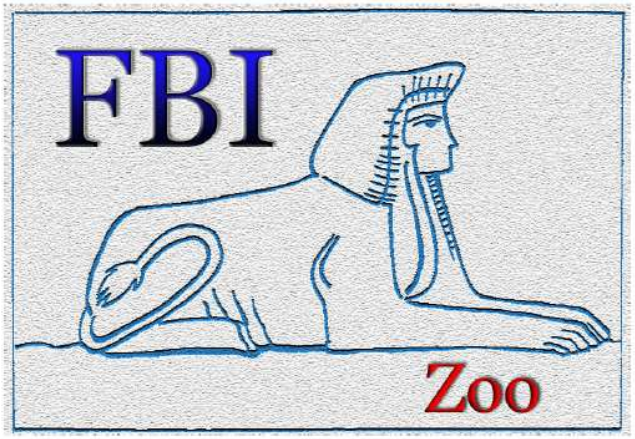
Interdisziplinäres Forschungsnetzwerk: Lebensmittel-übertragene zoonotische Infektionen beim Menschen

Food-Borne Zoonotic Infections of Humans (FBI-Zoo)



Sprecher: Lothar H. Wieler

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Yersinia enterocolitica
Salmonella enterica enterica
Escherichia coli
Campylobacter jejuni

Herbert Schmidt

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Lothar Kreienbrock
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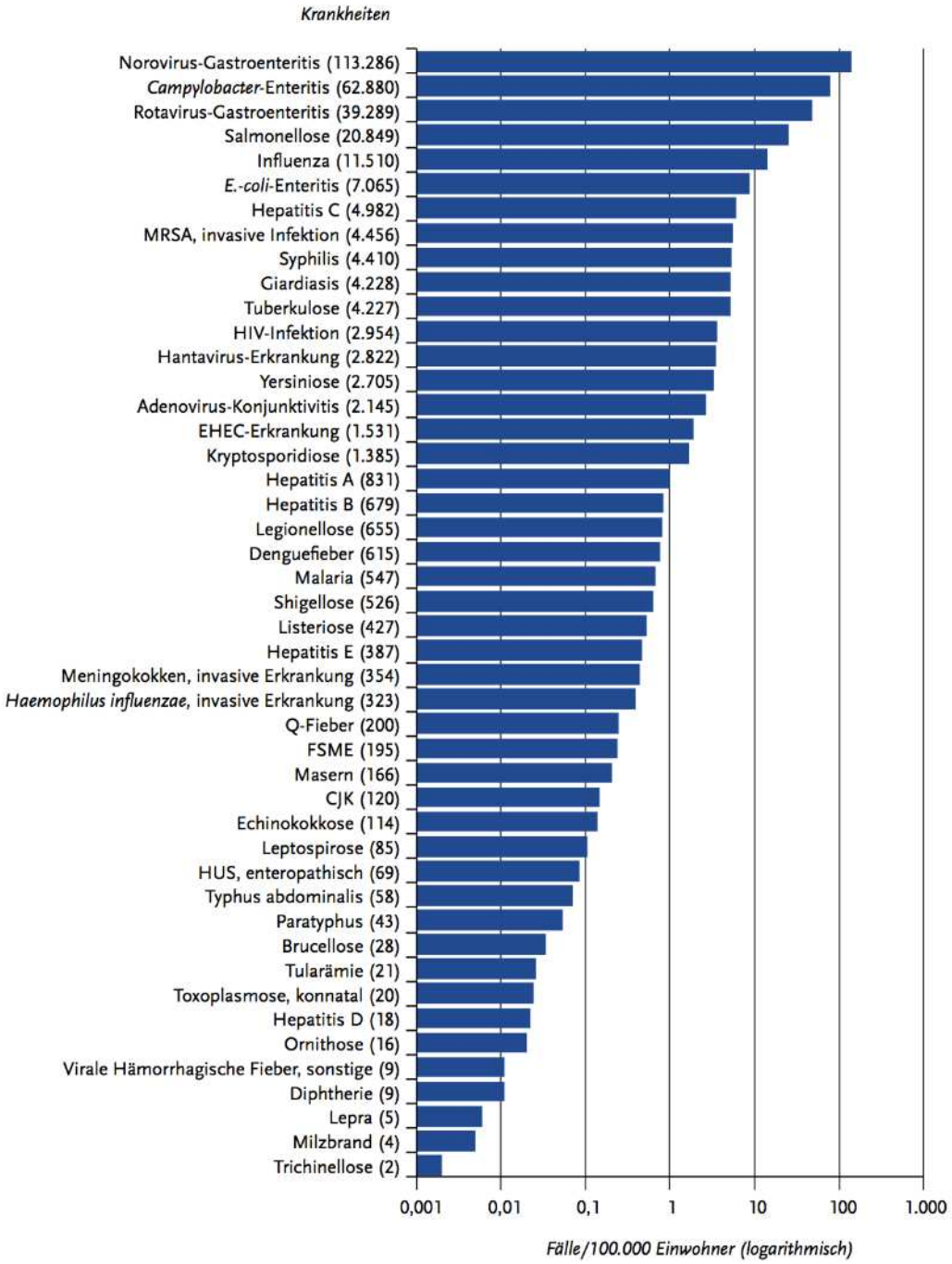
Abb. 4.1.1:
Inzidenz und Anzahl der Fälle aller meldepflichtigen Krankheiten, Deutschland, 2012



Cave: teilweise starkes „Underreporting“ (z.B. bei Lebensmittel-bedingten Infektionskrankheiten)

RKI: Infektionsepidemiologisches Jahrbuch für 2012

Fort- und Weiterbildungskonzept:

+++ FOKUS: Nachwuchsförderung +++

Tagungen:

- 12x Verbundtreffen (alternierend intern / international mit Themenschwerpunkt)
- Teilnahme an nationalen und internationalen Tagungen (DGHM, Zoonosensymposium)

Workshops:

- 5x (sequenzbasierte Typisierung, MLVA, NGS, Infektionsepidemiologie etc.)

Graduiertenkollegs / PhD-Programme:

- GRK1121, IRTG1273, IRTG1673, Summer Schools etc.
- Veterinary Research and Animal Biology, Biomedical Sciences, etc.

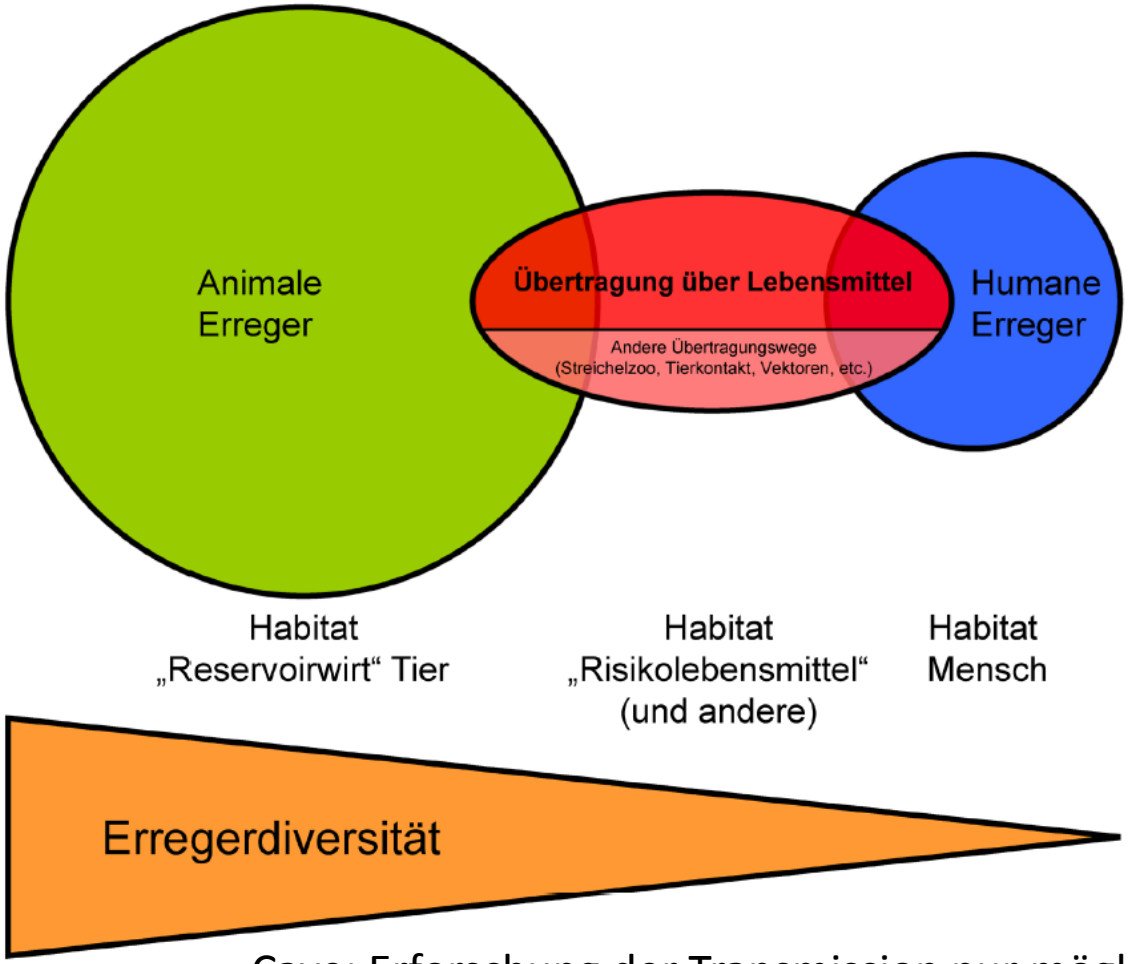
Networking:

- gemeinsame Abendveranstaltungen
- Laborbesuche (Verbund-intern und -extern)
- Teilnahme an internationalen Tagungen / Summer Schools
- Fachgruppe „Zoonosen“ (DGHM); Querschnittaktivität „PBA-Zoo“; mikrobiologische Primärdatenbank (TMF)

Forschungskonzept:

+++ FOKUS: Biologie des Erregers im spezifischen Habitat +++

Yersinia enterocolitica
Salmonella enterica enterica
Escherichia coli
Campylobacter jejuni



Cave: Erforschung der Transmission nur möglich nach Habitat-übergreifender Erregertypisierung
Warum: mögliche Einträge der Zoonose-Erreger über andere Habitate sowie Adaptation an Mensch!!!

