Epidemiology of campylobacteriosis and acute gastroenteritis from a human and health system's perspective in Switzerland

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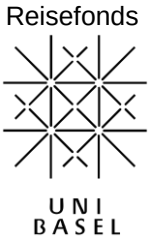

ii. Summary

Background: Campylobacteriosis is a zoonotic disease caused by an infection with bacteria from the genus *Campylobacter* spp. In humans, it manifests clinically as acute gastroenteritis (AG) of short duration i.e. a few days. The syndrome AG is mainly characterised by diarrhoea (>3 unformed stools per day), vomiting, nausea, dehydration and abdominal cramps and pain. Also other infectious intestinal diseases (IID) caused by a wide range of bacterial, viral or parasitic pathogens can lead to AG. Campylobacteriosis and many other IID are diagnosed by stool diagnostics (stool cultures, polymerase chain reactions). Major risk factors for an infection with *Campylobacter* spp. are foreign travel, eating undercooked chicken meat and exposure through environmental routes e.g. contaminated drinking water. Campylobacteriosis is the most prevalent bacterial zoonotic disease in European countries and other high-income countries around the world. Close to 230,000 cases were recorded in Europe in 2015, 7000 thereof from Switzerland. AG due to IID is a prevalent disease and 0.25 – 1.4 disease episodes per person per year are observed in high-income countries. In Switzerland, laboratory-confirmed cases of campylobacteriosis are registered in the National Notification System for Infectious Diseases (NNSID) at the Federal Office of Public Health. In line with the rest of Europe case numbers show an increasing and unexplainable trend since 2005. Human *Campylobacter* infections in Switzerland show a clear seasonality with a peak of infections during summer time and a second peak during winter time at the turn of the year. Determinants leading to the observed epidemic peak of campylobacteriosis case numbers in Switzerland in winter time

are unknown. The disease burden of campylobacteriosis measured by the NNSID is supposedly only the tip of the iceberg. Many cases suffering from a mild episode of AG which could be due to an infection with *Campylobacter* spp. do not seek health care, are never tested and hence not reported. Yet, only laboratory-confirmed cases of notifiable IID such as campylobacteriosis are registered in the NNSID. The paradigm of the burden-of-illness pyramid describes the chain of events that have to occur for a case of IID in the community to be reported to the surveillance system. These are: (i) affected individual seeks health care (ii) a stool test is performed and (iii) a positive result is reported to the surveillance system. It is unclear which determinants lead to health care seeking of campylobacteriosis and AG cases and which processes lead to the initiation of stool testing i.e. to registration in the NNSID.

Objectives: This work aimed at contributing to a better understanding of the epidemiology of human campylobacteriosis and AG and improving the interpretation of routine surveillance data from the NNSID. It seeks (i) to describe how campylobacteriosis and AG presents as disease and illness in the Swiss population and within the Swiss health care system and (ii) to create a basis for an improved interpretation and validity of routine surveillance data from the NNSID.

Methods: Six research components were conducted to assess the epidemiology of human campylobacteriosis and AG and the associated disease and economic burden from different perspectives along the burden-of-illness pyramid. Determinants of the campylobacteriosis winter peak in Switzerland were investigated conducting a matched case-control study at the turn of the year 2012/2013. Cases were recruited among laboratory-confirmed cases registered in the NNSID and controls matched

for sex, age group and canton of residence from the general Swiss population. Participants were interviewed by telephone using a sent-before photo illustrated questionnaire about different food and non-food exposures and cases were additionally questioned regarding their illness experience. Risk factors were assessed applying a pair-matched analysis. Results of the case-control study lead to an additional assessment of transmission dynamics of *Campylobacter* spp. in Europe. For this work case-based surveillance data for selected European countries were descriptively analysed with a focus on winter peaks as observed in Switzerland. Long-term epidemiological trends observed in campylobacteriosis and salmonellosis surveillance data of the NNSID were investigated by assessing laboratory positivity rates and merging case notification data and laboratory test data from eight large Swiss diagnostic laboratories. The retrospective analysis of positivity rates (positive tests divided by total tests conducted) included data on stool tests conducted between 2003 and 2012. The clinical presentation of campylobacteriosis cases, case management and disease burden of campylobacteriosis and AG at the primary care level were investigated using a mixed methods approach. First, general practitioners (GPs) managing cases of the aforementioned case-control study were interviewed with a semi-structured questionnaire on clinical presentation, case management and disease burden. Interviews were analysed by inductive content analysis based on Grounded Theory. Study results provided valuable inputs for the design of the following prospective quantitative study embedded in the Swiss Sentinel Surveillance Network *Sentinella*. Some 170 physicians practicing in primary care and paediatrics provided information on the number and aetiology of AG cases and also on the associated case presentation and management over one year. Data were descriptively

analysed and initial consultations due to AG per 100,000 population were estimated. This work portfolio finally provided data needed to estimate direct health care costs caused by campylobacteriosis and AG. Direct health care costs were estimated using expert opinions, official cost rates for health care and results of the preceding research components.

Results: The multivariable analysis of data from the case-control study identified the consumption of meat fondue (matched odds ratio [mOR] 4.0, 95 % confidence interval [CI] 2.3–7.1) and travelling abroad (mOR 2.7, 95 % CI 1.1–6.4) as major risk factors for an infection with *Campylobacter* spp. over Christmas and New Year. The consumption of meat fondues with chicken meat was associated with a significantly increased risk of disease compared to meat fondue without chicken meat (mOR 3.8, 95 % CI 1.1–13.5). Around 60% of campylobacteriosis cases received an antibiotic therapy and 14% were hospitalised. The assessment of transmission dynamics with national case-based surveillance data on *Campylobacter* spp. from several European countries showed that winter peaks similar to Switzerland can be observed in Austria, Belgium, Finland, Germany, Luxembourg, The Netherlands and Sweden. Disease onsets reported for cases point towards risk exposures around Christmas and New Year, and meat fondue or table top grilling also posing such a risk are prominent in several of these countries at this time of the year. The analysis of laboratory positivity rates from *Campylobacter* spp. and *Salmonella* spp. showed an increase of annual test numbers for both infections of 51% from 2003 to 2012. Positivity rates of *Campylobacter* spp. increased from 7.6% to 11.1% during the same time period while rates of *Salmonella* spp. decreased from 2.7% to 1.5%. A distinct

seasonality of test numbers and positivity rates was observed whereby the rate for *Salmonella* spp. peaked in autumn and for *Campylobacter* spp. in summer as well as at the turn of the year. The qualitative study among GPs revealed that a considerable proportion of AG patients consults and receives medical advice by telephone only. Interviewed physicians reported an estimated average disease burden of two AG cases per week and five campylobacteriosis cases per year. Four distinct strategies for the application of stool diagnostics ("test") and antibiotic therapy ("treat") were observed: "Wait & See", "Treat & See", "Treat & Test", and "Test & See". The subsequent quantitative study within the *Sentinella* network estimated the incidence of AG at the primary care level for 2014 at 2146 first consultations per 100,000 population. Stool diagnostics were performed for 11.6% of patients and *Campylobacter* spp. was the most frequently diagnosed pathogen. Antibiotics were prescribed for 8.5% of cases and 86.3% were on sick leave for a median duration of 4 days. Estimated 311,192 – 707,255 patients consult a physician due to AG or campylobacteriosis annually resulting in direct health care costs of €29 to €45 million.

Conclusions: The importance of human campylobacteriosis and AG due to IID for public health has been clearly underestimated in Switzerland so far. Both diseases cause a high disease and health system burden leading to remarkable health care costs. Cases are often severely affected by the disease and the proportion requiring hospitalisation and/or antibiotic therapy is considerable. Human exposure to chicken meat contaminated with *Campylobacter* spp. at meat fondues plays a major role for the epidemic increase of case numbers during winter time. The NNSID accurately reflects epidemiological

trends of campylobacteriosis and salmonellosis in the Swiss population. Public health authorities should regularly assess determinants of the burden-of-illness pyramid to maintain the system's validity. This work has significantly increased the knowledge on the disease burden of human campylobacteriosis and AG in Switzerland but the exact burden of disease in the community still needs to be further investigated.

iii. List of abbreviations

%	Percent
€	Euro
AG	Acute gastroenteritis
CFU	Colony-forming units
CFU/g	Colony-forming units per gram
CHF	Swiss Franc
DALYs	Disability-adjusted life years
ECDC	European Centre for Disease Prevention and Control
EEA	European Economic Area
EFSA	European Food Safety Authority
EHEC	Enterohaemorrhagic *Escherichia coli*
EKNZ	The Ethics Committee northwest/central Switzerland
EU	European Union
FERG	Foodborne Disease Burden Epidemiology Reference Group
FOPH	Federal Office of Public Health
FSVO	Federal Food Safety and Veterinary Office
FWD	Programme of Food- and Waterborne Diseases and Zoonoses
FWD-Net	Food- and Waterborne Diseases Network

g	Gram
GBS	Guillan-Barré syndrome
GP(s)	General practitioner(s)
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IID	Infectious intestinal diseases
ILI	Influenza-like illness
LMICs	low- and middle-income countries
$\log_{10}$	Logarithm to base 10
NNSID	National Notification System for Infectious Diseases
NORS	National Outbreak Reporting System
PCR	Polymerase chain reaction
PFGE	Pulsed-field gel electrophoresis
Sentinella	Swiss Sentinel Surveillance Network Sentinella
TESSy	The European Surveillance System
UK	United Kingdom
WGS	Whole genome sequencing
WHO	World Health Organization

1. Introduction including literature review

Campylobacteriosis is a zoonotic bacterial disease in humans leading to acute gastroenteritis (AG) and is caused by *Campylobacter* spp. Its disease burden increased continuously in Europe during the last decade. Switzerland was no exception and *Campylobacter* spp. got more attention from public health authorities. As a result, the Swiss Federal Food Safety and Veterinary Office (FSVO) founded the "*Campylobacter* platform" together with other authorities and partners from academia and the industry to address this public health problem in a One Health approach in December 2008[1]. The aim was to launch the control of *Campylobacter* spp. based on scientific evidence and thereby reduce the human disease burden. Therefore, the platform initiated several research projects regarding campylobacteriosis to close existing knowledge gaps in Switzerland.

Various risk assessments from abroad showed that the consumption of chicken meat contaminated with *Campylobacter* spp. is the main source of infection for humans. Consequently, a focus of the research was laid on the transmission pathway of *Campylobacter* spp. along the food chain including poultry production, food safety, consumer behaviour and risk exposures. Other sources of infection and routes of exposure than via poultry were investigated by source attribution studies with *Campylobacter* spp. isolates from animals, food, humans and the environment. The disease burden of campylobacteriosis and the associated health care costs in

[1] Abolished in 2016, see Chapter 10.2 for further information

Switzerland were largely unknown except case numbers registered by the National Notification System for Infectious Diseases (NNSID) of the Federal Office of Public Health (FOPH). The NNSID case numbers represent merely the tip of the iceberg in terms of disease burden. Only laboratory-confirmed cases are registered and not all cases suffer from severe disease and have stool diagnostics performed. Undiagnosed campylobacteriosis cases are clinically categorised as AG patients. Hence, estimating the disease burden and health care costs of campylobacteriosis need to take AG into account.

This work contributes to the endeavours of the *Campylobacter* platform by providing an understanding of the epidemiology of campylobacteriosis and AG in Switzerland. The disease burden, potential risk factors for infection, case management and health care costs associated with campylobacteriosis and AG were investigated from a human and health system's perspective. The subsequent introduction and literature review provides an overview on (i) campylobacteriosis and AG as diseases including risk factors for infection, (ii) the associated case management, (iii) the current knowledge on their disease burden and cost of illness in high-income countries and (iv) surveillance systems for campylobacteriosis and other gastrointestinal diseases in Switzerland.

1.1. Campylobacteriosis

1.1.1. Pathogenesis

Human campylobacteriosis is a zoonotic disease that is mainly caused by the bacteria *Campylobacter jejuni* and a smaller proportion by *Campylobacter coli* (Gillespie *et al.* 2002, Man 2011, Schielke *et al.* 2014, EFSA and ECDC 2016). The rela-

tionship of both species with the occurrence of diarrhoea in humans was first described by Skirrow as "*Campylobacter* enteritis" (Skirrow 1977). Other *Campylobacter* species causing gastrointestinal and extragastrointestinal infections include *C. concisus*, *C. upsaliensis*, *C. ureolyticus*, *C. lari* or *C. fetus* but their importance for humans and public health is largely unknown (Lastovica 2006, Man 2011, Kaakoush *et al.* 2015). However, traditional culture methods – which are still widely deployed in routine diagnostics - underestimate the prevalence of non-*C. jejuni/C. coli* spp. and recent studies suggest a higher importance of non-*C. jejuni/C. coli* spp. in human campylobacteriosis than previously assumed (Lastovica 2006, Bullman *et al.* 2012, On 2013, Underwood *et al.* 2016).

