

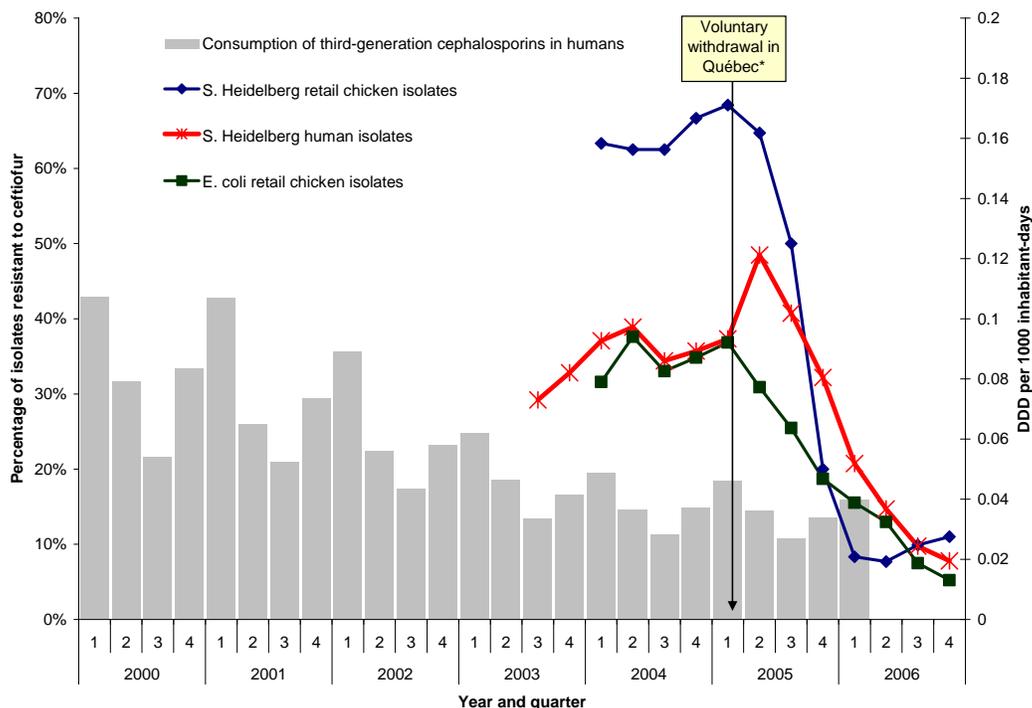


Salmonella Heidelberg – Ceftiofur-Related Resistance in Human and Retail Chicken Isolates

The Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS) provided data to stakeholders leading to a voluntary withdrawal in Québec chicken hatcheries of the extra-label¹ use of ceftiofur. After the withdrawal, a significant decrease in ceftiofur-resistance was seen in *Salmonella* Heidelberg isolates from retail chicken and humans (Figure 1). Such a reduction can protect the efficacy of related cephalosporin drugs, which are used to treat several types of infections, including severe cases of salmonellosis in children.

The Public Health Agency (PHAC) supports and encourages all Canadian hatcheries to apply similar efforts as those undertaken by Québec in order to limit the emergence and spread of cephalosporin-resistant S. Heidelberg from poultry to humans, via reductions in ceftiofur use. PHAC needs to enter into discussions with provincial and industry representatives to promote the CIPARS findings as an impetus to responsible use of antimicrobials in veterinary medicine across Canada.

Figure 1. Past three quarters moving average of the percentage of isolates resistant to ceftiofur for retail chicken *E. coli*, retail chicken and human clinical *S. Heidelberg* isolates, and quarterly human consumption of 3rd generation cephalosporins dispensed at retail pharmacies (IMS² Health) in Québec.



¹ Extra-label involves use other than what is on the label such as use for a different species, different age class, different indication, or at a different dose/duration. This use is considered unapproved although veterinarians have the legal authority to use drugs in this manner if the situation is warranted.

² IMS=Intercontinental Medical Statistics

*Voluntary withdrawal of ceftiofur use by Québec hatcheries in February 2005. At the time of publishing, human consumption data was only analyzed up to the first quarter of 2006.

Further details for the following sections can be found in the appendix or by CTRL+clicking on identified links.

1. Rationale for concern about this serovar and its resistance profile:

Salmonella Heidelberg is a prevalent serovar in North America ([Table 1](#)).

S. Heidelberg was the third most common serovar in humans in Canada in 2004, the fifth most common serovar in the US, but not found among the top six serovars for other continents.

Salmonella Heidelberg is a relatively invasive serovar and thus causes more severe illness in humans, including in children, than other non-typhoidal serovars (click on '[An invasive serovar](#)').

The resistance profile of this serovar often include resistance to ceftiofur and reduced susceptibility to the related antimicrobial ceftriaxone, which could limit the options for treatment of pregnant women and children (and possibly others) that develop extra-intestinal salmonellosis from this serovar (click on '[Resistance to ceftiofur and possible failure of ceftriaxone therapy in extra-intestinal *S. Heidelberg* human infections](#)').

2. Link between ceftiofur resistance in human and chicken isolates:

In order to prevent and control *Escherichia coli* infections, some broiler chicken hatcheries alternated the use of ceftiofur (extra-label use) with gentamicin until 2003, when the gentamicin formulation became unavailable. Published information (Boulianne, 2005¹) indicated that 100% of the Québec hatcheries surveyed were using ceftiofur in 2004 (in hatching eggs and/or day old chicks). No published information is available from other provinces and therefore we have no information to suggest that Québec was unique in terms of ceftiofur utilization at the hatchery level. Our CIPARS 2003 annual report highlighted higher rates of ceftiofur resistance in retail chicken and human isolates of *S. Heidelberg* from Québec compared to Ontario. In Québec, resistance was also higher in retail chicken than among human isolates. (click on '[Link between ceftiofur resistance in human and chicken isolates](#)'. Resistance had however risen in 2004 in Ontario to reach levels similar to those in Québec in 2003 and 2004 in both humans and chicken.

