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Sources and spatial patterns of STEC infection in the Netherlands

Lapo Mughini-Gras, DVM PhD

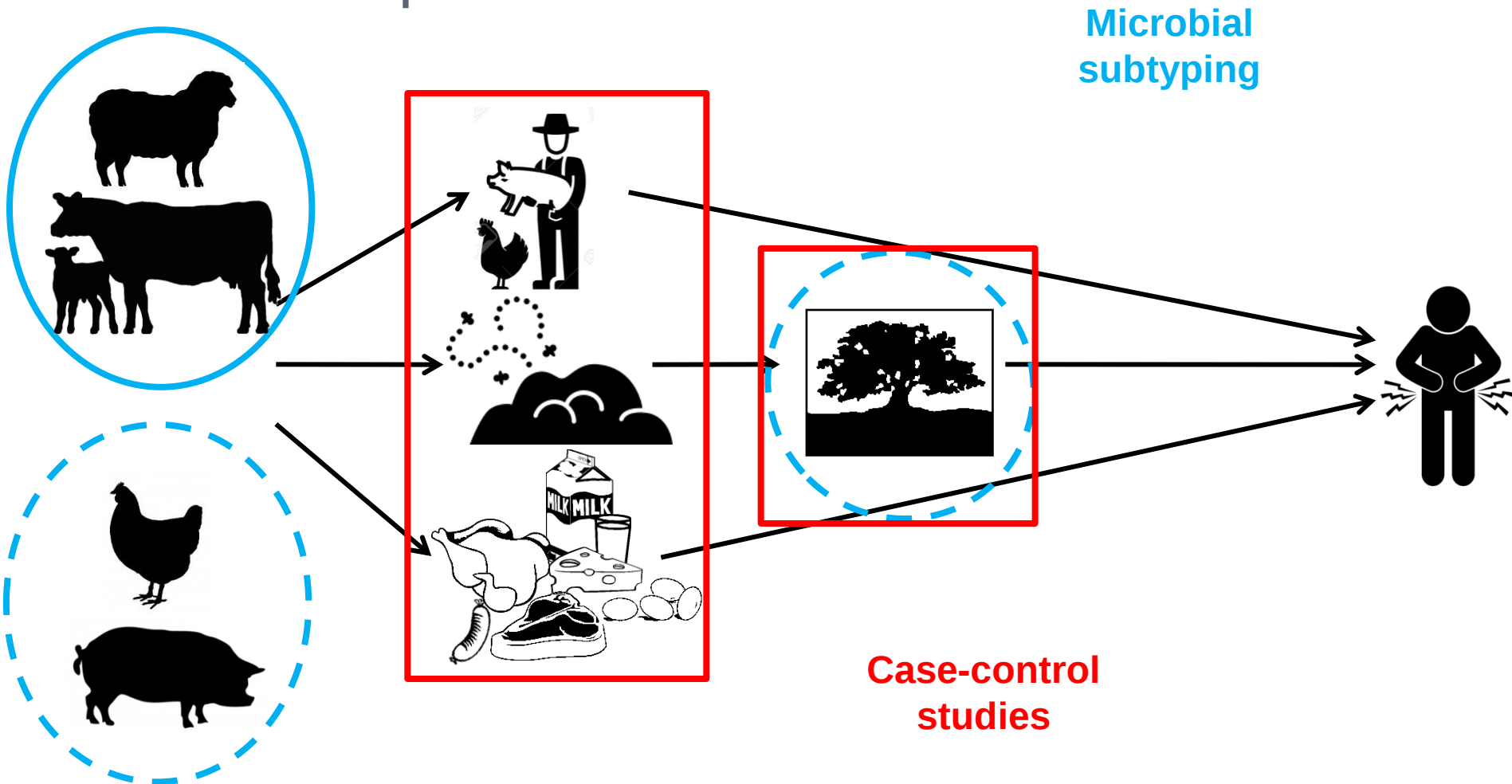
September 2020



Introduction

- Ruminants are the main reservoir for STEC, but there is evidence for (wild) birds, pigs, dogs and horses being significant spill-over hosts
- Source attribution studies based on microbial subtyping have mainly been performed for *Salmonella*, *Campylobacter* and *Listeria*
- Combined (source-assigned) case–control and source attribution analyses (as done for *Salmonella* and *Campylobacter*) may bridge the gap between attributing human cases at:
 - the start of the transmission chain (i.e. reservoir level)
 - the point of exposure (i.e. risk factors)to identify source-specific risk factors for human infection

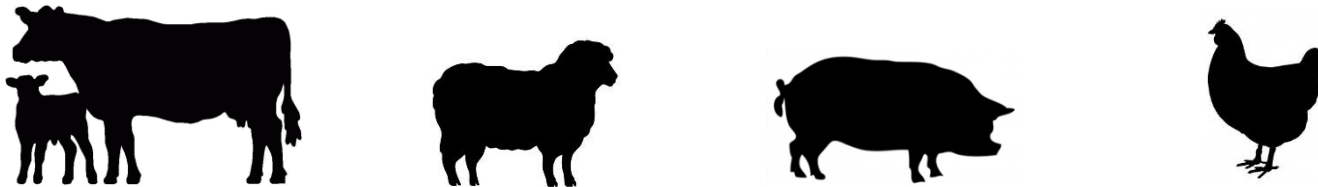
Reservoirs vs. exposure





Aim

To attribute human STEC infections to four putative livestock sources
(cattle, small ruminants, pigs, poultry)



To determine how the STEC strains attributed to each source may infect humans



Source attribution models



Wilfrid van Pelt

Dutch model

$$\lambda_{ij} = \frac{p_{ij} \times m_j}{\sum_j p_{ij} \times m_j} \times e_i$$



Danish model

$$e_i \approx \text{Poisson}(\sum_j \lambda_{ij})$$
$$\lambda_{ij} = m_j \times p_{ij} \times q_i \times a_j$$



Tine Hald

λ_{ij} estimated number of human isolates of type i from source j

p_{ij} prevalence of type i in source j

e_i observed number of human isolates of type i

m_j exposure weight (e.g. amount of food from source j consumed, probability of exposure to source j , etc.)

q_i type-dependent factor (i.e. virulence, pathogenicity, survivability, etc.)

a_j source-dependent factor (i.e. ability of sources j to act as a vehicle for the pathogen like source characteristics influencing bacterial growth, preparation/handling procedures, etc.)

