

# **Understanding the transfer of resistance from animals to man – an example: campylobacter in poultry**

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# Overview

- **What does the public health data say re *Campylobacter* and resistance transfer?**
- **What does laboratory science say?**
- **What do we need to consider moving forward?**

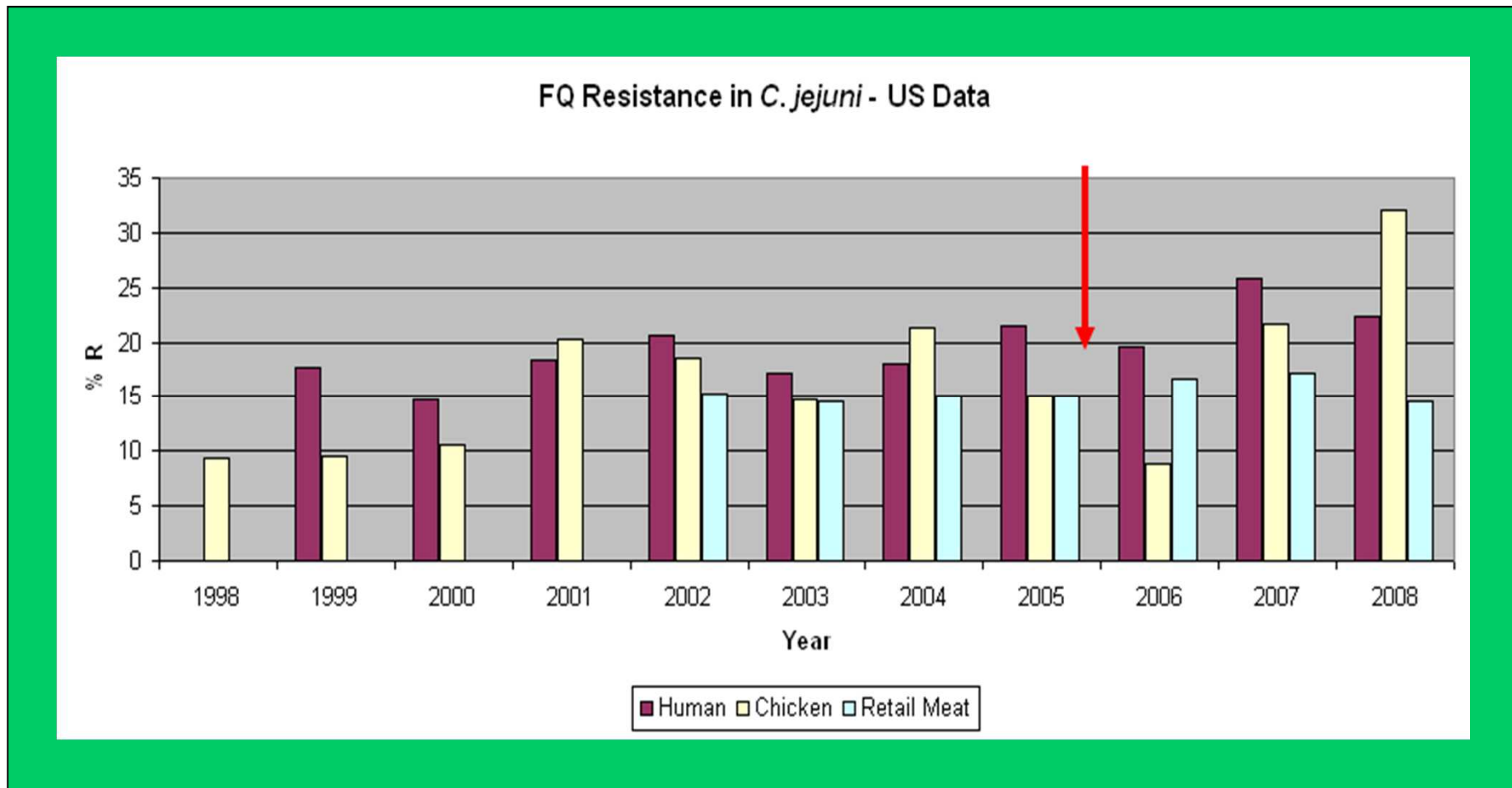


# Background

- ***Campylobacter jejuni***
  - Commensal intestinal bacteria in broilers & turkeys
  - Causes overt, self-limiting GI tract disease in man
  - Drugs of choice, although rarely necessary
    - Macrolides (erythromycin/azithromycin generally first choice)
    - Fluoroquinolones (ciprofloxacin, second line)
    - Note there is a distinction between approved drug indications & treatment realities (Sanford Guide); also differs from country to country
  
- **Raw poultry meat considered an important source of human campylobacteriosis in industrialised countries**
  - Directly or via cross-contamination
  - Travel an important risk factor
  
- **Potential transfer of antimicrobial resistant avian campylobacters into food chain perceived as public health hazard**



# One Health – Laboratory Science or Public Health?



# Many Studies .....

## Different Public Health Conclusions

### Public Health - *Campylobacter* Revisited

#### Short-Term and Medium-Term Clinical Outcomes of Quinolone-Resistant *Campylobacter* Infection

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CID (2009) 48, 1500-1506

**Methods.** A case-comparison study of patients infected with ciprofloxacin-resistant or ciprofloxacin-susceptible *Campylobacter* species was conducted in Wales during the period 2003–2004.

