

distrust whatever the wishes of a mind, the animal frame was well fitted to exercise them; the wily instincts of the throat, the brain, the eye, the nervous hands and lean giant arms, which were bared above the elbow, betrayed a form of intelligence of great extent, invention and resource.

"Calpurnia," said the Egyptian, "you will rise of the wiles which suggest you, and your voice will be heard. Always prosper your goal, for it is the will of the gods."

"Beside," added Calpurnia, "I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"Right, my Calpurnia," said the Egyptian, "I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"My dear Calpurnia," said the Egyptian, "I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

love to sing, to ripen their minds—to unfold the sweet blossom of their hidden passions, to be prepared the fruit to my taste. I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"Beside," added Calpurnia, "I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."

"I will do as I please, and if it comes to the point of death, I will die as I choose. I will not be the victim of any man's will, and I will not be the victim of any man's death."



Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Infezioni da *Campylobacter* nell'uomo

Serbatoi animali, fattori di rischio, vie di trasmissione e grado di esposizione al patogeno nei Paesi Bassi

Lapo Mughini Gras, DVM PhD
lapo.mughini.gras@rivm.nl

13 Dicembre 2017, Teramo



The RIVM

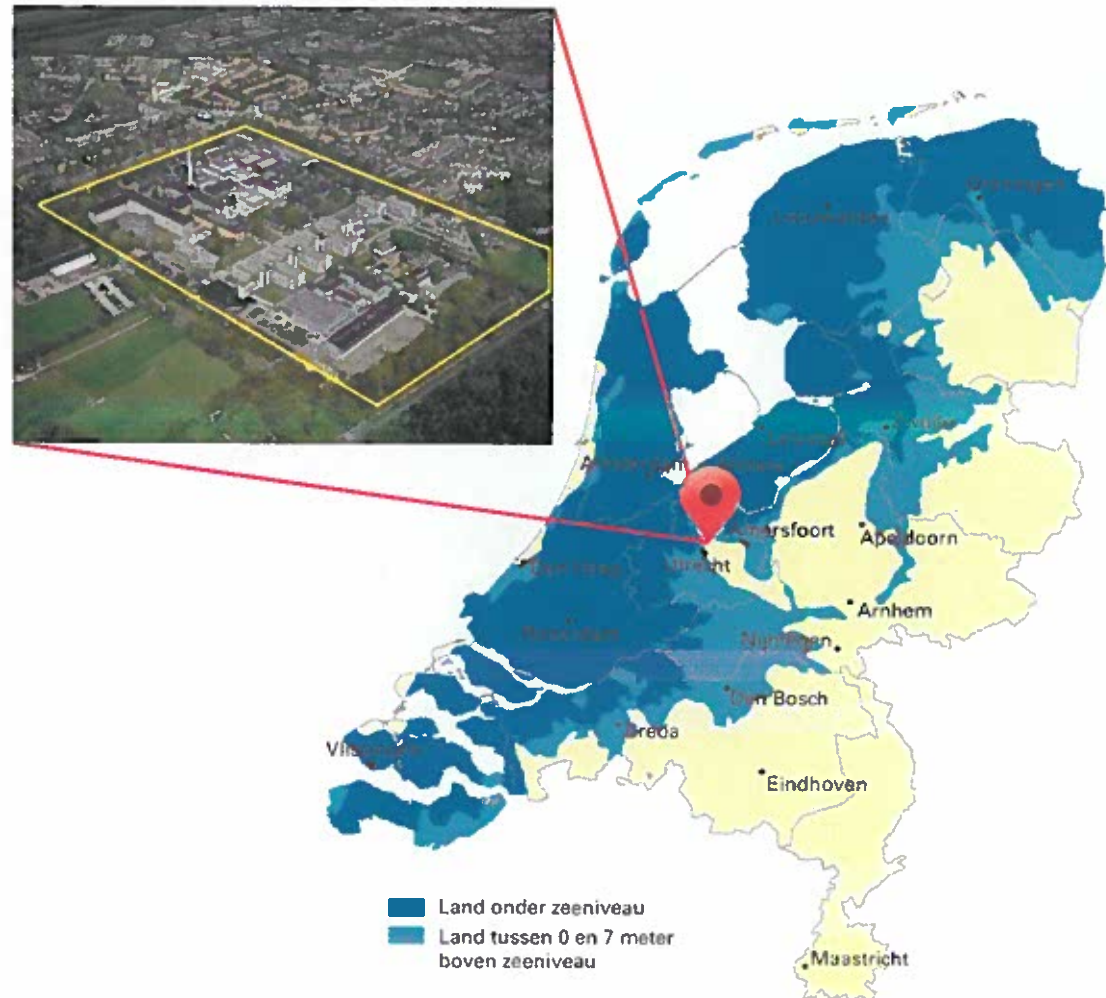
- Dutch National Institute for Public Health and the Environment
- Established in 1909
- Surveillance, monitoring, intervention planning & implementation, research, and scientific advisory for public and environmental health
- Main funders
 - Dutch Ministry of Health, Welfare and Sport
 - Dutch Ministry of Infrastructure and the Environment





Key figures

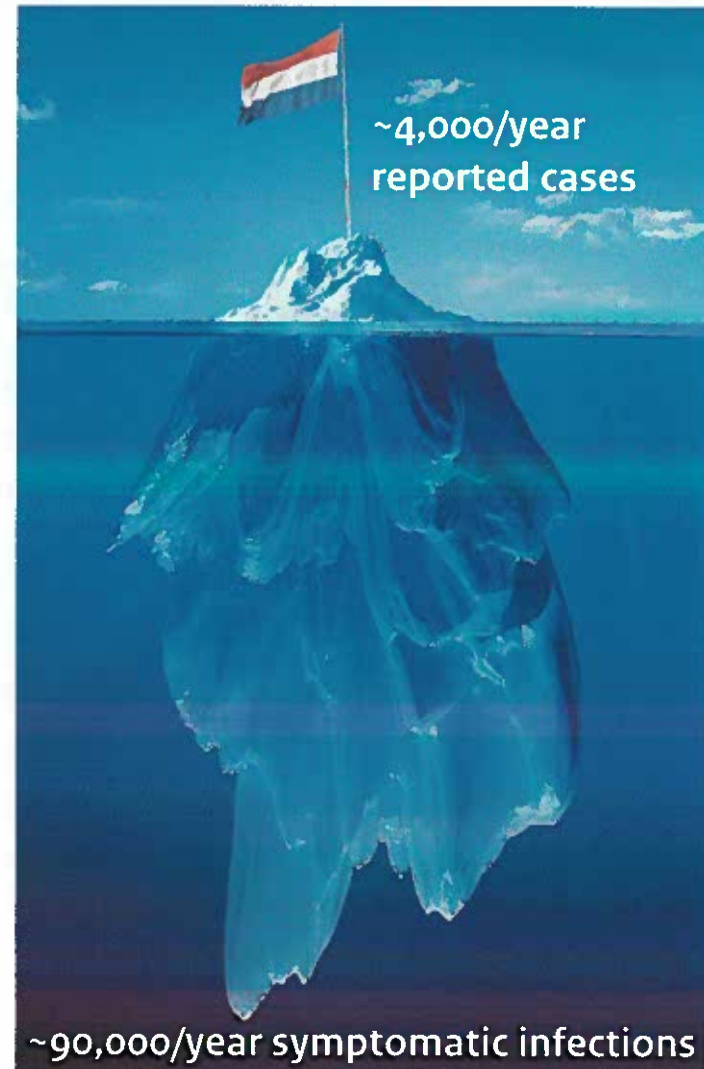
- 1470 employees
 - 54% ♀, mean age 47 years
 - 26 professorships
 - 5% expats
- ~300 research projects a year
- ~2600 publications a year
- € 323 million annual budget (2015)