- Frequentist approach
- Equal impact of types and sources on humans
- Source probabilities calculated independently of human subtype frequencies

- Bayesian approach
- Different impact of types and sources on humans
- Source probabilities fitted on human subtype frequencies

O-serotyping data



Borrowing livestock source data

How?

- Select data from different EU countries/time periods
- Choose countries/time periods similar in human data → comparable human data = exchangeable livestock source data

Why?

- Limited source data from NL
- Increase diversity of O-serotypes
- ~50% beef from other EU countries
- Improve model performance (less uncertainty, unknowns, convergence)

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

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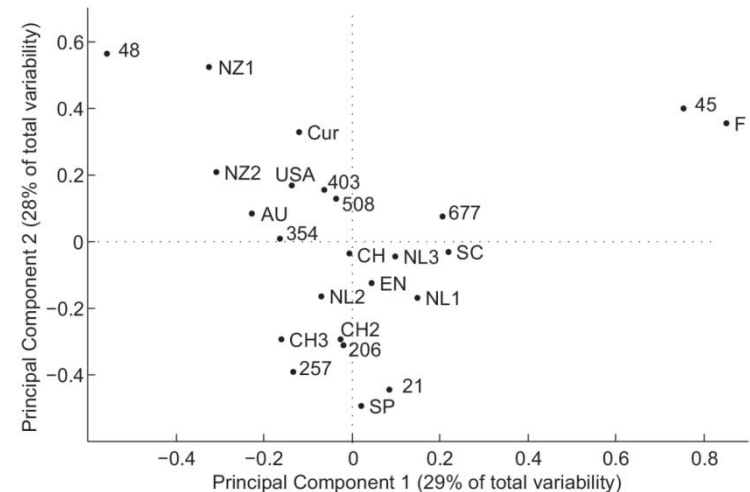




TABLE 1 Breakdown of the number of O-serotyped Shiga toxin-producing *Escherichia coli* (STEC) isolates used in the source attribution analysis, including the proportional similarity index (PSI) of the O-serotype frequency distribution of human STEC infections in the Netherlands with that of the human STEC infections in each of the other countries

	Netherlands	Germany	Sweden	Slovenia	France	Belgium	Denmark	Austria	Norway	Ireland	Hungary	Total
2011	270	0	6	1	1	17	1	97	0	75	12	480
Human	255	0	0	0	0	0	0	0	0	0	0	255
Cattle	7	0	2	1	1	11	1	50	0	40	9	122
Pig	3	0	0	0	0	0	0	0	0	5	3	11
Poultry	0	0	0	0	0	0	0	0	0	25	0	25
Sheep & goat	5	0	4	0	0	6	0	47	0	5	0	67
2012	357	39	12	2	1	17	1	96	0	31	6	562
Human	283	0	0	0	0	0	0	0	0	0	0	283
Cattle	32	32	11	2	1	11	1	44	0	13	5	152
Pig	14	4	0	0	0	0	0	0	0	2	0	20
Poultry	4	0	0	0	0	0	0	0	0	16	0	20
Sheep & goat	24	3	1	0	0	6	0	52	0	0	1	87
2013	495	10	6	2	4	13	1	89	1	77	6	704
Human	364	0	0	0	0	0	0	0	0	0	0	364
Cattle	79	8	6	2	4	7	1	43	0	50	5	205
Pig	38	0	0	0	0	0	0	0	0	6	0	44
Poultry	1	0	0	0	0	0	0	0	0	17	0	18
Sheep & goat	13	2	0	0	0	6	0	46	1	4	1	73
2014	505	18	4	0	0	17	1	79	0	22	3	649
Human	281	0	0	0	0	0	0	0	0	0	0	281
Cattle	89	8	4	0	0	15	1	33	0	15	3	168
Pig	54	6	0	0	0	0	0	0	0	2	0	62
Poultry	25	0	0	0	0	0	0	0	0	3	0	28
Sheep & goat	56	4	0	0	0	2	0	46	0	2	0	110
Total	1627	67	28	5	6	64	4	361	1	205	27	2395
PSI*		0.85	0.74	0.73	0.68	0.68	0.68	0.67	0.55	0.53	0.52	

Choose countries (go O-serotypes) with human PSI>0.50



Source-assigned case-control study

- Cases (#342)
 - O-serotyped STEC infection
 - period 2010–2014
 - interviewed within 1 month from symptoms onset
 - no travel 1 week before symptoms onset
 - Not part of outbreak or family cluster
- Controls (#2260)
 - thrice-yearly routine control interviews
 - period 2010–2014
 - no travel 1 week before interview
- 8 putative risk factors were tested for risk of human STEC infections of probable cattle, small ruminant, pig or poultry origin

Epidemiol. Infect. (2015), **143**, 1360–1367. © Cambridge University Press 2014
doi:10.1017/S0950268814002349