Forschungskonzept:
Im Zentrum steht der Erreger!!

Technisch / experimentelle Grundlage:

- Anzucht, Klassifizierung und Typisierung von Erregervarianten

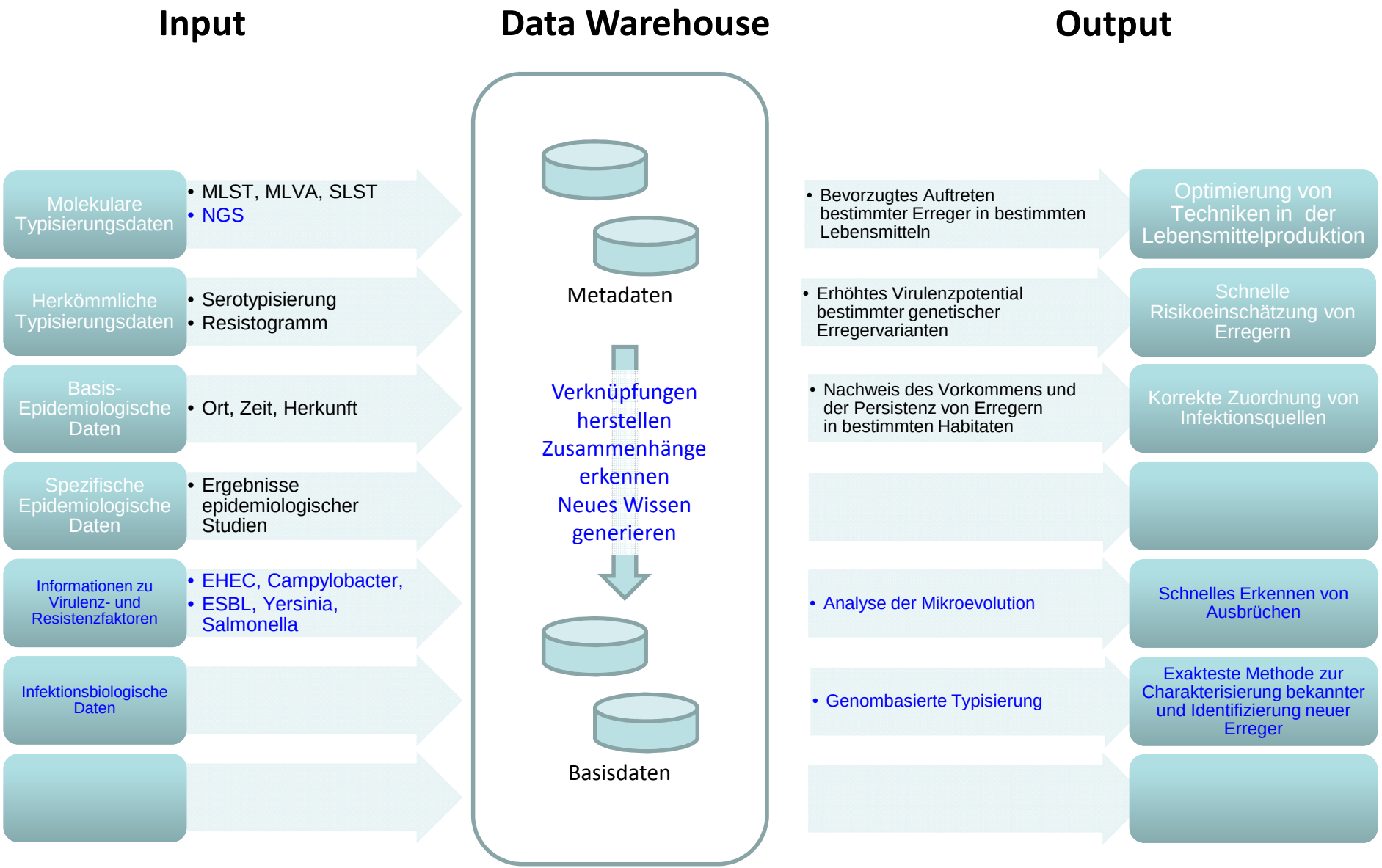
- eindeutige Assoziation zwischen Erregervariante und Habitat

- experimentelle funktionelle Analyse der Biologie identischer Erregervarianten in verschiedenen Habitaten

Grundprinzip:

- NUR durch **Verbindung** von Infektionsepidemiologie mit molekularer Typisierung und molekularer Infektionsbiologie können wirksame Interventions- und Präventions-Maßnahmen in den jeweiligen Habitaten etabliert werden

Data warehouse



Public Health:
Sichere Lebensmittel tierischer Herkunft

Highlights:

Habitat Tier (*in vivo / in vitro*):

- Etablierung Minipig-Infektionsmodell *Yersinia enterocolitica* / *Campylobacter jejuni*
- Etablierung Hühner-Infektionsmodell *Campylobacter jejuni* / *Salmonella enterica*

Forschungsergebnisse:

- Invasin ist essentieller Adhäsionsfaktor von *Yersinia enterocolitica* bioserotype 4/O:3 im Schwein, nicht aber in der Maus (im Gegensatz zu *Yersinia enterocolitica* bioserotype 4/O:8)
- *Campylobacter jejuni* besteht aus Generalisten (Zoonose-Erreger) und Spezialisten Hinweise, Hinweise auf unterschiedliche Nährstoffmetabolisierung

Handlungsoptionen:

- Invasin als möglicher Vakzine-Kandidat gegen *Yersinia enterocolitica* im Schwein
- Spezifische Futterrationen können Vermehrung von *C. jejuni* reduzieren

Minipig-Infektionsmodell

IAI Accepts, published online ahead of print on 16 December 2013
Infect. Immun. doi:10.1128/IAI.01001-13

An essential role of invasin for colonization and persistence of *Yersinia enterocolitica* in its natural reservoir host, the pig

Julia Schaake[1*], Anna Drees[2*], Petra Grüning[2*], Frank Uliczka[1], Fabio Pisano[1], Tanja Thiermann[1], Alexandra von Altrock[3], Frauke Seehusen[4], Peter Valentin-Weigand[2*], Petra Dersch[1*]

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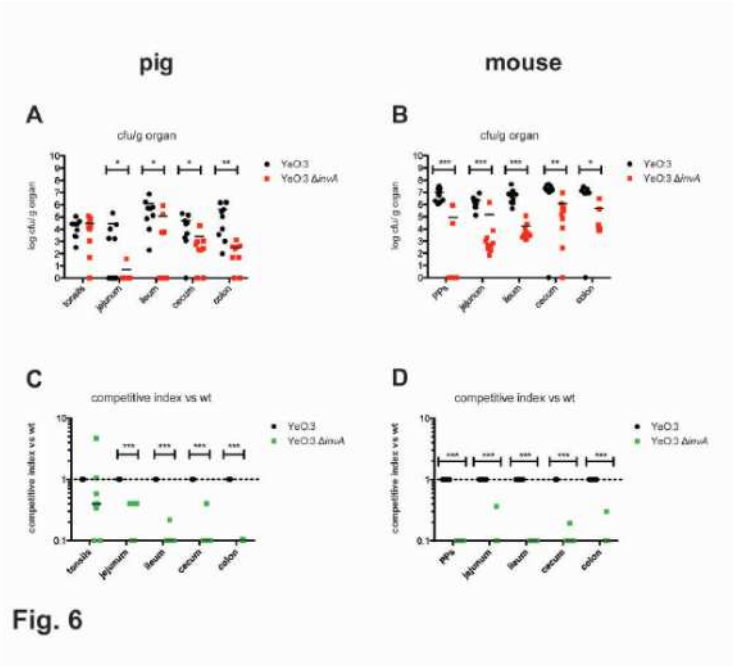
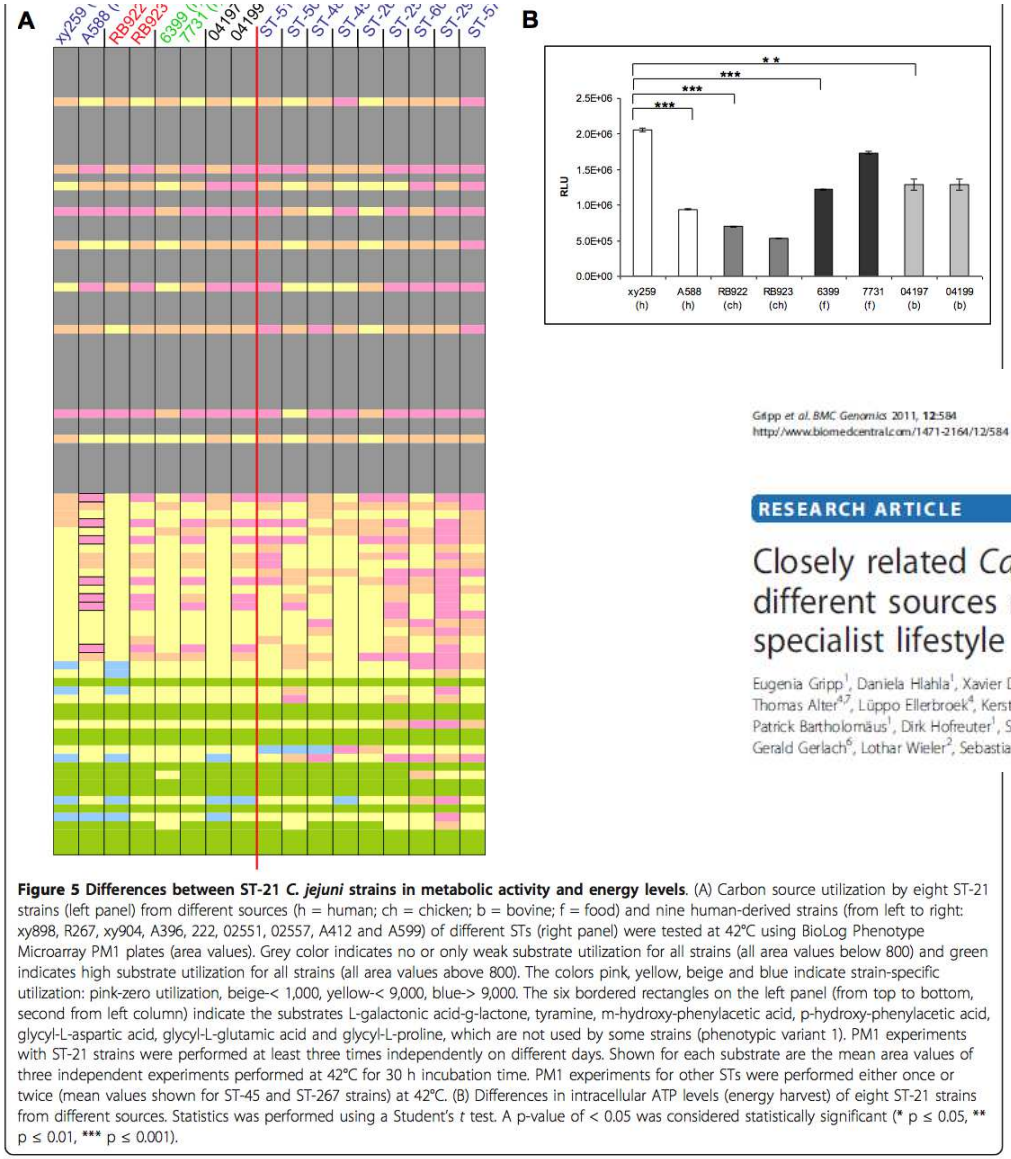


