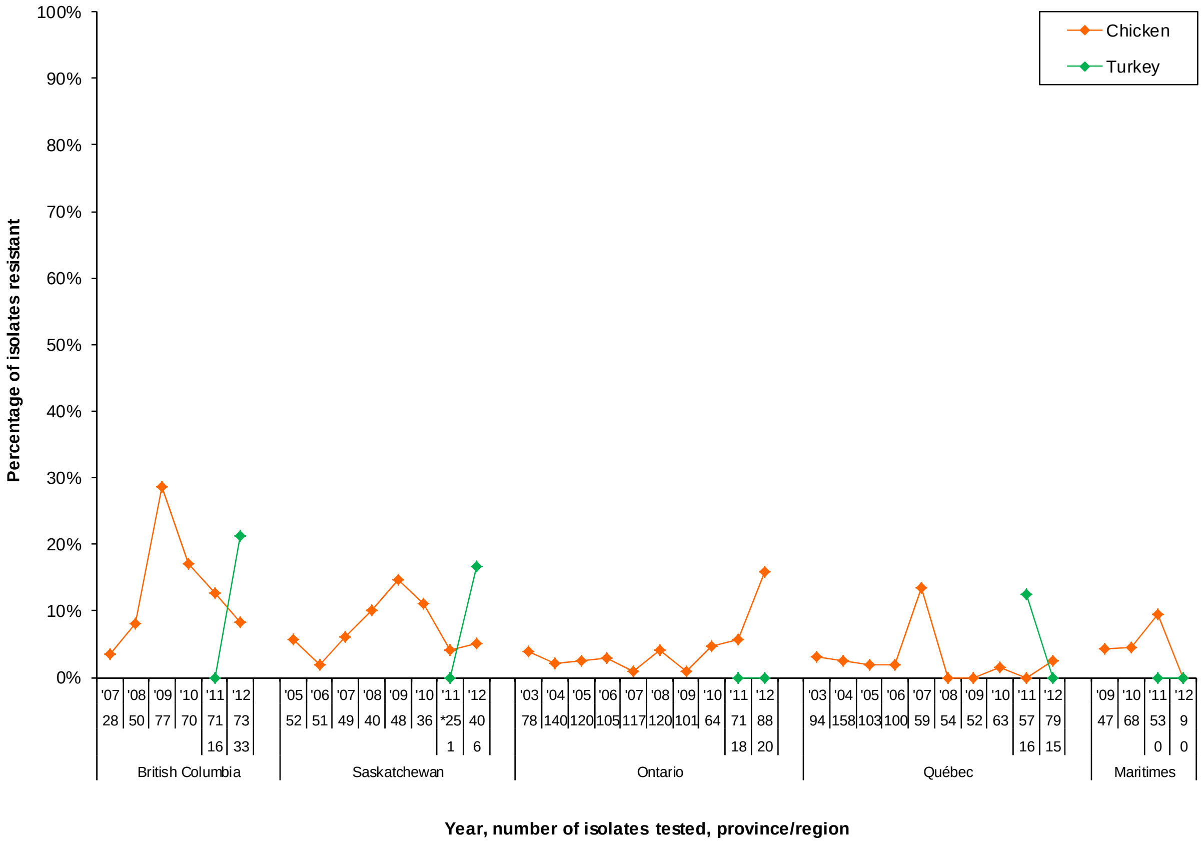
[12] Aarestrup FM, McDermott PF, Wegener HC. 2008. Transmission of antibiotic resistance from food animals to humans. In: Nachamkin I, Szymanski CM, Blaser MJ(eds). *Campylobacter, 3rd ed*. ASM Press pg 645.

[13] Nelson JM, Smith KE, Vugia DJ, Rabatsky-Ehr T, Segler SD, Kassenborg HD, et al. Prolonged diarrhea due to ciprofloxacin resistant *Campylobacter* infection. *J Infect Dis*. 2004 Sep 15; 190(6):1150−7.

data that may help explain the changing resistance patterns, particularly those seen in retail chicken.

Key Message: Human Campylobacter infections are primarily subspecies jejuni, which is commonly recovered from retail chicken. The pattern of ciprofloxacin resistance in retail chicken continues to change over time and across regions. In 2013, CIPARS will have antimicrobial use information for broiler flocks in the major chicken producing provinces which will provide an additional layer of data that may help explain the changing resistance patterns.

Figure 4. Temporal variation in resistance to ciprofloxacin in *Campylobacter* isolates from retail chicken and turkey, by province/region and year



*Sample testing not met.

MULTICLASS RESISTANCE ACROSS COMMODITIES

MULTICLASS RESISTANCE IN TURKEY SAMPLES

In 2012, several *E. coli* and *Salmonella* isolates recovered from turkey samples demonstrated resistance to multiple classes of antimicrobials. From retail turkey meat purchased in Ontario, 1 *E. coli* isolate was resistant to all classes of antimicrobials tested. In addition, 1 *S*. Indiana isolate from retail turkey in Ontario and 2 clinical *S*. Indiana isolates from turkeys in Ontario demonstrated resistance to 6 classes of antimicrobials (all except the quinolones). All of these isolates underwent further susceptibility testing to determine if they were resistant to the carbapenems, all were susceptible.

