Campylobacter: do not just blame the chickens

EW: When is a food-borne infection not a food-borne infection?

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Facts (1)

- **Campylobacteriosis is the most common cause of acute gastroenteritis in the EU and in industrialized countries**

  - most common recognized bacterial zoonosis

- **80% of *Campylobacter* infections are believed to be food-borne**

Mead PS et al, Emerg Infect Dis 1999

Skirrow MB. Int J Food Microbiol 1991

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Facts (2)

- **Campylobacteriosis is mainly caused by *C. jejuni* and to a lesser extent by *C. coli***

- **Other species can also be found in humans**

  - *C. fetus*, *C. lari*, *C. upsaliensis*

  **- non-*Campylobacters*: *Arcobacter*, enterohepatic *Helicobacter* (*H. pullorum, H. cinaedi*)

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Distribution of *Campylobacter* sp received at the french NRC (4,807 strains from 1986 to 2000)

	Stools	Blood	Other	Total
C. jejuni	3 071	156	44	3 271
C. coli	808	46	19	873
C. fetus	89	289	72	450
C. upsaliensis	33	4	3	40
C. lari	20	7	3	30
C. sputorum	3	3	2	8
C. hyointestinalis	4	-	-	4
A. cryaerophila	1	-	-	1
H. cinaedi	2	3	1	6
Campylobacter sp.	78	26	13	115
C. jejuni ssp doylii	5	-	2	7
Helicobacter pylori	-	-	2	2
Total	4 114	534	161	4 807

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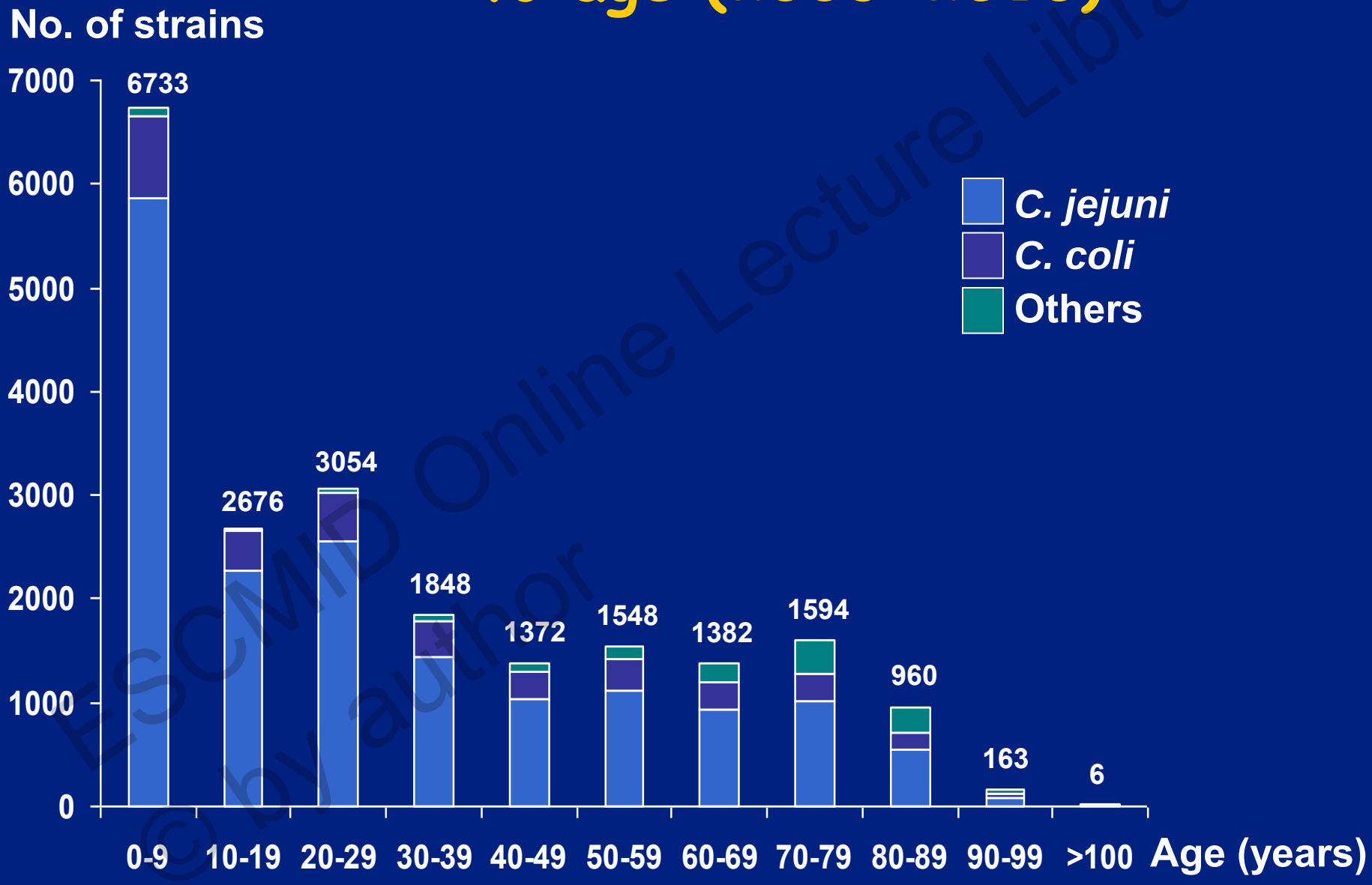
Distribution according to age (2003-2010)



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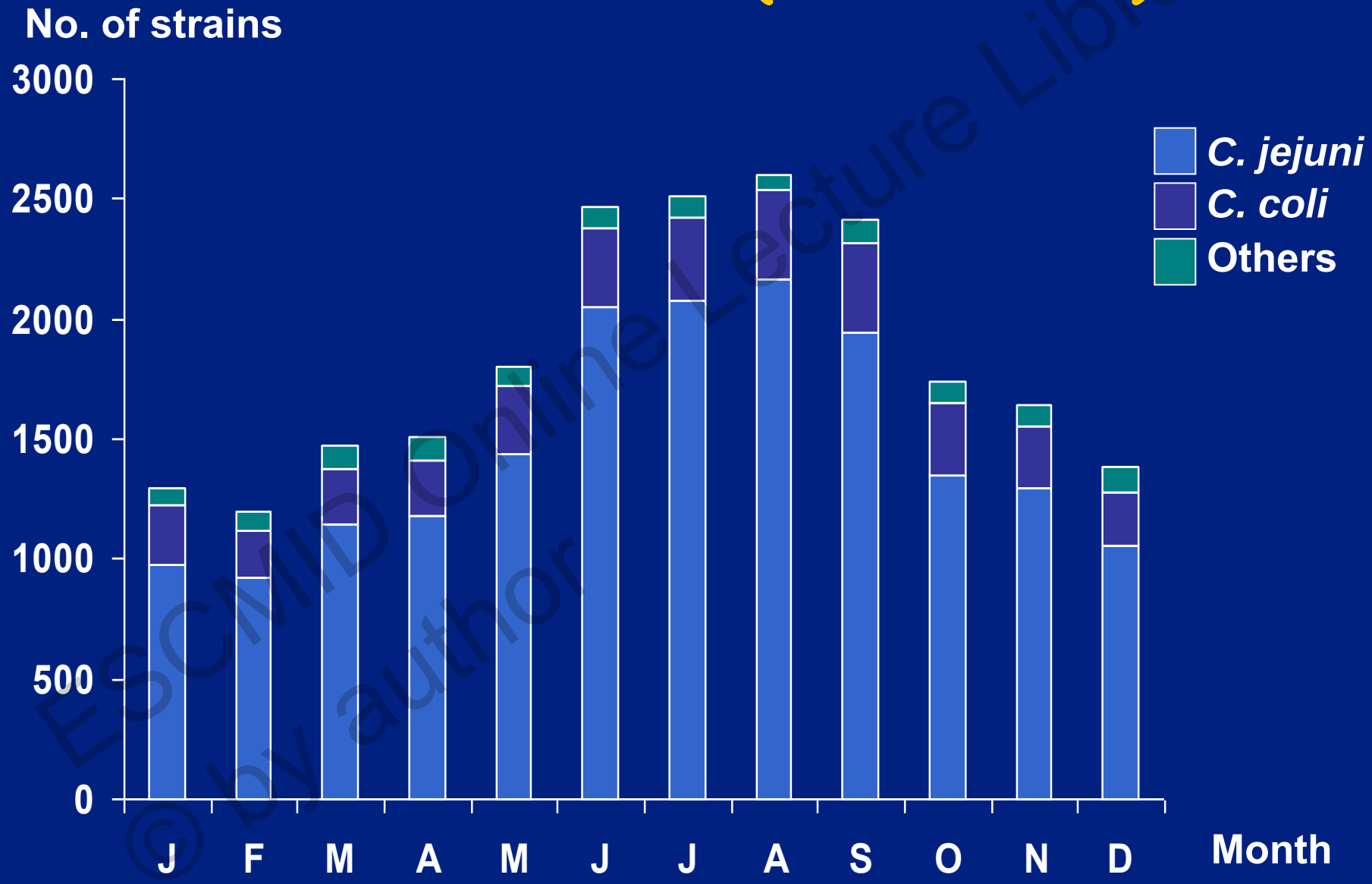
Monthly distribution of Campylobacter strains received (2003-2010)