Campylobacter spp. is transmitted by the faecal-oral route and the intake of as little as 500 organisms is sufficient to acquire an infection (Robinson 1981, Black *et al.* 1988, Kothary and Babu 2001). Following an incubation period of approximately 3 days the onset of campylobacteriosis is often marked by strong abdominal cramps and later includes diarrhoea (bloody, watery), fever, nausea, vomiting and abdominal and joint pain (Skirrow 1990, Kapperud *et al.* 1992, Ketley 1997, Braam 2004). A variety and mix of signs and symptoms occur in different combinations and severities. The disease manifests clinically as AG of short duration i.e. a few days and is usually self-limiting with an unproblematic recovery (Kapperud *et al.* 1992, Ketley 1997, Wassenaar and Blaser 1999, Zilbauer *et al.* 2008).

Rare complications of an infection with *Campylobacter* spp. include gastrointestinal and extragastrointestinal complications such as reactive arthritis, cholecystitis, pancreatitis, meningitis, bacteraemia, inflammatory bowel disease (IBS) or febrile con-

vulsions (Skirrow *et al.* 1993, Smith 1995, Allos 2001, Hannu *et al.* 2002). The so called Guillan-Barré syndrome (GBS) is an important and severe complication after an infection (Nachamkin *et al.* 1998, Allos 2001, Nachamkin 2001, Poropatich *et al.* 2010). GBS, an acute autoimmune-mediated disorder affecting the peripheral nervous system, results in neuromuscular paralysis such as weakness of limbs and respiratory muscles (Smith 1995, Hughes and Rees 1997, Nachamkin *et al.* 1998). An annual increase of 7% of cases with *Campylobacter*-associated GBS was observed in France between 1996 and 2007 while the number of GBS cases in New Zealand decreased due to campylobacteriosis control (Baker *et al.* 2012, Sivadon-Tardy *et al.* 2014).

1.1.2. Risk factors for contracting campylobacteriosis

Reservoirs for *Campylobacter* spp. are different domestic or wildlife birds and mammals where the human pathogen lives commensally in the intestine (Blaser *et al.* 1980, EFSA Panel on Biological Hazards 2010). As a result animal faeces contaminate the environment or carcasses - especially poultry - during the slaughter process (Engberg 2006, EFSA Panel on Biological Hazards 2010, Whiley *et al.* 2013, Kaakoush *et al.* 2015). Hence, the pathogen can be transmitted from its reservoir to humans over direct routes e.g. close contact with domestic animals or indirect routes such as contaminated drinking water or meat (EFSA Panel on Biological Hazards 2010, Whiley *et al.* 2013). A meta-analysis of case-control studies on risk factors for a sporadic *Campylobacter* spp. infection identified the following exposures being associated with an elevated risk for infection: foreign travel, eating undercooked chicken meat, exposure through environmental routes e.g. contaminated drinking water, direct contact with farm an-

imals and having a pre-existent chronic disease (Domingues *et al.* 2012).

Several studies have identified travelling abroad as one of the most important risk factor for contracting human campylobacteriosis (Schorr *et al.* 1994, Neimann *et al.* 2003, Friedman *et al.* 2004, Mossong *et al.* 2016). Concomitantly, high proportions of campylobacteriosis were reported among returning travellers suffering from bacterial diarrhoea (Swaminathan *et al.* 2009, Ravel *et al.* 2011, Zenner and Gillespie 2011, Kendall *et al.* 2012). The risk of infection depends on the destination of travel and is generally lower for travels to Northern and Western Europe and North America while it increases for travels to Asia, Africa or South America (Charlett *et al.* 2003, Ekdahl and Andersson 2004, Mughini-Gras *et al.* 2014). However, travel per se is not considered a source of infection or route of exposure as travellers are likely exposed to *Campylobacter* spp. by the common routes e.g. eating chicken meat (Pires *et al.* 2009, Domingues *et al.* 2012, Mughini-Gras *et al.* 2014).

The most important source for the foodborne transmission described in the literature is poultry whereas beef and pork seem to play a secondary role (Mullner *et al.* 2009, Sheppard *et al.* 2009, EFSA Panel on Biological Hazards 2010, Boysen *et al.* 2014). Poultry and cattle mainly harbour *Campylobacter jejuni* and to a lesser extent *Campylobacter coli* which is more common among pigs (Inglis *et al.* 2004, Milnes *et al.* 2008, Hannon *et al.* 2009, EFSA Panel on Biological Hazards 2010).

Especially carcasses of broilers become easily contaminated during the slaughter process and chicken meat often contains high loads of *Campylobacter* spp. when it reaches the retail level (EFSA Panel on Biological Hazards 2010, Ellerbroek *et*

al. 2010, Guerin *et al.* 2010, Hardy *et al.* 2013). Different risk assessments in high-income countries indicate that the consumption of poultry meat especially when undercooked is the main risk factor for an infection with *Campylobacter* spp. (Schorr *et al.* 1994, Neimann *et al.* 2003, Friedman *et al.* 2004, Mughini Gras *et al.* 2012, Mossong *et al.* 2016). Genetic studies investigating the sources of human *Campylobacter* spp. infections showed that exposure to chicken meat accounts for around 50-70% of human campylobacteriosis cases (Sheppard *et al.* 2009, Kittl *et al.* 2013a, Boysen *et al.* 2014, Jonas *et al.* 2015, Mossong *et al.* 2016).

The important role of poultry as an infection source could be observed 1999 in Belgium and 2003 in the Netherlands (Vellinga and van Loock 2002, van Pelt *et al.* 2004). Domestically produced poultry products and eggs were withdrawn from the retail market in Belgium due to the contamination of poultry products with dioxin (Vellinga and van Loock 2002). The number of human campylobacteriosis cases dropped by 40% during the two weeks following the withdrawn and returned to previous levels afterwards (Vellinga and van Loock 2002). An outbreak of avian influenza and the associated culling of poultry in the Netherlands from March to May 2003 resulted in higher prices for and consequently a lesser consumption of poultry meat (Friesema *et al.* 2012). A 10% - 70% reduction of reported campylobacteriosis cases was observed among public health laboratories until December 2003, with the largest reduction in areas where the culling took place (Friesema *et al.* 2012).

Beef, pork, sheep meat or game play also a role in in foodborne transmission of *Campylobacter* spp. e.g. if consumed raw as tartare (Mullner *et al.* 2009, Taylor *et al.* 2013, Whiley *et al.*

2013). While pigs, sheep and wild animals are the a source of infection for only a minority of human infections cattle account for around 20% of human cases (Sheppard *et al.* 2009, Kittl *et al.* 2013a, Boysen *et al.* 2014, Jonas *et al.* 2015). *Campylobacter* strains from cattle are mainly linked to campylobacteriosis outbreaks where contaminated unpasteurized milk or drinking water was identified as the source of infection (Clark *et al.* 2003, Heuvelink *et al.* 2009, Taylor *et al.* 2013, Fernandes *et al.* 2015).

Although *Campylobacter* spp. are generally perceived as food-borne pathogens other transmission pathways also contribute. Noteworthy are direct contact (e.g. petting) with infected domestic animals or pets and contaminated vegetables or fruits eaten raw (Neimann *et al.* 2003, Verhoeff-Bakkenes *et al.* 2011, Mughini Gras *et al.* 2012, Gras *et al.* 2013). However, the consumption of raw vegetables in relation to contracting campylobacteriosis is controversial and has also been identified as a protective factor (Neimann *et al.* 2003, Doorduyn *et al.* 2010, Mughini Gras *et al.* 2012, Whiley *et al.* 2013).

1.1.3. Risk factors for contracting campylobacteriosis in Switzerland

In Switzerland the major risk factors for a sporadic infection with *Campylobacter* spp. were already described more than 20 years ago by a case-control study using a ‘close-friend’-control sampling (Schorr *et al.* 1994). It showed that travelling abroad followed by the consumption and handling of poultry and poultry liver are the most important risk factors in Switzerland. Risk exposures and risk factors could have changed and likely vary during the year considering the increase of human campylobacteriosis cases since the 1990s (Schmutz *et al.* 2016).

It appears as travelling abroad was surpassed by poultry consumption as the main risk factor in Switzerland. One of the Swiss genotyping studies which distinguished between domestic and travel-associated human cases counted only 18% of travel-associated cases (Niederer *et al.* 2012). The population attributable fractions of travelling abroad and poultry consumption in Switzerland were equal (27%) in a risk attribution model using exposure modelling (Büttner *et al.* 2010).

In Switzerland several genotyping studies attributed human campylobacteriosis cases to different sources of infection. The comparison of human isolates with environmental isolates revealed that 40 – 84% of the human cases originated from the poultry reservoir (Kittl *et al.* 2011, Kittl *et al.* 2013a, Jonas *et al.* 2015). However, another study on domestic and travel-associated human isolates showed a much lower genetic overlap with poultry isolates (Niederer *et al.* 2012). Further, poultry as main cause of infection leading to human campylobacteriosis in Switzerland is supported by a risk attribution model which estimated a population attributable fraction of 27% for poultry consumption (Büttner *et al.* 2010).

Indeed Swiss broiler flocks show high levels of colonisation with *Campylobacter* spp. (BLV and BAG 2017). A Swiss study between autumn 2003 and summer 2004 found that 35.7% of broiler flocks were colonised by *Campylobacter* spp. whereby the five colonised flocks were tested positive in summer (Ring *et al.* 2005). Another study revealed a *Campylobacter* spp. prevalence of 29% among faecal swab samples collected from chickens of 100 Swiss poultry farms. This corresponds to a flock prevalence of 54% and on the farm level up to 69% of included farms were tested positive depending on the type of farm (Wittwer *et al.* 2005). On farms, the

pathogen is often transferred from chickens to other farm animals and vice versa (Zweifel *et al.* 2008). The latest available data from 2016 shows a flock prevalence for broiler chickens of 35% (BLV and BAG 2017).

The prevalence of *Campylobacter* in broilers at slaughter has a direct effect on the prevalence of campylobacteriosis in humans after two weeks (Wei *et al.* 2015). *Campylobacter* strains of broilers at slaughter were found at high levels in chicken meat at the Swiss retail level (Wirz *et al.* 2010, Kittl *et al.* 2013b). The contamination rate of chicken meat with *Campylobacter* spp. depends on the season of the year (higher in summertime) and can reach up to a 100% e.g. for chicken liver (Baumgartner and Felleisen 2011, BLV and BAG 2017). Domestic chicken meat products are significantly more often contaminated than chicken meat products imported from abroad (Baumgartner and Felleisen 2011). Hence, the indirect transmission of *Campylobacter* spp. from broilers to humans by chicken meat could play a major role for human campylobacteriosis in Switzerland.

Bovine *Campylobacter* spp. strains are also a source for human campylobacteriosis in Switzerland. Around 10-20% of human *Campylobacter* spp. isolates can be attributed to cattle (Wieland *et al.* 2006, Kittl *et al.* 2013a, Jonas *et al.* 2015). However, an earlier study did not find any *Campylobacter* spp. in bulk-tank milk samples from 206 different Swiss dairy farms (Stephan and Buhler 2002). *Campylobacter* spp. can also be found in pigs, dogs and cats but these seem to play a minor part as sources for human campylobacteriosis (Wieland *et al.* 2005, Keller *et al.* 2007, Kittl *et al.* 2013a, Amar *et al.* 2014).

1.1.4. Measures to reduce the burden of campylobacteriosis

The burden of human campylobacteriosis can be most effectively reduced by an interdisciplinary One Health approach along the food chain including all relevant stakeholders (Golz *et al.* 2014). Of special interest herein is chicken meat given it is deemed the main source of human infections in Europe (EFSA Panel on Biological Hazards 2010). Intervention methods and control measures should be implemented at different stages along the farm-to-fork chain i.e. from broiler farms over slaughter and retail levels to the consumer level (Wagenaar *et al.* 2013, Golz *et al.* 2014). The colonization of broiler flocks with *Campylobacter* spp. can theoretically be prevented with strict biosafety measures on farms (Wagenaar *et al.* 2013, Golz *et al.* 2014). Yet, *Campylobacter* spp. is ubiquitous in the environment of farms significantly hindering any prevention of its introduction into broiler flocks (Wagenaar *et al.* 2013). Promising control measures are the irradiation (e.g. gamma radiation) or chemical decontamination (e.g. by lactic acids, acidified sodium chlorite, peracetic acid) of broiler carcasses at the end of the slaughter process which aim at reducing the contamination rate and the load of *Campylobacter* spp. on broiler carcasses (EFSA Panel on Biological Hazards 2011). Today, these interventions and measures aim at lowering *Campylobacter* contamination levels of poultry products to an acceptable low risk as it is hardly possible to completely eliminate *Campylobacter* spp. from the poultry production (Wagenaar *et al.* 2013).