In 2012, there were 4 human cases of *S.* Indiana reported to NESP of which 1 was submitted to CIPARS for susceptibility testing. The human isolate was susceptible to all antimicrobials tested.

MULTICLASS RESISTANT *SALMONELLA* DUBLIN

In 2012, 4 human isolates of *S*. Dublin were recovered from bloodstream infections in people; 3 were from Québec, and 1 was from Ontario. The bloodstream infections were resistant to 6 classes of antimicrobials (all except the macrolides). Among agri-food sources, *S*. Dublin is most commonly recovered from cattle and historically has been more common in Western Canada. In Ontario, *S*. Dublin was observed in clinical diagnostic samples from cattle for the first time in 2012 and prior to 2011, the serovar was not observed in Québec. In 2012, 26% (7/27) clinical *S*. Dublin isolates from cattle showed the same resistance profile as the bloodstream infections in people; all of these resistant isolates were from Québec. At this time, CIPARS is using genome sequencing to determine possible relatedness between human and clinical diagnostic cattle isolates.

MULTICLASS RESISTANT *SALMONELLA* NEWPORT

Although still low, the proportion of human *S*. Newport displaying multiclass resistance has increased in recent years, with 6% (9/149) of isolates showing resistance to 5 classes of antimicrobials (all except the macrolides and quinolones) in 2012 compared to 1% (2/136) of isolates in 2009. A single multiclass resistant isolate was identified from a clinical cattle submission in 2009 and another was recovered from a clinical pig isolate in 2010. No multiclass resistant *S*. Newport isolates have been recovered from CIPARS farm, abattoir or retail components, suggesting that the resistant *S*. Newport infections in people did not originate from chicken, pork or beef raised in Canada. Further investigation of the resistant isolates from people and potential exposure sources is ongoing.

Key Message: Some human and agri-food isolates showed resistance to 5 or more antimicrobial classes. However, not all multiclass resistance trends observed among human Salmonella isolates were seen in isolates from the major agri-food commodities (cattle, pigs, and chickens).

INTEGRATED ANTIMICROBIAL USE FINDINGS AND DISCUSSION

KILOGRAMS OF ANTIMICROBIALS USED PER KILOGRAM OF WEIGHT IN HUMANS AND ANIMALS

Canada is a major producer of food animals, particularly poultry, swine, and cattle. As such, there are roughly 19 times more terrestrial food animals than people in Canada (Figure 5). Most of the animals represented in Figure 5 are poultry (approximately 600 million of the 655 million). Overall, the population is underestimated for animals as farmed fish statistics in Canada are reported as kilograms produced rather than counts of individual animals. In contrast, the human population in Canada in 2012 was roughly 34.8 million.

To be effective in the body, antimicrobials are given based upon body size. As some animals are heavier than people and some are lighter, this makes it difficult to directly compare use across species. Furthermore, comparative measures such as kilograms of active ingredient (with or without correction for the underlying population) do not account for the individual potencies of the drugs. For people, there is a common standard metric which accounts for both potency and underlying population: defined daily doses/1,000 inhabitant days (DIDs). Similar standard metrics for animal antimicrobial use do not currently exist, although CIPARS is working to develop Canadian metrics.

In the absence of standard metrics, an estimate of the weight (kg) of each population (animals and humans) has been calculated to be used as a denominator for distribution data. To do this, the average weight of the major food animal species was estimated using published data for the population estimates for each species. This is an approach similar to that used by the European Surveillance for Veterinary Antimicrobial Consumption (ESVAC)[14] for reporting animal antimicrobial sales data and similar to what the Swedish Veterinary Antimicrobial Monitoring (SVARM) program has used in the past for comparing human and animal use[15]. However, average weights of animals differ around the world. Hence, the animal analyses were carried out using 2 different estimates: European average weights and Canadian average weights. The European average weights were those used by ESVAC and the Canadian average weights are

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[14] European Medicines Agency. European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), 2013. Sales of veterinary antimicrobial agents in 25 EU/EEA countries in 2011 (EMA/236501/2013). Available at: www.ema.europa.eu/docs/en_GB/document_library/Report/2013/10/WC500152311.pdf. Accessed January 2015.

[15] SWEDRES-SVARM 2012. Use of antimicrobials and occurrence of antimicrobial resistance in Sweden. Solna/Uppsala ISSN 1650-6332. Available at: www.sva.se/upload/Redesign2011/Pdf/Om_SVA/publikationer/Swedres_Svarm2012.pdf. Accessed January 2015.