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Campylobacter reservoirs

Food production animals are considered to be the primary source of *Campylobacter sp* infection in humans

- poultry is estimated to account for 50%–70% of human *Campylobacter* infection

- consumption of beef, pork products…

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Chickens or not chickens?

Yes indeed ...

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Flock colonization

- **High metabolic temperatures (42°C) found in poultry species**

  - prominent reservoir for thermotolerant *Campylobacter*

- **Risk factors for colonization and transmission**

  - flock size, age of birds

  - environmental water supplies, insects

- **Prevention**

  - no vaccine, phages, chemical and physical decontamination (reduction 1-2 log units)

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Flock colonization

- **Broilers, turkeys, ducks and other types of poultry can become colonized with *Campylobacter***

  - one introduced *Campylobacter* spreads rapidly
  - vertical and horizontal transmission

- **10^8 *Campylobacter*/g of cecal contents**

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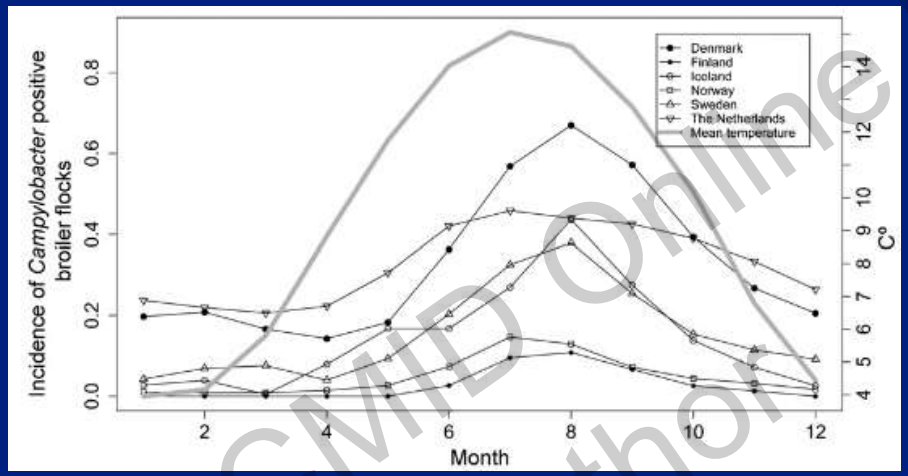
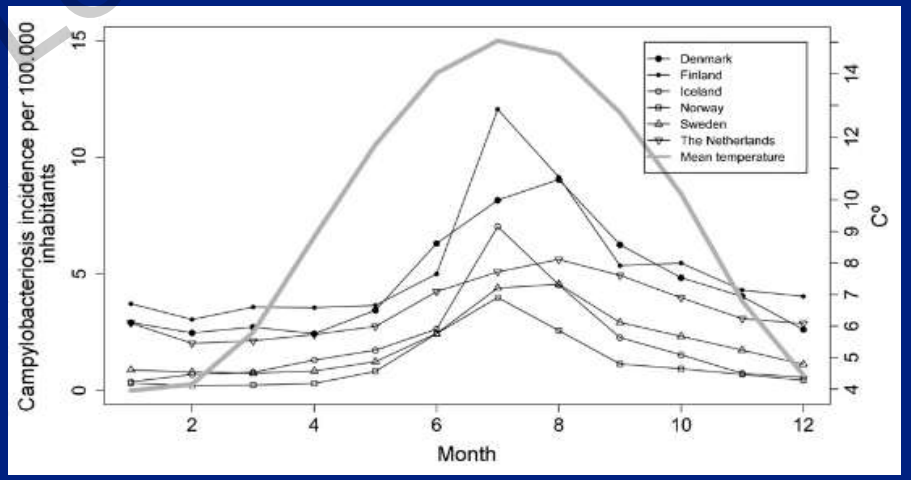
Trends in Campylobacter incidence

In broilers and humans in 6 European countries 1997-2007

- concordant seasonality for all the countries



Monthly incidence of broiler flocks



Monthly incidence in human

Jore S et al, Rev Vet Med 2010

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Poultry processing

- Campylobacters are predominantly found on the skin

- Inevitable contamination from cecal and gut contents

  - during evisceration process

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Horrocks SM S et al, Anaerobe 2009

The dioxin crisis-Belgium 1999

June 1999, dioxin-contaminated feed components

- **Belgian authorities ordered the withdrawal from sale of Belgian poultry and eggs**

⇨ **significant decline (40%) in the number of *Campylobacter* infections**

⇨ **the use of a disaster as an epidemiologic tool offers a unique opportunity to prove the importance of chicken in human campylobacteriosis**

Vellinga A and Van Loock F, Emerg Infect Dis 2002

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Risk factors for *C. jejuni* infection

- Handling chicken
- Eating not fully cooked chicken
- Eating commercially prepared chicken

⇨ case-control studies and outbreak investigations

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Chickens or not chickens?

not only….