**Results.** There was no difference between 145 persons with ciprofloxacin-resistant infection and 411 with ciprofloxacin-susceptible infection with regard to the severity or duration of acute illness. Mean duration of diarrhea was similar in patients with ciprofloxacin-resistant versus ciprofloxacin-susceptible infection (8.2 vs. 8.6 days;  $P = .57$ ) and did not alter significantly after adjustment for potential covariates, including age, underlying disease, foreign travel, use of antidiarrheal medication, and use of antimicrobials in a multiple linear regression model. There was no difference between case patients and comparison patients in the frequency of reported symptoms or in general practitioner consultation rates at either the 3-month or the 6-month follow-up interview.

**Conclusions.** In this study, there was no evidence of more-severe or prolonged illness in participants with quinolone-resistant *Campylobacter* infection, nor was there evidence of any adverse medium-term consequences. This suggests that the clinical significance of quinolone resistance in *Campylobacter* infection may have been overestimated.

Consistent with earlier review of Wassenaar *et al* (2007), IJAA 30, 195



# What Does Lab Science Say?



# Antibiotic Resistance Transfer

## – *in vitro* & *in vivo*?

- **Clearly occurs *in vitro* in laboratory setting among commensals and between commensals & pathogens**
  - Agerso & Sandvang (2005)
  - Jiang *et al* (2006)
  
- **Direct evidence is limited and indirect evidence does not always support transfer across animal species**
  - *“We determined the prevalence of plasmid-mediated quinolone resistance mechanisms among non-Typhi Salmonella spp. isolated from humans, food animals, and retail meat in the US, 2007. Unlike the human strains, no animal or retail meat isolates harboured a plasmid-mediated mechanism”*  
.....Sjölund-Karlsson *et al* (2010)



# Antibiotic Resistance Transfer – *Campylobacter* - different to selection of resistant clones

- *Campylobacter* capable of conjugation & natural transformation, lab studies suggest both play significant roles in resistance transfer
- Natural transformation considered a main mechanism for mediating transfer of genetic materials encoding resistance determinants in *C. jejuni*, but direct evidence that it happens is still lacking
  - Jeon *et al* (2008)
- Jeon *et al* (2008) showed natural transformation is key in mediating DNA transfer in *Campylobacter* co-cultures but natural transformation does not play a major role in the emergence of FQ-R mutants



# Experimental Infection Models - Not Real Life

- ***“Despite the wide acceptance and theoretical considerations, direct in vivo experimental evidence that horizontal transfer of DNA generates genetic diversity among bacteria in their natural habitat is sparse. The event requires the simultaneous presence of multiple strains at a distinct niche and active mechanisms that allow DNA transfer and integration into the chromosome”***
  - ***de Boer et al (2002)***
  
- **In experimental infection models conditions can be optimised such that data indicates unequivocally inter-strain genetic exchange as well as intra-genomic alterations occurring *in vivo* during *C. jejuni* infection**
  - **Data that this happens naturally for antimicrobial resistance markers is not forthcoming**



# Is the cat not already out of the bag?

## Functional Characterization of the

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resistance genes harbored by major pathogens. The immense diversity of resistance genes in the human microbiome could contribute to future emergence of antibiotic resistance in human pathogens.

Most of the resistance genes identified with culture independent metagenomic sampling from the same samples were novel when compared to all known genes in public databases. **This suggests that barriers exist to lateral gene transfer between these bacteria and readily cultured human pathogens**

Sommer *et al*, 2010

*Science (2009) 325:1128*



# Frequency of Resistance Transfer Within the Intestine

- **Issues to consider**
  - Ability of recipient & resistant strains to colonize the gut
  - Relative fitness of susceptible and resistant strains
  - Mutation rates, in the intestine not in the laboratory!
  - Efficiencies of horizontal transfer of resistance genes
  - *In vitro* does not equal *in vivo* and the gnotobiotic rodent model is not real life
    - Schjørring (2008)



# Data Sources for Resistance Development

## - Surveillance Data is Important

- We therefore must do it correctly.
- Methodology & analysis must be harmonized such that data can be used as a necessary input into risk analysis
- Intervention cannot simply be initiated in response to current surveillance data because of lack of robustness
- Robust data sets would better allow for appropriate risk management as a response to the public health issues arising from changes in antibiotic resistance in foodborne pathogens & commensal organisms
  - Silley *et al* (2011)
  - Giske *et al* (2010)



# Public Health & Lab Science Must Come Together

- Public health needs are to reduce *Campylobacter* transmission from poultry & poultry products to humans, appropriate intervention strategies have to be established & applied along the food chain
- Development of efficient intervention strategies still hindered by lack of knowledge on epidemiology of *Campylobacter* in the poultry house
  - Antimicrobial bans do not appear as effective strategies



# Thanks

- to all those colleagues who have over the years sharpened my thinking



**for their support to attend  
and present at this meeting**