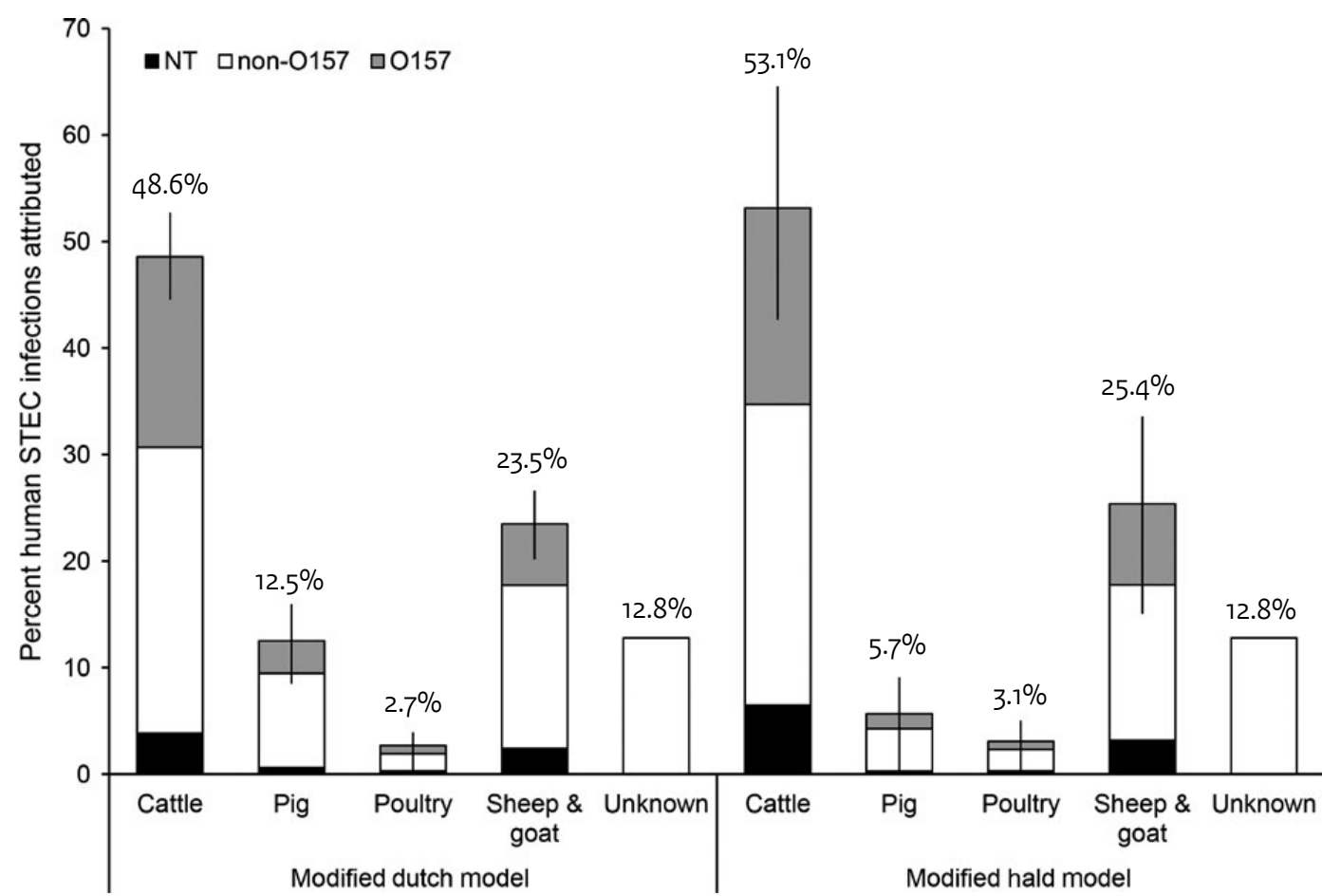
Risk factors for sporadic Shiga toxin-producing *Escherichia coli* O157 and non-O157 illness in The Netherlands, 2008–2012, using periodically surveyed controls

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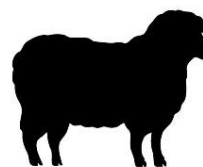
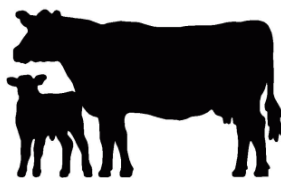


Overall attributions





Source attribution (%) most important O-serotypes



O157	321	68.8 (44.8-88.9)	21.4 (7.2-43.0)	5.0 (0.9-14.3)	4.7 (0.3-15.9)
Non-O157	604	56.1 (47.3-73.6)	32.0 (18.5-41.9)	7.1 (2.1-12.2)	4.8 (1.2-9.7)
O26	105	74.3 (47.4-99.3)	13.5 (2.6-34.0)	6.2 (0.8-19.0)	6.0 (0.3-21.2)
O91	87	67.3 (33.2-97.8)	24.8 (4.8-58.1)	6.3 (0.5-21.7)	1.6 (0.0-7.1)
O103	52	74.8 (38.4-100)	19.0 (2.4-51.8)	6.2 (0.4-23.2)	0.0 (0.0-0.0)
O146	50	16.9 (2.4-46.0)	76.8 (43.2-100)	4.6 (0.3-17.5)	1.7 (0.0-7.4)
O113	36	62.1 (30.0-98.7)	31.4 (9.0-64.8)	5.1 (0.5-17.1)	1.4 (0.0-5.8)
Others	274	48.9 (15.1-66.3)	35.5 (11.6-80.3)	8.5 (1.3-26.2)	7.1 (1.0-11.4)
Non-typeable	89	56.5 (27.4-86.2)	35.2 (12.2-65.8)	7.3 (1.1-21.9)	1.0 (0.0-4.1)