Campylobacter in the Netherlands

- 93% *C. jejuni* and 5% *C. coli*
- Rare outbreaks, mainly sporadic infections
- Largest burden of foodborne infections
~1,200 DALYs and € 21 million / year



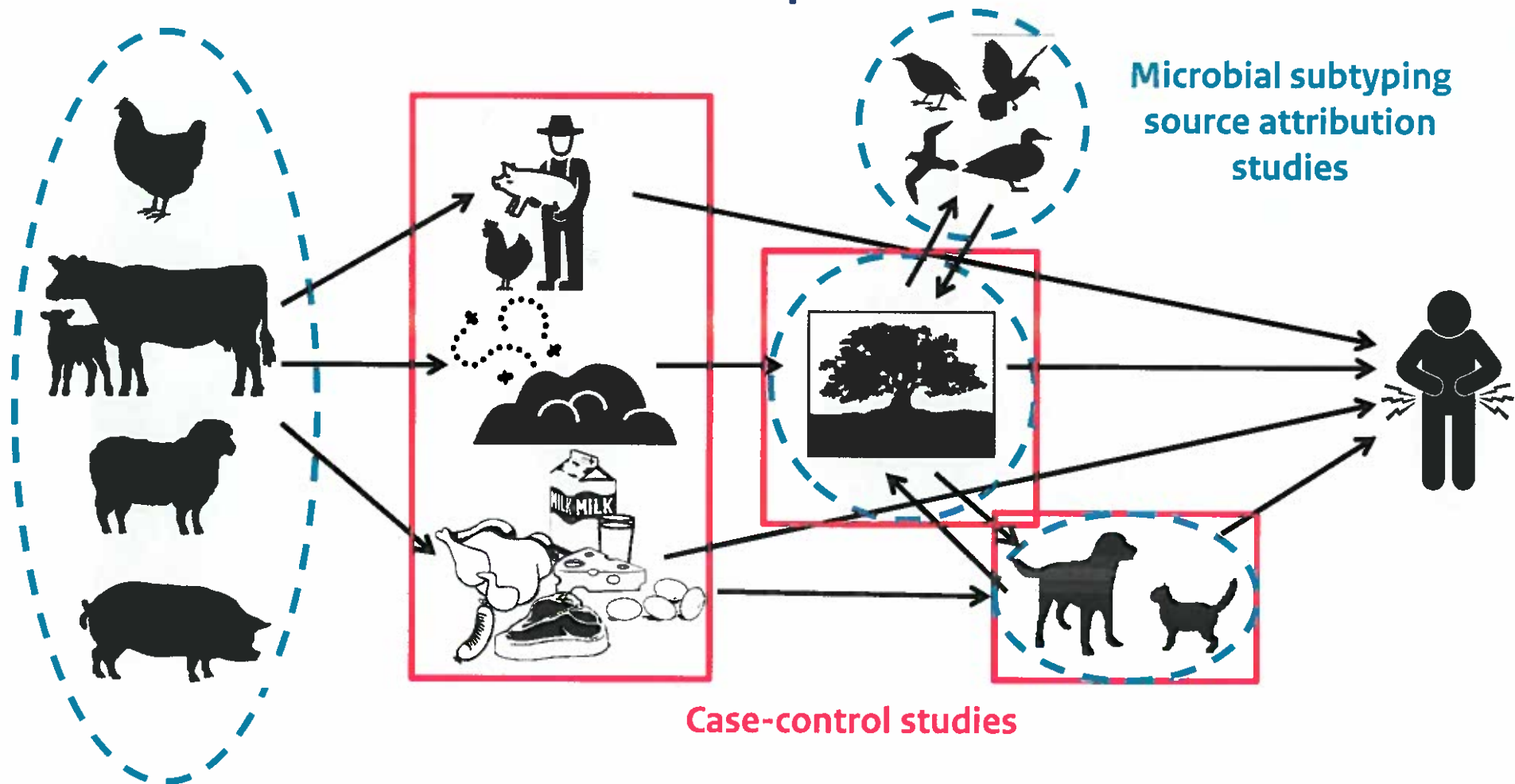


Source attribution

- To infer the **relative contributions** of different animal, food and environmental **sources** to the **human disease** burden
- **To guide targeted interventions** and to measure their impact
- **Several approaches** (Pires *et al.* Foodborne Pathog Dis 2009;6:417-24)
 - Microbial subtyping (top-down approach)
 - Comparative exposure assessment (bottom-up approach)
 - Case-control studies (traditional approach)
 - Analysis of outbreak investigations (meta-analysis like approach)
 - Intervention studies (learning from disasters)
 - Expert elicitations (last resort)
- Best approach depends on **research question** being addressed and **data availability**



Source attribution: reservoir & exposure



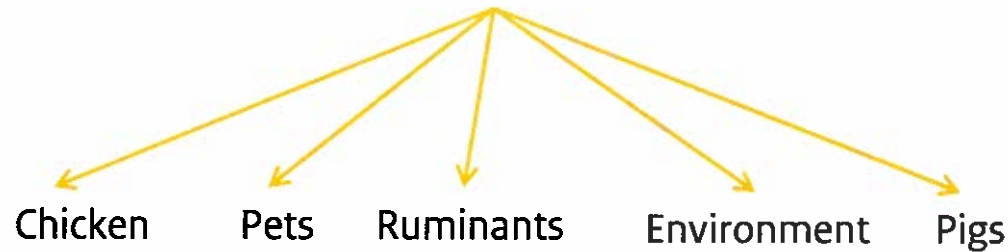


The CaSa Study

Epidemiol. Infect. (2010), 138, 1391–1404. © Cambridge University Press 2010
doi:10.1017/S095026881000052X