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Risk factors for Campylobacteriosis

A French national case-control study from Sept. 2002 to June 2006: identification of independent risk factors

- consumption of undercooked beef
- meal at a restaurant
- poor utensil hygiene in the kitchen

Gallay A et al, J Infect Dis 2014

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A case-control study in FoodNet Sites (USA)

Risk factor analysis (univariate analysis)

- international travel
- animal and farm exposure: living on farm, visiting a farm, having contact with farm animals, puppies and adult dogs
- having a household member with diarrhoea

Friedman CR et al, CID 2004

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A case-control study in FoodNet Sites (USA)

Risk factor analysis (multivariate analysis)

- drinking raw milk
- eating raw sea food
- non-food exposure: untreated water, having a puppy, contact with animal stools

⇨most of these factors remained similar regardless of age

Friedman CR et al, CID 2004

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Prevalence in animals

- **The intestines of warm blooded animals (mammals and birds) are the amplification vessel for *Campylobacter sp***
- ***Campylobacter sp* can be isolated from the feces of**
  - healthy food-producing animals (eg, pigs, cattle, sheep)
  - wild animals and pets (birds, dogs, cats)
- **Presence in these animals is usually asymptomatic**

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Prevalence in small ruminants at slaughter

- **Contamination rates per carcass category (80% positive)**
  - 78.4% for kids, 94.5% for lambs, 63.5% for goats and 72.2% for sheep

- **30% of intestinal content samples were positive**

- **Multiplex-PCR and RFLP analysis showed that**
  - *C. coli* was the most prevalent species (76.2%)
  - *C. jejuni* (21.4%)
  - both species (2.4%)

Lazou T et al Int J Food Microbiol 2014

FoCMB Online Lecture Library
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Prevalence in retail lamb and kid carcasses

- **Campylobacters were recovered from**

  - 32% meat surfaces and 44% liver surfaces

- **Multiplex-PCR and RFLP analysis showed that**
  - *C. coli* was the most prevalent species (59.2%)
  - *C. jejuni* (40.8%)
  - high heterogeneity among the strains

Lazou T et al Foodborne Pathog Dis 2014

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Prevalence in animals

- ⇨ **Putative vehicules for consumer consumption of thermotolerant *Campylobacter***
- ⇨ **What is the risk imposed by such products in the epidemiology of human campylobacteriosis cases?**

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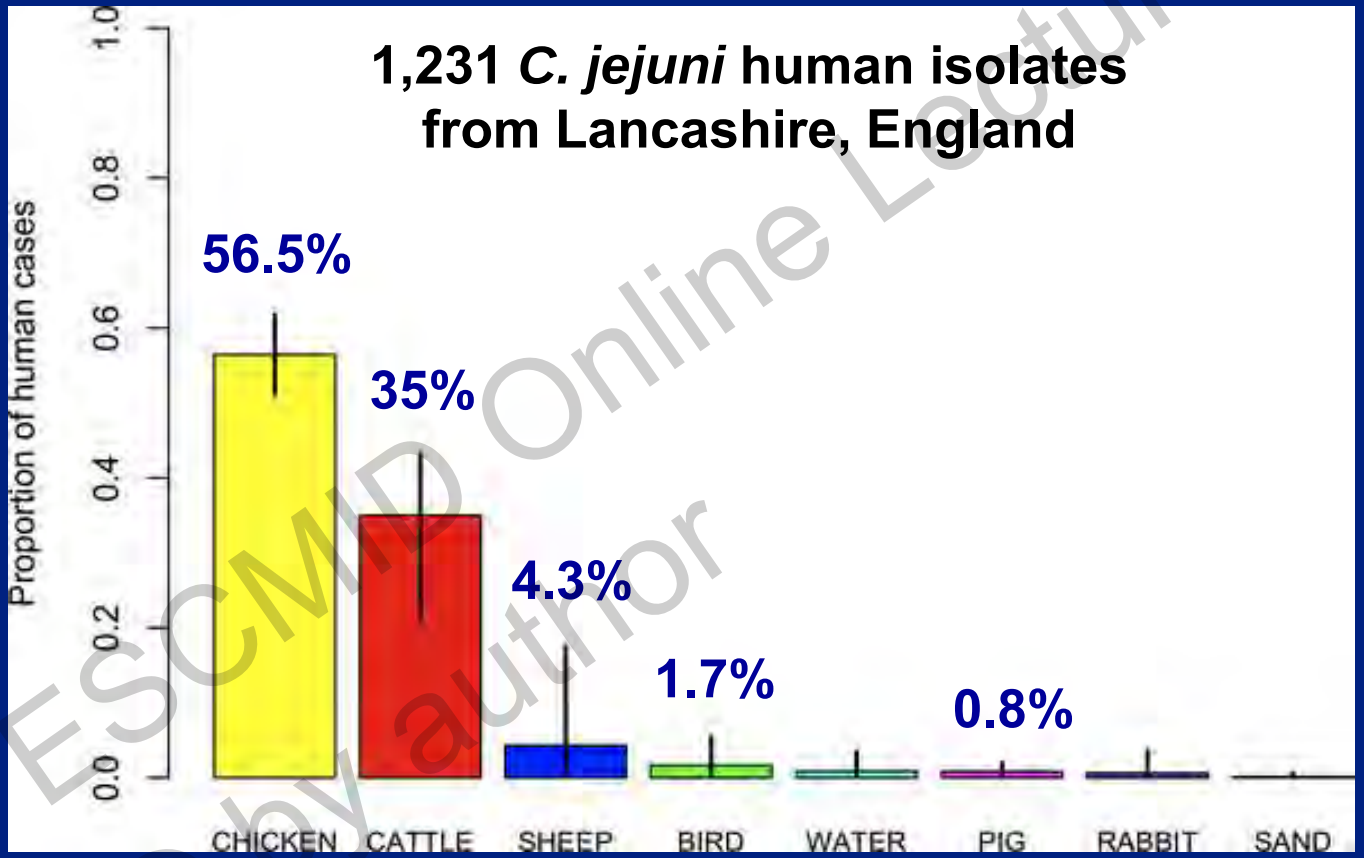
Lazou T et al Int J Food Microbiol 2014

Lazou T et al Foodborne Pathog Dis 2014

Tracing the source of Campylobacteriosis

MLST has become the dominant method used for reservoir and pathway attribution.



Wilson DJ, PLoS Genet 2008

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Tracing the source of Campylobacteriosis a Dutch study

Aims

- to better identify the original reservoirs compared to case-control studies
- to attribute Campylobacteriosis to 4 putative animal reservoirs (chicken, cattle, sheep, pig) and the environment

⇨ **MLST-based study:**

- 919 human strains (696 *C. jejuni* and 41 *C. coli*)

- 232 animal strains and 106 environmental strains

Mughini Gras L et al, PLoS One 2012

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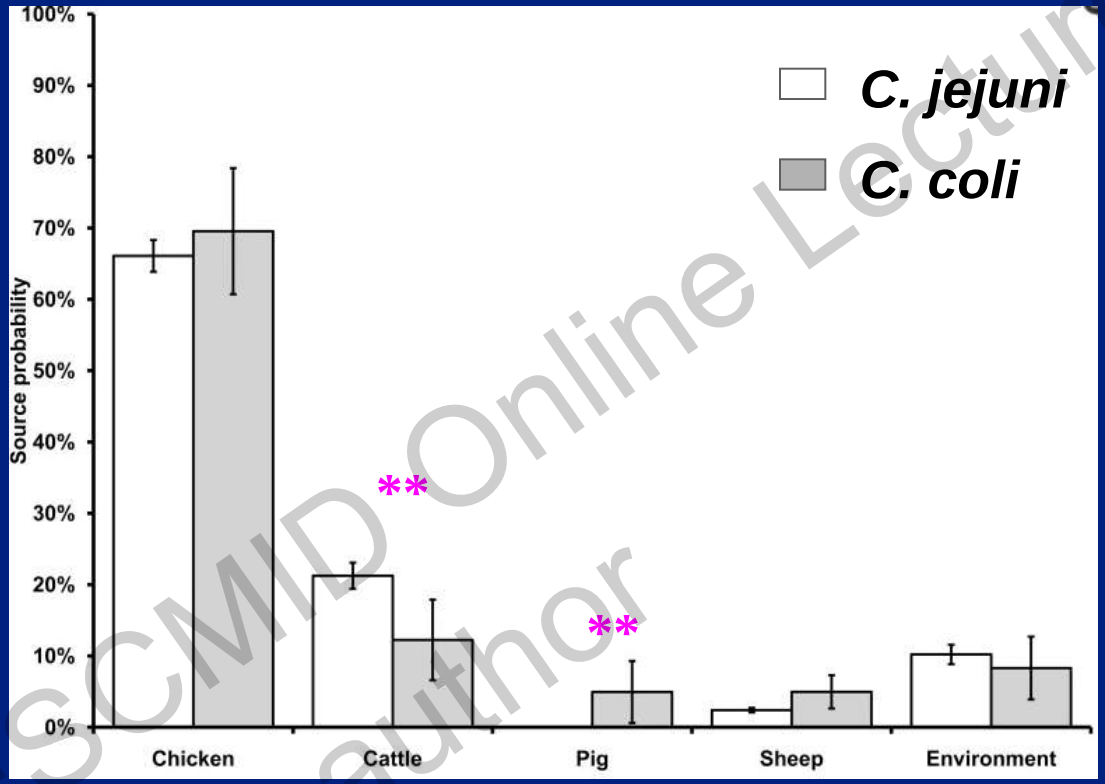
Tracing the source of Campylobacteriosis a Dutch study