3. Action:

To address these public health concerns raised by the publication of the 2003 CIPARS Report, all broiler chicken hatcheries in Québec voluntarily stopped all use of ceftiofur in February 2005. PHAC provided detailed information regarding this issue to other provincial agriculture representatives and the Canadian poultry industry via email, meetings, and presentations.

4. Effect of the withdrawal, other temporal changes, and current status:

We saw a marked decrease in the prevalence of ceftiofur-resistant isolates in both chicken and human *S. Heidelberg* isolates and chicken *Escherichia coli* following the voluntary withdrawal of ceftiofur in hatching and day-old chicks in Québec ([Figure 1](#)). Details, including current status of resistance levels, can be found at '[Effect of the withdrawal, temporal changes, and current status](#)'.

Since 2003, there has been a decline in the incidence of human *S. Heidelberg* cases in most of the largest Canadian provinces. Concurrently we observed a decline in the relative proportion of this serovar among abattoir and retail chicken *Salmonella* isolates from 2003-2006. CIPARS-Retail data in Ontario and Québec as well as CIPARS national abattoir data suggest that the niche occupied by *S. Heidelberg* may

¹ Boulianne, 2005. Results from a large poultry study in Québec examining antimicrobial use and antimicrobial resistance. Agriculture's Role in Managing Antimicrobial Resistance Conference. Toronto, October 2005.

have been replaced by *S. Kentucky* and to a lesser extent by *S. Enteritidis* from 2004 to 2006. (click on [‘Changes in the incidence of Salmonella serovars and relative ranking in Canada’](#)). However, these variations in the prevalence of the main chicken serovars are unlikely to be related to the voluntary ceftiofur withdrawal since these temporal changes started before February 2005.

5. Next Steps:

PHAC supports and encourages continuance of the efforts undertaken by Québec to limit the emergence and spread of cephalosporin-resistant *S. Heidelberg* from poultry to humans, via reductions in ceftiofur use. PHAC is interested in participating in discussions with provincial and industry representatives to promote similar actions on a national basis. This is an opportunity to use the CIPARS findings as an impetus to responsible use of antimicrobials in veterinary medicine.

PHAC will continue to monitor and communicate the situation through data collected and analyzed by CIPARS, and we will expand our retail surveillance to include additional provinces to better describe regional similarities and differences.

Summary:

CIPARS has identified and recognized the clinical significance of this prevalent, invasive, and often multi-drug resistant *Salmonella* serovar. We recognize that although ceftiofur is a veterinary drug only used in animals, cross-resistance to this drug can threaten the effectiveness of important human therapies for salmonellosis among other conditions. CIPARS data supports the hypothesis that the use of ceftiofur in broiler chicken hatcheries was selecting for the presence of ceftiofur-resistant *S. Heidelberg* strains in chicken meat and subsequently in human cases of *S. Heidelberg*. We have observed that resistance in commensal chicken *E. coli* follows the same long-term fluctuations as for *S. Heidelberg*. This supports the hypothesis that this resistance was driven by a common exposure to ceftiofur use, rather than solely the natural spread of a ceftiofur-resistant *S. Heidelberg* resistant clone.

Resistance data from Québec and Ontario tend to be very similar across time. In the absence of drug consumption data in broiler chickens in Canada, we cannot verify if the withdrawal in Québec subsequently led Ontario broiler chicken hatcheries to change their use of ceftiofur. However, a proportion of Ontario commercial broiler chickens may be raised from hatching eggs produced in Québec and some retail chicken meat sold in Ontario could have been from chickens grown in Québec. Similarly, a proportion of the chicken produced or purchased in Québec could have originated in Ontario. These inter-provincial exchanges could possibly explain some of the similarities observed between the two provinces. Exposure to sources of contamination other than chicken may also play a role in the resistance observed in human *S. Heidelberg* isolates.

To our knowledge, Québec is the only province that has taken voluntary action to stop the extra-label use of ceftiofur in broiler hatcheries. In 2006, resistance in retail chicken *E. coli* was significantly higher in Ontario than in Québec and Saskatchewan. Limited abattoir and retail data from British Columbia also indicates the presence of ceftiofur resistance among chicken *E. coli*. ***PHAC supports and encourages continuing the efforts undertaken by Québec to limit the emergence and spread of cephalosporin-resistant S. Heidelberg from poultry to humans, via reductions in ceftiofur use. PHAC will continue to monitor and communicate the situation through data collected and analyzed by CIPARS, and will expand the CIPARS retail program into other provinces. PHAC needs to enter into discussions with provincial and industry representatives to promote the CIPARS findings as an impetus to responsible use of antimicrobials in veterinary medicine.***

Since this issue was identified, Health Canada’s Veterinary Drugs Directorate has revised the ceftiofur prescription label to emphasize to veterinarians and producers that this product should not be used

outside of the specification on the label ¹. Although ceftiofur is labeled for use in turkey, ceftiofur should also be used judiciously in this commodity.

¹ *In Canada, ceftiofur has been labelled for use in certain food-producing animals but has not been labelled for use in chickens (or eggs). Thus, such use of ceftiofur in chicken eggs is considered to be extra-label drug use. Given the concern with the development and dissemination of antimicrobial resistance with such mass-medication in an extra-label manner, the labels of ceftiofur products in Canada have been updated with warning statements to include that extra-label drug use of ceftiofur products is not recommended.*

APPENDIX

A prevalent serovar in North America

Salmonella Heidelberg is one of the top three serovars isolated from human *Salmonella* cases in Canada and among the top five serovars in the United States. International comparisons of human data from 2000 to 2004 suggest that *S. Heidelberg* is more common in North America than in other regions of the world (Table 1).