Risk factors for indigenous *Campylobacter jejuni* and *Campylobacter coli* infections in The Netherlands: a case-control study

Y. DOORDUYN^{1*}, W. E. VAN DEN BRANDHOF¹, Y. T. H. P. VAN DUYNHOVEN¹,
B. J. BREUKINK¹, J. A. WAGENAAR^{2,3,4} AND W. VAN PELT¹



OPEN ACCESS Freely available online

August 2012 | Volume 7 | Issue 8 | e42599



Risk Factors for Campylobacteriosis of Chicken, Ruminant, and Environmental Origin: A Combined Case-Control and Source Attribution Analysis

Lapo Mughini Gras^{1,2,3,5*}, Joost H. Smid^{2,3}, Jaap A. Wagenaar^{4,5,6}, Albert G. de Boer⁴, Arie H. Havelaar^{2,7}, Ingrid H. M. Friesema², Nigel P. French⁸, Luca Busani¹, Wilfrid van Pelt²

Epidemiol. Infect., Page 1 of 10. © Cambridge University Press 2013
doi:10.1017/S0950268813000356

Increased risk for *Campylobacter jejuni* and *C. coli* infection of pet origin in dog owners and evidence for genetic association between strains causing infection in humans and their pets

L. MUGHINI GRAS^{1,2,3,5*}, J. H. SMID², J. A. WAGENAAR^{4,5,6}, M. G. J. KOENE¹,
A. H. HAVELAAR^{2,7}, I. H. M. FRIESEMA², N. P. FRENCH⁸, C. FLEMMING⁹,
J. D. GALSON⁹, C. GRAZIANI¹, L. BUSANI¹ AND W. VAN PELT²



MLST data



Country	Human	Chicken	Cattle	Sheep	Pig	Environment
The Netherlands	980†	210	9	0	13	106 (water)
United Kingdom	0	0	46	72	5	50 (sand)
Scotland	0	0	90	88	15	133 (wild birds)
Switzerland	0	0	23	0	100	0
Total	980	210	168	160	133	289

Mughini-Gras et al. PLoS One. 2012;7(8):e42599



Borrowing source data

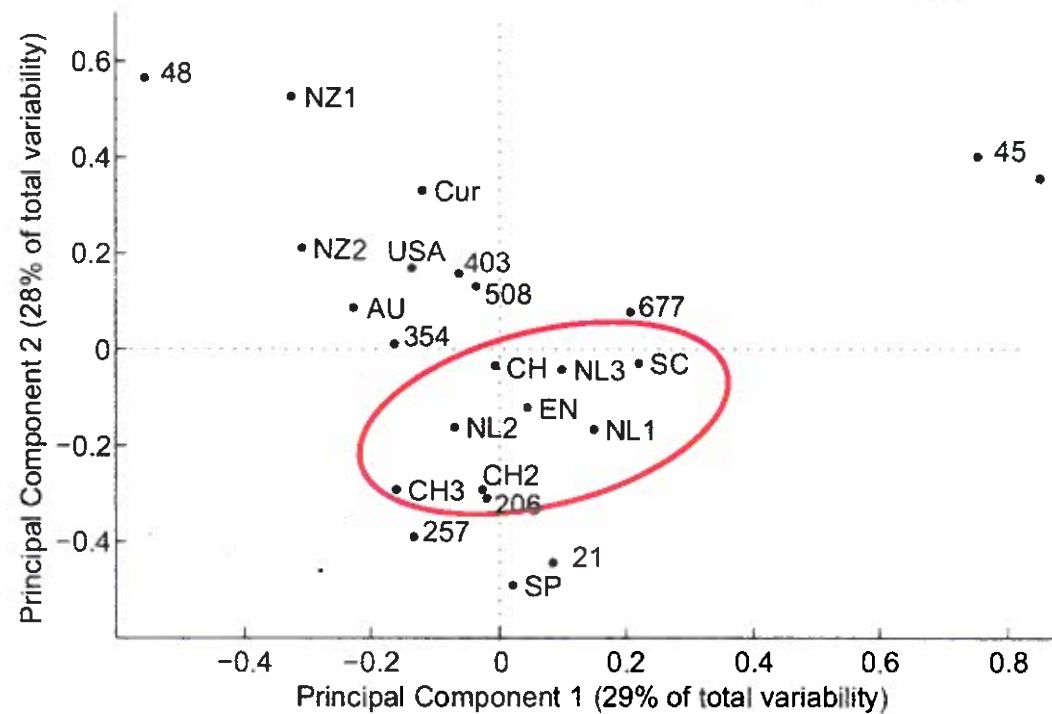
OPEN ACCESS Freely available online

February 2013 | Volume 8 | Issue 2 | e55029

PLOS ONE

Practicalities of Using Non-Local or Non-Recent Multilocus Sequence Typing Data for Source Attribution in Space and Time of Human Campylobacteriosis

Joost H. Smid^{1,2}, Lapo Mughini Gras^{3,4}, Albert G. de Boer⁵, Nigel P. French⁶, Arie H. Havelaar^{1,2}, Jaap A. Wagenaar^{3,7,8}, Wilfrid van Pelt¹