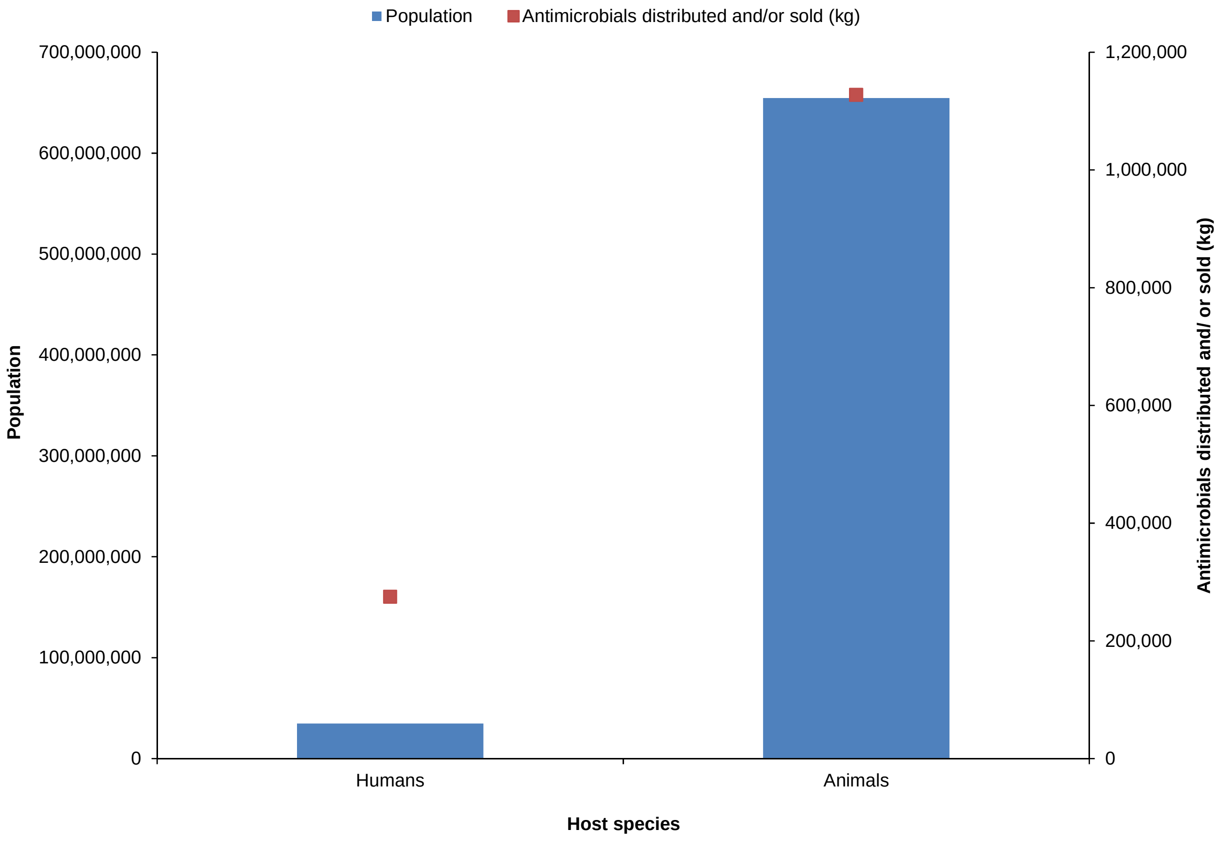
preliminary and based on early discussions between CIPARS and a small group of stakeholders representing different commodities and the pharmaceutical industry.

A similar total weight estimate was calculated for people; the Canadian population for 2012 was multiplied by an “average” weight of 70 kg per person to calculate this weight[16].

Figure 6 displays a comparison of the quantity of antimicrobials distributed and/or sold per kilogram of weight for humans and animals, using both estimations. Using European and Canadian animal weight estimates, the quantity of antimicrobials distributed and/or sold for use in animals was 1.4 or 1.2 times greater than the quantity distributed to people, respectively.

Key Message: In 2012, after adjusting for population sizes and weights, the quantity of antimicrobials distributed and/or sold for use in animals was 1.4 times greater than the quantity distributed to people (using European standard weights for animals).

Figure 5. Human and animal population estimates with total kilograms of antimicrobials distributed and/or sold for use