Table 1. International comparison of *Salmonella* serovars isolated from humans in 2004 (Canada and US) and in other continents (2000-2004).

Rank	Canada ¹	US ²	Africa ³	Asia ³	Central and South America and the Caribbean ³	Europe ³	Oceania ³
1	Typhimurium	Typhimurium	Typhimurium	Enteritidis	Enteritidis	Enteritidis	Typhimurium
2	Enteritidis	Enteritidis	Enteritidis	Weltevreden	Typhimurium	Typhimurium	Virchow
3	Heidelberg	Newport	Isangi	Anatum	Typhi	Hadar	Enteritidis
4	Thompson	Javiana	Livingstone	Stanley	Montevideo	Virchow	Saintpaul
5	Hadar	Heidelberg	Typhi	Typhimurium	Paratyphi B	Infantis	Birkenhead
6	Typhi	Montevideo	Corvallis	Rissen	Agona	Newport	Chester

¹ Government of Canada. Canadian Integrated Program for Antimicrobial Resistance Surveillance (CIPARS): 2004 Annual report. Public Health Agency of Canada, 2005.

² CDC. *Salmonella* Surveillance: Annual Summary, 2004. Atlanta, Georgia: US Department of Health and Human Services, CDC, 2005.

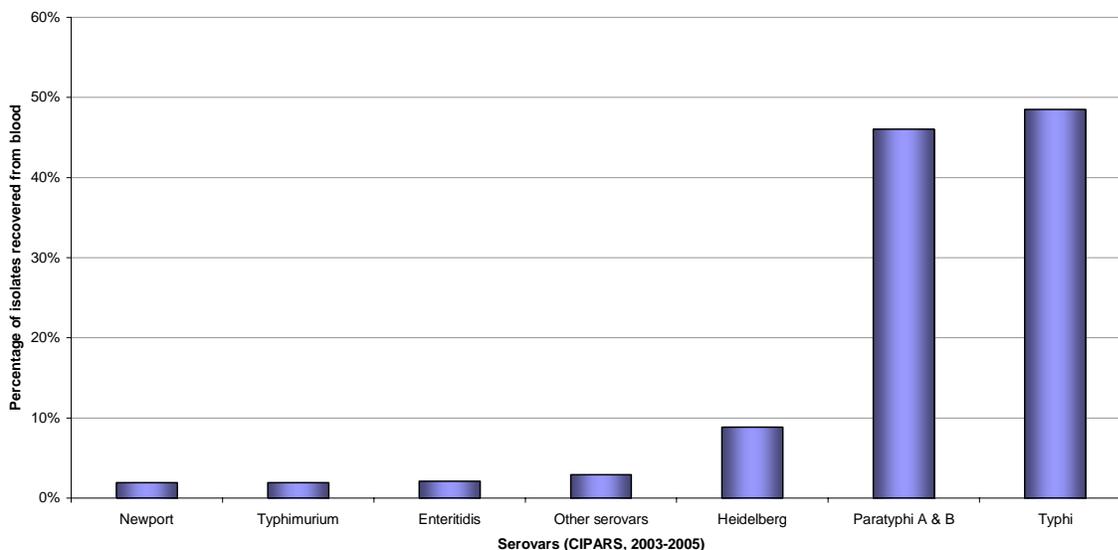
³ World Health Organization. WHO Global Salm-Surv. Progress Report (2000-2005). Department of Food Safety, Zoonoses and Foodborne Disease, WHO, 2006.

An invasive serovar

Salmonella Heidelberg appears to be more invasive¹ in humans than other non-typhoidal serovars. Overall, approximately 9% of human *S. Heidelberg* isolates collected since 2003 have been recovered from blood samples (Figure 2).

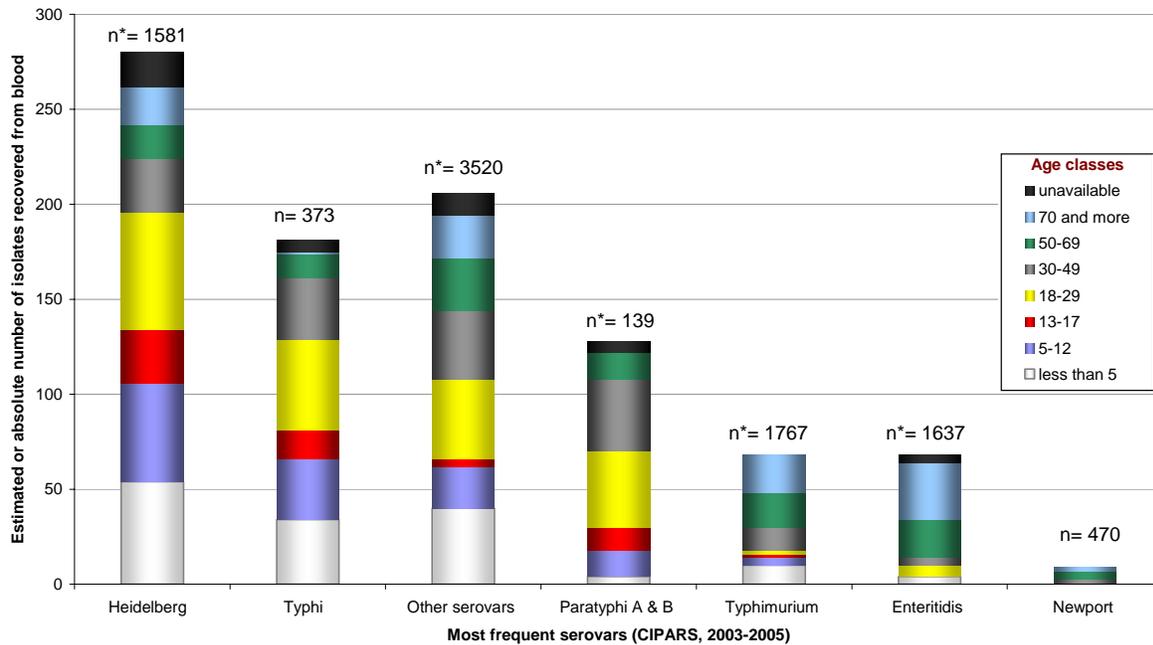
CIPARS receives *Salmonella* isolates (except for *S. Newport* and *S. Typhi*) during the first half of each month from the more populated provinces (British Columbia, Alberta, Ontario, and Québec) and all isolates from the remaining provinces. Assuming the beginning of the month is representative of the second half in the larger provinces, the total number of invasive *S. Heidelberg* cases between 2003 to 2005 was estimated at roughly 280 cases, with approximate 100 of them in children under the age of 13 (Figure 3). Of all serovars causing invasive salmonellosis in children under the age of 13, the largest numbers of cases were due to *S. Heidelberg* infection. Although *S. Paratyphi A*, *S. Paratyphi B*, and *S. Typhi* are more frequently associated with extra-intestinal/invasive infections (Figure 2), these serovars are less frequently observed in Canada.