1.2. Acute gastroenteritis and infectious intestinal diseases caused by *Campylobacter* spp. and other gastrointestinal pathogens

1.2.1. Acute gastroenteritis

Gastroenteritis also named gastrointestinal illness or diarrhoeal disease is a common and widespread disease worldwide especially among children (Majowicz *et al.* 2008, Fischer Walker *et al.* 2012, GBD 2015) (see Chapter 1.3). In general, gastroenteritis is physiologically characterised by inflammatory processes of the stomach or intestinal mucosal surface leading to enteric symptoms - predominantly diarrhoea (Tam *et al.* 2012a, DuPont 2014, Morgan *et al.* 2015). General characteristics of diarrhoea are increased water content, volume or frequency of stools (Guerrant *et al.* 2001). A frequent definition of diarrhoea is the passage of ≥3 unformed or liquid stools per day (in 24h) likewise accompanied by other enteric symptoms such as vomiting (Guerrant *et al.* 2001, WHO 2005, DuPont 2014). Diarrhoea can be categorised based on its duration as acute (<14 days), persistent (14 - 29 days) and chronic (≥30 days) (DuPont 2014).

AG usually last for less than 2 weeks and typical symptoms include diarrhoea (watery, with blood, mucus), vomiting, abdominal cramps and pain, fever, dehydration, nausea and loss of appetite occurring in various combinations (Guerrant *et al.* 2001, Thielman and Guerrant 2004, Majowicz *et al.* 2008, Morgan *et al.* 2015). Causes of AG include a range of gastrointestinal infections e.g. campylobacteriosis, non-infectious causes such as food poisonings (bacterial toxins, chemicals) or chronic conditions e.g. Crohn's disease, ulcerative colitis or food intolerance (Tam *et al.* 2012a). Yet, not all gastrointesti-

nal infections or food poisonings e.g. *Helicobacter pylori* or botulism lead to enteric symptoms (Tam *et al.* 2012a).

1.2.2. Infectious intestinal diseases

The term infectious intestinal diseases (IID)[2] generally refers to an infection with a gastrointestinal pathogen causing AG and is also known as acute infectious diarrhoea (Guerrant *et al.* 2001, Tam *et al.* 2012a, DuPont 2014, Morgan *et al.* 2015) (Figure 1.1). A wide range of pathogenic bacteria, viruses and protozoa mainly transmitted by the faecal-oral route have been identified as causes of IID (de Wit *et al.* 2001a, Huhulescu *et al.* 2009, Tam *et al.* 2012b, Morgan *et al.* 2015). Many of them are part of the ICD-10 group "Intestinal infectious diseases" (A00–A09) and are also summarised under the term food- and water-borne diseases.

The largest proportion of IID is caused by viruses whereby the main cause of viral IID at a global scale is considered to be norovirus accounting for nearly a fifth of all AG cases (Hall *et al.* 2013, Ahmed *et al.* 2014, Kirk *et al.* 2015, Pires *et al.* 2015). Other disease causing viruses include rotavirus, adenovirus, astrovirus and others (de Wit *et al.* 2001a, Huhulescu *et al.* 2009, Tam *et al.* 2012b, Morgan *et al.* 2015). Bacterial pathogens commonly causing IID are mainly food- and water-borne including, among others, *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Clostridium* spp., *Vibrio* spp., *Yersinia* spp. or pathogenic *E. coli* (de Wit *et al.* 2001a, DuPont 2009, Tam *et al.* 2012b). However, also bacterial pathogens potentially resulting in systemic infections with little

[2] Sometimes also called *intestinal infectious diseases*

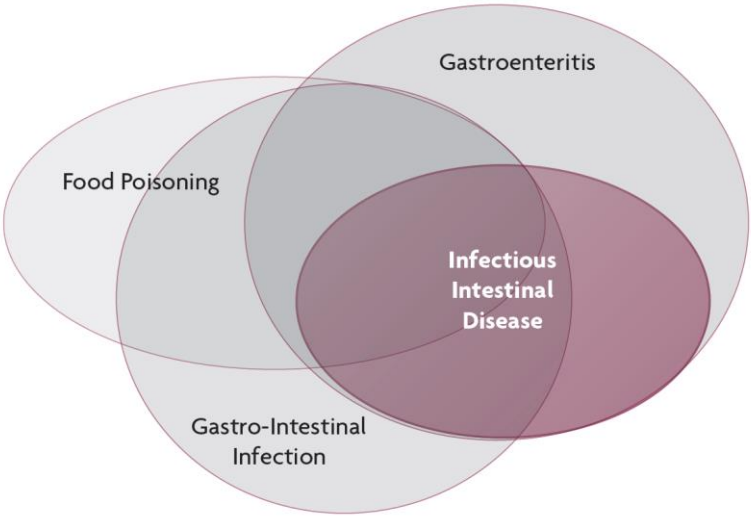

Figure 1.1: Graphical illustration of the term infectious intestinal disease in relation to similar terms.

Source: Tam *et al.* (2012a)

enteric symptoms (e.g. *Salmonella typhi*/*paratyphi*, *Listeria* spp.) are often included (DuPont 2009, Tam *et al.* 2012a).

Parasitic pathogens such as *Giardia* spp., *Cryptosporidium* spp., *Blastocystis* spp. or *Entamoeba* spp. are of less importance in high-income countries (de Wit *et al.* 2001a, Huhulescu *et al.* 2009, Tam *et al.* 2012b). In these countries they are often found in travellers returning from the tropics and sub-tropics (Shah *et al.* 2009, Majer and Neumayr 2015, Herbinger *et al.* 2016). Also other IID are frequently diagnosed in travellers with traveller's diarrhoea returning from low- and middle-income countries to high-income countries (Shah *et al.* 2009, Kendall *et al.* 2012, Herbinger *et al.* 2016).

1.3. Disease burden and epidemiology of acute gastroenteritis and human campylobacteriosis

1.3.1. Disease burden and epidemiology of acute gastroenteritis in high-income countries

An estimated 2.8 billion cases of diarrhoeal diseases occurred on a global level in 2013 according to the Global Burden of Disease Study (GBD 2015). Pires *et al.* (2015) estimated that *Campylobacter* spp., *Cryptosporidium* spp., *Salmonella* spp., *Shigella* spp., enterotoxigenic *E. coli*, enteropathogenic *E. coli*, *Entamoeba histolytica*, *Giardia lamblia* and norovirus transmitted by food in concert caused globally 1.8 billion cases of diarrhoeal disease and 599,000 deaths in 2010. Children under the age of 5 years accounted for around 40% of cases and deaths (Pires *et al.* 2015). The highest disease burden is observed in low- and middle income countries (LMICs) (GBD 2015, Pires *et al.* 2015)

In high-income countries incidences of AG on population level range from 0.3 to 3.5 episodes per person-year (Roy *et al.* 2006). In Europe, reports indicate that an individual experiences 0.5 to 1.4 episodes of AG on average per year. Specifically the number of episodes per person-year – often referred to as 'annual incidence'-, was estimated at 0.27 for the United Kingdom (UK) (Tam *et al.* 2012c), 0.29 for the Netherlands (Havelaar *et al.* 2012), 0.33 for France (van Cauteren *et al.* 2012), 0.42 for Malta (Gauci *et al.* 2007b) 0.60 for Ireland (Scallan *et al.* 2004), 0.90 for Poland (Baumann-Popczyk *et al.* 2012), 0.95 for Germany (Wilking *et al.* 2013), 1.08 for Italy (Scavia *et al.* 2012), 1.2 for Norway (Kuusi *et al.* 2003) and 1.4 for Denmark (Muller *et al.* 2012). The disease burden in the United States of America (US), Canada, Australia and New

Zealand was estimated at 0.60, 0.63, 0.92 and 1.11 episodes per person-year, respectively (Hall *et al.* 2006, Jones *et al.* 2007, Adlam *et al.* 2011, Thomas *et al.* 2013). Comparisons between countries should be interpreted with caution. Often, different study designs and case definitions were used leading to remarkable differences in the estimated disease burden (Scallan *et al.* 2005, Majowicz *et al.* 2008). By 2017 no such estimate was available for Switzerland.

These high incidences result in a high annual AG disease burden and significant health system use in these countries: In 2009, an estimated 16.9 million cases in the UK resulted in 18 physician consultations per 1000 person-years (Tam *et al.* 2012c). In the Netherlands, an estimated 4.8 million cases of AG result in 13 primary care attendances per 1000 person-years and 1.3 hospitalisations per 1000 person-years (Havelaar *et al.* 2012). Norwegian estimates assume 5.4 million cases, 200 consultations per 1000 person-years and 50 hospital admissions per 1000 person-years resulting in 800,000 hospital days (Kuusi *et al.* 2003). The disease burden for France was estimated at 21 million cases and 110 physician consultations per 1000 person-years (van Cauteren *et al.* 2012). The estimate for Poland is 33.3 million cases, 266 physician consultations per 1000 person-years and 40 hospitalisations per 1000 person-years (Baumann-Popczyk *et al.* 2012). In Italy, an estimated 48 million cases and 389 physician consultations occur per 1000 person-years (Scavia *et al.* 2012). A study in Germany estimated 64.9 million cases, 395 physician consultations per 1000 person-years and 32 admissions to hospital per 1000 person-years resulting in 19.9 million hospital days per year for the adult population only (Wilking *et al.* 2013).

Studies in high-income countries showed that the disease burden is generally highest in children and decreases with age (Baumann-Popczyk *et al.* 2012, Doorduyn *et al.* 2012, Muller *et al.* 2012, Tam *et al.* 2012c, van Cauteren *et al.* 2012). The incidence of AG in Danish children aged <9 years was 2.3 episodes per person-year compared to an all-age incidence rate of 1.4 (Muller *et al.* 2012). In France, children aged <5 years had an incidence rate of 0.76 episodes per person-year which was more than double the rate of all study participants (van Cauteren *et al.* 2012). The incidence rate of AG among Polish children was higher for those aged 5-14 years than for those aged <5years (1.4 vs. 1.1 episodes per person-year) (Baumann-Popczyk *et al.* 2012). The disease burden among children is comparable to Europe in Australia, Canada, New Zealand and the US (Scallan *et al.* 2005, Hall *et al.* 2006, Jones *et al.* 2007, Adlam *et al.* 2011).

The disease burden of AG in Europe generally peaks in winter and decreases at the beginning of spring (Huhulescu *et al.* 2009, Muller *et al.* 2012, Scavia *et al.* 2012, van Cauteren *et al.* 2012, Wilking *et al.* 2013). In Poland as an example, the highest rate was observed for January (1.48 episodes per person-years) and lowest in June (0.35 episodes per person-years) (Baumann-Popczyk *et al.* 2012). Interestingly, in Malta a slightly different seasonality with peaks in June–July and October–November is observed (Gauci *et al.* 2007b). The disease burden of AG in Australia peaks also in summer (Hall *et al.* 2006).

In some countries such as Austria, Italy, Norway or Poland an additional peak in late summer (July-September) can be observed (Kuusi *et al.* 2003, Huhulescu *et al.* 2009, Baumann-Popczyk *et al.* 2012, Scavia *et al.* 2012). Studies indicate that

the peak in winter is associated with viral gastrointestinal infections e.g. norovirus or rotavirus and the one in late summer with enteropathogenic bacteria e.g. *Campylobacter* spp. or *Salmonella* spp. (Huhulescu *et al.* 2009, Karsten *et al.* 2009, Baumann-Popczyk *et al.* 2012). The disease burden of specific bacterial and viral IID in Denmark shows a distinct seasonality (Muller *et al.* 2012). Norovirus infections are more prevalent in winter months, rotavirus infections in late winter and early spring and bacterial IID – especially *Salmonella* spp. – in summer (Muller *et al.* 2012).

1.3.2. Disease burden and epidemiology of campylobacteriosis in high-income countries

Human campylobacteriosis occurs worldwide (Kaakoush *et al.* 2015, Kirk *et al.* 2015). The global disease burden in 2010 is estimated at 166 million cases including 37,600 deaths or at 3.7 million disability-adjusted life years (DALYs) by the Foodborne Disease Burden Epidemiology Reference Group (FERG) (Kirk *et al.* 2015). The Global Burden of Disease Study 2010 estimated an even higher global burden of 7.5 million DALYs (Murray *et al.* 2012). The disease burden for Switzerland in 2013 was estimated at 1751 – 2852 DALYs (Babo Martins *et al.* 2017).

The available information on the disease burden of campylobacteriosis in high-income countries is diverse and includes surveillance data, population-based studies and national burden estimates. This information can be influenced by surveillance biases, different diagnostic methods and techniques, study designs and methods or population-level immunity (Havelaar *et al.* 2009, Kaakoush *et al.* 2015, EFSA and ECDC 2016). The disease burden of campylobacteriosis should thus be carefully

compared between countries and different study characteristics need to be considered.