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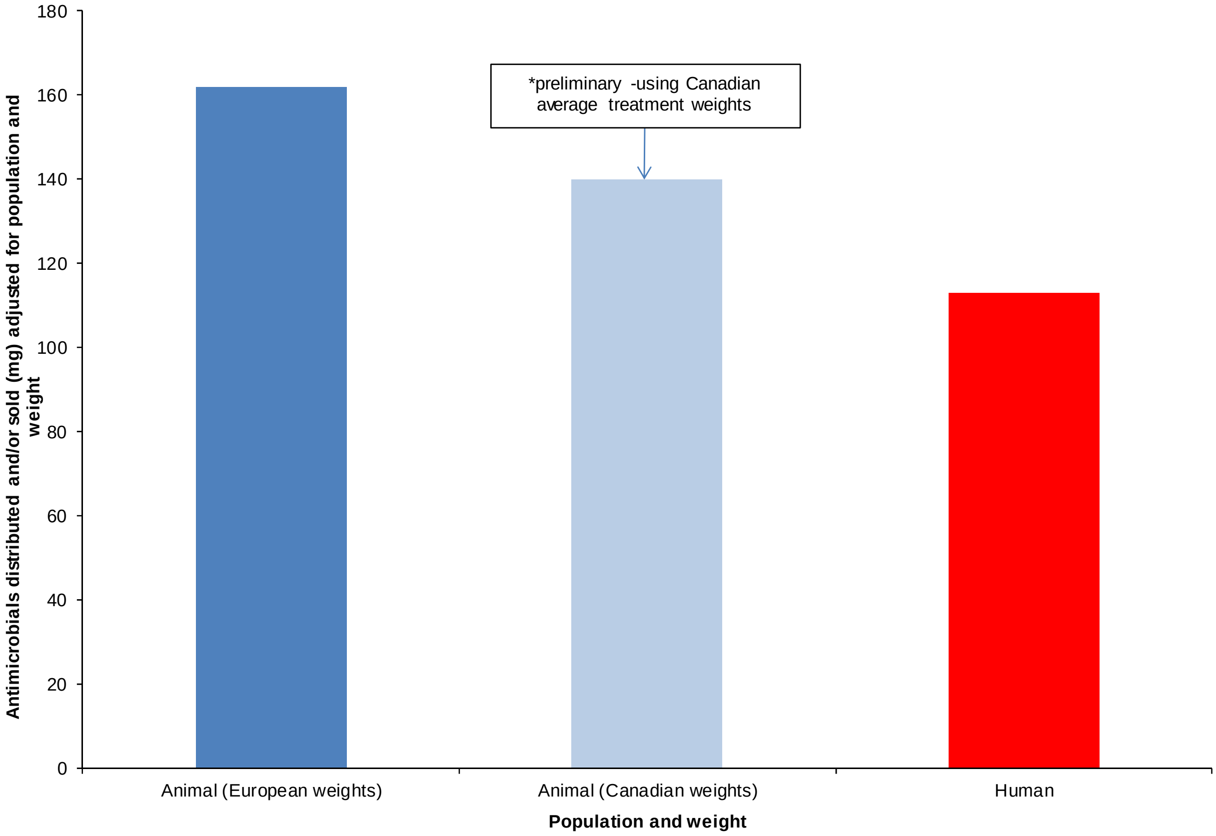
[16] World Health Organization. Definition and general considerations. WHO Collaborating Centre for Drug Statistics Methodology. Available at: www.whocc.no/ddd/definition_and_general_considera/. Accessed March 2015.

Figure 6. Quantity of antimicrobials distributed and/or sold for use in animals and people (adjusted for populations and weights)



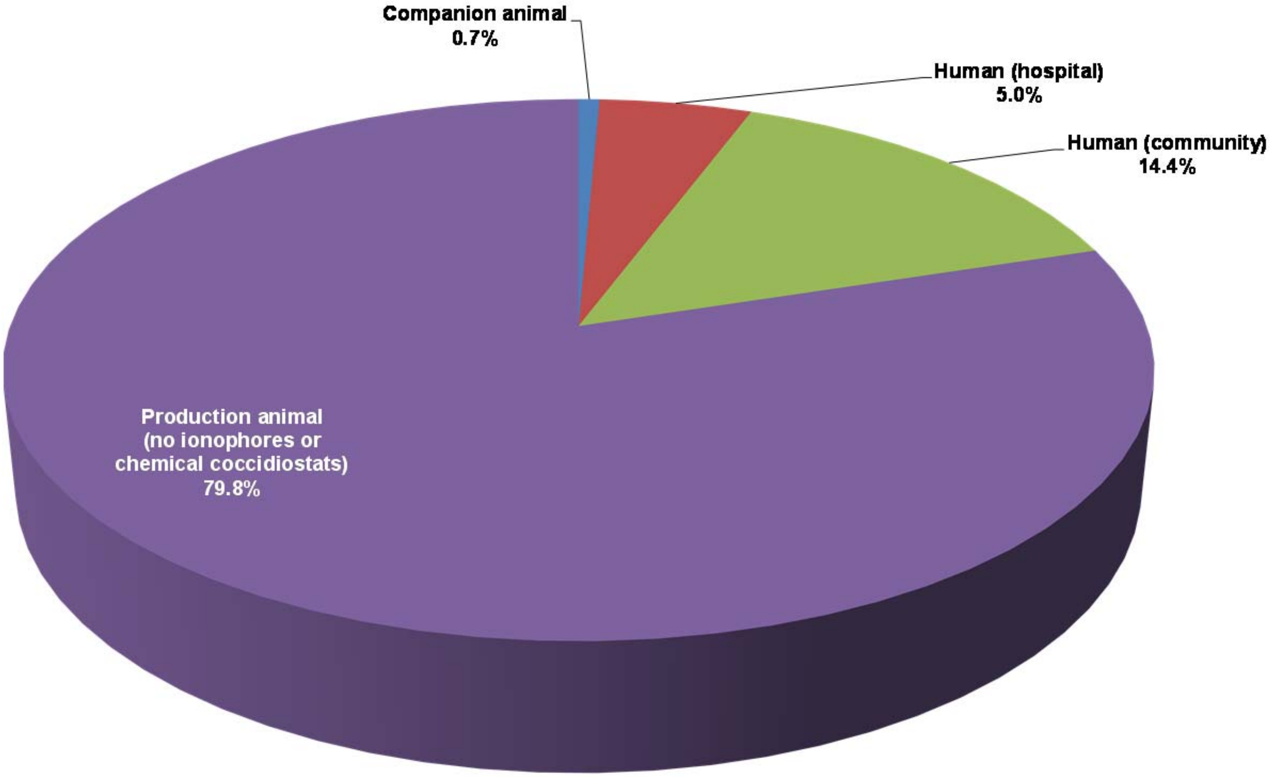
SECTORS USING ANTIMICROBIALS IN CANADA

Many of the same antimicrobial classes are used in animals and in people. Of the total kilograms of antimicrobials distributed and/or sold for use in people and animals (1.4 million kg; excluding ionophores, chemical coccidiostats, and arsenicals), 80% were intended for use in production animals (food animals and horses) (Figure 7). In people, 74% of the total kilograms of antimicrobials used occurred in the community setting and 26% in hospitals. In animals, less than 1% of the total kilograms of antimicrobials used was in companion animals (mainly dogs and cats).