Fig. 6

Hühner-Infektionsmodell und Next-generation Sequencing

Campylobacter jejuni Generalisten und Spezialisten



Gripp et al. BMC Genomics 2011, 12:584
http://www.biomedcentral.com/1471-2164/12/584

BMC Genomics

RESEARCH ARTICLE Open Access

Closely related *Campylobacter jejuni* strains from different sources reveal a generalist rather than a specialist lifestyle

Eugenia Gripp[1], Daniela Hlahla[1], Xavier Didelot[2], Friederike Kops[1], Sven Maurischat[3], Karsten Tedin[3], Thomas Alter[4,7], Lüppo Ellerbroek[4], Kerstin Schreiber[5], Dietmar Schomburg[5], Traute Janssen[3], Patrick Bartholomäus[1], Dirk Hofreuter[1], Sabrina Woltemate[1], Markus Uhr[1], Birgit Brenneke[1], Petra Grüning[6], Gerald Gerlach[6], Lothar Wieler[2], Sebastian Suerbaum[1*] and Christine Josenhans[1*]

Figure 5 Differences between ST-21 *C. jejuni* strains in metabolic activity and energy levels. (A) Carbon source utilization by eight ST-21 strains (left panel) from different sources (h = human; ch = chicken; b = bovine; f = food) and nine human-derived strains (from left to right: xy898, R267, xy904, A396, 222, 02551, 02557, A412 and A599) of different STs (right panel) were tested at 42°C using BioLog Phenotype Microarray PM1 plates (area values). Grey color indicates no or only weak substrate utilization for all strains (all area values below 800) and green indicates high substrate utilization for all strains (all area values above 800). The colors pink, yellow, beige and blue indicate strain-specific utilization: pink-zero utilization, beige-< 1,000, yellow-< 9,000, blue-> 9,000. The six bordered rectangles on the left panel (from top to bottom, second from left column) indicate the substrates L-galactonic acid-g-lactone, tyramine, m-hydroxy-phenylacetic acid, p-hydroxy-phenylacetic acid, glycyl-L-aspartic acid, glycyl-L-glutamic acid and glycyl-L-proline, which are not used by some strains (phenotypic variant 1). PM1 experiments with ST-21 strains were performed at least three times independently on different days. Shown for each substrate are the mean area values of three independent experiments performed at 42°C for 30 h incubation time. PM1 experiments for other STs were performed either once or twice (mean values shown for ST-45 and ST-267 strains) at 42°C. (B) Differences in intracellular ATP levels (energy harvest) of eight ST-21 strains from different sources. Statistics was performed using a Student's *t* test. A p-value of < 0.05 was considered statistically significant (* $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$).

Habitat Reservoirwirt:

Wenige „Supershedder“ verbreiten EHEC im Rinderbestand

Menrath et al. Gut Pathogens 2010, 2:7
http://www.gutpathogens.com/content/2/1/7

Gut Pathogens

RESEARCH Open Access

Shiga toxin producing *Escherichia coli:* identification of non-O157:H7-Super-Shedding cows and related risk factors

Andrea Menrath[1*], Lothar H Wieler[2], Katrin Heidemanns[2], Torsten Semmler[2], Angelika Fruth[3], Nicole Kemper[1]

Abstract

Background: Shiga toxin producing *Escherichia coli* (STEC) are an important cause of human gastro-enteritis and extraintestinal sequelae, with ruminants, especially cattle, as the major source of infection and reservoir. In this study, the fecal STEC shedding of 133 dairy cows was analyzed over a period of twelve months by monthly sampling with the aim to investigate shedding patterns and risk factors.

Results: Overall, 24.7% (in total 407) of 1,646 fecal samples were tested positive for *stx* by PCR with inner-herd prevalences on the different farms of 11.1% to 32.3%. At individual levels, cows were *stx*-positive on zero to eight consecutive samplings. According to a strictly longitudinal definition of Super-Shedding, in the present study 14 cows were identified as Super-Shedders of non-O157 serotypes.
Significant risk factors for the shedding of STEC were the month of sampling, the number of lactations and days in lactation, the nutritional condition, the somatic cell count and the content of protein in milk. Most notably, the presence of STEC Super-Shedding cows in the herd was a significant risk factor, revealing that STEC Super-Shedding is not restricted to STEC O157:H7 alone.

Conclusions: These data have implications for possible interventions, as removing single non-O157:H7 STEC Super-Shedding cattle from farms would significantly reduce STEC burden.

Public Health:
Sichere Lebensmittel tierischer Herkunft

Highlights:

Habitat Lebensmittel:

- Etablierung Hackfleisch-Kontaminationsmodell EHEC / *Yersinia*
- Etablierung Milch-Kontaminationsmodell *Campylobacter*

Forschungsergebnisse:

- EHEC O157:H7: bei Hitzestress in Hackfleisch erhöhte Expression von Adhäsionsgenen
- *C. jejuni*-Stoffwechsel: Casein (-); Caseinhydrolysat (+), tryptisch verdautes Casein (+)

Handlungsoptionen:

- Optimierung Herstellungs- und Konservierungsverfahren Lebensmittel tier. Herkunft

Hackfleisch-Kontaminationsmodell:

Stamm-spezifische Unterschiede – Beachtung bei Risikobewertung

Eur Food Res Technol
DOI 10.1007/s00217-013-2104-9

SHORT COMMUNICATION

Comparison of net growth of Shiga toxin-producing *Escherichia coli* strains of serogroups O26, O103, and O157 in ground meat at different temperatures

Andrea Kroj · Elisabeth Hauser · Herbert Schmidt

Received: 16 August 2013 / Revised: 16 September 2013 / Accepted: 21 September 2013

Abstract In this study, the net growth of 22 Shiga toxin-producing *Escherichia coli* O26, O103, and O157 strains originating from risk foods, animal feces, and patients suffering from hemolytic-uremic syndrome was compared in ground beef at 15 and 37 °C. The results of this study demonstrated that the ability to grow to high numbers in ground meat at these temperatures is strain-specific rather than serogroup- or origin-specific.

Enterohemorrhagic *E. coli* (EHEC) are a subgroup of STEC that can cause a spectrum of human gastrointestinal diseases ranging from mild diarrhea, hemorrhagic colitis, up to the life-threatening hemolytic-uremic syndrome (HUS) [4]. EHEC produce one or more Stx as well as other virulence factors encoded on the chromosome, on prophages, or on plasmids. Most EHEC strains carry the locus of enterocyte effacement (LEE), encoding several type III effector proteins, and the outer membrane protein

Journal of Food Protection, Vol. 74, No. 9, 2011, Pages 1434–1440
doi:10.4315/0362-028X.JFP-11-018

Specific Expression of Adherence-Related Genes in *Escherichia coli* O157:H7 Strain EDL933 after Heat Treatment in Ground Beef

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MS 11-018: Received 14 January 2011/Accepted 1 April 2011

ABSTRACT

In this study, the expression of particular stress- and virulence-associated genes of *Escherichia coli* O157:H7 strain EDL933 in ground beef was investigated using real-time PCR. Specific gene expression in the food matrix was found in combination with heat treatment. In contrast to a treatment at 37°C, treatment at 48°C for 10 min resulted in increased expression of the genes *eae*, *hcpA*, *iha*, *lpfA*, and *toxB*. Adherence to human intestinal HT-29 cells was enhanced in bacterial cells inoculated and heat treated in ground beef. The expression of *gadE*, which encodes a main regulator of the glutamate system of the acid response, was reduced under these conditions. However, expression of *rpoS* and *recA*, which are involved in the establishment of stress responses, and Shiga toxin genes was not significantly different under the same conditions.