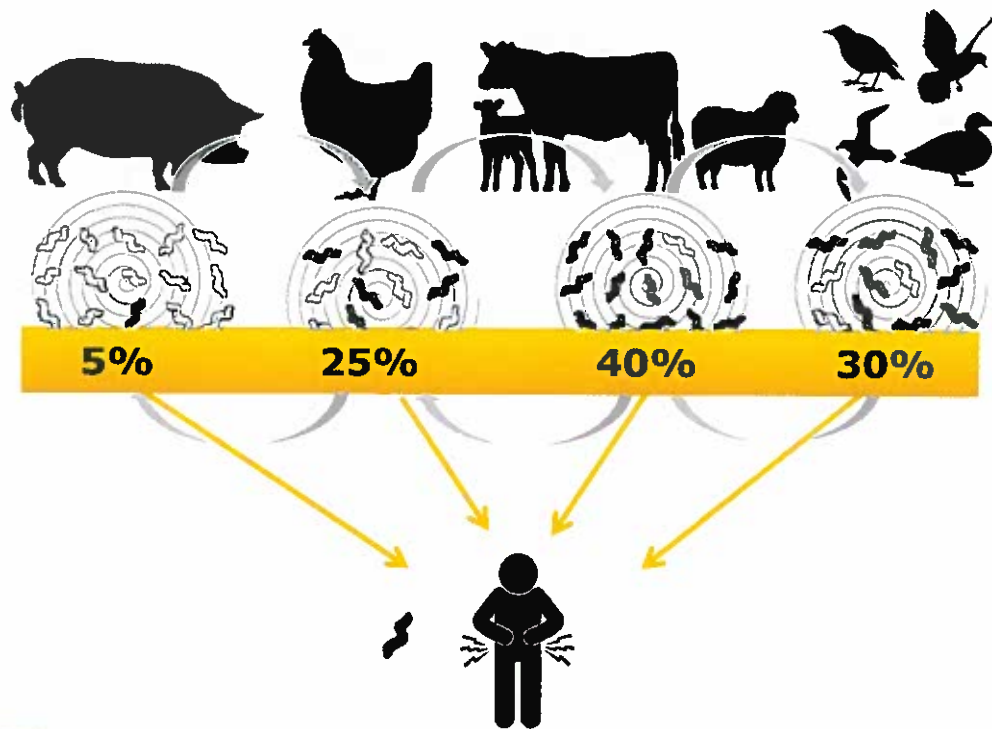


Selection of source data from countries/time periods that have their respective human data more similar to those you want to attribute



Source attribution analysis

- **Asymmetric Island Model** (Wilson et al. PLoS Genet 2008;4:e1000203)
 - Bayesian population genetics model that uses MLST data for probabilistic assignment of STs to sources
 - *Campylobacter* population is seen as separate islands where mutation, recombination and migration occur



Evolutionary stage

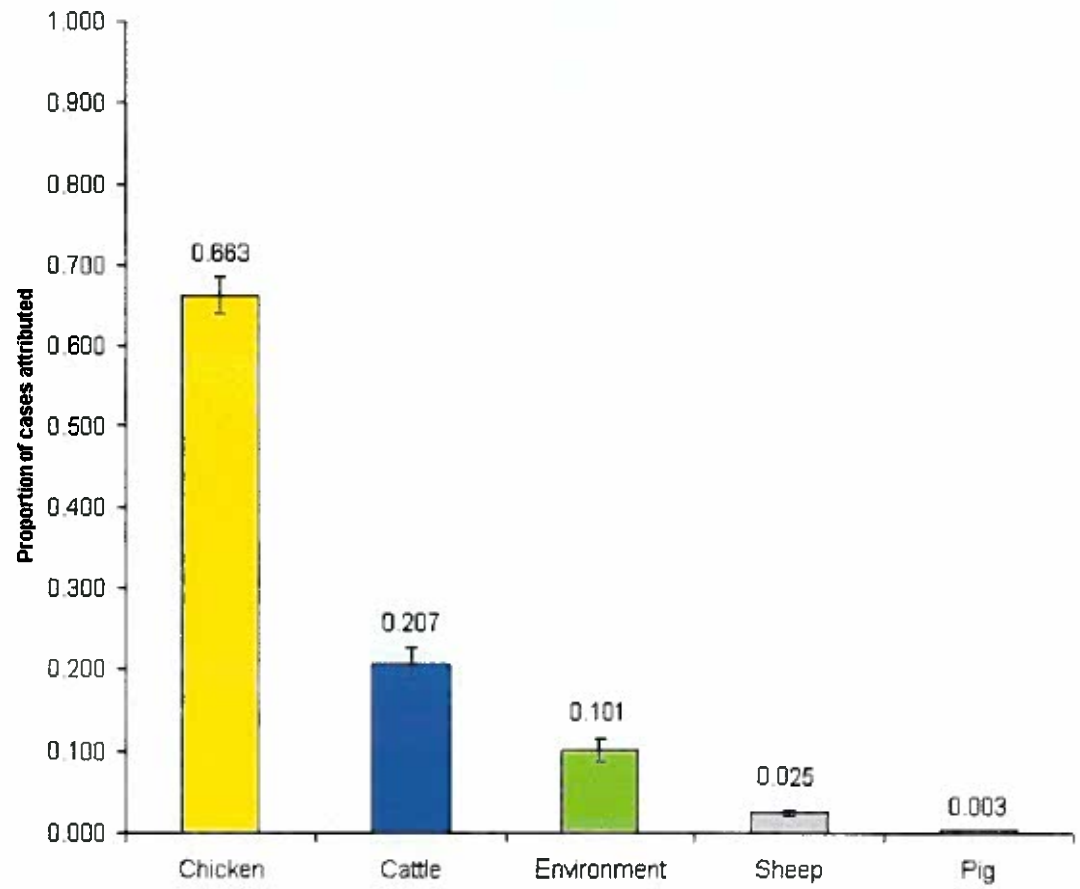
- Only source data
- Estimates mutation, recombination and migration rates to be used in the second stage

Attribution stage

- Relies on sampling probabilities: probability that a given human ST is randomly sampled from each host population
- Estimates an assignment posterior probability for each ST