Animal distribution data underestimate the total quantity of antimicrobials used in animals, as this information does not account for quantities imported for own use or as active pharmaceutical ingredients for further compounding. CAHI has recently estimated that for all animal pharmaceutical products, the loss of market share represented by own use importation or active pharmaceutical ingredient importation is roughly 13%. This estimate is for all animal health products; broader than just antimicrobials.

Key Message: Among all antimicrobials distributed for use in Canada (excluding ionophores, chemical coccidiostats, and arsenicals), 80% were used in production animals (food animals and horses). In humans, 74% of antimicrobial use occurred in the community setting and 26% in hospitals. In animals, less than 1% of antimicrobial use was for companion animals.

Figure 7. Proportion of total kilogram of antimicrobials distributed and/or sold in Canada by sector



USE BY ANTIMICROBIAL CLASS DIFFERS IN HUMANS AND ANIMALS

While the same or similar products may be licensed for use in people and animals, there are differences in the types of antimicrobials distributed and/or sold in each sector. For example, 53 times more fluoroquinolones and 9 times more cephalosporins are distributed and/or sold for use in people than for use in animals (Figure 8). Conversely, 4 times more macrolides and 78 times more tetracyclines are distributed for use in animals than are dispensed for use in people. It is important to note that there were no reported quantities of tetracyclines or macrolides distributed for use in companion animals. Similarly, for aminoglycosides, lincosamides, and sulfonamides with trimethoprim, the quantities distributed for use in animals were more than what used in people by 68, 7, and 3 times, respectively. The quantity of penicillins distributed for use was very similar between animals and people (1:1 ratio).

There are important differences in the relative frequency with which antimicrobials are distributed and/or sold in animals and people (Figure 9). In people, the predominant classes (by kilograms of active ingredients) are β-lactams, cephalosporins, macrolides, and fluoroquinolones. In animals, the predominant classes are tetracyclines, ionophores, chemical coccidiostats, and arsenicals, other antimicrobials, β-lactams, and macrolides.

Key Message: Although the same antimicrobial classes are used in humans and animals, some classes are used at much greater or lesser volumes in human medicine than veterinary medicine.

Figure 8. Kilograms of active ingredient of select antimicrobial classes distributed and/or sold for use in animals (production and companion animals) and people (hospital purchases and pharmacy dispensations)