Figure 2. Proportions of isolates recovered from human blood specimens for each of the most prevalent human non-typhoidal and typhoidal *Salmonella* serovars in Canada; CIPARS, 2003-2005.



¹ The proportion of strains isolated from "Blood" were used as a surrogate measure of invasiveness.

Figure 3. Number of human *Salmonella* isolates recovered from blood specimens across age classes and the main human serovars in Canada; CIPARS, 2003-2005.



* n=estimated total number of isolates received (except for *S. Typhi* and *S. Newport*). Values were corrected for differences in submission by the four largest provinces.

Resistance to ceftiofur and possible failure of ceftriaxone therapy in extra-intestinal *S. Heidelberg* human infections

Ceftiofur (a third-generation cephalosporin used only in animals) resistance among *S. Heidelberg* isolates is highly correlated with resistance to ampicillin, amoxicillin-clavulanic acid, and ceftiofur (A2C-AMP resistance pattern). It is also associated with reduced susceptibility (intermediate resistance) to ceftriaxone, another third generation cephalosporin used exclusively in humans. Ceftriaxone is identified as a drug of Very High Importance to Human Medicine according to Health Canada's Veterinary Drugs Directorate. It is a drug of choice for the treatment of extra-intestinal salmonellosis in children and pregnant women¹. Hence, patients with extra-intestinal infections caused by *S. Heidelberg* strains with intermediate resistance to ceftriaxone are at risk of ceftriaxone therapy failure.

¹ Katherine M. Shea, *Nontherapeutic Use of Antimicrobial Agents in Animal Agriculture: Implications for Pediatrics*. Committee on Environmental Health and Committee on Infectious Diseases. *Pediatrics* 2004; 114: 862-868.

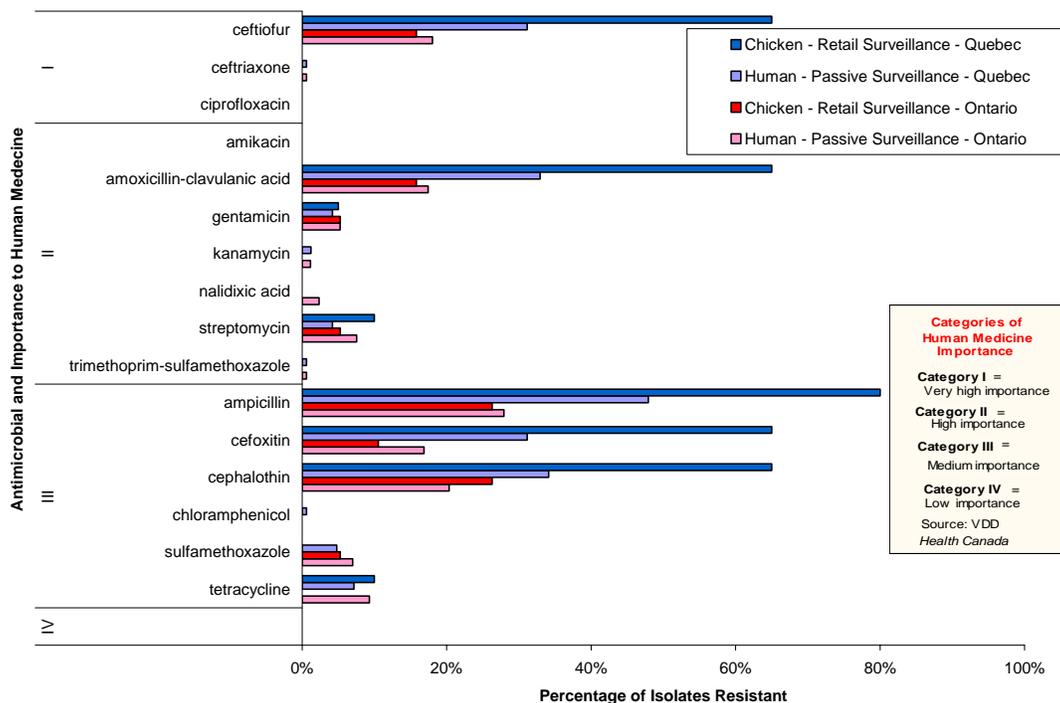
Link between ceftiofur resistance in human and chicken isolates

In order to prevent and control *Escherichia coli* infections, a certain number of broiler chicken hatcheries alternated the use of ceftiofur with gentamicin until 2003 when the gentamicin formulation became unavailable. Published information (Boulianne, 2005¹) indicated that 100% of the Québec hatcheries surveyed were using ceftiofur in 2004 (in hatching eggs and/or day old chicks). No published information is available from other provinces and therefore we have no information to suggest that Québec was unique in terms of ceftiofur utilization at the hatchery level. Anecdotal information also indicates that ceftiofur was also used in chickens outside of the province of Québec.