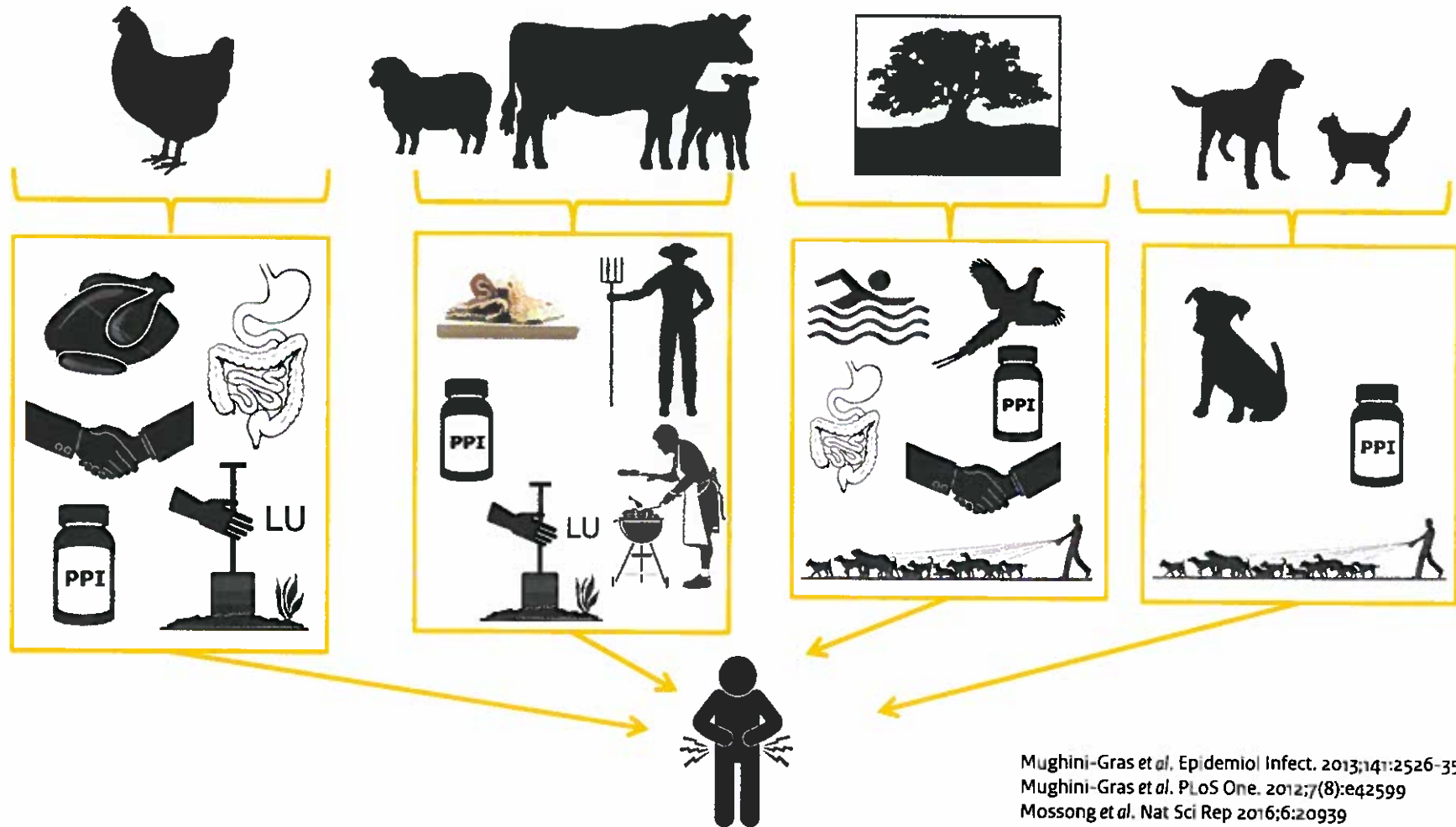
Attributions



Mughini-Gras et al. PLoS One. 2012;7(8):e42599



Source-specific risk factors



Mughini-Gras et al. Epidemiol Infect. 2013;141:2526-35
Mughini-Gras et al. PLoS One. 2012;7(8):e42599
Mossong et al. Nat Sci Rep 2016;6:20939