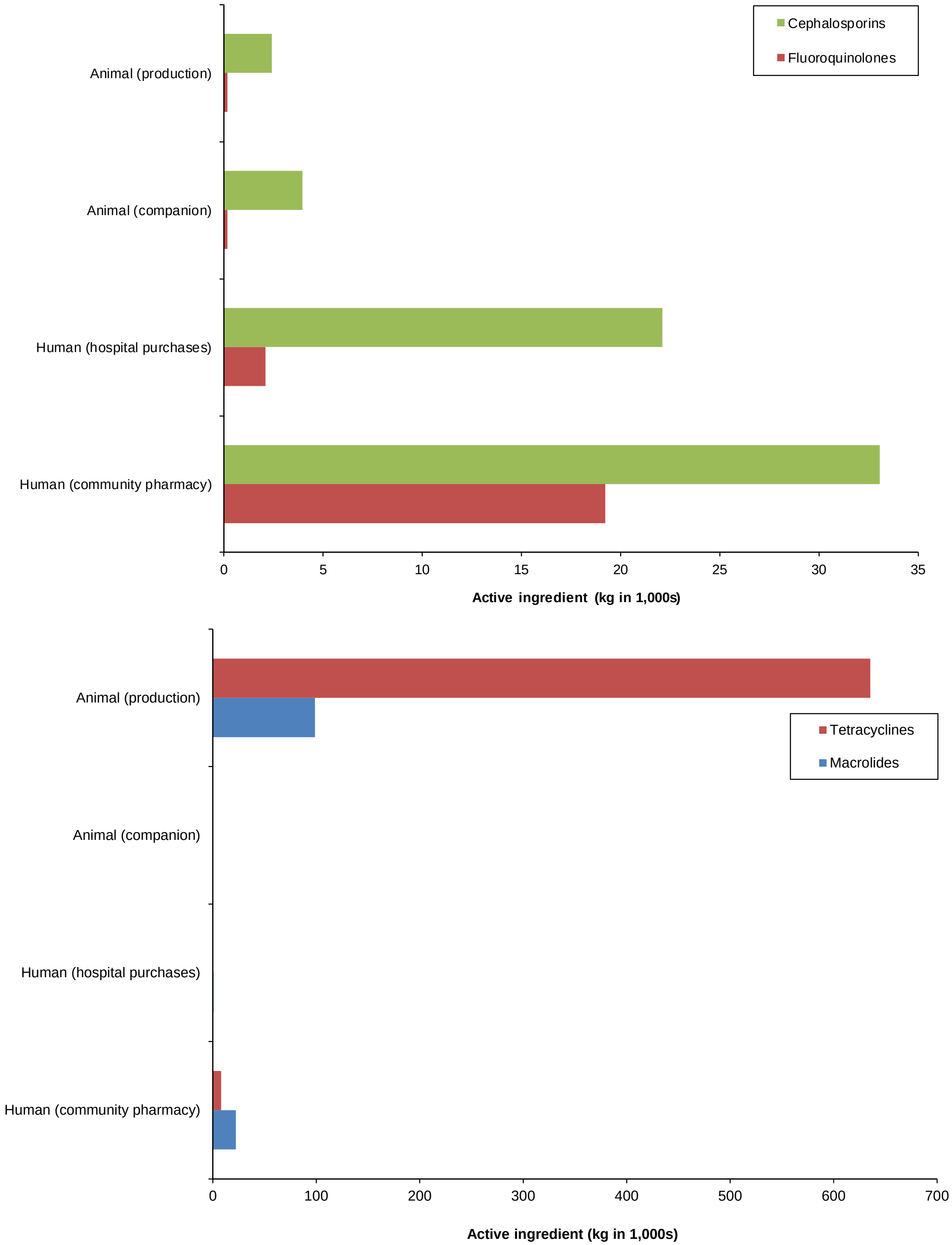
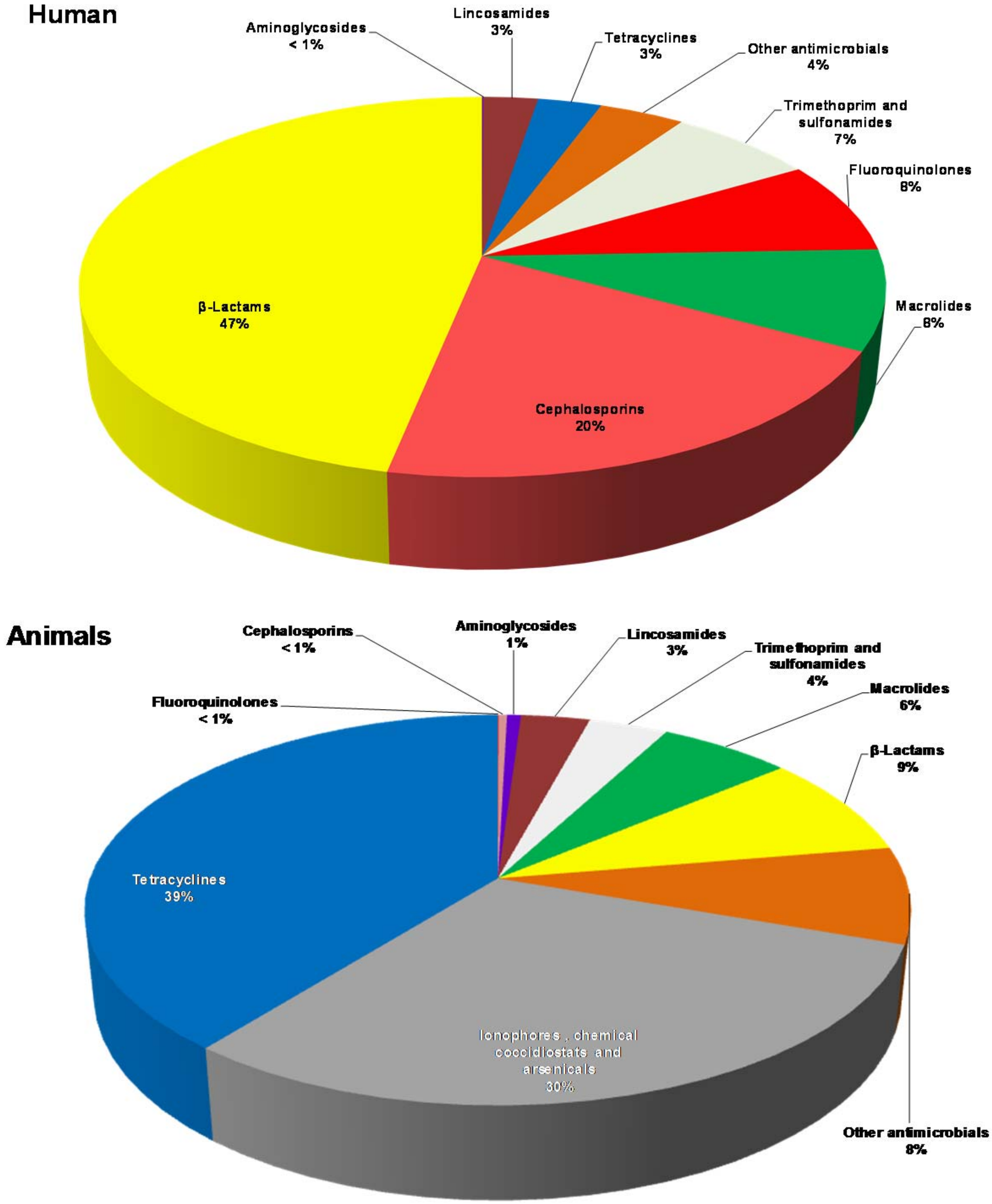


Figure 9. Relative proportion of antimicrobials distributed and/or sold for use in humans and animals, based on kilograms of active ingredients



INDICATIONS FOR USE AMONG HUMANS AND ANIMALS

Indication for antimicrobial use data in humans is obtained through the sentinel physician dataset[17]. In grower-finisher pigs data on reasons for use were collected through the sentinel farm program.