Our CIPARS 2003 annual report highlighted higher rates of ceftiofur resistance in retail chicken and human isolates of *S. Heidelberg* from Québec compared to Ontario (Figure 4). In Québec, resistance was also higher in retail chicken than among human isolates (Figure 4).

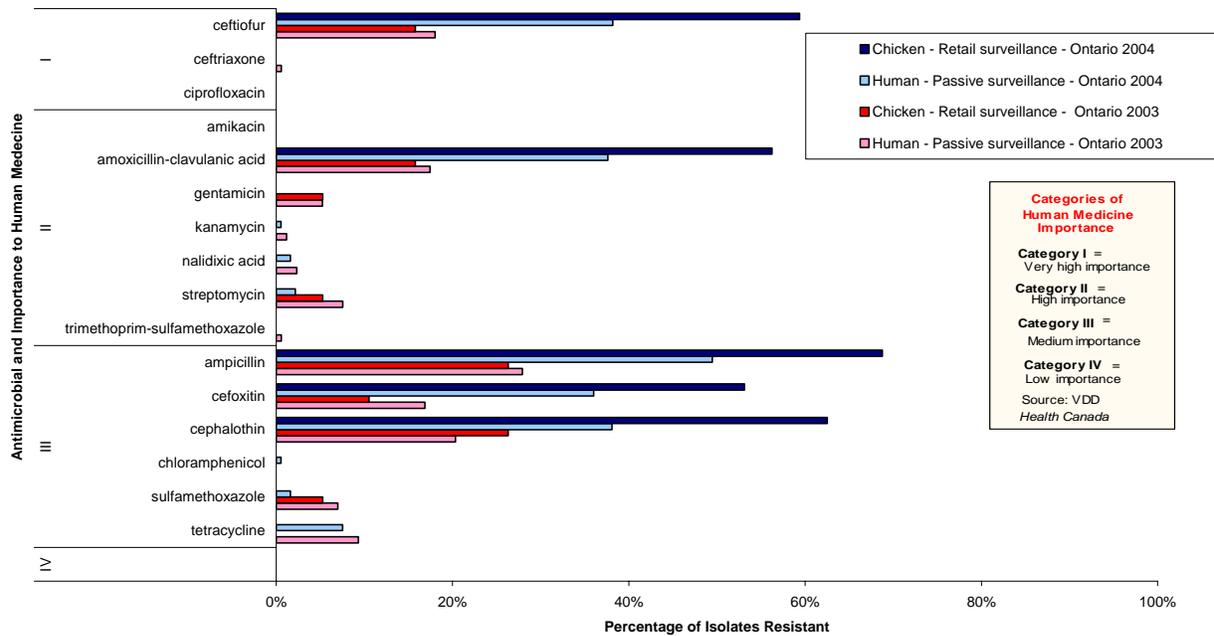
In Ontario in 2004 we saw increases in ceftiofur resistance levels in retail chicken and human *S. Heidelberg* isolates similar to those observed in Québec in 2003 and 2004 (Figure 5). Also in 2004, the level of ceftiofur resistance in Ontario retail chicken isolates was higher than that observed for human *S. Heidelberg* isolates (Figure 5). In Québec, ceftiofur resistance levels remained similar between 2003 and 2004.

Figure 4. Individual antimicrobial drug resistance in *Salmonella Heidelberg* isolated from retail chicken (n=20) and human cases (n=167) in Québec, and from retail chicken (n=19) and human cases (n=172) in Ontario in 2003.



¹ Boulianne, 2005. Results from a large poultry study in Québec examining antimicrobial use and antimicrobial resistance. Agriculture's Role in Managing Antimicrobial Resistance Conference. Toronto, October 2005.

Figure 5. Individual antimicrobial drug resistance in *Salmonella Heidelberg* isolated from human cases in Ontario in 2003 (n=172) and 2004 (n=186), and from retail chicken in Ontario in 2003 (n=19) and 2004 (n=32).



Action

To address public health concerns raised by the publication of the 2003 CIPARS Report, all broiler chicken hatcheries in Québec voluntarily stopped the use of ceftiofur in February 2005. PHAC provided detailed information regarding this issue to other provincial agriculture representatives and the Canadian poultry industry via email, meetings, and presentations.