Attribution of human infection



66.2% 20.7% 0.3% 2.5% 10.1%

Mughini Gras L et al, PLoS One 2012

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Tracing the source of Campylobacteriosis

Study from Switzerland (2001-2012)

- 730 human strains
- 610 chicken, 159 dog, 360 pig and 23 cattle strains

⇨ **MLST and *fla*B typing**

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Kittl S et al, PLoS One 2013

Tracing the source of Campylobacteriosis

Structure source attribution

C. jejuni *C. coli*

cattle chickens dogs chickens pigs

overall
- chickens (70.9%)
- cattle (19.3%)
- dogs (8.6%)
- pigs 1.2%

Kittl S, PLoS One 2013

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Campylobacteriosis is not only a food-borne disease

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Sources of *Campylobacter spp* contamination of river water

- **Study conducted in Brittany which is the region of large-scale poultry and pig production in France**
  - **local stream water is the source of 75% of the water destined for human consumption**
- **50% of river water samples were positive**
  - **observed during all four seasons**
  - ***C. jejuni* 74.1%, *C. coli* 17.8%, *C. lari* 8.1%**

Denis M et al, Path Biol 2011

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Role of water

- **Contamination of surface water by manure from animals**
  - risk factor if consumption of untreated water
  - indirect contact: swimming in contaminated water or consumption of raw products irrigated with surface water
- **Faecal contamination of a groundwater system**
  - failure in the chlorination system
  - waterborne community outbreak (France, August 2000)
  - multiple pathogens including *C. coli*

Gallay A et al, CMI 2006

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Role of wild birds

- **Wild birds can be positive for *Campylobacter sp***

  - *C. jejuni*, *C. lari*

- **Wild griffon vultures in eastern Spain:**

  - culture-based methods

  - *Campylobacter sp* and *Salmonella sp* detection

  ⇨ 52.6% *Salmonella* sp versus only 1.0% for *Campylobacter sp*

Marin C et al, PLos One 2014

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Role of milk

- **Unpasteurized milk can be contaminated by *C. jejuni***

  - milking **Humphrey TJ et al, J Applied Bacteriol 1988**

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Role of milk

- **Unpasteurized milk can be contaminated by *C. jejuni***

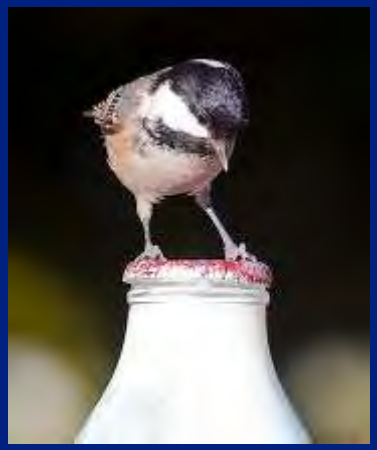
  - milking **Humphrey TJ et al, J Applied Bacteriol 1988**

- ***Campylobacter* infection related to bird-pecked milk**

  - magpies, jackdaws

  - sporadic cases of *C. jejuni* enteritis

  - small outbreaks



Riordan T et al, Epidemiol Infect 1993

Palmer SR et al, Lancet 1995

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C. fetus infection in humans: exposure and disease

- **Main species isolated from blood samples**
- **Predisposing factors**
  - **pregnancy, cancer, old age**
- **Reservoir of *C. fetus***
  - **veterinary pathogen causing fertility problem in cattle and sheep**
  - **no carriage in pigs**
  - **poultry do not appear to be a source of *C. fetus* (hostile T°)**

Wagenaar JA et al, CID 2014

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C. fetus in the food chain and source attribution

- **Food products from cattle and sheep are the most likely routes of transmission**

  - liver and meat products if consumed not fully cooked or even raw
  - cross-contamination in the kitchen with other foodstuffs

- **Other sources**

  - cheese has been implicated in an outbreak
  - vegetables in Malaysia
  - outbreaks in neonatal care-units suggestive of human-to human transmission

⇨ **no case-control studies and food microbiology methods not adapted to *C. fetus* isolation**

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Campylobacter: do not just blame the chickens

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Attribution of human Campylobacteriosis

- **Human exposure to animals is possible via multiple pathways including**

  - food (in particular poultry meat)

  - environment

  - direct animal contact

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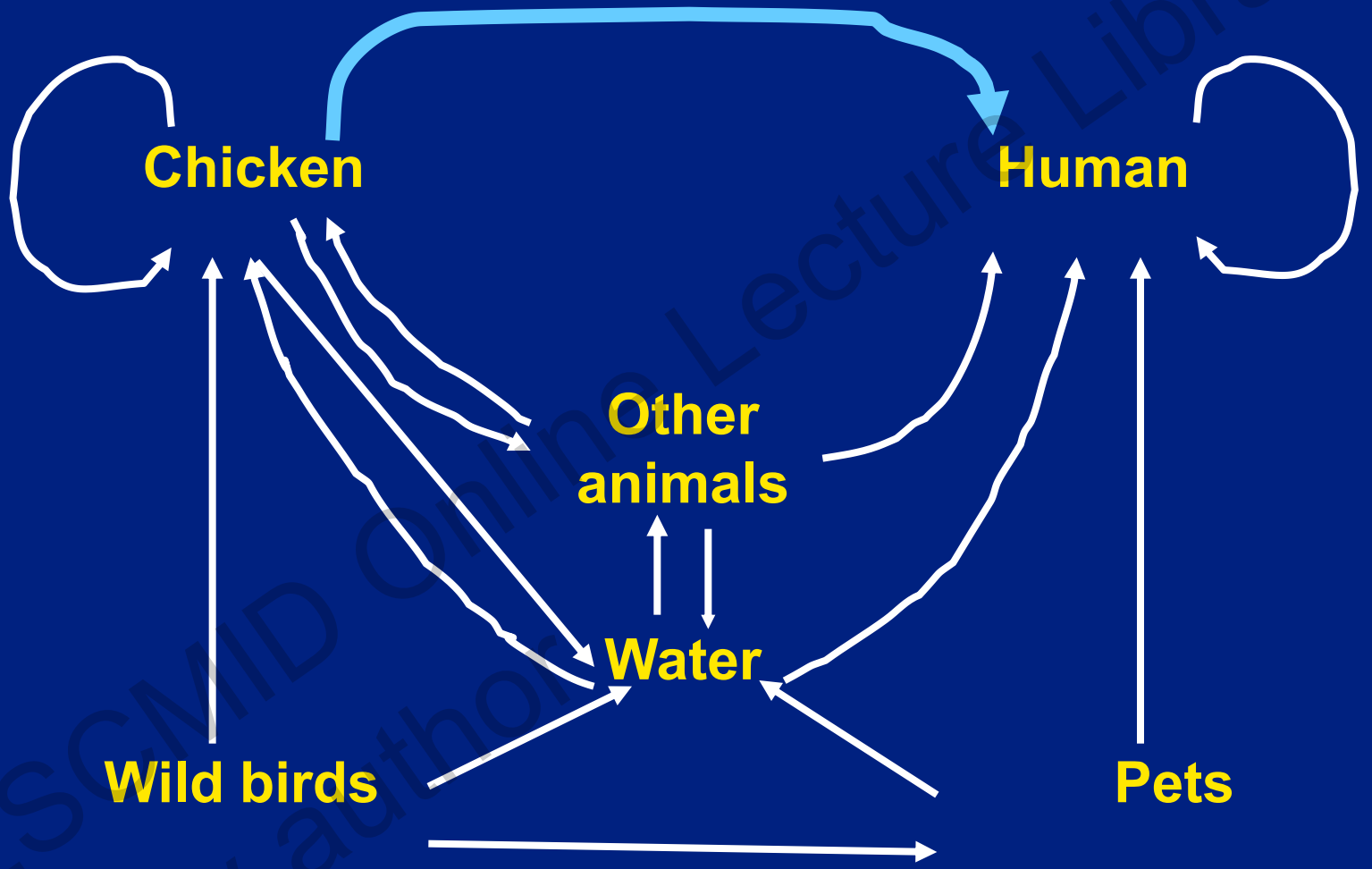
Complexes transmission cycle