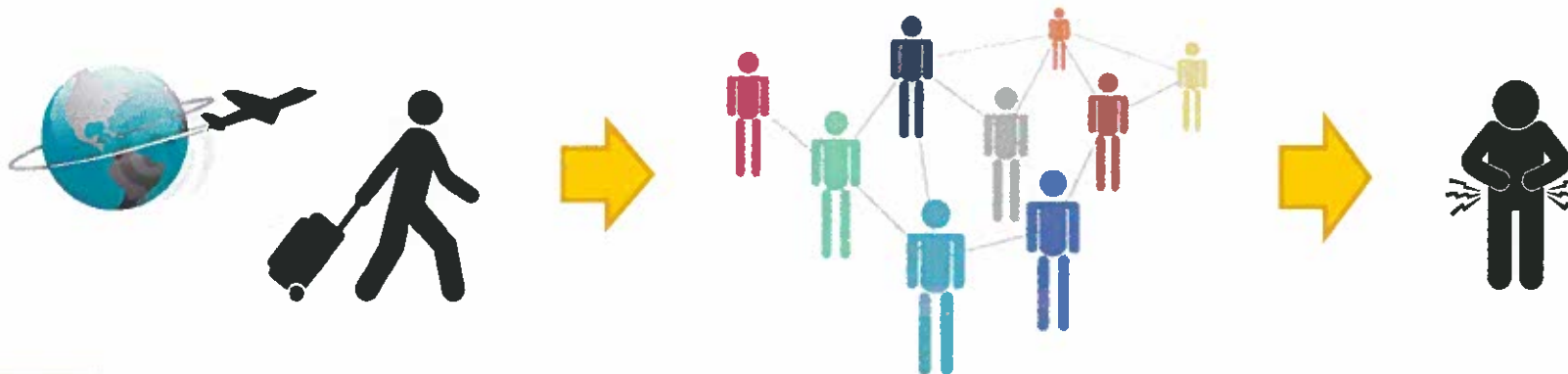


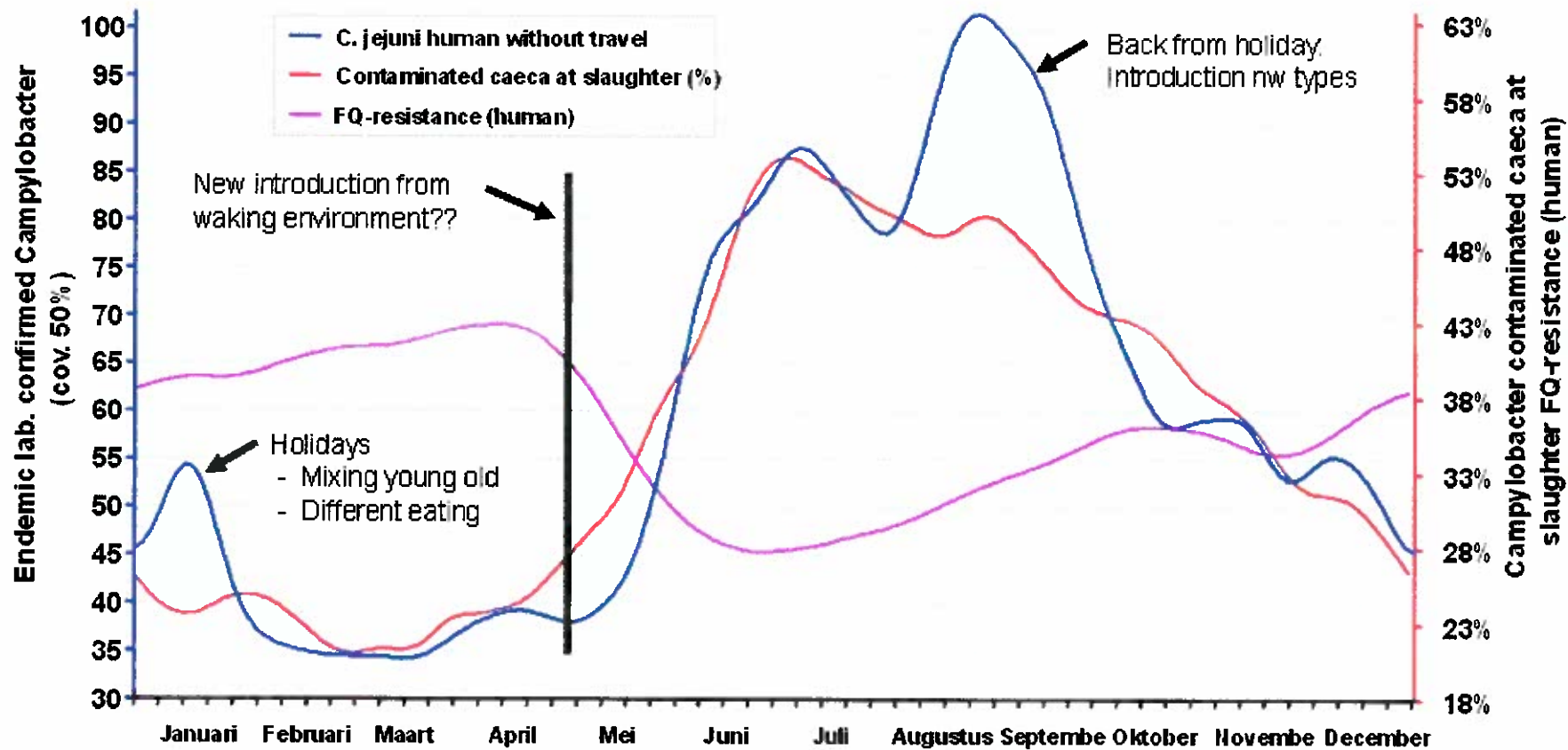
Exotic STs in domestic infections

Epidemiol. Infect., Page 1 of 12. © Cambridge University Press 2013
doi:10.1017/S0950268813002069

Campylobacteriosis in returning travellers and potential secondary transmission of exotic strains

L. MUGHINI-GRAS^{1,2,3*}, J. H. SMID^{2,6}, J. A. WAGENAAR^{1,4,5}, A. DE BOER⁴,
A. H. HAVELAAR^{2,6}, I. H. M. FRIESEMA², N. P. FRENCH⁷, C. GRAZIANI¹,
L. BUSANI¹ AND W. VAN PELT²

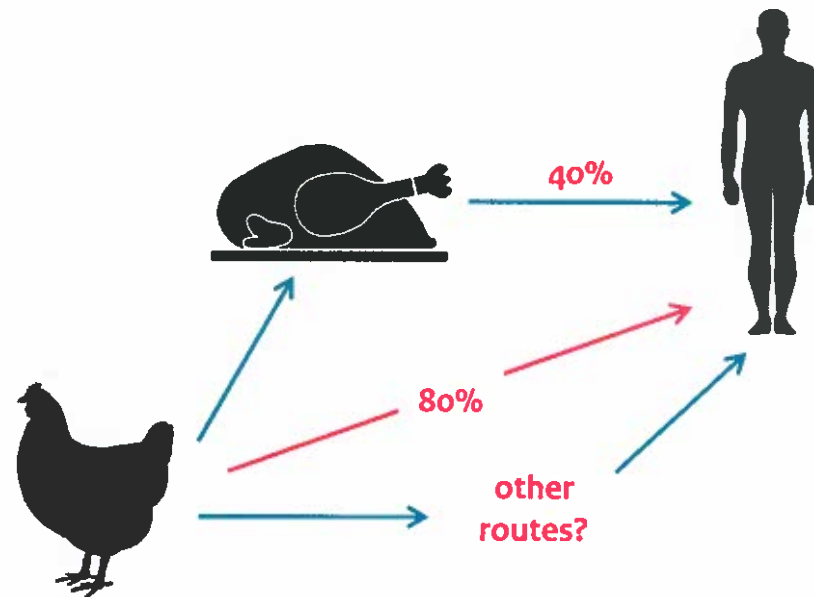






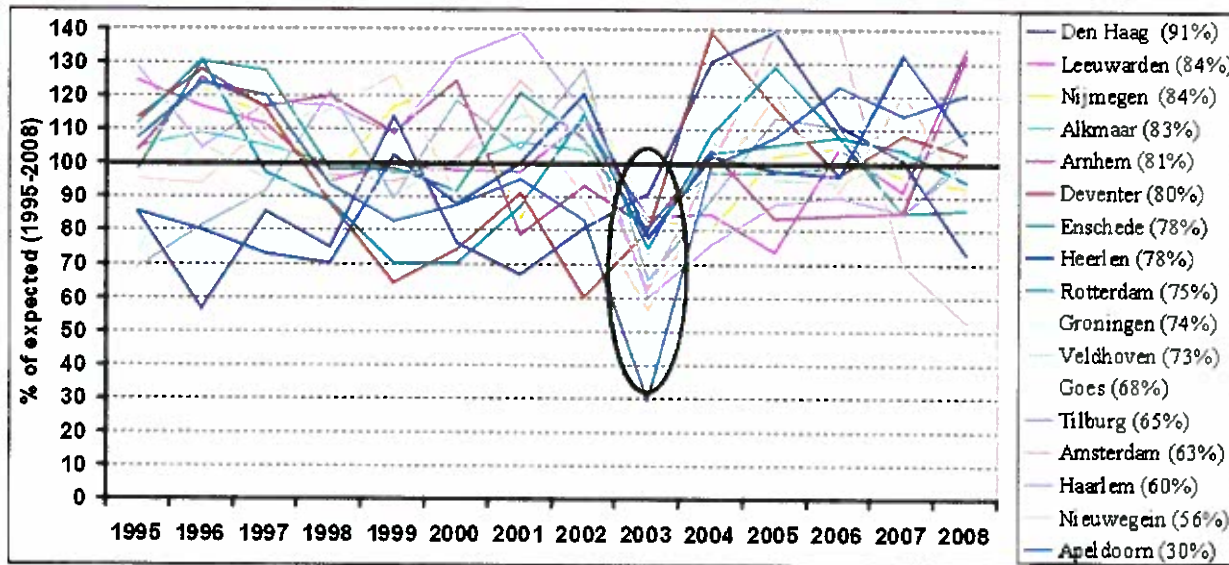
Non-poultry meat transmission

- Up to 80% of human infections can be attributed to the poultry reservoir as a whole
(Wagenaar et al. *Clin Infect Dis* 2013,57:1600-6)
- But only about 40% of human infections can be attributed to poultry consumption
(Mughini-Gras et al. *PLoS One* 2012,7:e42599; Doorduyn et al. *Epidemiol Infect* 2010,138:1391-404; Vellinga & Van Loock *Emerg Infect Dis* 2002,8:19-22)