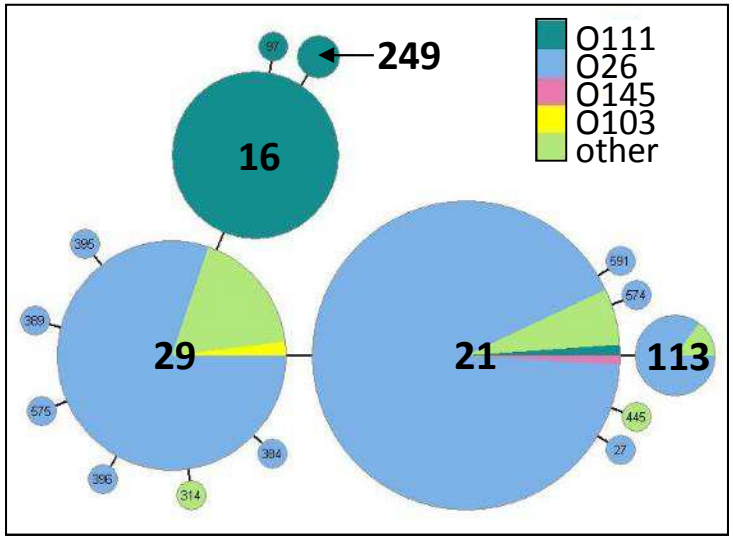
DNA-Sequenztypisierung:

Serotypisierung der wichtigsten non-O157 EHEC täuscht fehlende Verwandtschaft vor

- "**big five**" – die wichtigsten klassischen EHEC-Serotypen:

O157 (H7/H-)
O26 (H11/H-)
O103 (H2/H-)
O145 (H25/H28/H-)
O111 (H8/H-)

} non-O157



Sequenztyp-Komplex 29

Inga Eichhorn, 2013

Gesamtgenomsequenzierung mittels NGS:

Enterohämorrhagische und atypische Enteropathogene *E. coli* im Sequenztyp-Komplex 29 sind hochverwandt

hohe Prävalenz bei Rindern – Entstehung von EHEC durch Phagentransduktion?

Sequenztyp-Komplex 29

Inga Eichhorn, 2013

Public Health:
Sichere Lebensmittel tierischer Herkunft

Highlights:

Habitat Mensch:

- Etablierung NGS zum Nachweis und zur Diagnostik von EHEC (2011: EHEC O104:H4)
- Anwendung MLST/MLVA zur Typisierung von *Salmonella enterica enterica* Serovaren
- Fall-Kontroll-Studien zu Risikofaktoren von sporadischen Yersinia-, Salmonella und Campylobacter-Infektionen

Forschungsergebnisse:

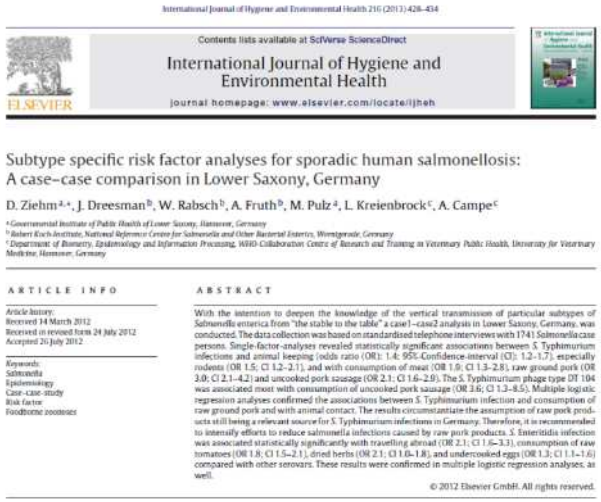
- EHEC-Ausbruch 2011: EHEC O104:H4 ist kein typischer Zoonoseerreger; vier der „big five“ sind genetisch nahe verwandt
- *Salmonella enterica enterica* Serovare sind polyphyletisch: Humaninfektionsquellen variieren in Abhängigkeit von der genetischen Linie

Handlungsoptionen:

- Etablierung und Validierung DNA-Sequenzbasierter Typisierungsmethoden
- Etablierung, Validierung und Anwendung einfacher diagnostischer Tests
- Aufklärung über Risikofaktoren

Molekulare Typisierung von Salmonella:

Identische Serovare bestehen aus mehreren habitatspezifischen genetischen Linien: verschiedene Infektionsquellen für den Menschen innerhalb eines Serovares → „Source attribution“



International Journal of Hygiene and Environmental Health 216 (2013) 426–434

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journal homepage: www.elsevier.com/locate/ijheh

Subtype specific risk factor analyses for sporadic human salmonellosis: A case–case comparison in Lower Saxony, Germany

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[b] Robert Koch-Institute, National Reference Centre for Salmonella and Other Bacterial Enterics, Wernigerode, Germany
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ABSTRACT

With the intention to deepen the knowledge of the vertical transmission of particular subtypes of *Salmonella enterica* from "the stable to the table" a case1–case2 analysis in Lower Saxony, Germany, was conducted. The data collection was based on standardised telephone interviews with 1741 *Salmonella* case persons. Single-factor-analyses revealed statistically significant associations between *S.* Typhimurium infections and animal keeping (odds ratio (OR): 1.4; 95%-Confidence-interval (CI): 1.2–1.7), especially rodents (OR 1.5; CI 1.2–2.1), and with consumption of meat (OR 1.9; CI 1.3–2.8), raw ground pork (OR 3.0; CI 2.1–4.2) and uncooked pork sausage (OR 2.1; CI 1.6–2.9). The *S.* Typhimurium phage type DT 104 was associated most with consumption of uncooked pork sausage (OR 3.6; CI 1.3–8.5). Multiple logistic regression analyses confirmed the associations between *S.* Typhimurium infection and consumption of raw ground pork and with animal contact. The results circumstantiate the assumption of raw pork products still being a relevant source for *S.* Typhimurium infections in Germany. Therefore, it is recommended to intensify efforts to reduce salmonella infections caused by raw pork products. *S.* Enteritidis infection was associated statistically significantly with travelling abroad (OR 2.1; CI 1.6–3.3), consumption of raw tomatoes (OR 1.8; CI 1.5–2.1), dried herbs (OR 2.1; CI 1.6–1.8), and undercooked eggs (OR 1.3; CI 1.1–1.6) compared with other serovars. These results were confirmed in multiple logistic regression analyses, as well.

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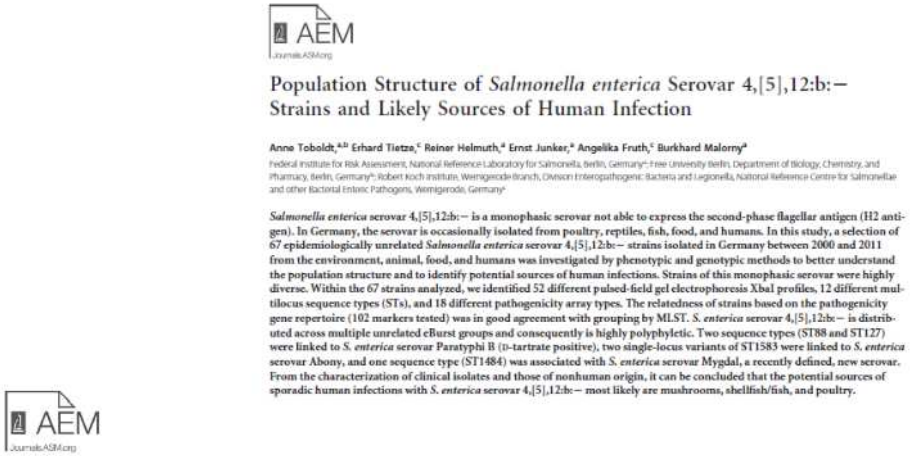

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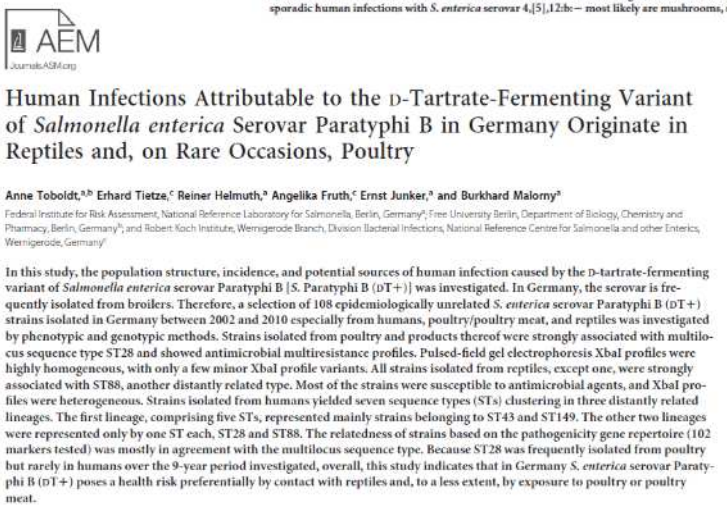
Population Structure of *Salmonella enterica* Serovar 4,[5],12:b:− Strains and Likely Sources of Human Infection

Anne Toboldt,[a,b] Erhard Tietze,[c] Reiner Helmuth,[a] Ernst Junker,[a] Angelika Fruth,[c] Burkhard Malorny[a]

Federal Institute for Risk Assessment, National Reference Laboratory for Salmonella, Berlin, Germany[a]; Free University Berlin, Department of Biology, Chemistry, and Pharmacy, Berlin, Germany[b]; Robert Koch Institute, Wernigerode Branch, Division Enteropathogens: Bacteria and Legionella, National Reference Centre for Salmonellae and other Bacterial Enteric Pathogens, Wernigerode, Germany[c]