Effect of the withdrawal, temporal changes, and current status

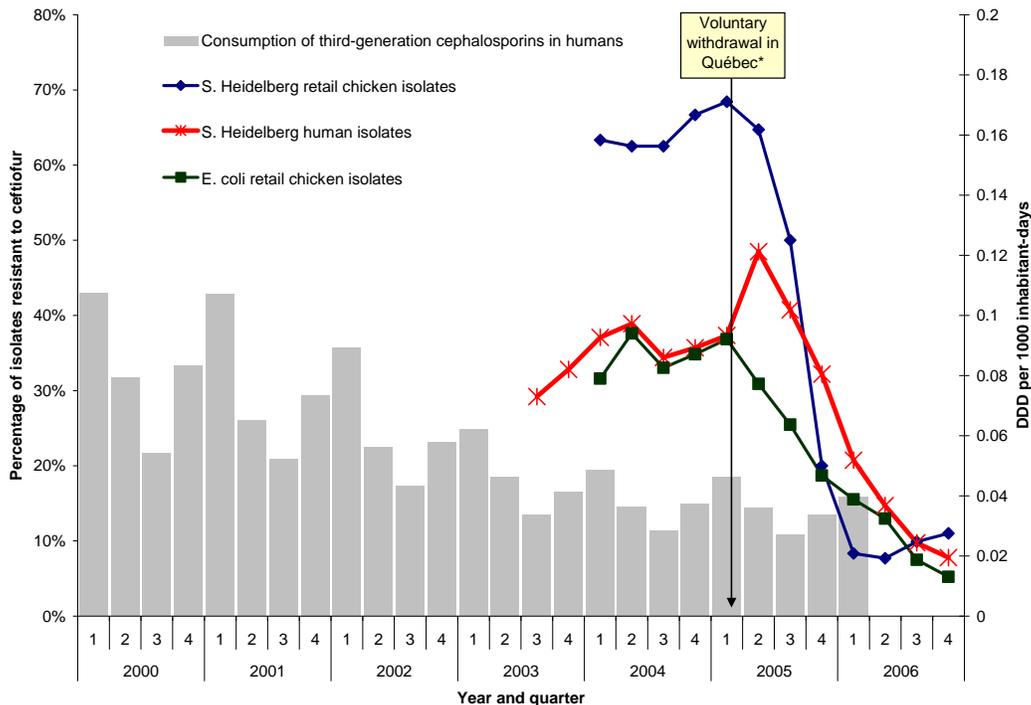
Figure 1 shows the marked decrease in prevalence of ceftiofur-resistant isolates in both chicken and human *S. Heidelberg* isolates and chicken *E. coli* following the voluntary withdrawal of the use of ceftiofur in hatching and day-old chicks in Québec. Ceftiofur resistance in chicken generic *E. coli* isolates is used in these figures as a surrogate indicator for ceftiofur use. To reduce variation due to the small number of *S. Heidelberg* and *E. coli* recovered in retail chicken on a quarterly basis and in order to use the same time scale for all ceftiofur resistance data, resistance results are presented as the moving average of the past three quarters.

Data available at time of web-posting indicated that in Québec, ceftiofur resistance in chicken *E. coli* and human *S. Heidelberg* is continuing to decline, while resistance in chicken *S. Heidelberg* seems to be stabilizing around 10%. The estimated use of 3rd-generation cephalosporins in humans in this province shows a steady decreasing trend since 2000 (with seasonal fluctuations of use), but this does not correlate well with the fluctuation of ceftiofur resistance observed in human *S. Heidelberg* isolates. However, the drug use data do not include hospital use of cephalosporins (data not available at the time of analysis).

Generally, similar trends have been seen in Ontario (Figure 7) since the voluntary withdrawal in Québec. However, resistance to ceftiofur among *S. Heidelberg* and *E. coli* from Ontario retail chicken started increasing again in 2006 to around 20% by the end of 2006. Ceftiofur resistance among human isolates decreased after 2004 until the third quarter of 2006 where it seems to stabilize around 10%. The estimated use of 3rd-generation cephalosporins in humans in Ontario has been higher from 2000 to 2006 than in Québec, but it too has steadily declined since 2000 and does not correlate well with resistance data in human isolates, although again, hospital drug use information is lacking.

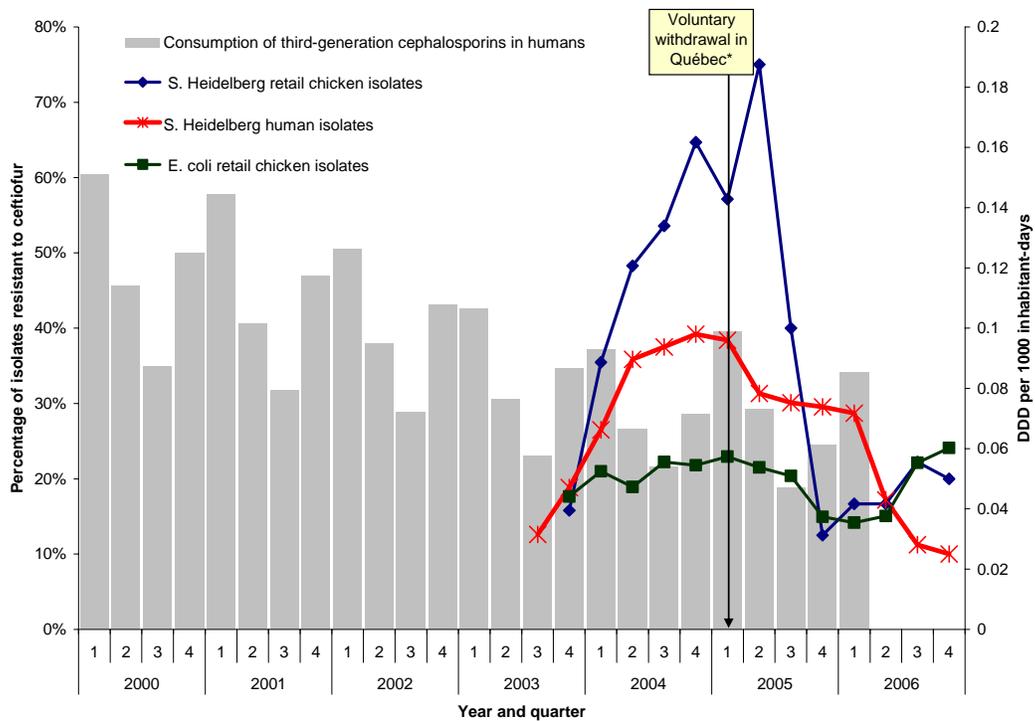
In 2006, resistance to ceftiofur was significantly higher for Ontario retail chicken *E. coli* isolates than for Québec or Saskatchewan isolates (Figure 8). Resistance to ceftiofur for chicken *Salmonella* isolates was not apparently different across any of the three provinces (Figure 9), but the number of *Salmonella* recovered in 2006 in each province was not sufficient to detect significant differences of resistance for such small differences.