	Overall (unweighted)				
Age (years)					
≤5	Reference	Reference	Reference	Reference	Reference
6–15	0.93 (0.56–1.55)	1.00 (0.58–1.71)	1.14 (0.62–2.10)	0.96 (0.53–1.74)	0.64 (0.28–1.44)
16–45	0.56 (0.36–0.87)	0.56 (0.35–0.89)	0.85 (0.49–1.47)	0.57 (0.34–0.95)	0.58 (0.30–1.10)
46–65	0.12 (0.08–0.20)	0.10 (0.06–0.18)	0.24 (0.12–0.48)	0.12 (0.07–0.22)	0.16 (0.06–0.42)
≥66	0.20 (0.12–0.31)	0.18 (0.11–0.29)	0.31 (0.17–0.55)	0.24 (0.14–0.43)	0.25 (0.08–0.81)
Gender (♂ vs. ♀)	1.31 (1.01–1.70)	1.28 (0.97–1.69)	1.28 (0.92–1.77)	1.39 (1.02–1.88)	1.59 (0.76–3.35)
Year					
2010	Reference	Reference	Reference	Reference	Reference
2011	1.86 (1.19–2.90)	2.04 (1.23–3.38)	2.27 (1.26–4.11)	2.11 (1.19–3.72)	1.42 (0.75–2.69)
2012	1.37 (0.87–2.16)	1.45 (0.87–2.42)	1.22 (0.68–2.18)	1.48 (0.87–2.53)	2.48 (0.68–9.03)
2013	2.19 (1.41–3.42)	2.29 (1.36–3.86)	3.65 (1.88–7.08)	2.86 (1.56–5.23)	9.94 (0.87–114.03)
2014	2.46 (1.57–3.86)	2.96 (1.75–5.01)	3.63 (1.85–7.10)	3.39 (1.81–6.32)	9.23 (1.15–74.00)
Season					
Winter	Reference*	Reference	Reference	Reference	Reference
Spring	0.55 (0.35–0.89)	0.65 (0.39–1.08)	0.70 (0.40–1.23)	0.77 (0.44–1.35)	0.27 (0.06–1.20)
Summer	5.71 (3.77–8.64)	7.20 (4.48–11.55)	8.54 (4.72–15.46)	8.28 (4.77–14.37)	13.82 (0.66–291.36)
Autumn	2.15 (1.46–3.16)	2.57 (1.66–3.99)	2.41 (1.44–4.04)	2.26 (1.40–3.66)	1.02 (0.29–3.58)
SES	1.17 (1.02–1.34)	1.19 (1.02–1.40)	1.10 (0.92–1.31)	1.25 (1.03–1.50)	1.29 (0.86–1.95)
Urbanization					
Urban	Reference	Reference	Reference	Reference	Reference
Intermediate	1.37 (0.92–2.04)	1.34 (0.89–2.02)	0.93 (0.58–1.49)	1.30 (0.83–2.04)	2.71 (1.29–5.68)
Rural	1.62 (1.04–2.54)	1.61 (1.01–2.57)	1.03 (0.60–1.75)	1.41 (0.86–2.33)	3.75 (1.27–11.04)
Raw meat spreads	n.s.	1.67 (1.24–2.25)	n.s.	n.s.	n.s.
Beef	1.39 (1.15–1.92)	1.60 (1.15–2.23)	n.s.	n.s.	n.s.
Raw vegetables	0.27 (0.19–0.40)	0.27 (0.18–0.42)	0.22 (0.14–0.36)	0.32 (0.20–0.52)	0.43 (0.19–0.96)
Minced meat	n.s.	n.s.	1.57 (1.03–2.40)	n.s.	1.90 (1.08–3.34)
Undercooked meat	1.67 (1.24–2.24)	n.s.	1.81 (1.26–2.58)	2.03 (1.49–2.78)	2.12 (1.06–4.26)
Cured meat	1.35 (1.03–1.77)	n.s.	n.s.	n.s.	2.84 (1.46–5.53)



Received: 9 November 2016
DOI: 10.1111/zph.12403

ORIGINAL ARTICLE

WILEY

Attribution of human infections with Shiga toxin-producing *Escherichia coli* (STEC) to livestock sources and identification of source-specific risk factors, The Netherlands (2010–2014)

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Summary

Shiga toxin-producing *Escherichia coli* (STEC) is a zoonotic pathogen of public health concern whose sources and transmission routes are difficult to trace. Using a combined source attribution and case-control analysis, we determined the relative contributions of four putative livestock sources (cattle, small ruminants, pigs, poultry) to human STEC infections and their associated dietary, animal contact, temporal and socio-economic-demographic risk factors in the Netherlands in 2010/2011–2014. Dutch source data were supplemented with those from other European countries with similar STEC epidemiology. Human STEC infections were attributed to sources using both the modified Dutch model (mDM) and the modified Hald model (mHM) supplied with the same O-serotyping data. Cattle accounted for 48.6% (mDM) and 53.1% (mHM) of the 1,183 human cases attributed, followed by small ruminants (mDM: 23.5%; mHM: 25.4%), pigs (mDM: 12.5%; mHM: 5.7%) and poultry (mDM: 2.7%; mHM: 3.1%), whereas the sources of the remaining 12.8% of cases could not be attributed. Of the top five O-serotypes infecting humans, O157, O26, O91 and O103 were mainly attributed to cattle (61%–75%) and O146 to small ruminants (71%–77%). Significant risk factors for human STEC infection as a whole were the consumption of beef, raw/undercooked meat or cured meat/cold cuts. For cattle-attributed STEC infections, specific risk factors were consuming raw meat spreads and beef. Consuming raw/undercooked or minced meat were risk factors for STEC infections attributed to small ruminants. For STEC infections attributed to pigs, only consuming raw/undercooked meat was significant. Consuming minced meat, raw/undercooked meat or cured meat/cold cuts were associated with poultry-attributed STEC infections. Consuming raw vegetables was protective for all STEC infections. We concluded that domestic ruminants account for approximately three-quarters of reported human STEC infections, whereas pigs and poultry play a minor role and that risk factors for human STEC infection vary according to the attributed source.