DISEASE TREATMENT

In 2012, when antimicrobials were recommended for use in humans by physicians, the most common antimicrobial classes recommended were the β-lactams, macrolides, and quinolones. From CIPARS swine data in 2012, when antimicrobials were used in swine the most commonly reported classes were macrolides, β-lactams (penicillins), and lincosamides.

Similarly, and not surprisingly, there was overlap in the diseases that were being treated with antimicrobials among humans and swine. In humans, the most common disease classifications that recommended an antimicrobial for treatment were respiratory tract infections (46%), infections of the genitourinary tract (20%), and infections of the skin (16%). In swine, antimicrobials were most commonly administered for the prevention or treatment of respiratory tract infections (29%) and to a lesser extend for the treatment of enteric infections (23%) and lameness (17%). Included in “other” reasons for use in swine were production claim uses in feed and treatments for systemic bacterial infections and wound management.

However, antimicrobial classes were not used identically among human and swine populations in 2012 (Figure 10 and Figure 11). For example, when β-lactams were recommended for use in human medicine, 57% were for respiratory disease (Figure 10). When β-lactams were used in swine, 35% were used for the treatment and prevention of respiratory disease, but 45% were used to treat and/or prevent lameness (Figure 11). Figure 10 and Figure 11 also highlight where antimicrobial classes were used among swine but not among humans (e.g. flavophospholipids, phenicols, pleuromutilins, and ionophores) and among humans but not swine (e.g. quinolones).

Key Message: Most of the antimicrobial use in humans was for treatment of respiratory and urinary tract infections; most of the use in pigs was to prevent or treat respiratory infections. Most use of antimicrobials of high importance to human medicine reported in pigs was to treat and/or prevent respiratory infections.