Figure 6. Past three quarters moving average of the percentage of isolates resistant to ceftiofur for retail chicken *E. coli*, retail chicken and human clinical *S. Heidelberg* isolates, and quarterly human consumption of 3rd generation cephalosporins dispensed at retail pharmacies (IMS' Health) in Québec.



* Voluntary withdrawal of ceftiofur use by Québec hatcheries in February 2005. At the time of publishing, human consumption data was only analyzed up to the first quarter of 2006.

Figure 7. Past three quarters moving average of the percentage of isolates resistant to ceftiofur for retail chicken *E. coli*, retail chicken and human clinical *S. Heidelberg* isolates, and quarterly human consumption of 3rd generation cephalosporins dispensed at retail pharmacies (*IMS Health*) in Ontario.



* Voluntary withdrawal of ceftiofur use by Québec hatcheries in February 2005. At the time of publishing, human consumption data was only analyzed up to the first quarter of 2006.

Figure 8. Individual antimicrobial drug resistance in retail chicken *E. coli* isolates from Ontario, Québec, and Saskatchewan; *Retail Meat Surveillance*, 2006.

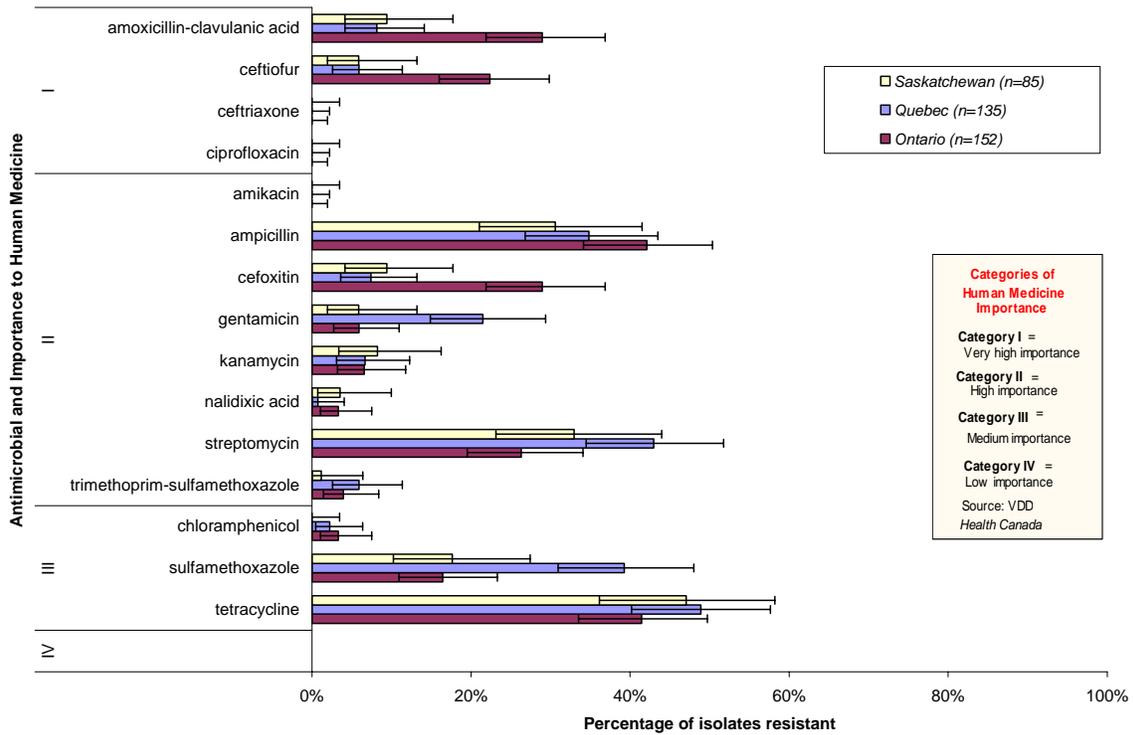
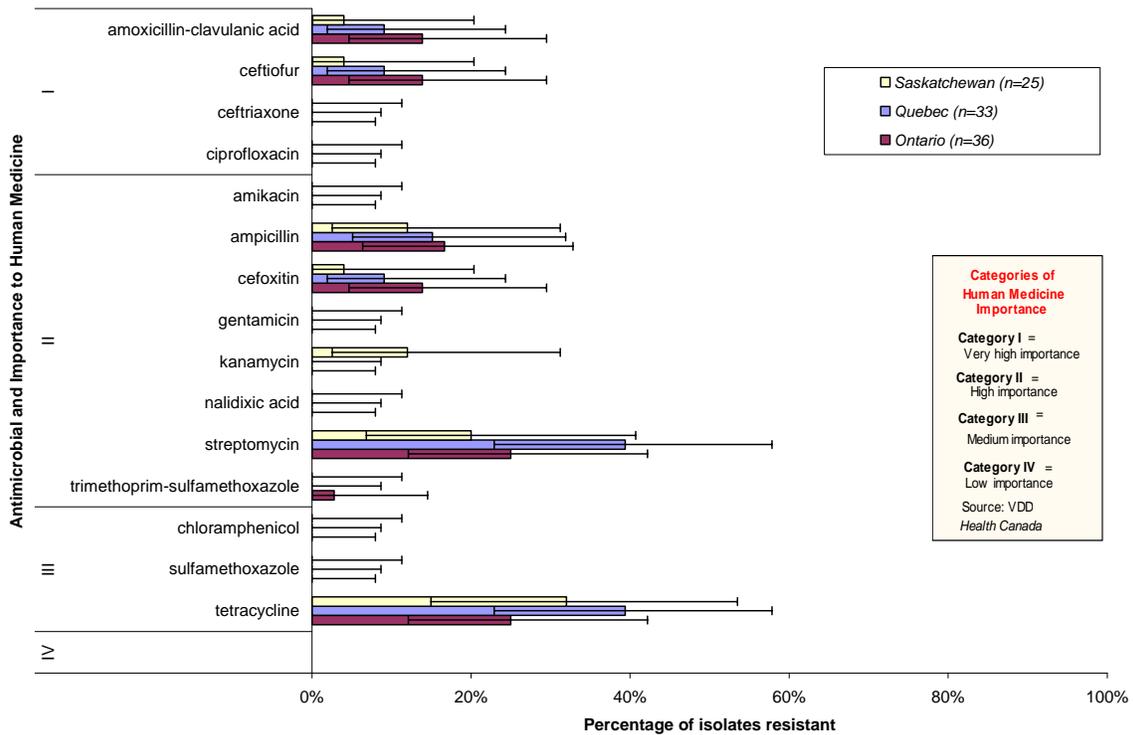