KEYWORDS

animal reservoirs, *E. coli*, risk factors, shiga toxin-producing *Escherichia coli*, source attribution, transmission routes



Aim

To study the spatial association between STEC O157 human infections and livestock densities in the Netherlands



Methods

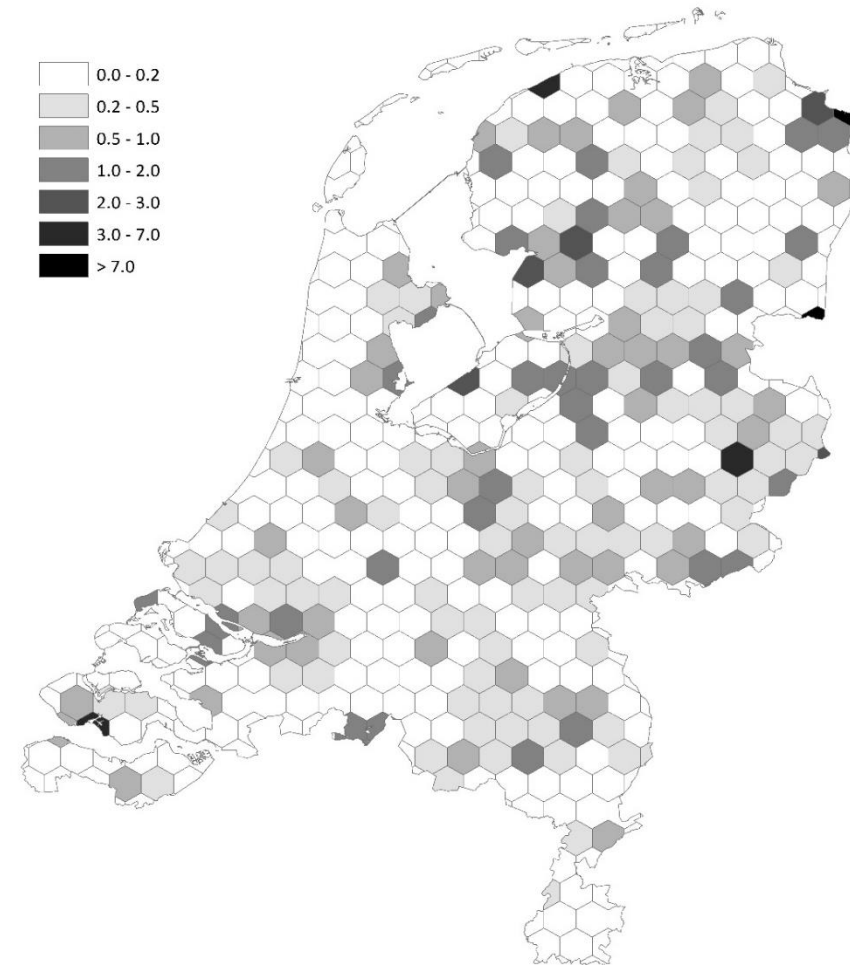
Spatial analysis

- Hexagons ~90 km²
- Spatial regression analyses (INLA)

STEC O157 cases 2009-2016 (OSIRIS)

Population (CBS)

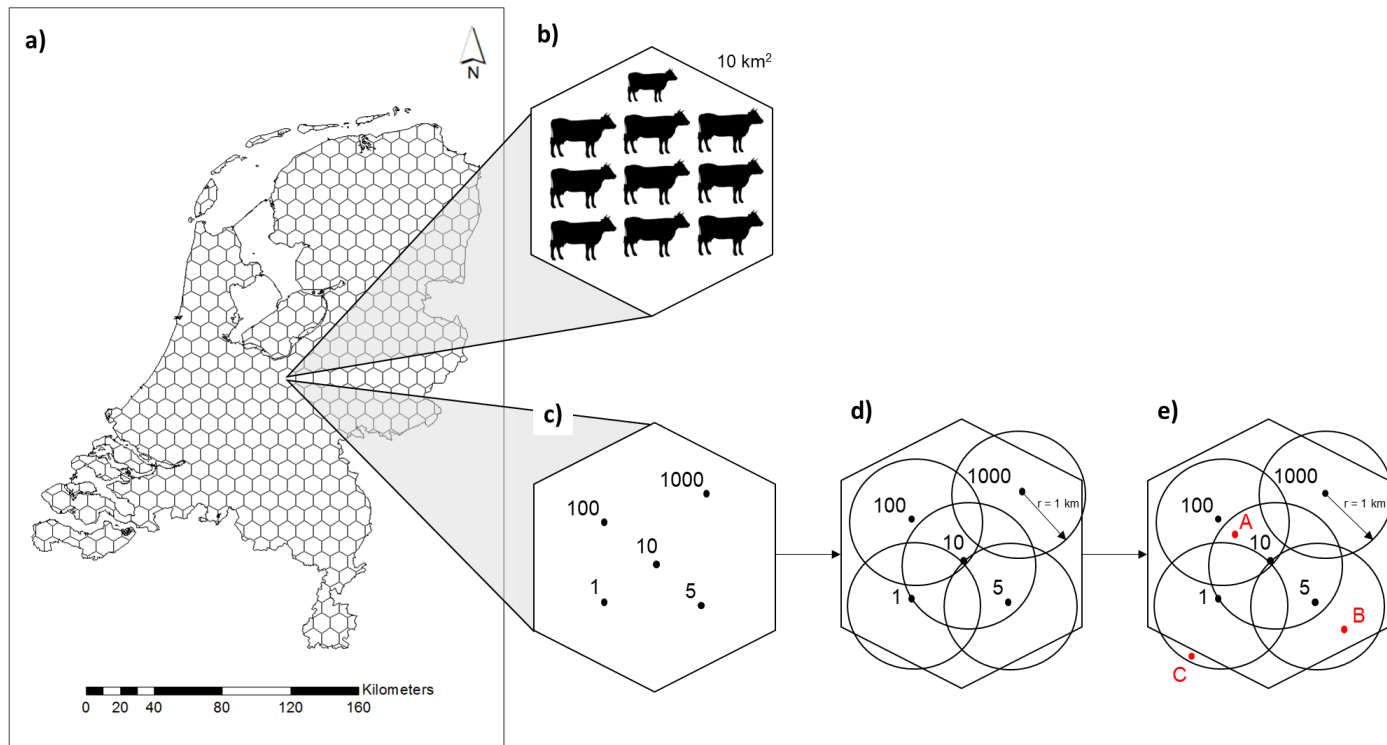
Animals per farm (I&R – RVO)