Epidemiological disasters: H7N7 in the NL

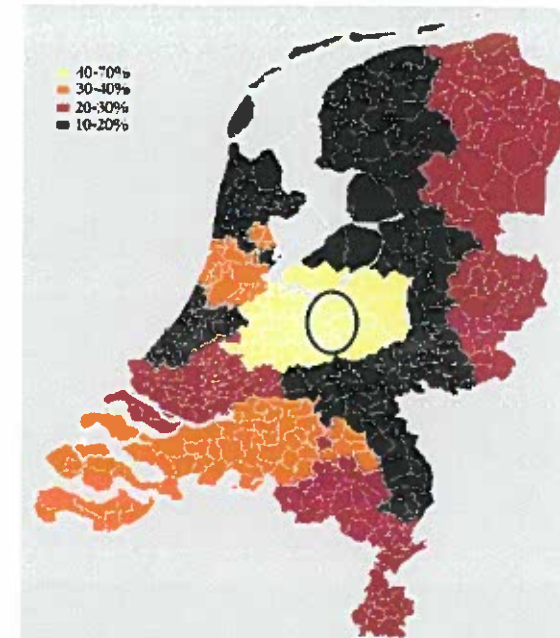


In 2003, an **epidemic of avian influenza** resulted in **extensive poultry culling** (~30 million birds) in the Netherlands. Concurrently, human **campylobacteriosis cases decreased by 44-70% in the culling areas**

Poultry Culling and Campylobacteriosis Reduction among Humans, the Netherlands

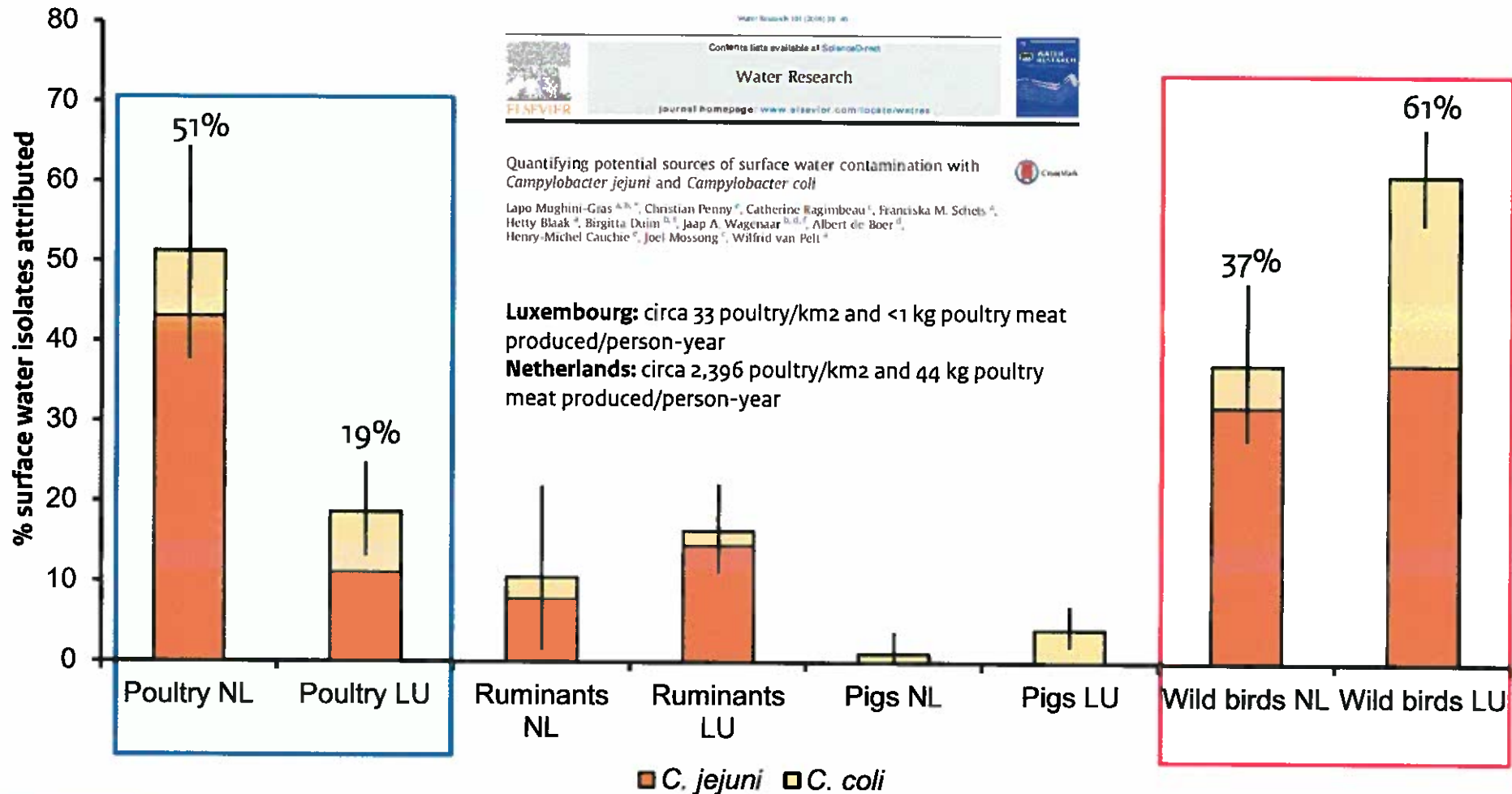
Ingrid H.M. Friesema, Arie H. Havelaar, Paul P. Westra, Jaap A. Wagenaar, and Wilfrid van Pelt