Salmonella enterica **serovar 4,[5],12:b:− is a monophasic serovar not able to express the second-phase flagellar antigen (H2 antigen). In Germany, the serovar is occasionally isolated from poultry, reptiles, fish, food, and humans. In this study, a selection of 67 epidemiologically unrelated *Salmonella enterica* serovar 4,[5],12:b:− strains isolated in Germany between 2000 and 2011 from the environment, animal, food, and humans was investigated by phenotypic and genotypic methods to better understand the population structure and to identify potential sources of human infections. Strains of this monophasic serovar were highly diverse. Within the 67 strains analyzed, we identified 52 different pulsed-field gel electrophoresis XbaI profiles, 12 different multilocus sequence types (STs), and 18 different pathogenicity array types. The relatedness of strains based on the pathogenicity gene repertoire (102 markers tested) was in good agreement with grouping by MLST. *S. enterica* serovar 4,[5],12:b:− is distributed across multiple unrelated eBurst groups and consequently is highly polyphyletic. Two sequence types (ST88 and ST127) were linked to *S. enterica* serovar Paratyphi B (D-tartrate positive), two single-locus variants of ST1583 were linked to *S. enterica* serovar Abony, and one sequence type (ST1484) was associated with *S. enterica* serovar Mygdal, a recently defined, new serovar. From the characterization of clinical isolates and those of nonhuman origin, it can be concluded that the potential sources of sporadic human infections with *S. enterica* serovar 4,[5],12:b:− most likely are mushrooms, shellfish/fish, and poultry.**



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Human Infections Attributable to the D-Tartrate-Fermenting Variant of *Salmonella enterica* Serovar Paratyphi B in Germany Originate in Reptiles and, on Rare Occasions, Poultry

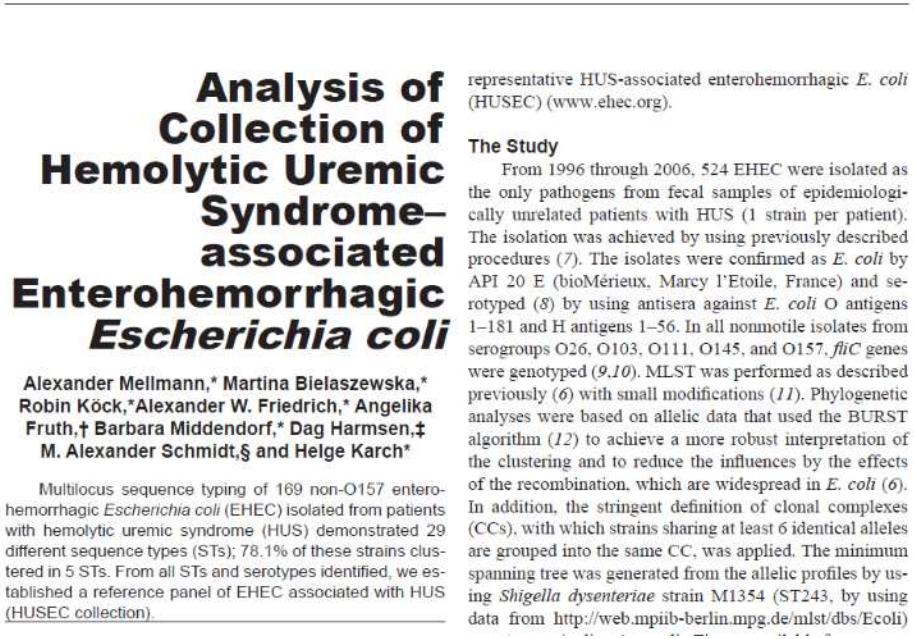
Anne Toboldt,[a,b] Erhard Tietze,[c] Reiner Helmuth,[a] Angelika Fruth,[c] Ernst Junker,[a] and Burkhard Malorny[a]

Federal Institute for Risk Assessment, National Reference Laboratory for Salmonella, Berlin, Germany[a]; Free University Berlin, Department of Biology, Chemistry and Pharmacy, Berlin, Germany[b]; and Robert Koch Institute, Wernigerode Branch, Division Bacterial Infections, National Reference Centre for Salmonella and other Enterics, Wernigerode, Germany[c]

In this study, the population structure, incidence, and potential sources of human infection caused by the D-tartrate-fermenting variant of *Salmonella enterica* serovar Paratyphi B [*S.* Paratyphi B (DT+)] was investigated. In Germany, the serovar is frequently isolated from broilers. Therefore, a selection of 108 epidemiologically unrelated *S. enterica* serovar Paratyphi B (DT+) strains isolated in Germany between 2002 and 2010 especially from humans, poultry/poultry meat, and reptiles was investigated by phenotypic and genotypic methods. Strains isolated from poultry and products thereof were strongly associated with multilocus sequence type ST28 and showed antimicrobial multiresistance profiles. Pulsed-field gel electrophoresis XbaI profiles were highly homogeneous, with only a few minor XbaI profile variants. All strains isolated from reptiles, except one, were strongly associated with ST88, another distantly related type. Most of the strains were susceptible to antimicrobial agents, and XbaI profiles were heterogeneous. Strains isolated from humans yielded seven sequence types (STs) clustering in three distantly related lineages. The first lineage, comprising five STs, represented mainly strains belonging to ST43 and ST149. The other two lineages were represented only by one ST each, ST28 and ST88. The relatedness of strains based on the pathogenicity gene repertoire (102 markers tested) was mostly in agreement with the multilocus sequence type. Because ST28 was frequently isolated from poultry but rarely in humans over the 9-year period investigated, overall, this study indicates that in Germany *S. enterica* serovar Paratyphi B (DT+) poses a health risk preferentially by contact with reptiles and, to a less extent, by exposure to poultry or poultry meat.

Molekulare Typisierung von EHEC:

Diagnostik sowie Aussagen zum Virulenzpotential und zur Verwandtschaft im Rahmen von Ausbrüchen wird erleichtert



Analysis of Collection of Hemolytic Uremic Syndrome–associated Enterohemorrhagic *Escherichia coli*

Alexander Mellmann,* Martina Bielaszewska,* Robin Köck,*Alexander W. Friedrich,* Angelika Fruth,† Barbara Middendorf,* Dag Harmsen,‡ M. Alexander Schmidt,§ and Helge Karch*

Multilocus sequence typing of 169 non-O157 enterohemorrhagic *Escherichia coli* (EHEC) isolated from patients with hemolytic uremic syndrome (HUS) demonstrated 29 different sequence types (STs); 78.1% of these strains clustered in 5 STs. From all STs and serotypes identified, we established a reference panel of EHEC associated with HUS (HUSEC collection).

representative HUS-associated enterohemorrhagic *E. coli* (HUSEC) (www.ehec.org).

The Study

From 1996 through 2006, 524 EHEC were isolated as the only pathogens from fecal samples of epidemiologically unrelated patients with HUS (1 strain per patient). The isolation was achieved by using previously described procedures (*7*). The isolates were confirmed as *E. coli* by API 20 E (bioMérieux, Marcy l'Etoile, France) and serotyped (*8*) by using antisera against *E. coli* O antigens 1–181 and H antigens 1–56. In all nonmotile isolates from serogroups O26, O103, O111, O145, and O157, *fliC* genes were genotyped (*9*,*10*). MLST was performed as described previously (*6*) with small modifications (*11*). Phylogenetic analyses were based on allelic data that used the BURST algorithm (*12*) to achieve a more robust interpretation of the clustering and to reduce the influences by the effects of the recombination, which are widespread in *E. coli* (*6*). In addition, the stringent definition of clonal complexes (CCs), with which strains sharing at least 6 identical alleles are grouped into the same CC, was applied. The minimum spanning tree was generated from the allelic profiles by using *Shigella dysenteriae* strain M1354 (ST243, by using data from http://web.mpiib-berlin.mpg.de/mlst/dbs/Ecoli)

HUSEC-Kollektion ermöglicht Risiko-Empfehlung im Umgang mit Patienten

Molekulare Typisierung von Yersinia / EHEC:

Diagnostik, Einschätzung von Virulenzpotential und Verwandtschaft erleichtert Ausbruchsuntersuchung und Patientenmanagement

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A molecular scheme for *Yersinia enterocolitica* patho-serotyping derived from genome-wide analysis

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ABSTRACT

Yersinia enterocolitica is a food-borne, gastro-intestinal pathogen with world-wide distribution. Only 11 serotypes have been isolated from patients, with O:3, O:9, O:8 and O:5,27 being the serotypes most commonly associated with human yersiniosis. Serotype is an important characteristic of *Y. enterocolitica* strains, allowing differentiation for epidemiology, diagnosis and phylogeny studies. Conventional serotyping, performed by slide agglutination, is a tedious and laborious procedure whose interpretation tends to be subjective, leading to poor reproducibility. Here we present a PCR-based typing scheme for molecular identification and patho-serotyping of *Y. enterocolitica*. Genome-wide comparison of *Y. enterocolitica* sequences allowed analysis of the O-antigen gene clusters of different serotypes, uncovering their formerly unknown genomic locations, and selection of targets for serotype-specific amplification. Two multiplex PCRs and one additional PCR were designed and tested on various reference strains and isolates from different origins. Our genotypic assay proved to be highly specific for identification of *Y. enterocolitica* species, discrimination between virulent and non-virulent strains, distinguishing the main human-related serotypes, and typing of conventionally untypeable strains. This genotyping scheme could be applied in microbiology laboratories as an alternative or complementary method to the traditional phenotypic assays, providing data for epidemiological studies.