Since 2005 *Campylobacter* spp. is the most common gastrointestinal bacterial pathogen reported in humans in the European Union (EU) and the European Economic Area (EEA) (EFSA and ECDC 2016). The annual notification rate of campylobacteriosis in the EU increased significantly from 2008 to 2015 but has been rather stable in the last 5 years (EFSA and ECDC 2016). For 2015, an average notification rate of 65.5 laboratory-confirmed cases per 100,000 population corresponding to totally 229,213 laboratory-confirmed cases was reported (EFSA and ECDC 2016). This is a decrease of 5.8% compared to the notification rate of 2014 (69.5 per 100,000 population) and comparable with notification rates of 2012 and 2013 (65.4 and 64.3 per 100,000 population, respectively) (EFSA and ECDC 2016).

Highest national notification rates (>90 cases per 100,000 population) were reported from the Czech Republic, Slovakia Sweden and the UK and lowest rates (≤3.7 cases per 100,000 population) from Bulgaria, Cyprus, Latvia, Poland, Portugal and Romania (EFSA and ECDC 2016). In Germany, the notification rate of campylobacteriosis has increased considerably from 2001 (67 cases per 100,000 population) to 2014 (86 cases per 100,000 population) (Schielke *et al.* 2014, EFSA and ECDC 2016). Switzerland reported a notification rate of 85.3 cases per 100,000 population for 2015 (EFSA and ECDC 2016)[3].

[3] Further, annual notification rates of campylobacteriosis for European countries in 2015 are summarised in EFSA and ECDC (2016).

Some of the highest notification rates for campylobacteriosis were observed in New Zealand in the early 2000s with an average annual rate of 354 laboratory-confirmed cases per 100,000 population (Sears *et al.* 2011). The notification rate dropped to 162 cases per 100,000 population in 2008 after the successful implementation of poultry-focused food safety interventions (Sears *et al.* 2011). The notification rate of neighbouring Australia was 117.3 cases per 100,000 population in 2011 and an estimated 774,000 cases resulting in 18,200 DALYs occurred at the population level in 2010 (Gibney *et al.* 2014, Gibney *et al.* 2016).

Laboratory-confirmed cases represent only the tip of the iceberg of the total campylobacteriosis disease burden. Individuals suffering of campylobacteriosis do not always seek health care and if they do, they are not always tested with stool diagnostics. This leads to a considerable number of undetected cases in the community and at the healthcare level as often only laboratory-confirmed cases are registered in national surveillance systems. An estimated 9.25 million cases of human campylobacteriosis corresponding to an incidence rate of 1860 cases per 100,000 population occurred in the European community in 2009 (Havelaar *et al.* 2013). This means that for each of the 198,252 cases reported an additional 47 cases occur in the community without being registered (Havelaar *et al.* 2013).

The annual incidence rate of campylobacteriosis in the UK population was estimated at 1100 cases per 100,000 population (572,000 cases) and the disease lead to an estimated 80,000 medical consultations (Tam *et al.* 2012c). In the Netherlands, the estimated number of campylobacteriosis cases at the population level for 2009 was around 92,000 (557 cases per 100,000 population) which resulted in approximately 22,000 medical

consultations and 1000 hospitalizations (Havelaar *et al.* 2012). The Dutch disease burden including sequela of campylobacteriosis in the same year was estimated at 3250 DALYs (Havelaar *et al.* 2012). The annual incidence rate of campylobacteriosis in the French population was estimated at 842 cases per 100,000 population or 528,800 cases (van Cauteren *et al.* 2015). Around 327,000 of them consult a physician and close to 5200 cases are hospitalised (van Cauteren *et al.* 2015). Annual incidence rates for the German and Swiss population in 2009 were estimated at 338 and 350 cases per 100,000 population (277,000 cases and 26,900 cases), respectively (Havelaar *et al.* 2013)[4].

For the US population, 845,000 cases of domestically acquired foodborne campylobacteriosis including 8500 hospitalisations and 76 deaths were estimated for 2006 which equals 22,500 DALYs (Scallan *et al.* 2011, Scallan *et al.* 2015). In 2016, the American Foodborne Diseases Active Surveillance Network (FoodNet) notified around 8500 cases of *Campylobacter* spp. infections in its surveillance area which correspond to an incidence of 17.43 cases per 100,000 population (Marder *et al.* 2017). The incidence of campylobacteriosis in the US had increased since 2006 and the rate of 2014 was 13% higher compared to the average of the period from 2006-2008 (Crim *et al.* 2015). An estimated 213,700 cases of domestically acquired campylobacteriosis occurred in Canada in 2006 and 145,400 cases thereof were assumed to be foodborne (Thomas

[4] Further population incidence rates for other European countries can be found in Havelaar *et al.* (2013).

et al. 2013). However, only 7861 laboratory-confirmed cases were recorded in Canada in 2006 (Thomas *et al.* 2013).

Sporadic foodborne *Campylobacter* spp. infections represent the majority of cases whereas outbreaks – mainly waterborne and foodborne - are responsible for a small proportion of all infections (Skirrow 1990, 1991, Engberg 2006, Silva *et al.* 2011). Sources of infection for outbreaks are mainly contaminated poultry (often chicken liver), unpasteurized cow milk and contaminated drinking water (Heuvelink *et al.* 2009, Gubbels *et al.* 2012, Wensley and Coole 2013, Kaakoush *et al.* 2015, Mungai *et al.* 2015). In 2015, 385 foodborne outbreaks with 1421 cases and 2 waterborne outbreaks (unknown case numbers) were reported by EU/EEA member states - slightly less than in the previous five years (EFSA and ECDC 2016). Milk as source of infection was reported for more than half (56%) of the 25 foodborne outbreaks with strong evidence while around a quarter (24%) of these outbreaks were associated with broiler meat and products thereof (EFSA and ECDC 2016). A study by Taylor *et al.* (2013) reported that 86% of *Campylobacter* outbreaks in the US between 1997 and 2008 were foodborne and dairy exposures accounted for the majority of outbreaks (29%).

In high income countries the disease burden is generally largest among children less than 5 years of age and decreases with increasing age (Havelaar *et al.* 2009, Nichols *et al.* 2012, Schielke *et al.* 2014, ECDC 2015). Persons aged between 20 and 30 years are the second most affected group (Nichols *et al.* 2012, Schielke *et al.* 2014, Schmutz *et al.* 2016). The disease burden among older people increased since around 2005 while it decreased for young children (Nichols *et al.* 2012, Schielke *et al.* 2014, Schmutz *et al.* 2016). In general males are more

affected by campylobacteriosis than females (Nichols *et al.* 2012, Schielke *et al.* 2014, ECDC 2015, Schmutz *et al.* 2016). An exception is observed for young adults in their twenties where campylobacteriosis is more prevalent among females (Nichols *et al.* 2012, Schielke *et al.* 2014, Schmutz *et al.* 2016).

In LMICs, symptomatic infections affect mainly children less than 2 years of age while in high-income countries humans of all age groups are affected (Coker *et al.* 2002, Havelaar *et al.* 2009, Platts-Mills and Kosek 2014, ECDC 2015). A possible reason is the early and frequent exposure to *Campylobacter* spp. of children in LMICs resulting in individual protective immunity and population-level immunity (Rao *et al.* 2001, Havelaar *et al.* 2009, Amour *et al.* 2016). As a result, the incidence rate of symptomatic infections decreases with age and the proportion of asymptomatic carriers is bigger than in high-income countries (Havelaar *et al.* 2009).

A seasonal trend in human infections with *Campylobacter* spp. is observed in many high-income countries (Kovats *et al.* 2005, Lal *et al.* 2012). In Europe, the disease burden of campylobacteriosis shows a distinct seasonality with higher case numbers in all age groups during the summer months (ECDC 2015). Generally, case numbers start to increase rapidly at the beginning of April, peak between June and August and are lowest in February (ECDC 2015). The incidence of campylobacteriosis in Germany starts to increase in May and peaks in August (Schielke *et al.* 2014). An additional small peak of the incidence can be observed at the beginning of January (Schielke *et al.* 2014). In England and Wales case numbers – particularly in children - increase between May and June which is related to a rise in ambient temperature (Louis *et al.* 2005, Tam *et al.* 2006, Nichols *et al.* 2012). Ambient temperature likely acts as an

indirect driver of intermediate ecological pathways of transmission (Louis *et al.* 2005, Tam *et al.* 2006).

1.3.3. Disease burden and epidemiology of acute gastroenteritis and campylobacteriosis in Switzerland

In Switzerland the burden of disease of AG at population and health care levels are largely unknown. Available information is restricted to notifiable IID which are reported to the NNSID of the FOPH. Only bacterial IID have to be reported to the NNSID including *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Vibrio cholerae*, *Listeria* spp. and enterohaemorrhagic *Escherichia coli* (EHEC) (EDI 2015). As only laboratory-confirmed cases are recorded no numbers or even estimates of notifiable IID at population level are available. On the other side, information on the epidemiology and disease burden of non-notifiable IID caused by viruses or protozoa is very limited. Case numbers of notifiable IID for the year 2016 are summarised in Table 1.1.

In 2012, 8480 cases of human campylobacteriosis were reported to the NNSID – the highest number of cases since the establishment of the NNSID in 1988 (Schmutz *et al.* 2016). This is equivalent to an annual notification rate of 105 cases per 100,000 population and higher than the average of EU member states (65.4 cases per 100,000 population) in the same year (EFSA and ECDC 2016, Schmutz *et al.* 2016). In the 1990s, the yearly numbers steadily increased and reached a first peak in the year 2000 with 7024 cases (Figure 1.2).

Table 1.1: Case numbers of notifiable IID in Switzerland for 2016

Pathogen	**Case numbers**	**Incidence per 100,000 population**
Campylobacter spp.	7810	93.40
Salmonella spp.	1508	18.00
Salmonella typhi/*paratyphi*	24	0.03
Shigella spp.	186	2.20
Enterohaemorrhagic *E. coli*	478	5.70
Listeria spp.	51	0.60

Source: BAG (2017b)

Thereafter a decline in the yearly numbers was observed reaching the lowest level of 5061 cases in 2006 (Schmutz *et al.* 2016). Ever since, the yearly numbers increased steadily and campylobacteriosis was the most frequently notified zoonotic IID in 2016 (Schmutz *et al.* 2016, BLV and BAG 2017). The reasons still remain unexplained.

The rise in case numbers concurs with data from the EU where an increase in the number of cases was observed as well since 2005 (EFSA and ECDC 2016). The reasons for these increasing trends in Switzerland and the EU are not fully understood. It is assumed that improvements of surveillance systems and of diagnostics for campylobacteriosis could contribute to potential trends changes (EFSA and ECDC 2015).

The number of cases in Switzerland exhibits a seasonal pattern (Figure 1.3) (Schmutz *et al.* 2016). Peaks are observed during the summer months from June to August and over the festive season at the end of December and the beginning of January

(Schmutz *et al.* 2016). The reasons for this seasonal pattern are largely unknown. It is assumed that the summer peak is most likely related to the frequency of barbequing, thus also known as the "BBQ-peak". However, scientific evidence for this assumption is not available. Yet, chicken meat is more frequently contaminated with *Campylobacter* spp. in Switzerland during summer months (Baumgartner and Felleisen 2011). The winter peak is also named the "Fondue chinoise-peak" and is according to experts related to the consumption of dishes whereby raw meat is directly prepared at the table e.g. Fondue chinoise (Baumgartner *et al.* 2012). In agreement with this assumption group outbreaks of campylobacteriosis during the festive season due to Fondue chinoise have already been described (Schmid and Baumgartner 2003).