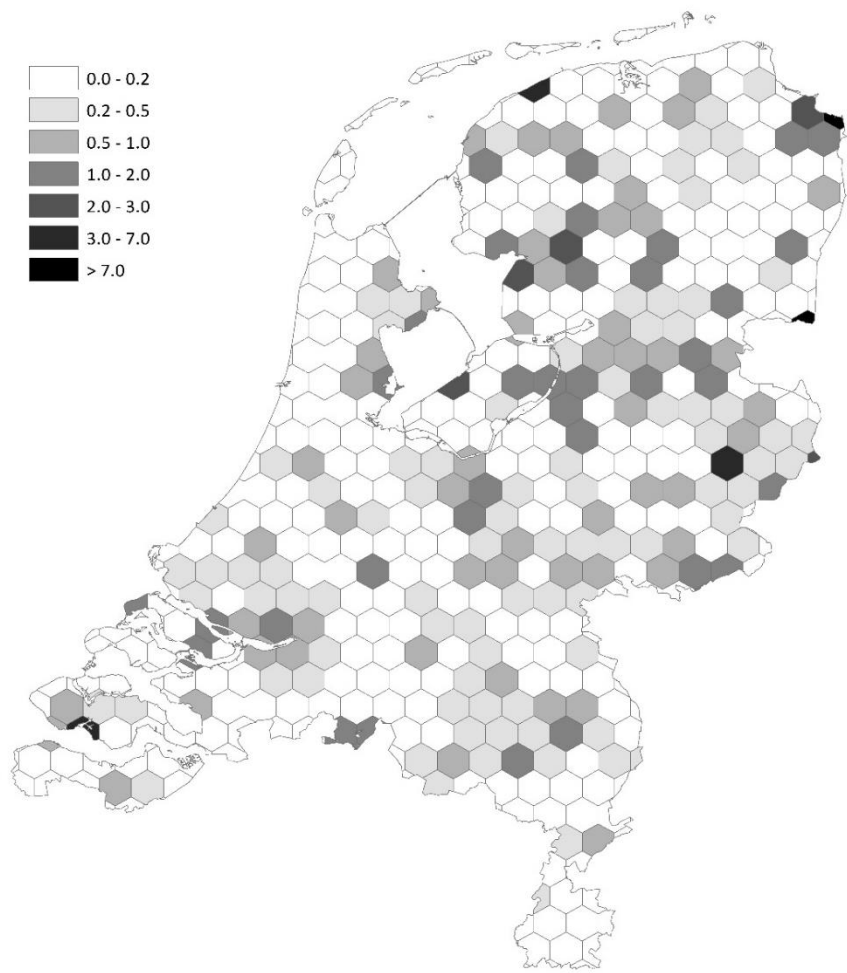


Cumulative human STEC O157 incidence rate (x 100,000 person-years)