⇨ difficult to present a precise estimate of the contribution of each reservoir and pathway to human disease

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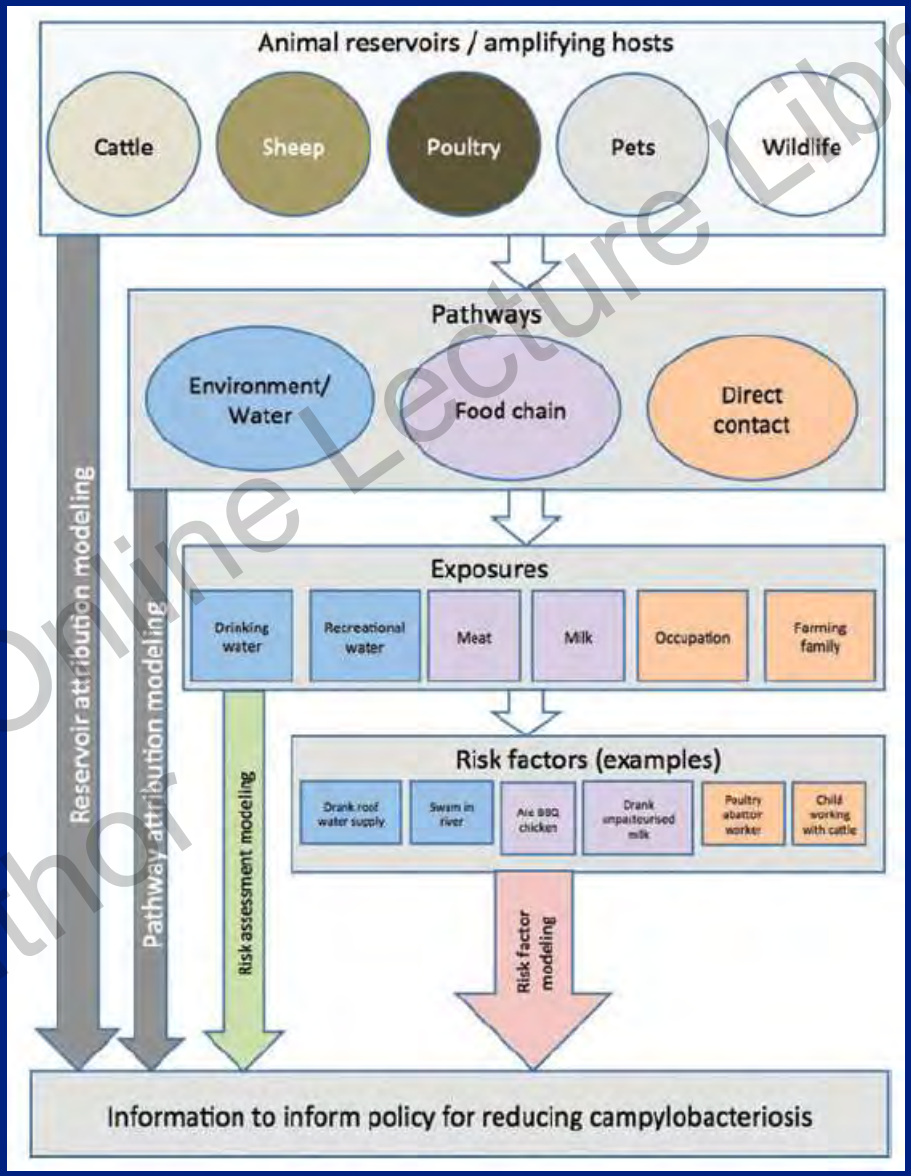
Attribution of human Campylobacteriosis



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Wagenaar JA CID 2013

Attribution of human Campylobacteriosis

- **Epidemiological approaches - meta-analysis of case-control studies**
  - travelling abroad
  - eating undercooked chicken
  - environmental sources
  - eating in a restaurant (particularly chicken)
  - direct contact with farm animals

- **Targeted interventions**
  - in Iceland (72% reduction in human incidence)
  - in New Zealand (54% decline in humans, and 74% reduction in the number of cases attributed to poultry)
  - in Belgium (dioxin crisis)
  - in the Netherlands (avian influenza epidemic in 2003)

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Human infections

- **Campylobacters are the leading bacterial cause of zoonotic disease worldwide**

  - affects around 1% of the human population in the EU/year

  - 13/1,000 in the USA annually

- **Intestinal clinical manifestations**

  - largely indistinguishable from other bacterial gut infections

  - fever, abdominal cramps, diarrhea (+/- blood), leukocytes

  - symptoms can last from 3 days to one week

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Human infections

- **Other clinical manifestations**

  - auto-immune diseases: Guillain-Barré or Miller Fisher syndromes

  - secondary infections: arthritis, abscess, meningitis

- **Epidemiology**

  - infection occurs in all age groups

  - in 2012 the CDC reported a 14% increase in campylobacteriosis illness caused by *C. jejuni*

  - in 2005 the CDC reported 1M cases/year in the USA

  - the ESFA and ECDC reported that campylobacteriosis has become the most often reported zoonosis in the EU followed by salmonellosis

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Comparison of risk factors for *C. jejuni* & *C. coli* infections – Univariate analysis

- ***C. jejuni* is associated with:**

- occurrence during the summer (May-September)
- more frequent resistance to ampicillin
- male gender

- ***C. coli* is associated with:**

- occurrence at a more advanced age
- more frequent resistance to quinolones
- existence of a trip abroad

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Comparison of risk factors for *C. jejuni* & *C. coli* infections Multivariate analysis

- ***C. jejuni* is associated with:**

- occurrence during the summer (May-September)