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BMC Genomics

RESEARCH ARTICLE Open Access

Tracing genomic variations in two highly virulent *Yersinia enterocolitica* strains with unequal ability to compete for host colonization

Debora Garzetti[1], Hicham Bouabe[1,2], Juergen Heesemann[1] and Alexander Rakin[1*]

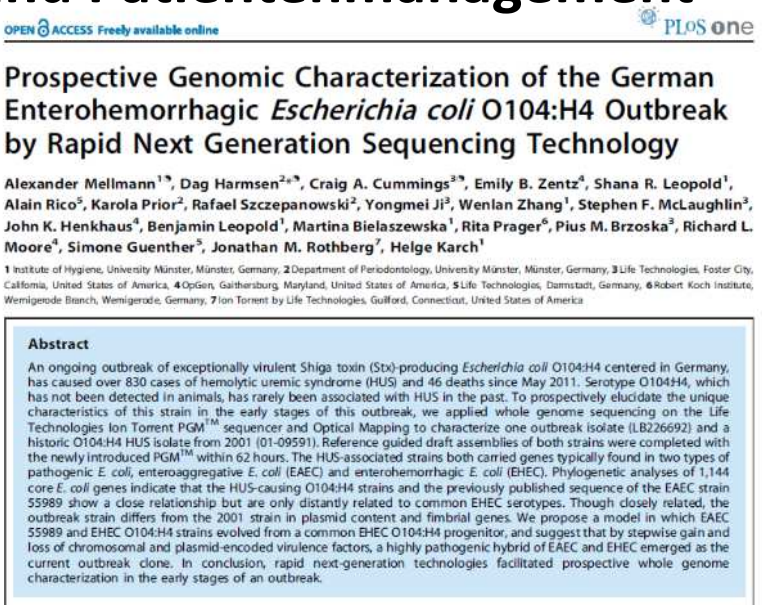
Abstract

Background: *Yersinia enterocolitica* is a gastrointestinal foodborne pathogen found worldwide and which especially affects infants and young children. While different bioserotypes have been associated with varying pathogenicity, research on *Y. enterocolitica* is mainly conducted on the highly virulent mouse-lethal strains of biotype 1B and serotype O:8. We demonstrate here that two *Y. enterocolitica* bioserotype 1B/O:8 strains, 8081 and WA-314, display different virulence and fitness properties in a mouse model. *In vivo* co-infection experiments revealed that strain WA-314 overcomes strain 8081 in the colonization of spleen and liver. To trace the reasons of this incongruity, we present here the first high-quality sequence of the whole genome of strain WA-314 and compare it to the published genome of strain 8081.

Results: Regions previously accepted as unique to strain 8081, like the YAPI and YGI-3 genomic islands, are absent from strain WA-314, confirming their strain-specificity. On the other hand, some fitness- and bacterial competition-associated features, such as a putative colicin cluster and a xenobiotic-acyltransferase-encoding gene, are unique to strain WA-314. Additional acquisitions of strain WA-314 are seven prophage-like regions. One of these prophages, the 28-kb P4-like prophage YWA-4, encodes a PilV-like protein that may be used for adhesion to and invasion of the intestinal cells. Furthermore, a putative autotransporter and two type 1 fimbrial proteins of strain WA-314 show a sequence similarity <50% with the orthologous proteins in strain 8081. The dissimilar sequences of these proteins indicate possible different functions or interaction modes, reflecting the specific adhesion properties of *Y. enterocolitica* strains 8081 and WA-314 and thus the different efficiency of host colonization. Further important differences were found in two pYV plasmid-encoded virulence factors, YopM and YscP. The impact of these differences on virulence is discussed.

Conclusions: Our study emphasizes that the virulence of pathogens can be increased, by acquiring new genes and/or improving the function of essential virulence proteins, resulting in permanently hyper-virulent strains. This work also highlights the importance of addressing genetic and phenotypic variations among closely related bacterial strains, even those belonging to the same bioserotype.

Keywords: Yersinia enterocolitica, Hyper-virulent, Genome comparison, Diversity, Host colonization, Virulence factors, YscP, YopM



OPEN ACCESS Freely available online PLoS one

Prospective Genomic Characterization of the German Enterohemorrhagic *Escherichia coli* O104:H4 Outbreak by Rapid Next Generation Sequencing Technology

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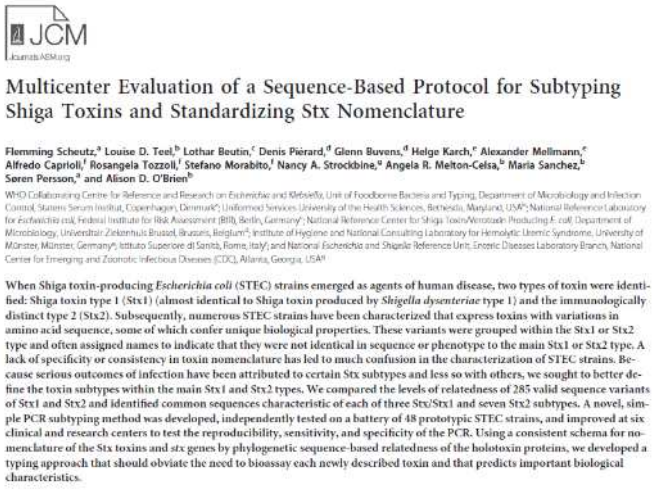
Abstract

An ongoing outbreak of exceptionally virulent Shiga toxin (Stx)-producing *Escherichia coli* O104:H4 centered in Germany, has caused over 830 cases of hemolytic uremic syndrome (HUS) and 46 deaths since May 2011. Serotype O104:H4, which has not been detected in animals, has rarely been associated with HUS in the past. To prospectively elucidate the unique characteristics of this strain in the early stages of this outbreak, we applied whole genome sequencing on the Life Technologies Ion Torrent PGM™ sequencer and Optical Mapping to characterize one outbreak isolate (LB226692) and a historic O104:H4 HUS isolate from 2001 (01-09591). Reference guided draft assemblies of both strains were completed with the newly introduced PGM™ within 62 hours. The HUS-associated strains both carried genes typically found in two types of pathogenic *E. coli*, enteroaggregative *E. coli* (EAEC) and enterohemorrhagic *E. coli* (EHEC). Phylogenetic analyses of 1,144 core *E. coli* genes indicate that the HUS-causing O104:H4 strains and the previously published sequence of the EAEC strain 55989 show a close relationship but are only distantly related to common EHEC serotypes. Though closely related, the outbreak strain differs from the 2001 strain in plasmid content and fimbrial genes. We propose a model in which EAEC 55989 and EHEC O104:H4 strains evolved from a common EHEC O104:H4 progenitor, and suggest that by stepwise gain and loss of chromosomal and plasmid-encoded virulence factors, a highly pathogenic hybrid of EAEC and EHEC emerged as the current outbreak clone. In conclusion, rapid next-generation technologies facilitated prospective whole genome characterization in the early stages of an outbreak.



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Multicenter Evaluation of a Sequence-Based Protocol for Subtyping Shiga Toxins and Standardizing Stx Nomenclature

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When Shiga toxin-producing *Escherichia coli* (STEC) strains emerged as agents of human disease, two types of toxin were identified: Shiga toxin type 1 (Stx1) (almost identical to Shiga toxin produced by *Shigella dysenteriae* type 1) and the immunologically distinct type 2 (Stx2). Subsequently, numerous STEC strains have been characterized that express toxins with variations in amino acid sequence, some of which confer unique biological properties. These variants were grouped within the Stx1 or Stx2 type and often assigned names to indicate that they were not identical in sequence or phenotype to the main Stx1 or Stx2 type. A lack of specificity or consistency in toxin nomenclature has led to much confusion in the characterization of STEC strains. Because serious outcomes of infection have been attributed to certain Stx subtypes and less so with others, we sought to better define the toxin subtypes within the main Stx1 and Stx2 types. We compared the levels of relatedness of 285 valid sequence variants of Stx1 and Stx2 and identified common sequences characteristic of each of three Stx/Stx1 and seven Stx2 subtypes. A novel, simple PCR subtyping method was developed, independently tested on a battery of 48 prototypic STEC strains, and improved at six clinical and research centers to test the reproducibility, sensitivity, and specificity of the PCR. Using a consistent schema for nomenclature of the Stx toxins and *stx* genes by phylogenetic sequence-based relatedness of the holotoxin proteins, we developed a typing approach that should obviate the need to bioassay each newly described toxin and that predicts important biological characteristics.

Epidemiologische Studien zu sporadischen Infektionen:

gezielte Aufklärung der Bevölkerung möglich

Rosner et al. BMC Infectious Diseases 2013, 13:236
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BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Clinical aspects and self-reported symptoms of sequelae of *Yersinia enterocolitica* infections in a population-based study, Germany 2009–2010

Bettina M Rosner*, Dirk Werber, Michael Höhle and Klaus Stark

Abstract

Background: Foodborne *Yersinia enterocolitica* infections continue to be a public health problem in many countries. Consumption of raw or undercooked pork is the main risk factor for yersiniosis in Germany. Small children are most frequently affected by yersiniosis. In older children and young adults, symptoms of disease may resemble those of appendicitis and may lead to hospitalization and potentially unnecessary appendectomies. *Y. enterocolitica* infections may also cause sequelae such as reactive arthritis (ReA), erythema nodosum (EN), and conjunctivitis.

Methods: We studied clinical aspects of yersiniosis, antimicrobial use, and self-reported occurrence of appendectomies, reactive arthritis, erythema nodosum and conjunctivitis. To assess post-infectious sequelae participants of a large population-based case–control study on laboratory-confirmed *Y. enterocolitica* infections conducted in Germany in 2009–2010 were followed for 4 weeks.

Results: Diarrhea occurred most frequently in children ≤4 years (99%); abdominal pain in the lower right quadrant was most common in children 5–14 years of age (63%). Twenty-seven per cent of patients were hospitalized, 37% were treated with antimicrobials. In 6% of yersiniosis patients ≥5 years of age, appendectomies were performed. Self-reported symptoms consistent with ReA were reported by 12% of yersiniosis patients compared to 5% in a reference group not exposed to yersiniosis. Symptoms consistent with EN were reported by 3% of yersiniosis patients compared to 0.1% in the reference group. Symptoms of conjunctivitis occurred with the same frequency in yersiniosis patients and the reference group.

Conclusions: Acute *Y. enterocolitica* infections cause considerable burden of illness with symptoms lasting for about 10 days and hospitalizations in more than a quarter of patients. The proportion of yersiniosis patients treated with antimicrobial drugs appears to be relatively high despite guidelines recommending their use only in severe cases. Appendectomies and post-infectious complications (ReA and EN) are more frequently reported in yersiniosis patients than in the reference group suggesting that they can be attributed to infections with *Y. enterocolitica*. Physicians should keep recent *Y. enterocolitica* infection in mind in patients with symptoms resembling appendicitis as well as in patients with symptoms of unclear arthritis.