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 18, No. 3, March 2012





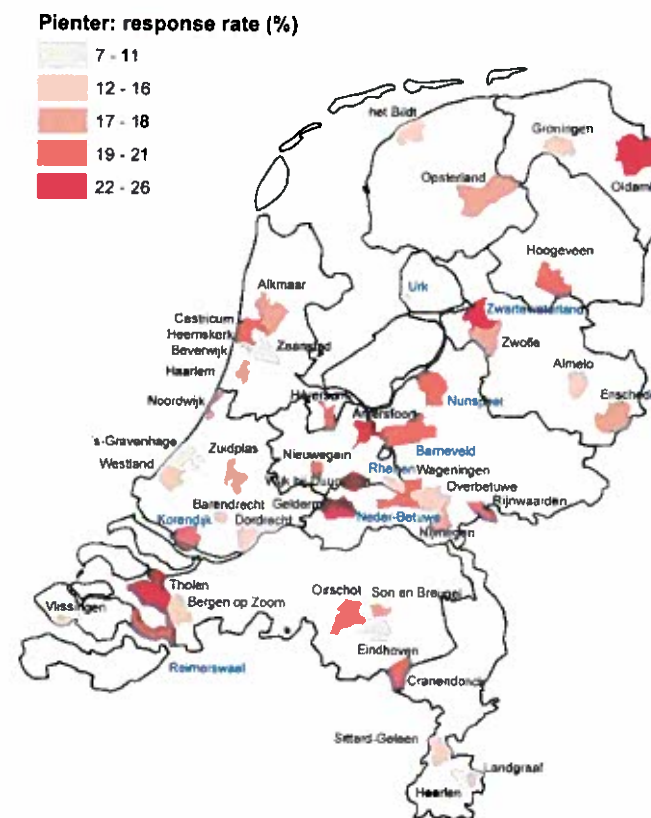
Attribution of water strains





Estimating *Campylobacter* infection pressure

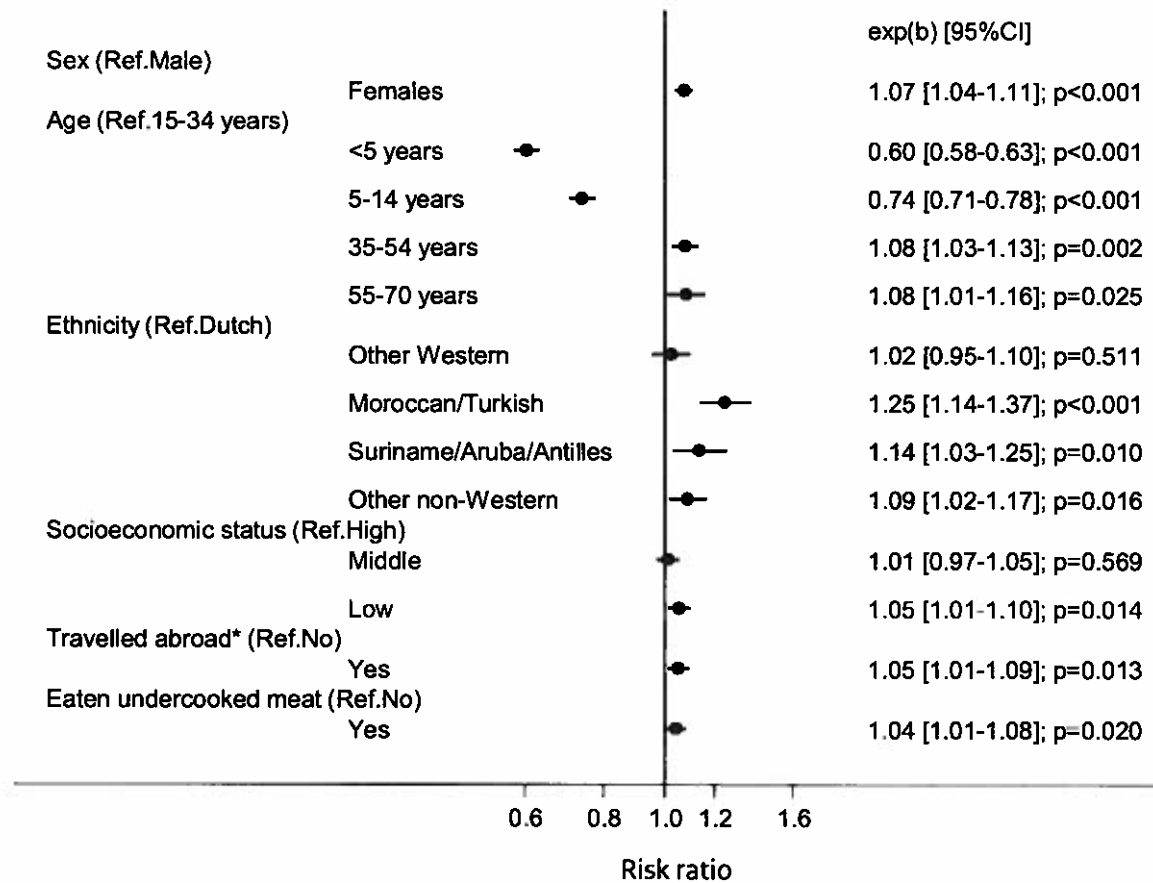
- Nationwide cross-sectional serosurvey, 2006-2007 (n=6,386)
van der Klis *et al.* Neth J Med 2009;67(7):301-8
 - 40 municipalities within 5 regions of similar population size
 - Age-stratified random sampling of municipal population registries
 - Sera and epidemiological data (questionnaire) collected
- Anti-*Campylobacter* IgG, IgM and IgA using ELISA (n=1,559)
Ang *et al.* Clin Microbiol Infect 2007;13:915-22
 - Antigen acid glycine extract of *C. jejuni* strain SSDZ-01
 - Results expressed as OD values
- Seroincidence calculation (no. infections/person/year)
Teunis *et al.* Stat Med 2012;31(20):2240-8 (ECDC serocalculator)
 - Based on post-infection reference peak and decay levels of IgG, IgM and IgA
 - Sampling weights applied
- Risk factors for increased infection pressure (seroincidence)
 - GLMs on individual log-transformed seroincidences
 - Accounted for clustered survey design, including sampling weights





Seroincidence estimations

1.61 *Campylobacter* infections per person-year (95%CI 1.58-1.64)





Rijksinstituut voor Volksgezondheid
en Milieu

*Ministerie van Volksgezondheid,
Welzijn en Sport*



**Grazie per
l'attenzione!**

lapo.mughini.gras@rivm.nl



Take-home messages

- Besides 'universal' risk factors, there are **risk factors that vary according to the attributable reservoir**
- Combined source attribution and case-control analysis may **improve risk factor identification/characterization and help uncover underlying transmission pathways**
- Controlling *Campylobacter* at **primary poultry production** is expected to affect also **non-poultry meat transmission routes**
- *Campylobacter* **infection pressure is high** (1.6 infections/person/year), several orders of magnitude higher than incidence of clinical cases
- **Risk factors for increased *Campylobacter* infection pressure are similar to those for clinical cases**



Potential sources of *Campylobacter*

- Many (all?) animal species...
- Data-driven selection
 - chicken, cattle, sheep/goat, pig, pets (dogs/cats), the environment (water/wild birds)