- ***C. coli* is associated with:**

- occurrence at higher age

- more frequent existence of a trip abroad

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Domestic animals and other "emerging species"

- ***C. ureolyticus*** **was recently identified as the second most common species after *C. jejuni* in Irish patients presenting gastroenteritis**

- **Putative sources**

  - **porcine samples (18%)**
  - **cat samples (32%)**
  - **dog faecal samples (9%)**

Koziel M et al, Gut Pathog 2014

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Other animals

- **Rodents, insects (flies)**

  - possible vectors for *Campylobacter sp* transmission to agricultural animals

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Campylobacter pathogenesis and disease

***C. jejuni* virulence involves**

- motility
- host cell adherence
- host cell invasion
- alteration of the host cell signaling pathways
- induction of host cell death
- evasion of the host immune system defenses, and acquisition of iron which serves as a micronutrient for growth

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Campylobacter pathogenesis and disease

The biochemical effects on cellular events are as follows:

- cytoskeletal rearrangement
- host cell death
- tight junction disruption and cytokine induction that lead to loss of epithelial cell function
- a compromised barrier and absorptive functions
- tissue destruction and disease manifestation
- adherence can also lead to an early inflammatory response that causes stimulation of innate immune functions

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Risk factors for Campylobacteriosis of chicken, ruminant and environmental origin

- **Risk factors for chicken-associated Campylobacteriosis**

  - consumption of chicken
  - recent use of PPI
  - having a chronic gastrointestinal disease
  - having contact with people with gastroenteritis

- **Risk factors for ruminant-associated Campylobacteriosis**

  - consumption of barbecued meat
  - consumption of tripe
  - recent use of PPI
  - occupational exposure to animals

Mughini Gras L, PLoS One 2012

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Risks factors for other *Campylobacter sp* infection

- Eating sausages and barbecued meat
- Exposure to farm or domesticated animals
- Consumption of raw milk
- Consumption of contaminated water

⇨ case-control studies and outbreak investigations

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A national epidemic of campylobacteriosis in Iceland, lessons learned

In 1999, an epidemic of campylobacteriosis was reported in Iceland

- **the recent availability of fresh poultry products in the marketplace was suggested as the source of infection**

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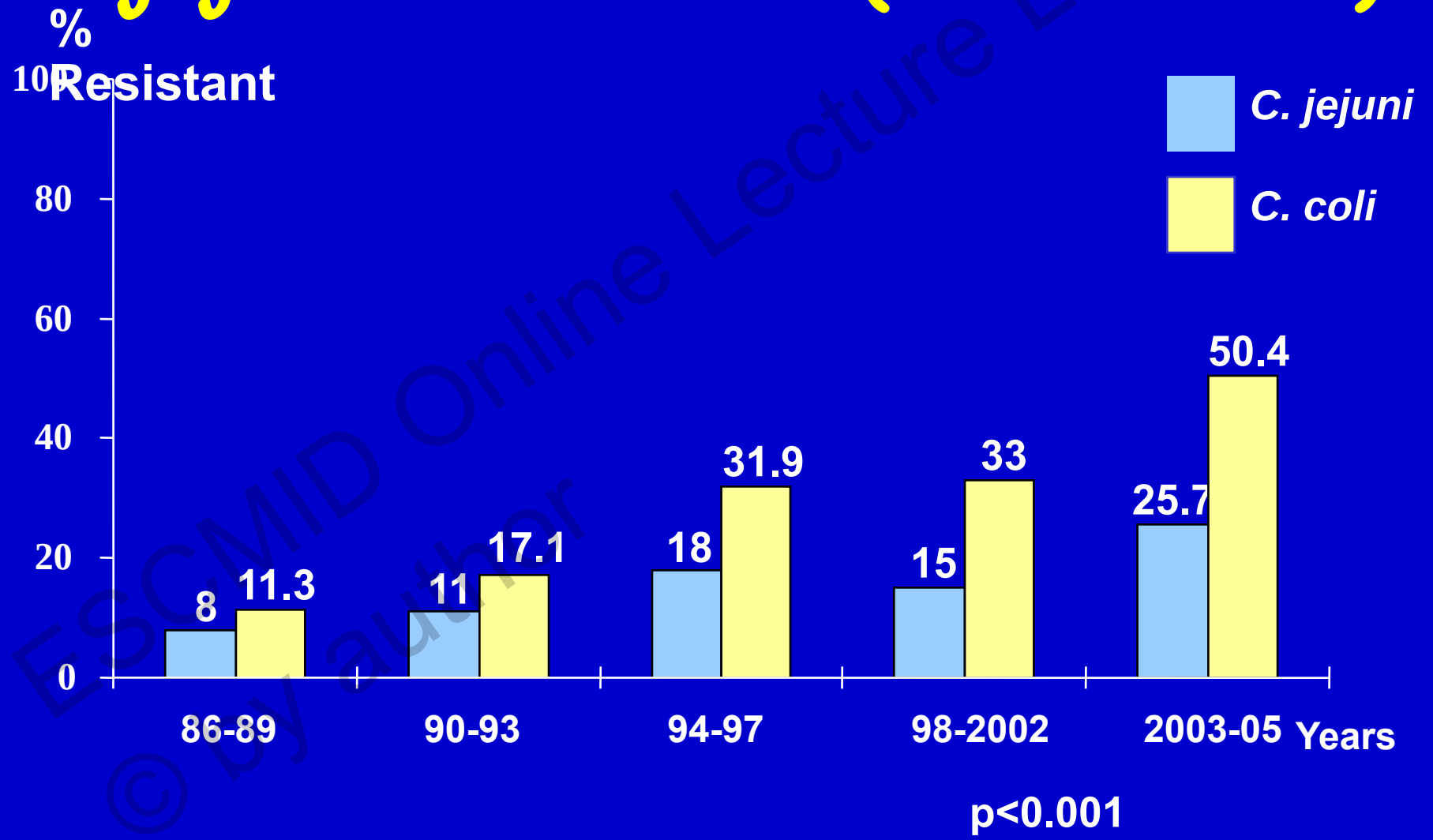
Tustin J et al Zoonoses Public Health 2011

Evolution of tetracycline resistance for *C. jejuni* and *C. coli* (1986-2005)