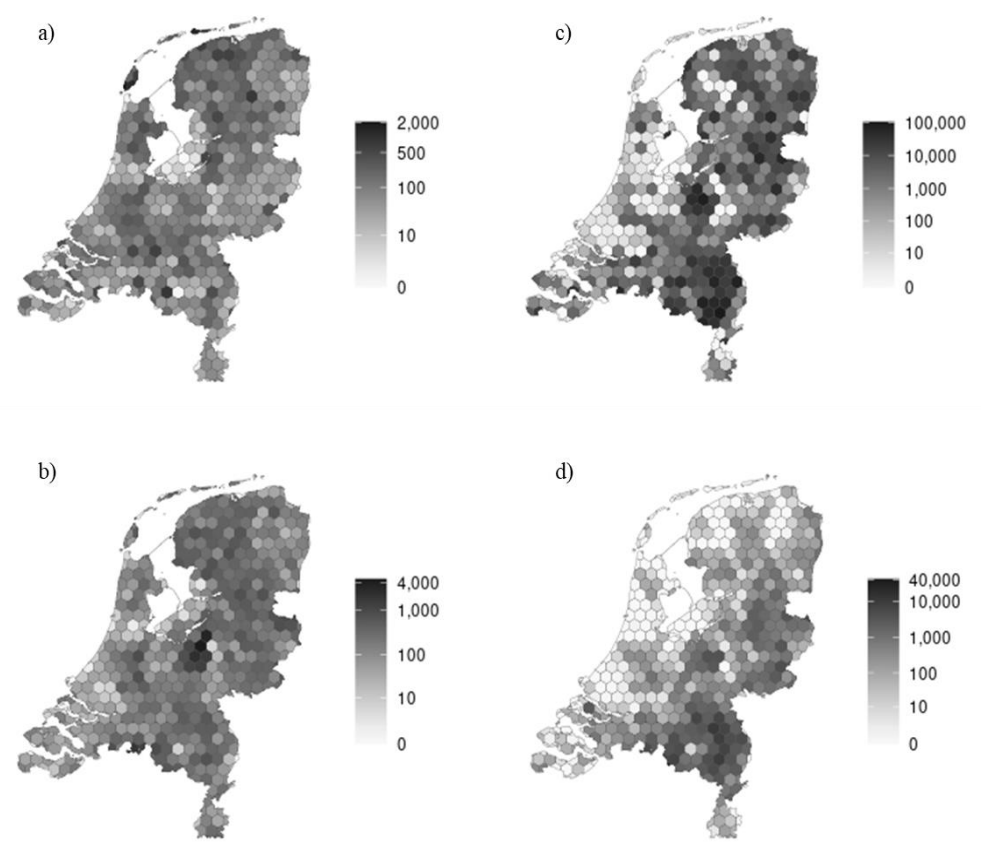
Population-weighted number of animals

$$\text{Exposure measure} = \frac{100 * A + 1000 * 0 + 10 * A + 5 * B + 1}{100 + 1000 + 10 + 1 + 5}$$





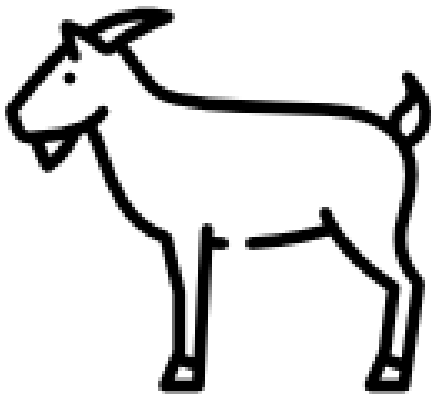
Cumulative human STEC O157 incidence rate (x 100,000 person-years)



Population-weighted number of animals for small ruminants (a), cattle (b), poultry (c) and pigs (d)



Small ruminants



Variable	P-value	RR	95% CI
Gender			
Males	Reference category		
Females	<0.001	1.74	1.40-2.17
Age category (years)			
0-4	<0.001	4.05	2.91-5.59
5-9	<0.001	2.01	1.32-2.97
10-49	0.27	1.15	0.90-1.49
≥ 50 (ref)	Reference category		
Livestock			
Small ruminants	0.03	1.13	1.01-1.26
Cattle	0.69	0.97	0.86-1.11
Poultry	0.50	1.01	0.97-1.06
Pigs	0.83	1.01	0.94-1.07



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**Thank you for
listening!**

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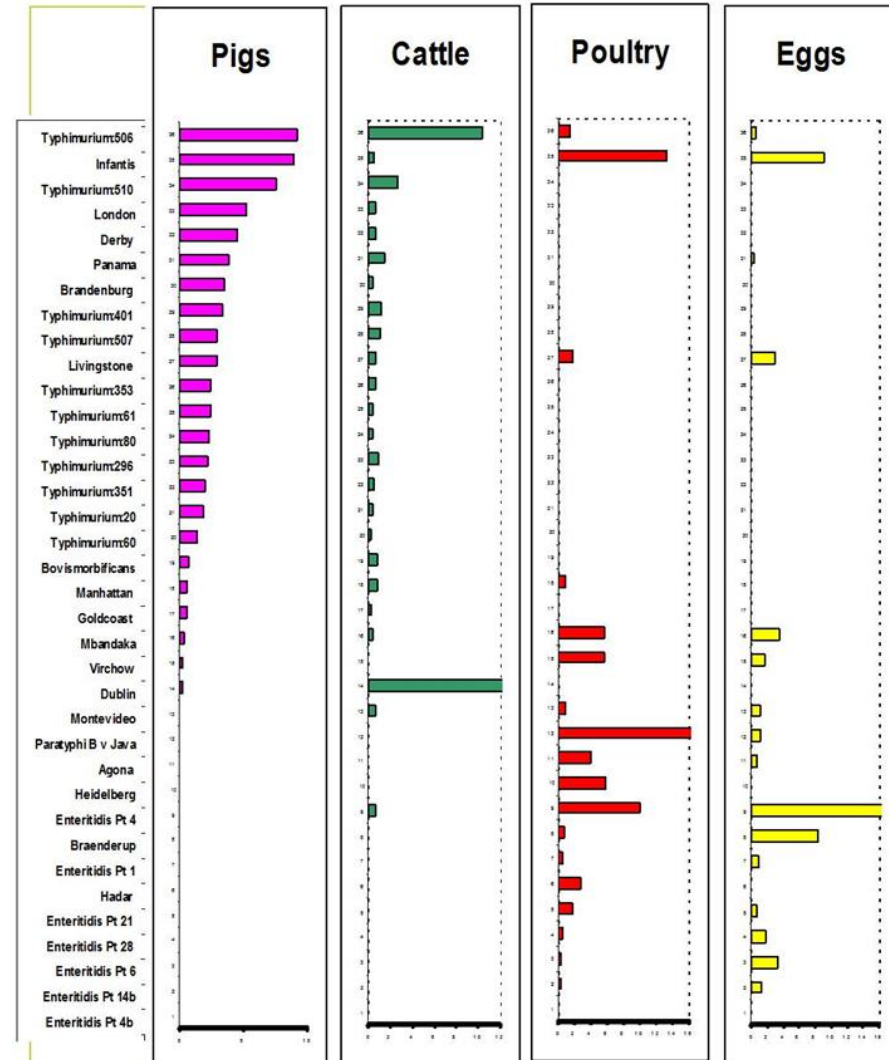
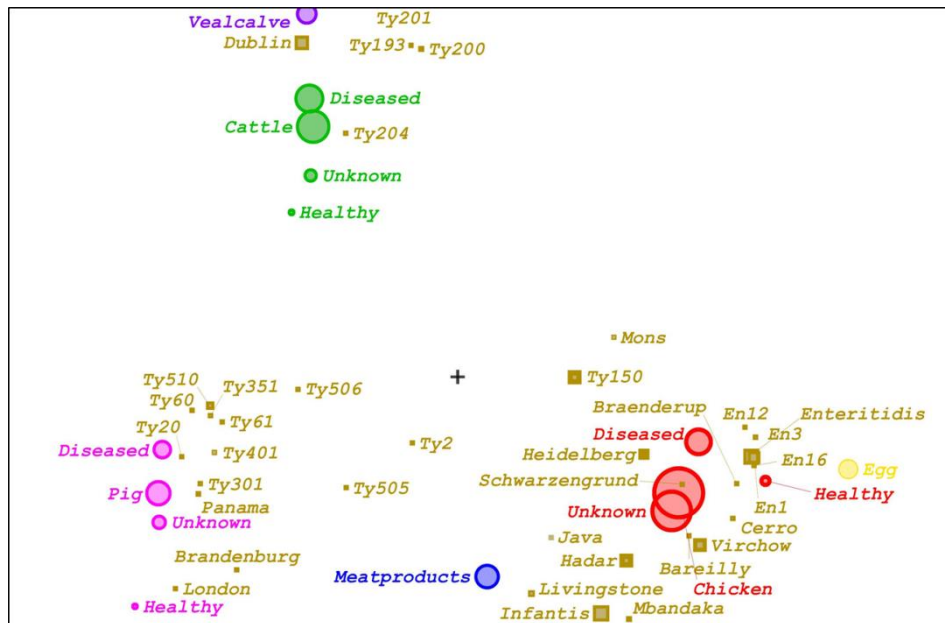