Keywords: *Yersinia enterocolitica*, Sequelae, Reactive arthritis, Erythema nodosum

ROBERT KOCH INSTITUT

Epidemiologisches Bulletin

15. Februar 2012 / Nr. 6 AKTUELLE DATEN UND INFORMATIONEN ZU INFEKTIONSKRANKHEITEN UND PUBLIC HEALTH

Yersiniose – Risikofaktoren in Deutschland

Die Yersiniose ist eine gastrointestinale, meist lebensmittelbedingte Erkrankung, die durch Infektion mit dem Bakterium *Yersinia enterocolitica* verursacht wird. Sie kann die Gesundheit erheblich beeinträchtigen, insbesondere im Kleinkindesalter. Typische Symptome einer akuten Yersiniose sind Durchfall, Bauchschmerzen, schmerzhafter Stuhldrang (Tenesmen), Fieber und Erbrechen. Die Symptome treten nach einer Inkubationszeit von etwa 5 Tagen auf (Zeitspanne 1–11 Tage). Bei Jugendlichen können die Symptome mit Schmerzen im rechten Unterbauch denen einer Appendizitis ähneln („Pseudoappendizitis") und vereinzelt auch zu unnötigen Appendektomien führen. Die Symptome einer Yersiniose klingen meist nach ein bis zwei Wochen ab. In seltenen Fällen können jedoch Folgeerkrankungen, wie reaktive Arthritis oder Erythema nodosum, auftreten. Seit 2002 ist ein kontinuierlicher Rückgang der an das Robert Koch-Institut (RKI) übermittelten Yersiniosen zu beobachten, von 7.540 im Jahr 2002 auf 3.364 im Jahr 2010. Die Inzidenz lag im Jahr 2010 bei 4,1 Erkrankungen / 100.000 Einwohner. Männliche Personen waren etwas häufiger betroffen als weibliche (4,8 Erkr. / 100.000 Einw. bzw. 3,5 Erkr. / 100.000 Einw.).[1] Yersiniosen treten am häufigsten bei Kindern unter 5 Jahre auf. Die Inzidenz ist bei einjährigen Kindern am höchsten (2010: 48,0 Erkr. / 100.000 Einw., s. Abb. 1). Inzidenzunterschiede zwischen den Bundesländern lassen sich vor allem auf Inzidenzunterschiede bei Kindern unter 5 Jahre zurückführen (s. Abb. 2, S. 48).[2] Etwa 98% aller übermittelten *Y. enterocolitica*-Infektionen werden als sporadische Fälle übermittelt, Krankheitsausbrüche sind selten.[2]

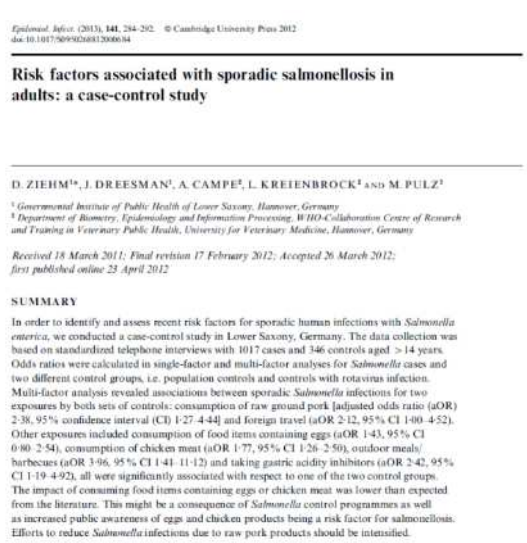
Diese Woche 6/2012

Yersiniose
Risikofaktoren in Deutschland

Hinweise auf Veranstaltungen und Ausschreibungen
- Ausschreibung von Stellen für die 5. EUPHEM-Kohorte auf der ECDC-Internetseite erschienen
- 14. Münchner AIDS- und Hepatitis-Tage
- Fortbildungsveranstaltung für den Öffentlichen Gesundheitsdienst

Meldepflichtige Infektionskrankheiten
Aktuelle Statistik
3. Woche 2012

ARE/Influenza
Zur Situation in der



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Risk factors associated with sporadic salmonellosis in adults: a case-control study

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SUMMARY

In order to identify and assess recent risk factors for sporadic human infections with *Salmonella enterica*, we conducted a case-control study in Lower Saxony, Germany. The data collection was based on standardized telephone interviews with 1017 cases and 346 controls aged >14 years. Odds ratios were calculated in single-factor and multi-factor analyses for *Salmonella* cases and two different control groups, i.e. population controls and controls with rotavirus infection. Multi-factor analysis revealed associations between sporadic *Salmonella* infections for two exposures by both sets of controls: consumption of raw ground pork [adjusted odds ratio (aOR) 2·38, 95% confidence interval (CI) 1·27–4·44] and foreign travel (aOR 2·12, 95% CI 1·00–4·52). Other exposures included consumption of food items containing eggs (aOR 1·43, 95% CI 0·80–2·54), consumption of chicken meat (aOR 1·77, 95% CI 1·26–2·50), outdoor meals/barbecues (aOR 3·96, 95% CI 1·41–11·12) and taking gastric acidity inhibitors (aOR 2·42, 95% CI 1·19–4·92), all were significantly associated with respect to one of the two control groups. The impact of consuming food items containing eggs or chicken meat was lower than expected from the literature. This might be a consequence of *Salmonella* control programmes as well as increased public awareness of eggs and chicken products being a risk factor for salmonellosis. Efforts to reduce *Salmonella* infections due to raw pork products should be intensified.

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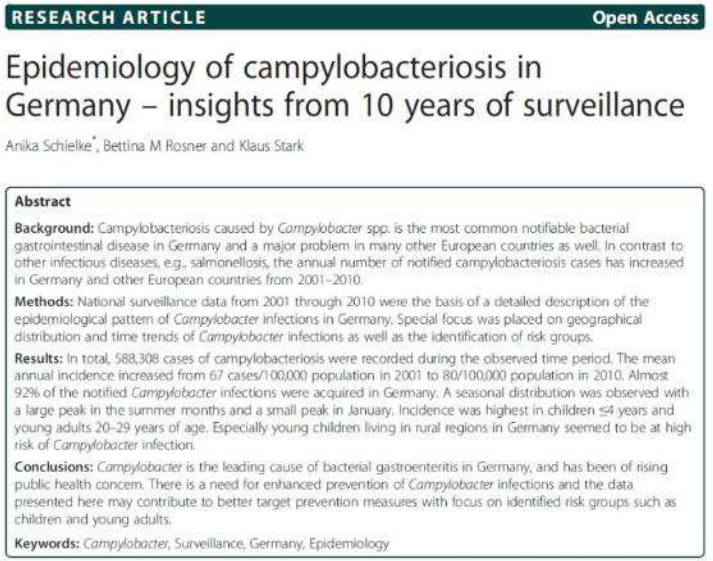
http://www.biomedcentral.com/1471-2334/14/30

BMC Infectious Diseases



RESEARCH ARTICLE Open Access

Epidemiology of campylobacteriosis in Germany – insights from 10 years of surveillance

Anika Schielke*, Bettina M Rosner and Klaus Stark

Abstract

Background: Campylobacteriosis caused by *Campylobacter* spp. is the most common notifiable bacterial gastrointestinal disease in Germany and a major problem in many other European countries as well. In contrast to other infectious diseases, e.g., salmonellosis, the annual number of notified campylobacteriosis cases has increased in Germany and other European countries from 2001–2010.

Methods: National surveillance data from 2001 through 2010 were the basis of a detailed description of the epidemiological pattern of *Campylobacter* infections in Germany. Special focus was placed on geographical distribution and time trends of *Campylobacter* infections as well as the identification of risk groups.

Results: In total, 588,308 cases of campylobacteriosis were recorded during the observed time period. The mean annual incidence increased from 67 cases/100,000 population in 2001 to 80/100,000 population in 2010. Almost 92% of the notified *Campylobacter* infections were acquired in Germany. A seasonal distribution was observed with a large peak in the summer months and a small peak in January. Incidence was highest in children ≤4 years and young adults 20–29 years of age. Especially young children living in rural regions in Germany seemed to be at high risk of *Campylobacter* infection.

Conclusions: *Campylobacter* is the leading cause of bacterial gastroenteritis in Germany, and has been of rising public health concern. There is a need for enhanced prevention of *Campylobacter* infections and the data presented here may contribute to better target prevention measures with focus on identified risk groups such as children and young adults.

Keywords: *Campylobacter*, Surveillance, Germany, Epidemiology

Molekulare Pathogenese:

Grundlage für prophylaktische und therapeutische Interventionen

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DOI 10.1007/s00018-012-1060-z

Cellular and Molecular Life Sciences

REVIEW

Facing glycosphingolipid–Shiga toxin interaction: dire straits for endothelial cells of the human vasculature

Andreas Bauwens · Josefine Betz · Iris Meisen · Björn Kemper · Helge Karch · Johannes Müthing

Received: 13 March 2012 / Revised: 25 May 2012 / Accepted: 14 June 2012 / Published online: 6 July 2012

Abstract The two major Shiga toxin (Stx) types, Stx1 and Stx2, produced by enterohemorrhagic *Escherichia coli* (EHEC) in particular injure renal and cerebral microvascular endothelial cells after transfer from the human intestine into the circulation. Stxs are AB_5 toxins composed of an enzymatically active A subunit and the pentameric B subunit, which preferentially binds to the glycosphingolipid globotriaosylceramide (Gb3Cer/CD77). This review summarizes the current knowledge on Stx-caused cellular injury and the structural diversity of Stx receptors as well as the initial molecular interaction of Stxs with the human endothelium of different vascular beds. The varying lipoforms of Stx receptors and their spatial organization in lipid rafts suggest a central role in different modes of receptor-mediated endocytosis and intracellular destiny of the toxins. The design and development of tailored Stx neutralizers targeting the oligosaccharide–toxin recognition event has become a very real prospect to ameliorate or prevent life-threatening renal and neurological complications.