Figure 9. Individual antimicrobial drug resistance in retail chicken *Salmonella* isolates from Ontario, Québec, and Saskatchewan; *Retail Meat Surveillance*, 2006.



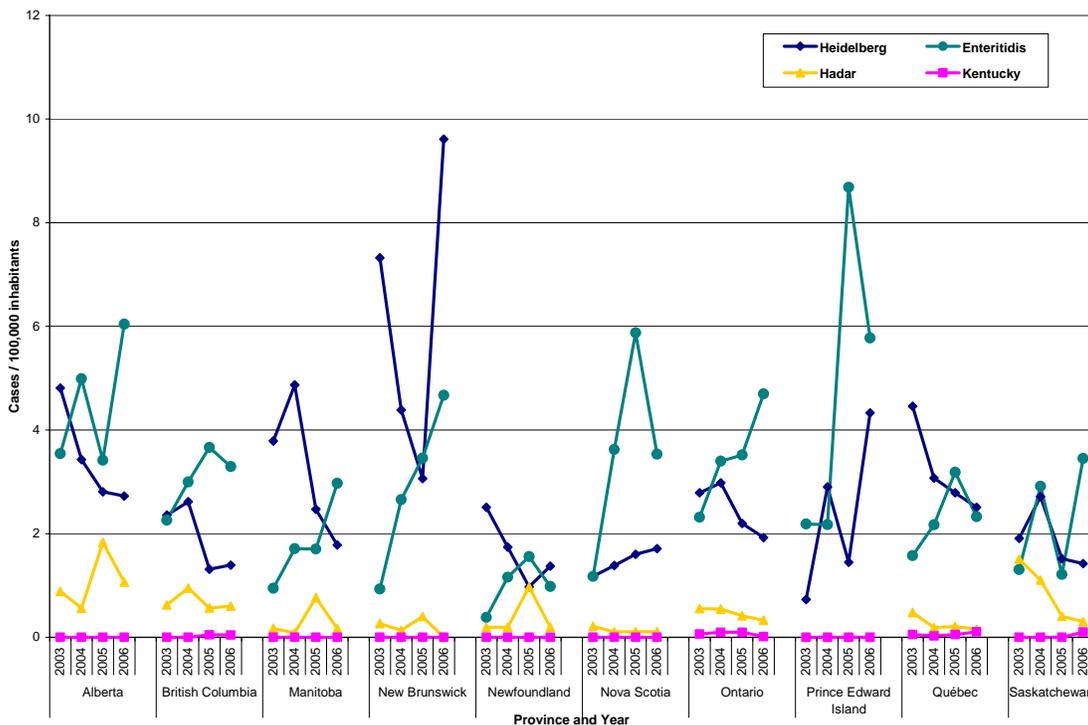
Changes in the incidence of *Salmonella* serovars and relative ranking in Canada

Since 2003, a decline in the incidence of human *S. Heidelberg* cases (based on extrapolated numbers of laboratory submissions to CIPARS) has been noted in most of the largest Canadian provinces (Figure 10). Concurrently CIPARS also observed a decline in the relative proportion of this serovar among abattoir and retail chicken *Salmonella* isolates from 2003-2006. CIPARS-Retail data in Ontario and Québec as well as CIPARS national abattoir data suggest that the niche occupied by *S. Heidelberg* may have been replaced by *S. Kentucky* and to a lesser extent, by *S. Enteritidis* from 2004 to 2006 (Figure 11).

Although *S. Kentucky* was relatively more frequent than *S. Enteritidis* among chicken samples, this was not reflected in human incidence rates where *S. Enteritidis* was more frequent than *S. Kentucky* (Figure 11). These variations may be explained by differences of the infectivity and virulence of the various serovars, by unidentified outbreaks and by the fact that chicken exposure is not the only risk factor for *S. Enteritidis* infections in humans¹.

Although there is an apparent correlation between the frequency of certain serovars in chicken and in humans, we believe these variations of the prevalence of the main chicken serovars are unlikely to be a result of the voluntary ceftiofur withdrawal since these temporal changes were started before February 2005.

Figure 10. Estimated incidence of reported human cases per 1,000 inhabitants by province for the most frequent serovars identified in chicken; CIPARS, 2003-2006.



¹ Consumption of poultry (particularly chicken, chicken strips and chicken nuggets) and shell eggs are documented risk factors for *S. Heidelberg* infection¹. Consumption of shell eggs, beansprouts and almonds are documented risk factors for *S. Enteritidis* infection¹.

Figure 11. Proportions of the three most prevalent *Salmonella* serovars and of *S. Enteritidis* among **chicken** isolates from abattoir and retail meat samples; CIPARS, 2003-2005.