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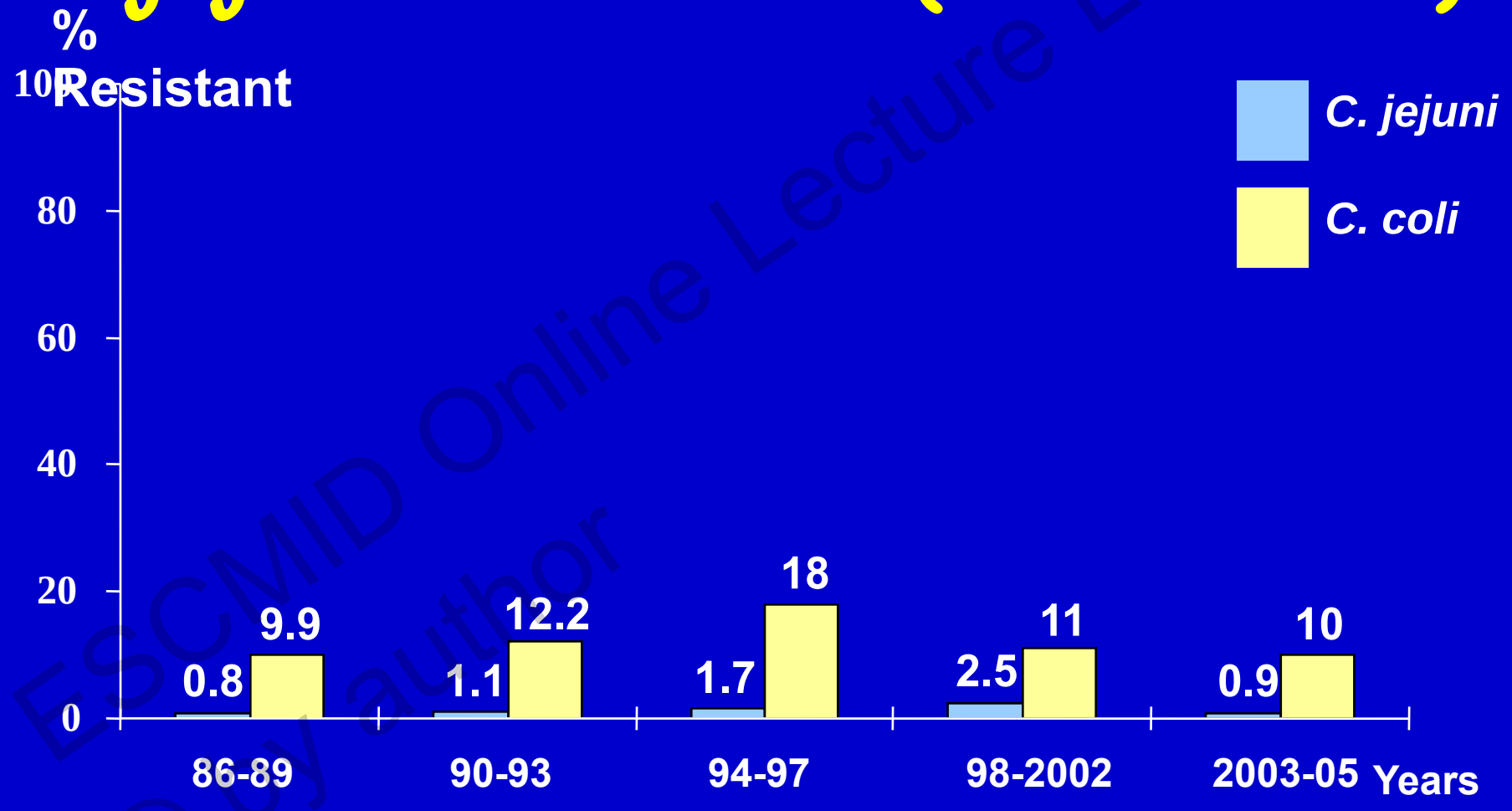
Evolution of erythromycin resistance for *C. jejuni* and *C. coli* (1986-2005)



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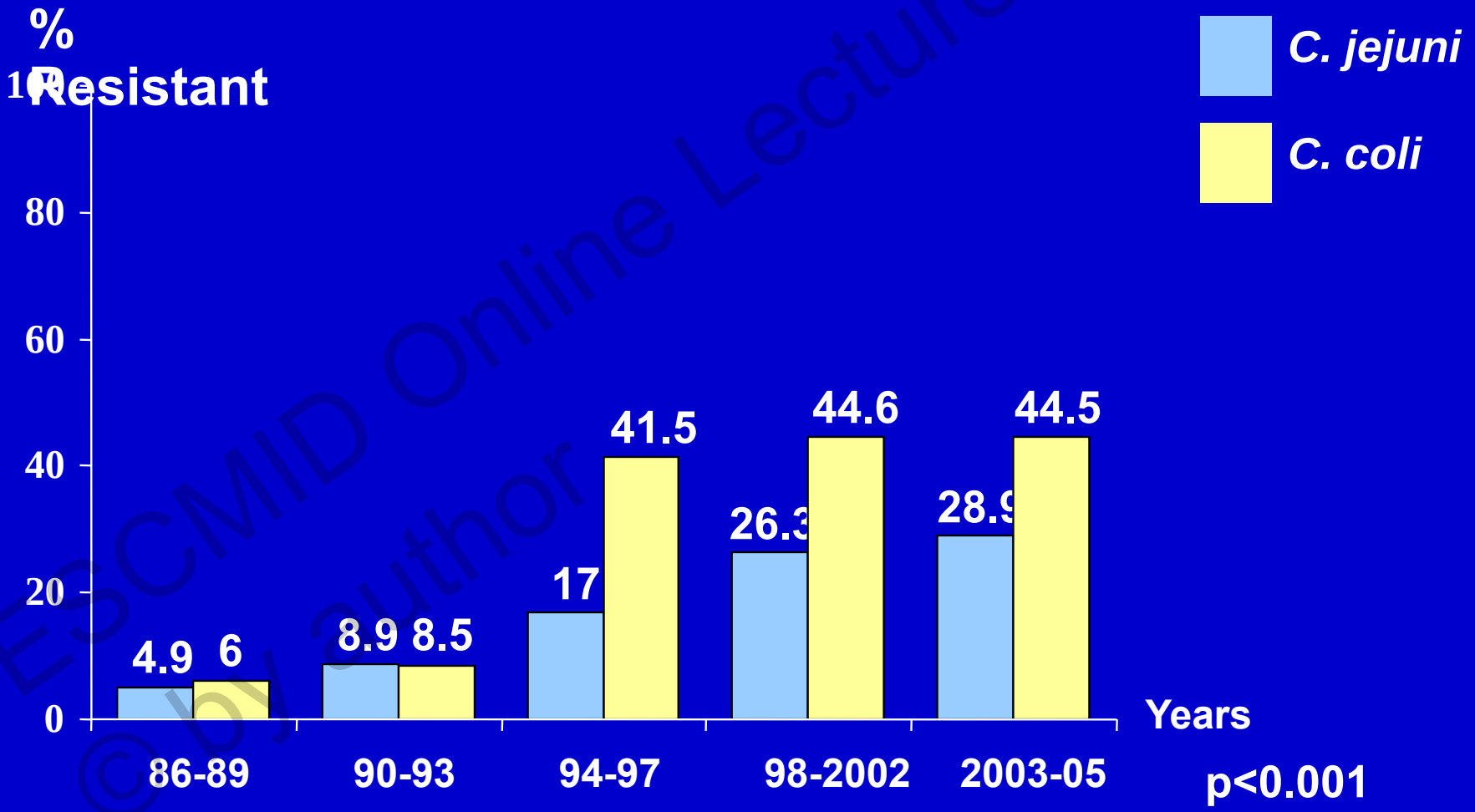
Evolution of nalidixic acid resistance for *C. jejuni* and *C. coli* (1986-2005)