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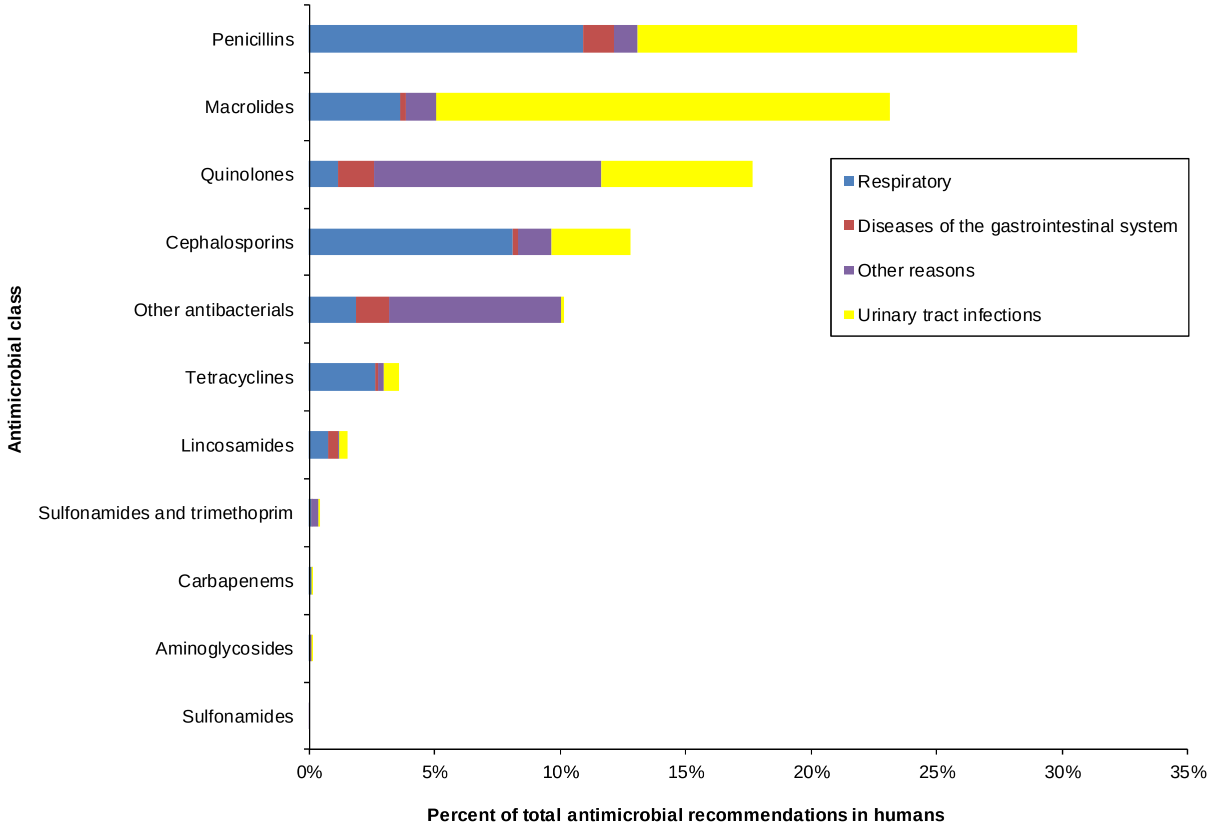
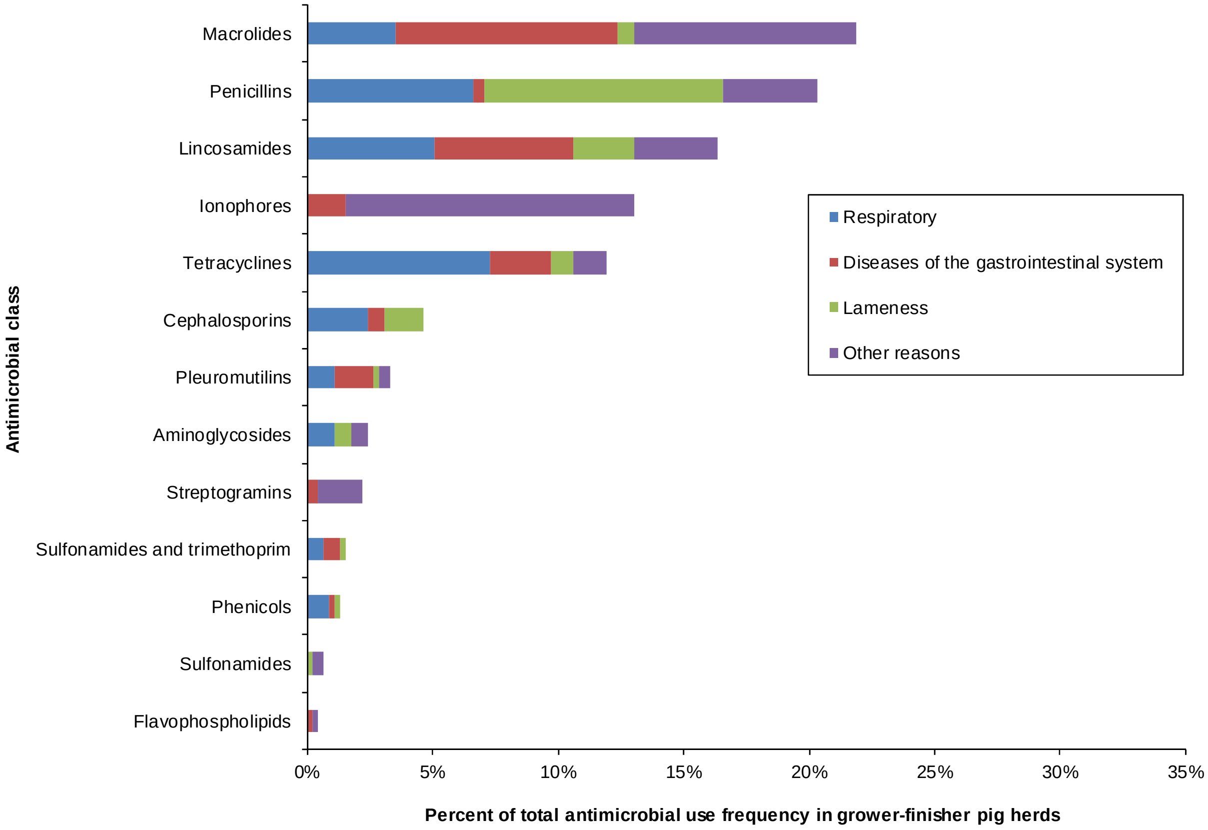
[17] Public Health Agency of Canada, 2014. Human antimicrobial drug use report 2012/2013. Available at: www.phac-aspc.gc.ca/publicat/hamdur-rumamh/2012-2013/index-eng.php. Accessed January 2015.

Figure 10. Percentage of antimicrobial recommendations by antimicrobial class and reason for use in humans



Other antibacterial classes included bacteriostatic antibiotics, carbapenems, glycopeptide antibiotics, nitrofuran derivatives, nitroimidazoles, and oxazolidinones.
Other diagnoses included congenital anomalies, diseases of the central nervous system, diseases of the circulatory system, diseases of the ear, diseases of the sense organs, endocrine, nutritional, metabolic, and immunity diseases, injuries and poisonings, musculoskeletal diseases, neoplasms, symptoms and ill-defined conditions, and supplementary classifications.

Figure 11. Percentage of antimicrobial recommendations by antimicrobial class and reason for use in swine



"Other reasons" include antimicrobial use for growth promotion and the treatment of systemic infections and wound management.

There was no reported use of quinolones or bacitracin in 2012.

Swine producers were instructed to select only one of three primary reasons for antimicrobial use: Growth promotion, Disease prevention or Disease treatment; respondents could "Check all that apply" from a list of secondary reasons for an antimicrobial use (Respiratory disease, Enteric disease, Lameness, and Other) under either Disease prevention or Treatment.