TABLE 4 Proportional similarity index values (%) and corresponding 95% bootstrap confidence intervals between the O-serotype frequency distributions of the Dutch and non-Dutch isolates from humans and from each livestock source

Dutch isolates	Human	Non-Dutch livestock isolates			
		Cattle	Small ruminants	Pigs	Poultry
Human	-	65.5 (55.2–75.8)	48.9 (30.5–67.1)	31.5 (3.0–60.0)	39.6 (8.5–70.9)
Cattle	32.8 (7.0–58.5)	39.3 (8.5–70.1)	-	-	-
Small ruminants	45.6 (61.6–29.7)	-	63.5 (49.7–76.8)	-	-
Pigs	30.1 (7.0–53.0)	-	-	14.6 (0.0–59.5)	-
Poultry	38.6 (14.2–63.2)	-	-	-	16.7 (0.0–65.5)

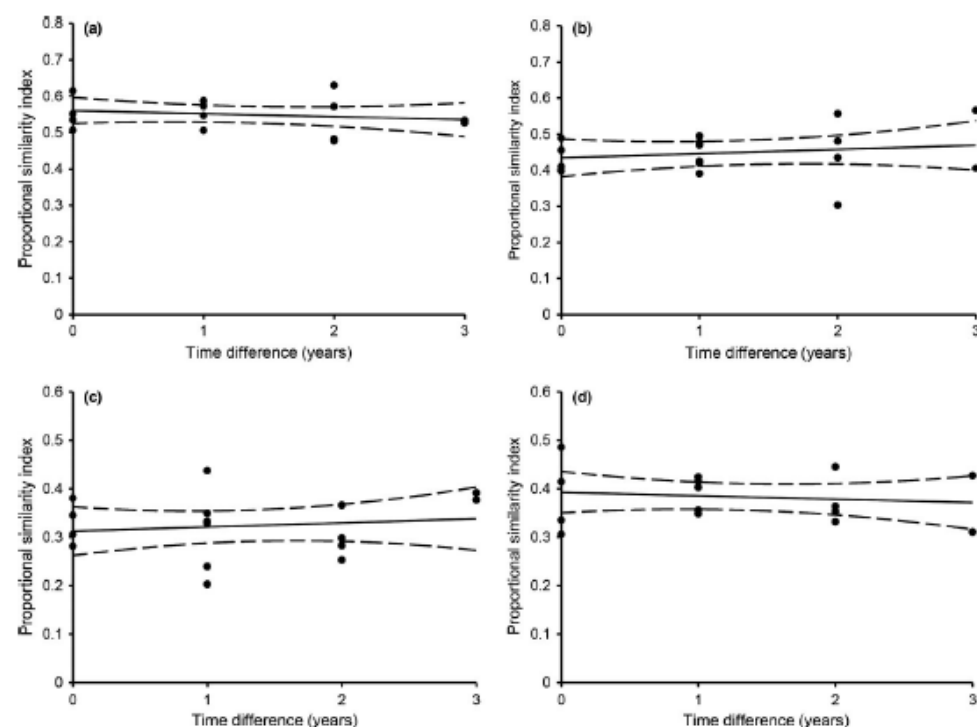


FIGURE 2 Similarity of O-serotype frequency distributions between human and cattle (a), small ruminant (b), pig (c) and poultry (d) isolates collected in different years (2011 to 2014)