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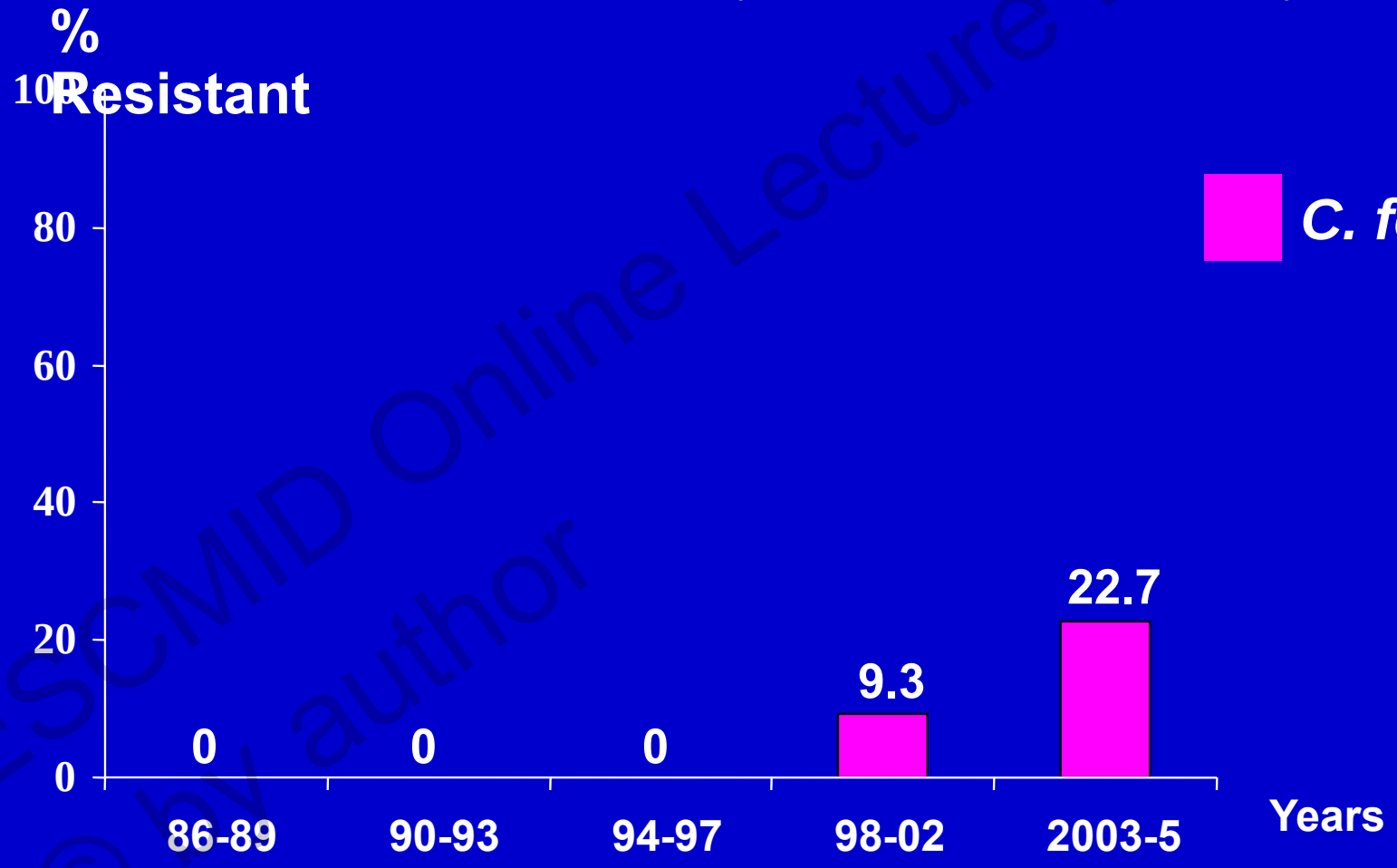
Evolution of fluroquinolone resistance for *C. fetus* (1986-2005)



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Origin of fluoroquinolone resistance

- Increased use of fluoroquinolones in human infections?
- Use of fluoroquinolones (enrofloxacin) in animals?

Arguments:

- children (<10 years) have the same resistance rates as adults (20% versus 23%, respectively; p= 0.3, 2002)
- countries where enrofloxacin is not used, have low fluoroquinolone resistance rates

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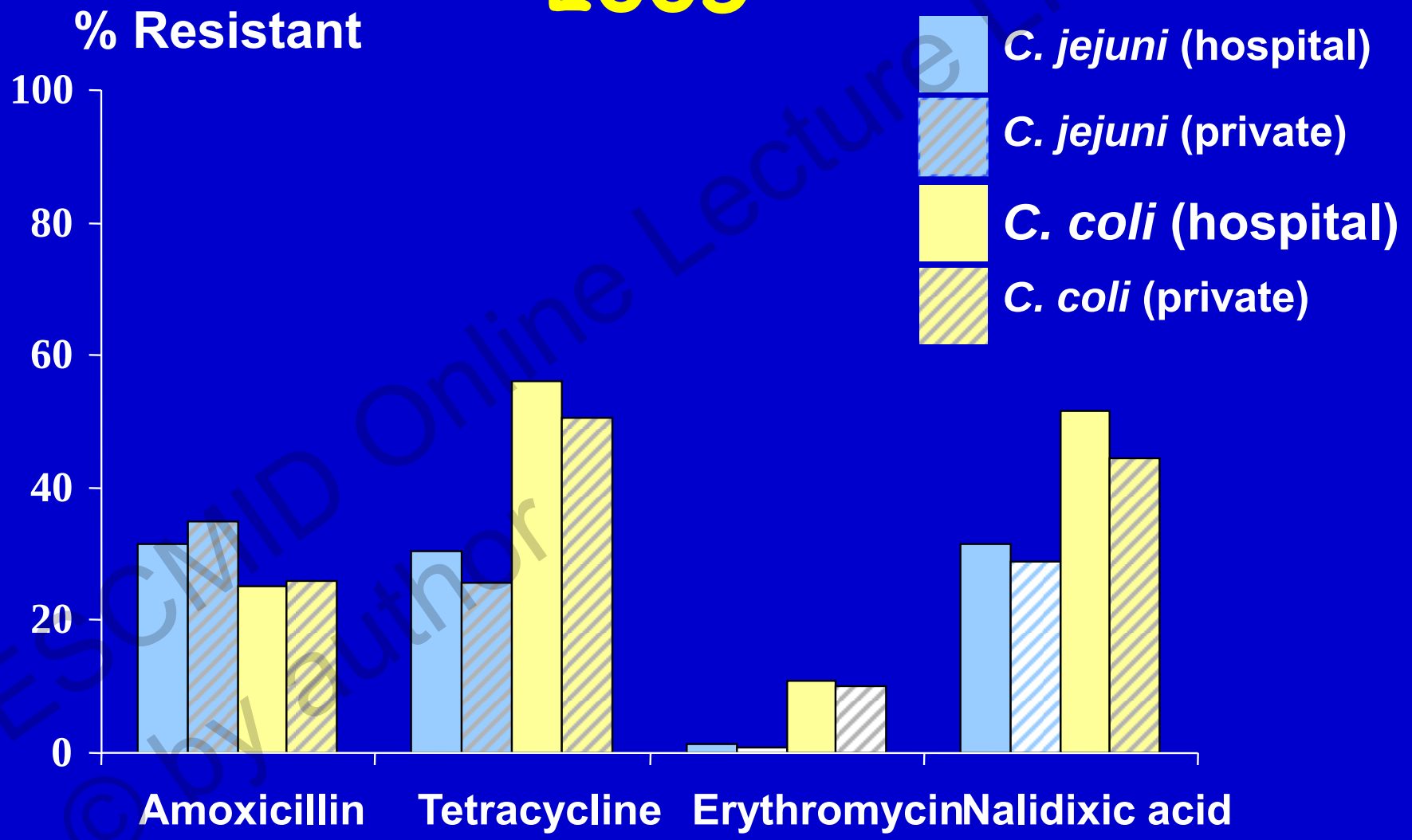
Comparison with data from the network of private laboratories in 2005



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Conclusions

- *C. coli* more resistant than *C. jejuni*
- Resistance to macrolides is low and stable
- Decrease of amoxicillin resistance
- Increase of tetracycline and fluoroquinolone resistance
- Importance to implement measures to limit the increase of quinolone resistance

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