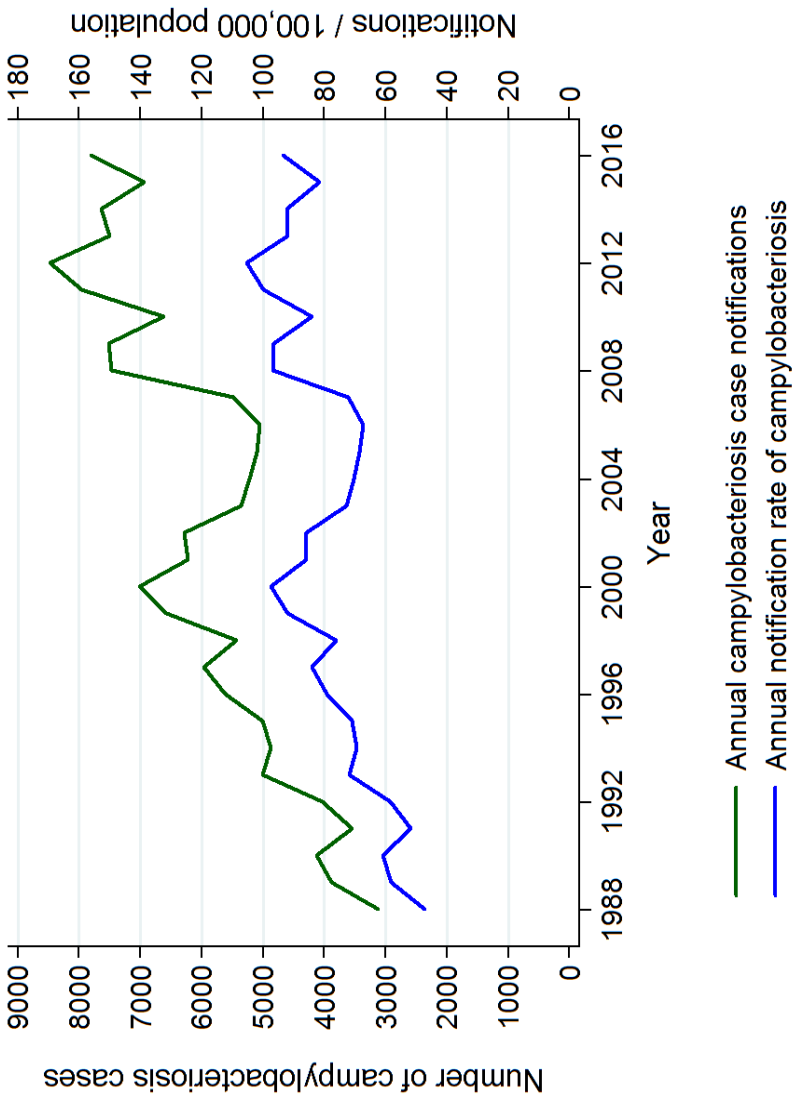

Figure 1.2: Notification rates and number of campylobacteriosis cases notified to the FOPH, Switzerland, 1988–2016

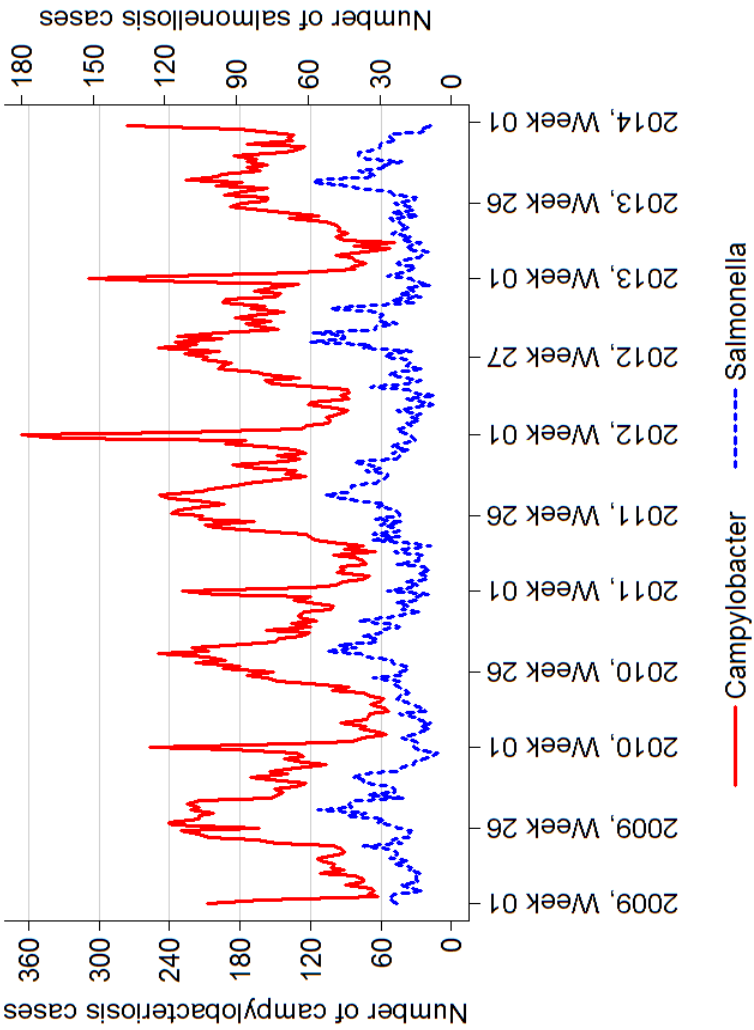

Figure 1.3: Seasonality of human campylobacteriosis and salmonellosis case notifications in Switzerland, 2009-2013.

Adapted from: Schmutz *et al.* (2016)

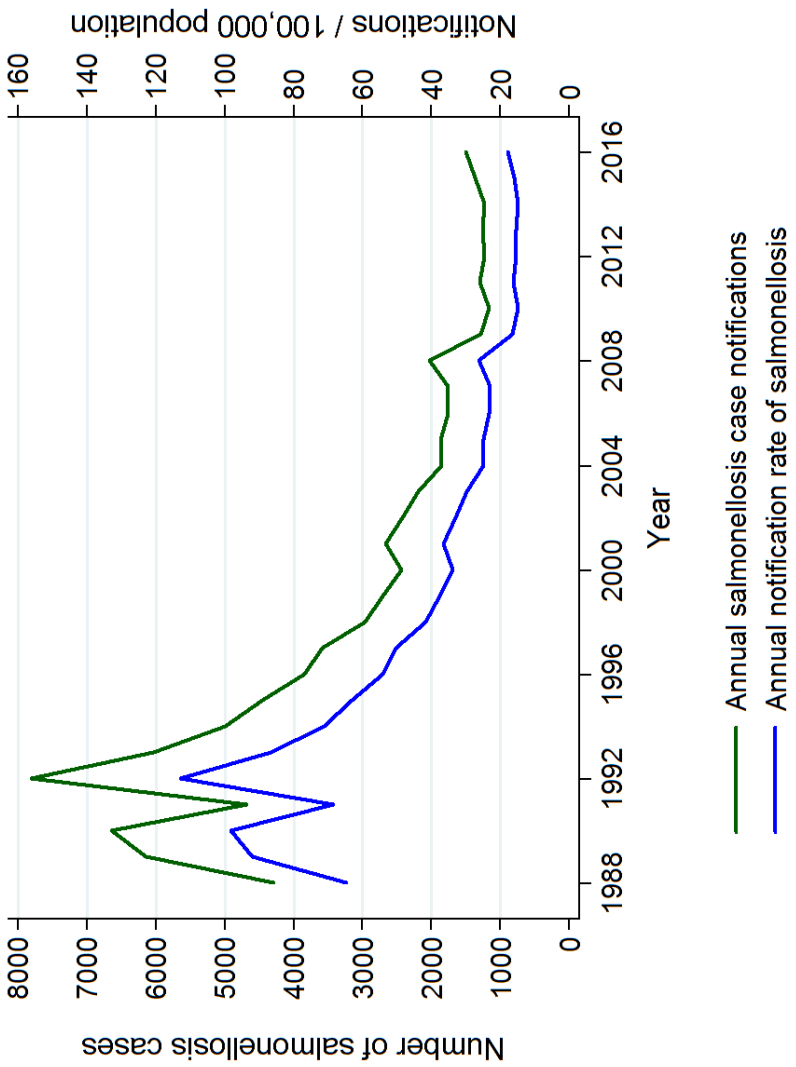

Figure 1.4: Notification rates and number of salmonellosis cases notified to the FOPH, Switzerland, 1988–2016

The situation of human campylobacteriosis in Switzerland stands in contrast to human salmonellosis. *Salmonella* spp. was more frequently diagnosed than *Campylobacter* spp. in clinical isolates of AG patients until 1995 (Schmid and Baumgartner 2012). A decline in the annual case numbers and notification rates was observed from the early 1990s until the 2010s (Figure 1.4) (Schmutz *et al.* 2016). This development was the result of concerted efforts and legal regulations of the poultry- and food-production industries to reduce the contamination of food with *Salmonella* spp. (Schmutz *et al.* 2016). As a consequence the proportion of travel-associated salmonellosis cases among notified cases increased from 28.7% in 1993 to 35.7% in 2011/12 (Schmid and Baumgartner 2013). Case notifications of human salmonellosis show a distinct seasonality with an increased number of notifications in late summer (July-October) (Figure 1.3) (Schmutz *et al.* 2016). Since 2010, the most frequent serovars were *S.* Enteritidis (54.0%) and *S.* Typhimurium (13.7%) (Schmutz *et al.* 2016).

1.4. Economic burden of acute gastroenteritis and campylobacteriosis

The high levels of disease burden associated with AG and campylobacteriosis generate a considerable economic burden. This burden is associated with different types of costs incl. direct healthcare costs (e.g. medication costs, consultation costs, hospital inpatient costs) and direct and indirect non-healthcare costs (e.g. loss of income and productivity). Economic burdens of different countries are difficult to compare as case definitions, cost items and approaches included for cost estimates vary between studies. Additionally, prices for health

care or medicines, loss of income and health care systems in general vary from country to country.

The economic burden of AG due to IID per case in the community of high income countries ranges from €14 in Australia to €1305 in the US (Hellard *et al.* 2003, Hoffmann *et al.* 2015). The total annual economic burden per country depends on the population size and is lowest in Malta (€17 million) and highest in the US (€12 billion) (Gauci *et al.* 2007a, Hoffmann *et al.* 2015). Annual health care costs account for €12 million in Malta and for €1.4 billion in the US (Gauci *et al.* 2007a, Hoffmann *et al.* 2015). In terms of direct health care costs per case in the community, the costs vary between €3 in Australia and €155 in the US (Hellard *et al.* 2003, Hoffmann *et al.* 2015).

Cases of campylobacteriosis result in annual costs (expenditures of public health systems and productivity losses) of €2.4 billion in the EU (EFSA 2016). Costs estimates for campylobacteriosis cases are highly variable depending on included sequela and mode of transmission e.g. foodborne cases only. National annual economic burdens range from €9 million in the Netherlands to €1.4 billion in the US (van den Brandhof *et al.* 2004, Hoffmann *et al.* 2015). This corresponds to costs of €117 per case in the Netherlands and of €1,710 in the US (van den Brandhof *et al.* 2004, Hoffmann *et al.* 2015). Total direct health care costs are also highest in the US (€213 million) and lowest in New Zealand (€0.6 million) (Scott *et al.* 2000, Hoffmann *et al.* 2015). Lowest health care costs per case were reported for New Zealand (€8) while these costs were highest in the Netherlands (€280) (Scott *et al.* 2000, Mangen *et al.* 2015).

The section above is a summary of the introduction of Chapter 9. A detailed overview and discussion on costs of illness of AG

and campylobacteriosis in high income countries can be found in this chapter.

1.5. Health care seeking of and case management for patients suffering from campylobacteriosis and other infectious intestinal diseases

1.5.1. Health care seeking of individuals affected by AG

The onset of AG due to IID can be abrupt or rather slow and individual symptoms occur in different combinations, severities and orders mainly depending on the infectious cause. As a result not every individual affected by an IID seeks medical care and many manage their illness themselves (DuPont 2014, Zollner-Schwetz and Krause 2015). The overall perceived severity of illness by the individual and the resulting need for medical care are important factors for health care seeking (Herikstad *et al.* 2002, Gibbons *et al.* 2014). There is evidence that cases with higher disease severity and longer disease duration are more likely to consult a physician (de Wit *et al.* 2001b, Kuusi *et al.* 2003, Tam *et al.* 2003, Hall *et al.* 2008).

Individuals with disease duration of ≥3 days were six times more likely to consult medical services than individuals with a shorter duration (Scallan *et al.* 2006). Bloody diarrhoea, vomiting, fever and abdominal cramps are important symptoms positively associated with medical consultations (de Wit *et al.* 2001b, Herikstad *et al.* 2002, Voetsch *et al.* 2004, MacDougall *et al.* 2008). Seeking medical care also depends on sex and age whereby male, children and elderly seek more frequently medical care than the rest of the population (de Wit *et al.* 2000, Scallan *et al.* 2006). These differences could be related to education and health literacy e.g. disease awareness, severity and

duration, previous illness and treatment experiences or when to seek care (Tam *et al.* 2003, Gibbons *et al.* 2014). Also not directly disease-related factors of legal, administrative and financial origin e.g. having health insurance, income, access to health care play a role (Tam *et al.* 2003, Scallan *et al.* 2006, Gibbons *et al.* 2014).

Additional contributing factors can be of cultural or religious origin (Gibbons *et al.* 2014). Health and medical care seeking differs e.g. between Bosnian migrants, Turkish/Kurdish migrants and Swiss (Gilgen *et al.* 2005). Differences were observed in the preferred medical outpatient setting (general practitioner vs. hospital) and the importance of different health care providers (Gilgen *et al.* 2005). Swiss patients considered the biomedical sector more important than self-treatment compared to Bosnian and Turkish/Kurdish patients (Gilgen *et al.* 2005).

1.5.2. Anamnesis and clinical evaluation of patients with AG

Assessing the medical history and a clinical evaluation of patients presenting with AG are important first steps for the further evaluation of the disease (Guerrant *et al.* 2001, Schweiger *et al.* 2005, Switaj *et al.* 2015). A thorough anamnesis and evaluation of the patient contributes to cost-effective and evidence-based initial diagnostic testing and therapy (Guerrant *et al.* 2001, Thielman and Guerrant 2004). The course and magnitude of the disease episode is evaluated by the onset, occurrence and severity of diarrhoea, abdominal pain, vomiting, nausea, fever and other symptoms (Guerrant *et al.* 2001, DuPont 2014). Thereby, the frequency, volume and presentation of stools e.g. stool with blood, mucus or pus need particular attention (Guerrant *et al.* 2001). Additionally, pa-

tient-specific epidemiological risk factors should be collected. Of interest are: recent travel activities, diet, contact to animals, individuals with similar disease in the environment, previous drug intake (antibiotics, immunosuppressive medications), co-morbidity (immunosuppressive disorders), occupational exposures like working in the food sector or at a day care centre (Guerrant *et al.* 2001, DuPont 2014).