Keywords Gb3Cer · Gb4Cer · Glycolipids · HUS · Lipid rafts · Mass spectrometry · Membrane microdomains

Introduction

Humans become infected with enterohemorrhagic *Escherichia coli* (EHEC, a certain subtype of pathogenic *E. coli*) through contaminated food and water via the oral route. Furthermore, EHEC have a high potential for person-to-person transmission since a very low infective dose is required and ingestion of as few as 10 bacteria may be sufficient to cause infection. EHEC survive the acidic human stomach, colonize the intestine, and release Shiga toxins (Stxs, also referred to as verotoxins, verocytotoxins, or Shiga-like toxins) which then enter the circulation by an as yet unknown mechanism. Current models suggest that Stxs preferentially bind to microvascular endothelial cells of the renal glomeruli and the brain and inhibit protein

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0019-9567/10/$12.00 doi:10.1128/IAI.00006-10

Distribution and Phylogeny of Immunoglobulin-Binding Protein G in Shiga Toxin-Producing *Escherichia coli* and Its Association with Adherence Phenotypes[▽]

Viktor Merkel,[1]# Barbara Ohder,[1]# Martina Bielaszewska,[1] Wenlan Zhang,[1] Angelika Fruth,[2] Christian Menge,[3] Erika Borrmann,[3] Barbara Middendorf,[1] Johannes Müthing,[1] Helge Karch,[1] and Alexander Mellmann[1]*

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eibG **in Shiga toxin-producing *Escherichia coli* (STEC) O91 encodes a protein (EibG) which binds human immunoglobulins G and A and contributes to bacterial chain-like adherence to human epithelial cells. We investigated the prevalence of *eibG* among STEC, the phylogeny of *eibG*, and *eibG* allelic variations and their impact on the adherence phenotype. *eibG* was found in 15.0% of 240 *eae*-negative STEC strains but in none of 157 *eae*-positive STEC strains. The 36 *eibG*-positive STEC strains belonged to 14 serotypes and to eight multilocus sequence types (STs), with serotype O91:H14/H⁻ and ST33 being the most common. Sequences of the complete *eibG* gene (1,527 bp in size) from *eibG*-positive STEC resulted in 21 different alleles with 88.11% to 100% identity to the previously reported *eibG* sequence; they clustered into three *eibG* subtypes (*eibG*-α, *eibG*-β, and *eibG*-γ). Strains expressing EibG-α and EibG-β displayed a mostly typical chain-like adherence pattern (CLAP), with formation of long chains on both human and bovine intestinal epithelial cells, whereas strains with EibG-γ adhered in short chains, a pattern we termed atypical CLAP. The same adherence phenotypes were displayed by *E. coli* BL21(DE3) clones containing the respective *eibG*-α, *eibG*-β, and *eibG*-γ subtypes. We propose two possible evolutionary scenarios for *eibG* in STEC: a clonal development of *eibG* in strains with the same phylogenetic background or horizontal transfer of *eibG* between phylogenetically unrelated STEC strains.**

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In Vivo-Induced InvA-Like Autotransporters Ifp and InvC of *Yersinia pseudotuberculosis* Promote Interactions with Intestinal Epithelial Cells and Contribute to Virulence

Fabio Pisano,[a] Annika Kochut,[a] Frank Uliczka,[a] Rebecca Geyer,[a] Tatjana Stolz,[a] Tanja Thiermann,[a] Manfred Rohde,[b] and Petra Dersch[a]

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The *Yersinia pseudotuberculosis* Ifp and InvC molecules are putative autotransporter proteins with a high homology to the invasin (InvA) protein. To characterize the function of these surface proteins, we expressed both factors in *Escherichia coli* K-12 and demonstrated the attachment of Ifp- and InvC-expressing bacteria to human-, mouse-, and pig-derived intestinal epithelial cells. Ifp also was found to mediate microcolony formation and internalization into polarized human enterocytes. The *ifp* and *invC* genes were not expressed under *in vitro* conditions but were found to be induced in the Peyer's patches of the mouse intestinal tract. In a murine coinfection model, the colonization of the Peyer's patches and the mesenteric lymph nodes of mice by the *ifp*-deficient strain was significantly reduced, and considerably fewer bacteria reached liver and spleen. The absence of InvC did not have a severe influence on bacterial colonization in the murine infection model, and it resulted in only a slightly reduced number of *invC* mutants in the Peyer's patches. The analysis of the host immune response demonstrated that the presence of Ifp and InvC reduced the recruitment of professional phagocytes, especially neutrophils, in the Peyer's patches. These findings support a role for the adhesins in modulating host-pathogen interactions that are important for immune defense.

FBI-Zoo:
Schlussfolgerungen

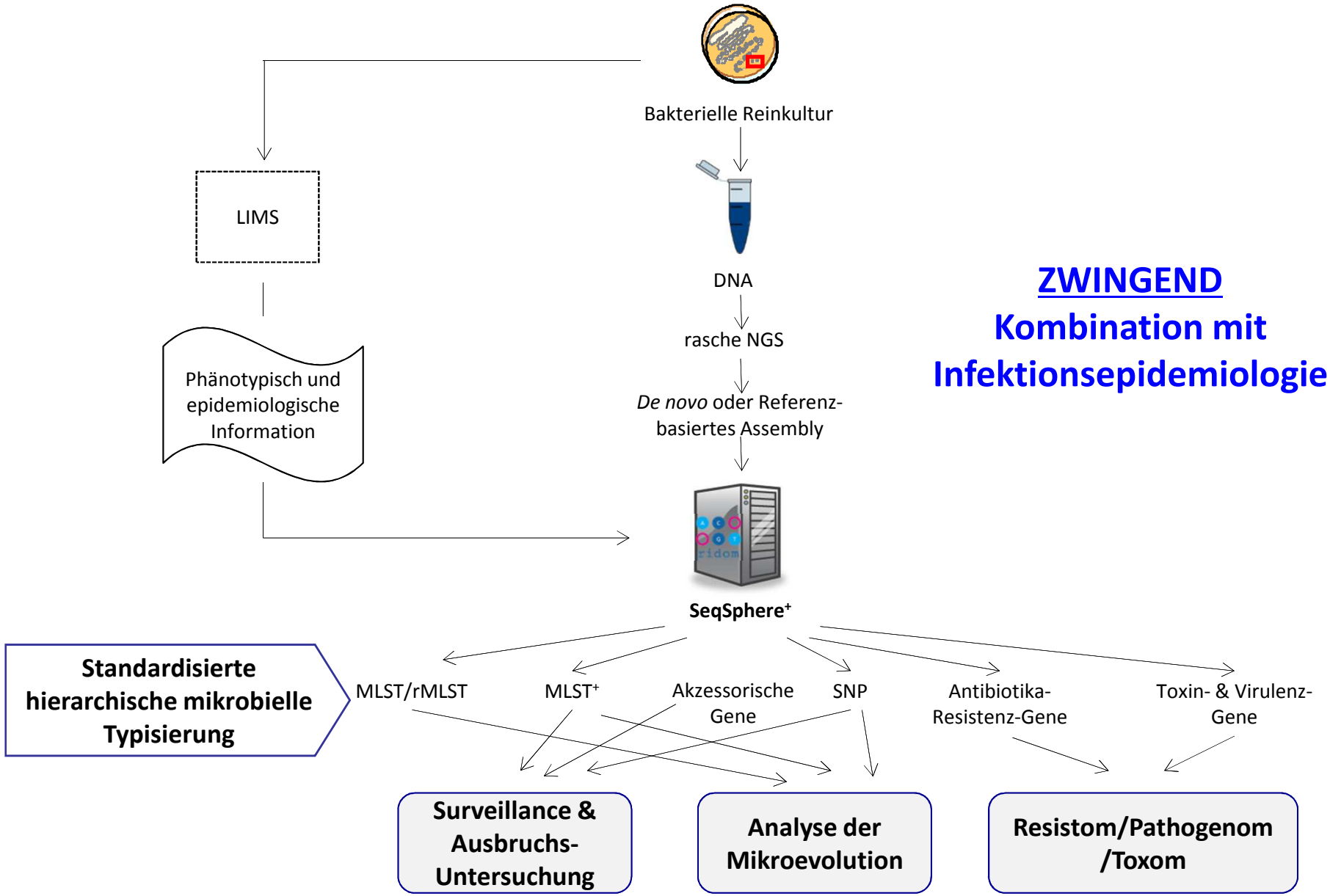
Eine leistungsfähige Surveillance (= Monitoring + Intervention) ist zwingend erforderlich, sie sollte auf einer eindeutigen, normierten und harmonisierten Typisierungsmethode beruhen

Experimentelle *in vivo* / *ex vivo* / *in vitro*-Analysen sollten vergleichend mit eindeutig identifizierten Erregervarianten durchgeführt werden

Handlungsoptionen:

- Etablierung und Validierung DNA-Sequenzbasierter Typisierungsmethoden
- Vernetzung infektionsepidemiologischer mit Typisierungsdaten aus verschiedenen Habitaten
- Etablierung translational nutzbarer Tierversuchsmodelle
- Entwicklung von Vakzinen und Mikrobiota-Konzepten (Human- und Tiermedizin)
- Verbesserung Herstellungs- und Konservierungsverfahren von Lebensmitteln tier. Herkunft
- Fort- und Weiterbildung im „One Health“ Sinne (transsektoral, interdisziplinär)
- Patienten- und Ausbruchsmanagement kontinuierlich aktualisieren bezogen auf Forschungsergebnisse
- Risiko-basierter Umgang mit Tier, Lebensmittel und Patient
- Anreize für mikrobiologische Primärdiagnostik sollten erhöht werden
- Intensivierung sozialwissenschaftlicher Forschung zur Kommunikation des Wissens

Typisierung der Wahl: Next generation sequencing



ZWINGEND
Kombination mit Infektionsepidemiologie

!!! Danke für ihre Aufmerksamkeit !!!