The clinical evaluation of the patient entails the assessment of the abdomen (tenderness, pain localisation), vital signs (fever, blood pressure, heart rate and state of consciousness), bacteraemia, inflammation parameters (C-reactive protein level, blood count), hydration status or hypovolemia (Guerrant *et al.* 2001, DuPont 2014, Switaj *et al.* 2015). The anamnesis and clinical evaluation can provide hints about the likely cause of disease and some authors have summarised clinical and epidemiological features of individual IID in detail (Thielman and Guerrant 2004, DuPont 2009, Switaj *et al.* 2015). However, the predictive value is generally low due to often similar disease patterns among individual IID and other possible non-infectious causes of AG (Slutsker *et al.* 1998, Guerrant *et al.* 2001).

1.5.3. Diagnostic tests for infectious intestinal diseases in patients with AG

Specific diagnostic tests for IID should be considered if the clinical features of the disease and the epidemiological setting point towards an infectious cause or if possible public health implications are likely (Thielman and Guerrant 2004, DuPont 2009, 2014). Patients with mild symptoms or a recent disease onset (<24h) do usually not require microbiological investigations as AG episodes are often self-limiting and frequently last

less than a day (Herikstad *et al.* 2002, Thielman and Guerrant 2004, DuPont 2014). General indications for diagnostic tests are: severe diarrhoea with blood, mucus or pus (dysentery), protracted diarrhoea, profuse cholera-like watery diarrhoea, fever, dehydration or the suspicion of an outbreak (Guerrant *et al.* 2001, DuPont 2009, 2014). Immunocompromised and elderly patients and patients working in the food industry, health care sector and at day care centres should be tested as their diseases could point towards an outbreak in these settings (Guerrant *et al.* 2001, DuPont 2014).

In the past, medical laboratories applied mainly culture-based methods, microscopy, antigen detection or individual real-time multiplex polymerase chain reaction (PCR) assays for routine diagnostics of IID (Binnicker 2015, Humphries and Linscott 2015). Since a few years so-called syndromic panels or PCR panels for the diagnosis of IID-causing pathogens are used for routine diagnostics (de Boer *et al.* 2010, Allerberger 2015, Humphries and Linscott 2015). In the meantime such panels are also frequently deployed in diagnostic laboratories of high-income countries including Switzerland (DuPont 2014, Hächler and Stephan 2015). Some of these panels are able to detect more than 20 gastrointestinal pathogens in one test with higher sensitivity than conventional methods (Khare *et al.* 2014, Binnicker 2015, Buss *et al.* 2015, Spina *et al.* 2015). A reduced need for labour and timeliness of diagnosis are additional benefits compared to conventional methods (Binnicker 2015).

The usefulness in daily routine diagnostics and in regard to clinical practice and disease surveillance are currently discussed (Langley *et al.* 2015, Schreckenberger and McAdam 2015). Multiple infections are more often detected with panels and the detection of DNA does not allow distinguishing be-

tween viable disease-causing pathogens and non-viable or passage pathogens (Khare *et al.* 2014, Binnicker 2015, Buss *et al.* 2015). It is currently unclear how to meaningfully interpret such results for an appropriate treatment in clinical practice (Binnicker 2015). Pathogens are often not isolated when panels are applied and hence, isolates for antimicrobial susceptibility testing or subtyping for outbreak detection can be lacking (Hächler and Stephan 2015, Humphries and Linscott 2015, Langley *et al.* 2015). As a result, conventional methods are still needed and will likely remain the gold standard for antimicrobial susceptibility testing, strain characterisation and public health purposes such as outbreak investigations (Guerrant *et al.* 2001, Hächler and Stephan 2015, Langley *et al.* 2015).

In the near future whole genome sequencing (WGS) with next-generation sequencing technologies is likely to become a solid and fast method for the routine diagnostic and surveillance of infectious diseases incl. IID (Deng *et al.* 2016, Tang *et al.* 2017). Together with bioinformatics tools it opens a whole range of new possibilities for disease surveillance and outbreak detection compared to older technologies such as pulsed-field gel electrophoresis (PFGE). Thereby sequenced genomes of pathogens from humans, food items or the environment are stored in a central database and through the comparison of different isolates by bioinformatics tools foodborne disease outbreaks and their sources can be discovered and investigated. A recent study in Denmark on the routine typing, surveillance, and outbreak detection of verocytotoxin-producing *E. coli* infections, for example, showed that WGS is indeed suitable for routine diagnostics and surveillance and that it is faster and cheaper than currently deployed routine methods (Joensen *et al.* 2014).

1.5.4. Treatment of acute gastroenteritis and infectious intestinal diseases

The fundamental therapeutic aim of up most importance for AG patients is to maintain their fluid and electrolyte balance to avoid dehydration (Guerrant *et al.* 2001, DuPont 2014). Oral fluid and electrolyte replacement by an appropriate and additional food and liquid intake e.g. through juices or soups is often sufficient for patients with mild disease (Guerrant *et al.* 2001, Thielman and Guerrant 2004, DuPont 2009). Intermediate to severerly dehydrated patients are more likely to require glucose-based electrolyte solutions or rehydration by intravenous fluids if oral rehydration is not possible (Guerrant *et al.* 2001, Thielman and Guerrant 2004). Antidiarrhoeals play a major role in the therapy besides maintenance of patients' fluid and electrolyte balance and antimotility drugs like loperamide can be helpful to reduce the frequency of stools (DuPont 2009, DuPont 2014). However, their use does not shorten the disease duration and they should be used in combination with antimicrobials for patients with bloody or febrile diarrhoea (Thielman and Guerrant 2004, DuPont 2009, 2014).

Antimicrobials or antibiotics can be important for the treatment of inflammatory and invasive bacterial IID. However, they are indicated in only a small proportion of patients as the disease is mostly self-limiting and symptomatic therapy is usually sufficient (DuPont 2009, 2014, Zollner-Schwetz and Krause 2015). Empirical treatment of patients is mainly indicated if the anamnesis and the clinical evaluation reveal a severe course of disease pointing towards a bacterial cause. Indicators are bloody stools, fever, signs of systemic infection, immunocompromised patients or watery and severe traveller diarrhoea (Guerrant *et al.* 2001, DuPont 2014, Zollner-Schwetz and

Krause 2015). In these urgent cases an empirical treatment with azithromycin (macrolide) is recommended nowadays while in the past often quinolone antibiotics (e.g. ciprofloxacin) were used (Guerrant *et al.* 2001, Zollner-Schwetz and Krause 2015).

The initiation of a targeted antimicrobial therapy is indicated in only a small number of patients with a laboratory-confirmed bacterial infection (DuPont 2014). The macrolides azithromycin and erythromycin are recommended antimicrobial agents for the treatment of human campylobacteriosis (DuPont 2009, 2014). Further detailed recommendations for targeted antimicrobial therapies of bacterial IID have been summarised by DuPont (2009, 2014). Specific national guidelines for Switzerland are not available so far.

Antibiotic resistance rates are increasing in gastrointestinal bacterial pathogens such as *Campylobacter* spp. or *Salmonella* spp. and local resistance patterns should be considered for a successful antimicrobial therapy (Guerrant *et al.* 2001, Zollner-Schwetz and Krause 2015). *Campylobacter* spp. one of the most common causes of bacterial IID in Europe shows high levels of resistance to fluoroquinolones (EFSA and ECDC 2016, 2017). In 2015, the level of resistance to ciprofloxacin (fluoroquinolone) among human *Campylobacter jejuni* isolates ranged from 96.6% in Portugal to 27.4% in Norway while the European average was at 60.8% (EFSA and ECDC 2017). Resistance to erythromycin (macrolide) of the same human isolates was on average very low (1.5%) with the highest rate observed in Romania (8.7%) (EFSA and ECDC 2017). Fluoroquinolones are not anymore recommended for the empirical treatment of human campylobacteriosis by the European Food Safety Authority (EFSA) and the European

Centre for Disease Prevention and Control (ECDC) (EFSA and ECDC 2017).

The situation in Switzerland is similar and resistance levels of 58.0% for fluoroquinolones and of 1.2% for erythromycin were observed among *Campylobacter jejuni* isolates from humans undergoing routine susceptibility testing in 2015 (FOPH and FSVO 2016). A comparison of domestic and travel-associated *C. jejuni* and *C. coli* isolates showed that quinolone-resistant strains were more prevalent in travellers (56% vs. 39%) (Niederer *et al.* 2012). An earlier analysis of *C. jejuni* isolates from campylobacteriosis patients revealed a proportion of quinolone-resistance of 37.5% (Kittl *et al.* 2011). However, only two out of the total 603 isolates tested in both studies were resistant to macrolides.

1.6. Surveillance of infectious intestinal diseases

Infectious disease surveillance like the surveillance of IID is part of public health surveillance and corresponding data is nowadays often collected through voluntary or mandatory reports of diagnostic laboratories, physicians and other health care providers (Chorba *et al.* 1990, Choi 2012). The concept of mandatory reporting of infectious diseases was introduced when the colony of Rhode Island in North America passed a law on the mandatory reporting of smallpox, yellow fever and cholera in 1743 (Thacker and Berkelman 1988, Choi 2012). William Farr coined the modern concept of surveillance by his work on vital statistics in the 19th century (Langmuir 1976, Choi 2012). The systematic reporting of various diseases by physicians on a weekly basis was first introduced in Massachusetts, US (1874) and later mandatory reporting was also implemented in Europe (Italy 1888, UK 1890) (Chorba *et al.*

1989, Choi 2012). Surveillance data on infectious diseases reported by diagnostic laboratories and physicians in Switzerland was published for the first time in 1894 (Schmid and Baumgartner 2012).

In 1963, Alexander Langmuir - chief epidemiologist of the US Centers for Disease Control (CDC, Atlanta, US) - defined disease surveillance as:

"Surveillance, when applied to a disease, means the continued watchfulness over the distribution and trends of incidence through the systematic collection, consolidation and evaluation of morbidity and mortality reports and other relevant data. Intrinsic in the concept is the regular dissemination of the basic data and interpretations to all who have contributed and to all others who need to know." (Langmuir 1963)

The definition of Langmuir let to today's broad concept of public health surveillance which is defined by the World Health Organisation (WHO 2017) as:

"Public health surveillance is the continuous, systematic collection, analysis and interpretation of health-related data needed for the planning, implementation, and evaluation of public health practice. Such surveillance can:

- *serve as an early warning system for impending public health emergencies;*
- *document the impact of an intervention, or track progress towards specified goals; and*
- *monitor and clarify the epidemiology of health problems, to allow priorities to be set and to inform public health policy and strategies."*

1.6.1. Laboratory surveillance systems for infectious intestinal diseases

Public health surveillance systems are ongoing data systems which collect data on health from populations (individuals and communities), healthcare providers (physicians, hospitals, laboratories) and governmental agencies (Thacker and Stroup 1994). Their data is linked directly to the practice of public health at different levels and can be used for research, public policies, decision making, treatment, and prevention and intervention programs (Thacker and Stroup 1994). *"An ideal surveillance system is representative of the population, flexible, economic, and resilient, with timely reporting and validation of its outputs (Declich and Carter 1994, Thacker and Stroup 1994)"* (Simonsen *et al.* 2016). Multiple surveillance data streams capturing the whole range of clinical outcomes and laboratory data are needed to be fully aware of the situation (Simonsen *et al.* 2016). Laboratory surveillance systems are the core of infectious disease surveillance (Simonsen *et al.* 2016).

The Foodborne Diseases Active Surveillance Network (FoodNet) is a collaborative effort of the CDC and other partners that conducts laboratory-based surveillance of foodborne diseases including IID in several states in the US (Allos *et al.* 2004). For this purpose the FoodNet introduced a paradigm which is nowadays known as the surveillance or burden-of-illness pyramid (Allos *et al.* 2004). It considers the chain of events which have to occur for an episode of IID in the community to be recorded by the laboratory-based surveillance system (Figure 1.5).

For *Campylobacter* spp. and other IID the chain of events that have to occur are: (i) being exposed to and infected by a gastrointestinal pathogen (ii) experience of symptomatic disease i.e. AG (iii) seek medical care e.g. at general practitioner (iv) phy-

sician requests a faecal specimen (v) positive test result i.e. laboratory-confirmed case (vi) reported to notification system (Allos *et al.* 2004, Gibbons *et al.* 2014). Obviously a case of IID will only be recorded by the notification system if every event of the chain arrives (Allos *et al.* 2004, Scallan *et al.* 2006, Gibbons *et al.* 2014). As a consequence, passive notification systems often underestimate the true burden of disease in the community resulting in an uncertainty around the population incidence of campylobacteriosis and other IID derived from the system (Wheeler *et al.* 1999, Gibbons *et al.* 2014).

Underestimation is an indicator of the extent to which notification systems fail to describe the real burden of disease in a given population i.e. the number of cases occurring in the population that are not captured by the system in relation to the number of notified cases (Gibbons *et al.* 2014). It consists of two components at different levels of the burden-of-illness pyramid: under-ascertainment of cases occurring at the population level and underreporting of cases occurring at the healthcare level (Gibbons *et al.* 2014).

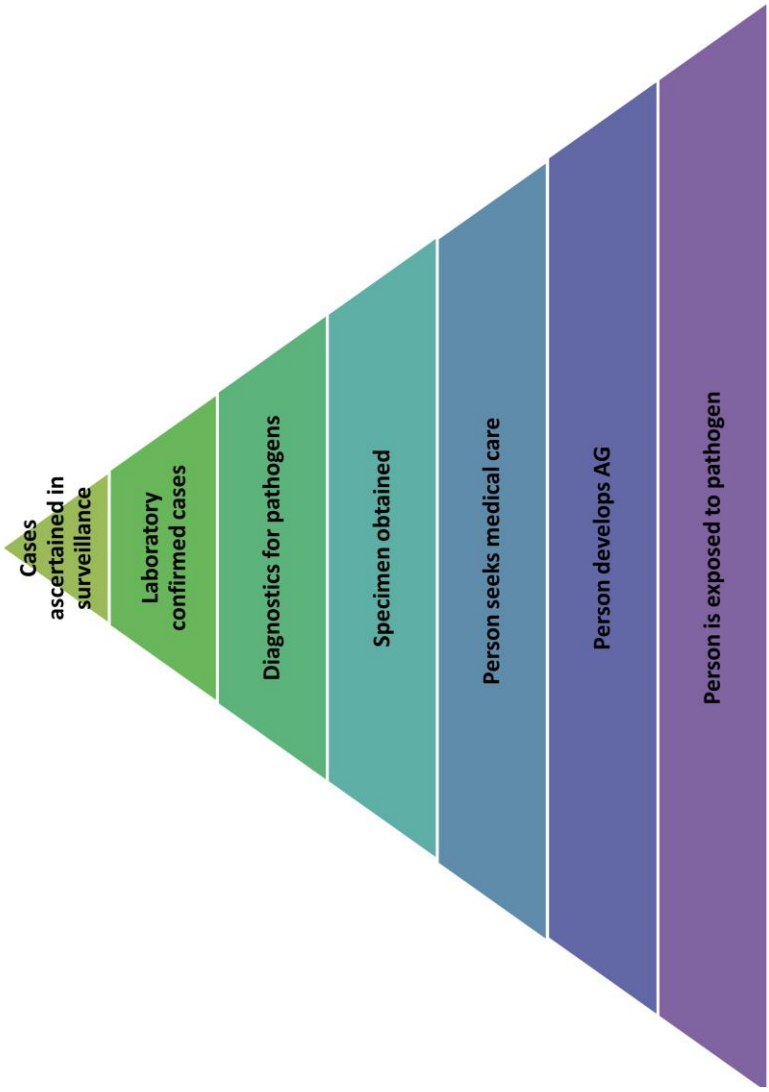

Figure 1.5: Burden-of-illness pyramid showing the chain of events required for a case of IID to be ascertained in the surveillance system

Adapted from Allos *et al.* (2004)

Notification systems capture only cases attending health care and hence, under-ascertainment can be seen as the proportion of cases not attending health care to cases attending health care (Gibbons *et al.* 2014). Reasons for not attending health care include asymptomatic infection, mild symptoms, the knowledge on the self-limiting nature of many IID and more (see 1.5.1). Underreporting refers to cases attending health care but not being recorded by the notification system and can be quantified as the proportion of cases attending healthcare to cases being recorded in the system (Hardnett *et al.* 2004, MacDougall *et al.* 2008, O'Brien *et al.* 2010, Gibbons *et al.* 2014). Under-diagnosis (pathogen is not diagnosed or misdiagnosed, see 1.5.3) and under-notification (failure to report) are both reasons for underreporting (Hardnett *et al.* 2004, MacDougall *et al.* 2008, Gibbons *et al.* 2014). The opposite of underreporting is referred to as reporting completeness which refers to the proportion of cases correctly diagnosed and reported among cases attending health care (Doyle *et al.* 2002).

The extent to which cases are underestimated in a notification system i.e. the extent of under-ascertainment and underreporting can be quantified by different study designs e.g. community-based studies, serological surveys, returning traveller studies, capture-recapture studies or modelling (Gibbons *et al.* 2014). Community-based studies such as the recent IID-2 study in the UK are frequently used to estimate the extent of underestimation in a notification system (Tam *et al.* 2012c, Gibbons *et al.* 2014).

1.6.2. Surveillance of campylobacteriosis and other infectious intestinal diseases in Europe

EU member states, Iceland, Liechtenstein and Norway report national surveillance data on a total of 52 communicable diseases to the ECDC. The ECDC coordinates the EU-wide surveillance of communicable diseases and enters the data in its database system, known as The European Surveillance System (TESSy) (ECDC 2015). The surveillance of the seven priority food- and waterborne diseases non-typhoidal salmonellosis, typhoid and paratyphoid fever, campylobacteriosis, Shiga toxin/verocytotoxin-producing *E. coli*, listeriosis, yersiniosis, and shigellosis is carried out by the ECDC Food- and Waterborne Diseases Network (FWD-Net) within the Programme of Food- and Waterborne Diseases and Zoonoses (FWD) (ECDC 2015).

In 2012, surveillance of campylobacteriosis was done by mandatory notification systems with full population coverage in 21 countries and by voluntary systems in six countries while three did not report at all. Surveillance data of campylobacteriosis reported to TESSy entails 27 variables common to all monitored communicable diseases (such as patient characteristics and diagnostics) and eight variables specifically for campylobacteriosis (for details see ECDC (2015)). The national notification systems vary among countries in regard to case definitions for campylobacteriosis, population coverage or diagnostic methods and hence a direct comparison of countries is hampered. A common case definition for the EU exists but further harmonisation of surveillance systems is needed for comparable surveillance data on national levels (ECDC 2015).

1.6.3. Surveillance of campylobacteriosis and other infectious intestinal diseases by the NNSID in Switzerland

In Switzerland, human campylobacteriosis and other IID are monitored through the NNSID run by the FOPH (Der Schweizerische Bundesrat 2015, EDI 2015). Only laboratory-confirmed bacterial IID including *Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Vibrio cholerae* (incl. clinical report), *Listeria* spp. (incl. clinical report) and EHEC (incl. clinical report) have to be reported to the NNSID (EDI 2015). Until 2015, laboratories reported confirmed cases to the FOPH and the cantonal physician of the cases' canton of residence within 24 hours or one week according to the Epidemics Act of 1970 and its related ordinances (Die Bundesversammlung 1970, Der Schweizerische Bundesrat 1999, EDI 1999).

The reporting period for laboratory-confirmed cases of all these diseases was set to 24 hours when the new Epidemics Act was implemented in 2016 (Die Bundesversammlung 2012, EDI 2015). Additionally, the total number of tests conducted for *Campylobacter* spp. and *Salmonella* spp., including the number of positive results, must now be reported annually as aggregated numbers, stratified by month and test method (EDI 2015) (reporting form see Appendix 14.1). Personal information on cases such as name, address, sex or date of birth has also to be reported but varies between notifiable pathogens. For cases of campylobacteriosis only initials, place of residence, date of birth and sex are required while e.g. full name, address, telephone number, whereabouts, date of birth, nationality and occupation have to be reported for cases infected with EHEC (EDI 2015) (reporting form see Appendix 14.2). Surveillance data on IID are made publically available on the website

(https://www.bag.admin.ch) and the weekly *BAG-Bulletin* of the FOPH.

Cases of campylobacteriosis and other notifiable IID are only diagnosed and later registered in the NNSID after a patient has consulted a physician, stool testing has been conducted and the stool test rendered a positive result. Consequently, patients registered in the NNSID represent only a (self-)selected proportion of all cases occurring in the population. This underestimation is thus, intrinsically linked to individual illness experience when suffering from an AG episode and related to individual steps in health care seeking and case management (see 1.6.1). The paradigm of the burden-of-illness pyramid introduced by FoodNet could be applied within the NNSID to interpret campylobacteriosis case numbers in regard to the disease burden in the general population. Unfortunately, required surveillance parameters e.g. the ratio of the campylobacteriosis rate in the community to the national surveillance rate are not available for Switzerland. Other European countries like the UK can do such interpretations based on country-specific surveillance parameters (Tam *et al.* 2012c).

1.6.4. The Swiss Sentinel Surveillance Network Sentinella

Established in 1986, the Swiss Sentinel Surveillance Network *Sentinella* is a cooperative voluntary surveillance and research network of primary care physicians and the FOPH which is operated and funded by the FOPH. The network's aim is to perform surveillance of non-notifiable infectious diseases and to conduct research in primary care. *Sentinella* consists of around 170 general practitioners, internists and paediatricians allocated to six geographical regions covering entire Switzerland. Approximately 2.5% of all physicians practicing in the

ambulatory care sector participate. The lead is with a steering committee consisting of representatives of the six regions, the Division of Communicable Diseases of the FOPH, the medical faculties of Basel, Bern, Geneva, Lausanne and Zurich plus individual primary care physicians. A biannual newsletter informs participating physicians about the latest administrative news, research projects and (scientific) publications of the network.

The network performs sentinel surveillance of influenza-like illness (ILI), mumps, pertussis, tick bites, Lyme disease, herpes zoster and post herpetic neuralgia. Additionally, research projects selected by the steering committee are included in the annual program of the network each year. Case numbers and the number of physician-patient contacts are reported weekly on a standard form with a unique identifier for each physician (paper-based or online). The standard form and/or paper-based supplementary forms or questionnaires are used for data collection in research projects. Further, physicians report detailed information on physician-patient contacts including age, sex and region twice a year during two weeks. This information together with reported case numbers is used to extrapolate the number of first consultations ("Erstkonsultationen") due to a disease or health condition per 100,000 inhabitants. A detailed description of the extrapolation method can be found in Altpeter *et al.* (2013). Latest results of the surveillance are published weekly in the *BAG-Bulletin* of the FOPH and its website (https://www.bag.admin.ch). Results from research projects are published in scientific journals. For more information see www.sentinella.ch.

2. Context and background for this work

2.1. Rationale and identified research needs

There is an unclear observed increase in campylobacteriosis case notifications in Switzerland since 2006. The interpretation of routine NNSID data is challenged given insufficient knowledge of how campylobacteriosis disease and illness presents in the general population and which determinants lead to health care seeking and case registration in the NNSID. The existing routine NNSID data do not allow estimating the annual incidence of campylobacteriosis in the Swiss general population. It allows only calculating the annual notification rate per 100,000 population. This clearly underestimates the incidence in the Swiss population as not all individuals affected by campylobacteriosis seek health care and have stool diagnostics performed.

Risk factors to contract campylobacteriosis are generally well described yet short-lived and transient risk factors relevant for the Swiss setting are unknown. The consumption of fondue chinoise is supposed to be relevant for Switzerland (Schmid and Baumgartner 2003). However, its importance as a risk factor during the observed campylobacteriosis winter peak is unclear. Similarly, the relationship of travelling and *Campylobacter* infections could play a role over Christmas and New Year considering that travelling is a risk factor in several countries and has been described more than 20 years ago as a cause for human campylobacteriosis in summer time in Switzerland (Schorr *et al.* 1994). Also, specific determinants for the apparent differences in age- and sex distributions of campylobacteriosis as observed in the NNSID are not fully understood.

It is actually unknown if the observed increase in campylobacteriosis case notification represents a real epidemiological increase or is only the result of an increased stool diagnostic rate and disease awareness on the part of the physicians and/or patients. A similar phenomenon has already been described with data from the NNSID on *Chlamydia trachomatis* infections (a sexually transmitted disease). The epidemic upward trend of case numbers observed in NNSID data could not be confirmed by analysing positivity rates using laboratory data (Schmutz *et al.* 2013).

Moreover, the burden of disease, aetiology and economic burden of AG in general, and due to IID in particular, are unknown at the population and the health system level in Switzerland. This is largely driven by the fact that individuals experiencing an episode of AG are not formally recorded neither at the health care level nor in other routine health information or surveillance systems apart from the NNSID. Consequently, interpretation of data from the NNSID, specifically from the case numbers published by the FOPH is limited and does not allow drawing inference on the burden of disease of AG in the community. There is a clear need to have a closer look at the NNSID data quality and relate and better explain it in regard to the corresponding burden of disease in Switzerland.

Also our understanding of the aetiological pattern of AG and the frequency of the pathogens at the primary care level and in the general Swiss population is equally hampered, i.e. only known from the "self-selected" subgroup of cases that is seeking medical care and that is registered in the NNSID. Information on the aetiology of AG in Switzerland is crucial to

establish interventions which reduce the burden of AG caused by IID.

The full economic burden of AG consisting of direct medical costs and direct and indirect non-medical costs is neither known from an individual patient-case nor from a national macro-economic perspective. Given the potentially significant nation-wide burden of AG there is a clear need to calculate the total monetary costs of an episode of AG due to IID arising from direct healthcare costs (medication costs, consultation costs, hospital inpatient costs) and direct and indirect non-healthcare costs (e.g. loss of income and productivity). It is likely that those diseases generate a considerable portion of national health expenditure and a substantial productivity loss in Switzerland that may be partially preventable.

2.2. Aim and objectives

2.2.1. Overall aim

The overall aim of the PhD thesis is to contribute to a better understanding of the epidemiology of human campylobacteriosis and AG and to improve the interpretation of routine surveillance data from the Swiss NNSID.

2.2.2. General objective 1

To describe how campylobacteriosis and AG present as diseases and illnesses in the Swiss population and within the Swiss health care system.

Specific objectives:

1) To assess the relative importance of alimentary, behavioural and environmental determinants to acquire a *Campylobacter* infection in Switzerland
2) To estimate the burden of AG and campylobacteriosis at the primary care level
3) To estimate direct health care costs associated with campylobacteriosis and AG in Switzerland

2.2.3. General objective 2

To create a basis for an improved interpretation and validity of routine surveillance data from the NNSID.

Specific objectives:

4) To analyse the validity of infectious disease surveillance data by assessing laboratory positivity rates of *Campylobacter* and *Salmonella* infections
5) To describe medical practitioners' diagnosis including stool testing rate, and treatment approaches for patients with AG and campylobacteriosis in particular

3. Research concept and methodological overview

This research consists of six research components aiming at a better understanding of the epidemiology of campylobacteriosis and AG especially in Switzerland and improving the interpretation of infectious disease surveillance data from the NNSID. The individual research components contributed to this aim by generating results at different levels of the burden-of-illness pyramid (Figure 3.1). Determinants of the transmission of *Campylobacter* spp. during winter time and disease presentation were investigated by a matched case-control study at the turn of the year 2012/2013 (Chapter 4). Transmission dynamics of *Campylobacter* spp. in Europe were analysed with a focus on winter peaks as observed in Switzerland using TESSy surveillance data for selected European countries (Chapter 5). Laboratory positivity rates of *Campylobacter* spp. and *Salmonella* spp. were analysed to assess the validity of the NNSID i.e. if corresponding surveillance data of the NNSID reflect what is observed at the laboratory level (Chapter 6). The presentation, case management and disease burden of campylobacteriosis and AG at the primary care level were first assessed in an explorative manner implementing a qualitative study among 69 Swiss general practitioners (GPs) in 2013 (Chapter 7). Based on these findings a one-year quantitative study within *Sentinella* was designed and implemented (Chapter 8). Additionally, direct health care costs caused by campylobacteriosis and AG were estimated for the first time in Switzerland (Chapter 9).

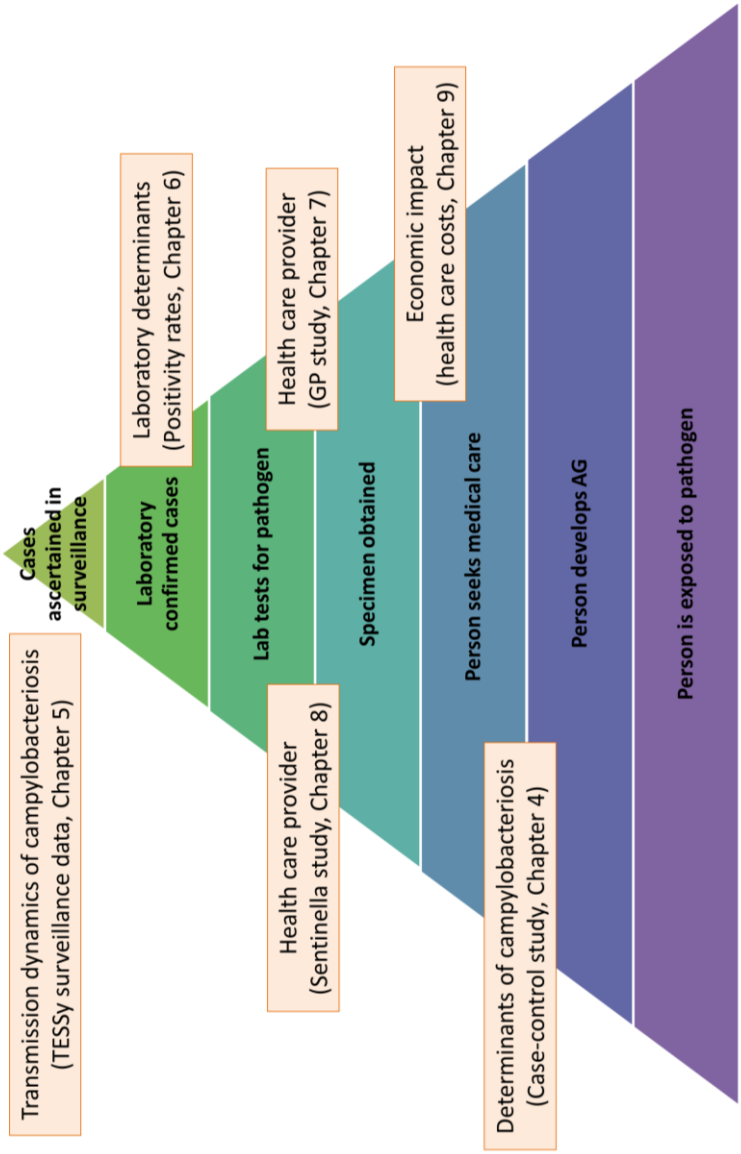

Figure 3.1: Graphical representation of the research components along the burden-of-illness pyramid

3.1. Collaborations

The present PhD thesis was conducted in close collaboration with cantonal and federal authorities, diagnostic laboratories, internal and external academic partners and the Swiss Sentinel Surveillance Network *Sentinella*.

The FOPH showed openness to scrutinise the NNSID and to assess determinants of campylobacteriosis and AG in the Swiss population and health care system. It was the main partner and played a major role in many aspects of conducting research by providing resources, expertise, surveillance data and its normative powers to foster collaboration with other stakeholders. In particular, it supported the research to understand the transmission of *Campylobacter* spp. in winter times (Chapter 4) and to describe the disease situation at the primary care level (Chapter 7 and 8). Contacts with diagnostic laboratories to obtain the necessary data to assess the positivity rates of *Campylobacter* and *Salmonella* were established with the help of the FOPH (Chapter 6).

The Swiss Sentinel Surveillance Network *Sentinella* under the lead of the FOPH provided the framework to conduct the longitudinal study to assess the incidence and aetiology of AG at the medical practice level (Chapter 8). *Sentinella* is managed entirely by the FOPH and our collaborative agreement with the FOPH enabled us to work through their channels.

GPs professional experience with campylobacteriosis and AG in regard to case management and disease burden (Chapter 7) was investigated together with colleagues from the Swiss branch of Pass International, Tessenderlo, Belgium and the Medical Anthropology Research Center, Universitat Rovira i Virgili, Tarragona, Spain; and with colleagues from the Centre

for Primary Health Care, University of Basel, Basel, Switzerland.

Direct health care costs for campylobacteriosis and AG (Chapter 9) were estimated in close collaboration with the Medical Services unit and Diagnostics unit of the Department of Medicine, Swiss TPH, Basel and colleagues from the Institute of Pharmaceutical Medicine, University of Basel and the Biostatistics and Prevention Institute, University of Zurich, Switzerland.

3.2. Summary of research approaches and study designs

3.2.1. A tradition and an epidemic: determinants of the campylobacteriosis winter peak in Switzerland

A prospective laboratory-based matched case-control study was conducted to elucidate risk exposures related to the campylobacteriosis winter peak such as food consumption or journeys abroad between December 2012 and February 2013. The principal aim of the study was to identify risk factors for a *Campylobacter* infection and corresponding risk factor patterns over the festive season in Switzerland. Secondary outcomes included symptomatology, illness perception and -experience, morbidity, health seeking behaviour and case management of laboratory-confirmed campylobacteriosis patients presenting to the health care system.

The study was performed among males and females aged ≥5 years living in Switzerland. Controls were selected from a random sample of the Swiss population. Cases and Controls were sent an information letter with a photo-illustrated questionnaire by postal mail and data was collected via computer-assisted

telephone interviews (CATI) working through the photo-illustrated questionnaire at both participant- and interviewer sides. A pair-matched analysis was performed to identify risk factors and corresponding matched odds ratios were reported. Data on secondary outcomes were descriptively analysed.

A detailed description of the methods applied for this research component can be found in Chapter 4 i.e. Bless *et al.* (2014).

3.2.2. The recurrent campylobacteriosis epidemic over Christmas and New Year in European countries, 2006-2014

This part of the thesis analyses surveillance data of Switzerland, neighbouring countries (Austria, Belgium, France, Germany, Italy, Luxembourg, and The Netherlands), countries of the British Isles (Ireland, United Kingdom) and Nordic countries (Denmark, Finland, Norway, Sweden) in regard to campylobacteriosis winter peaks at the turn of the year between 2006 and 2014. Surveillance data was obtained from the NNSID for Switzerland and from TESSy for the remaining countries.

A descriptive analysis of country-specific weekly notification data (case numbers and notification rates) focusing on the period of calendar weeks 45 to 8 was performed. Additionally, dates of disease onset or diagnosis were analysed for countries with an observable winter peak and possible causes for the observed transmission patterns are discussed.

A detailed description of the methods applied for this research component can be found in Chapter 5 i.e. Bless *et al.* (2017a).

3.2.3. Time trends of positivity rates from foodborne pathogen testing in Switzerland, 2003-2012

In this part laboratory positivity rates of *Campylobacter* spp. and *Salmonella* spp. in Switzerland were calculated to better understand their epidemiology. Essential retrospective nominator (positive tests) and denominator data (total number of tests performed) between 2003 and 2012 was collected from 8 Swiss medical diagnostic laboratories. The retrospective data collected included information on test characteristics (test method applied, test result, test date) and on tested patients (sex, age, canton of residence).

The positivity rate was defined as number of positive tests divided by all tests performed. The descriptive analysis included positivity rates for each of the two pathogens by year, laboratory, sex, age, test month, test week and combinations thereof. Additionally, determinants for a positive test result and the seasonality of positivity rates were analysed by univariable and multivariable regression. Results allowed drawing conclusions about the epidemiological situation of campylobacteriosis and salmonellosis and were compared with corresponding data of the NNSID to evaluate the validity of surveillance data.

A detailed description of the methods applied for this research component can be found in Chapter 6 i.e. Bless *et al.* (2017b).

3.2.4. Acute gastroenteritis and campylobacteriosis in Swiss primary care: the viewpoint of general practitioners

A qualitative study was conducted among Swiss GPs who treated campylobacteriosis patients invited for the previous case-control study (Chapter 5). GPs' perception of and profes-

sional experience with campylobacteriosis and AG including clinical presentation, case management and disease burden was investigated to evaluate the disease situation at the primary care level.

GPs were invited by an information letter explaining the study and contacted for an interview appointment by telephone. Interviews were conducted face-to-face with a semi-structured questionnaire which was pre-tested in a pilot. Data collected continuously underwent inductive content analysis based on Grounded Theory which allowed adapting the questionnaire for the next interviews based on preliminary results. Theoretical saturation was reached and results extensively discussed with the study team before drawing conclusions.

A detailed description of the methods applied for this research component can be found in Chapter 7 i.e. Bless *et al.* (2016).

3.2.5. Acute gastroenteritis in primary care: a longitudinal study in the Swiss Sentinel Surveillance Network, Sentinella

The incidence and aetiology of AG and the routine faecal specimen testing rate among patients with AG at the primary care level in Switzerland was assessed by a prospective longitudinal study within the Sentinel Surveillance Network *Sentinella*. Over the study period of one year (December 2013 to December 2014) sentinel physicians reported weekly the number of consultations per week (denominator data) and the number of patients initially consulting with AG including information on date of birth, sex, stool diagnostics performed (yes/no) and hospitalisation (yes/no). Additional information on cases of AG was collected by a supplementary questionnaire covering the total number of consultations, clinical presentation, stool test

result if available, treatment approaches and information on sick leave certification, travel activities and suspected risk factors.

During the first half of the study period the supplementary questionnaire was applied to a third of patients and in the second half to every patient due to lower case numbers than expected. Consequently, a weighted descriptive analysis was applied to the collected data and weighted, univariable logistic regression was used to assess the significance of differences. The burden of AG at the primary care level was estimated as initial consultations due to AG per 100,000 population with the established extrapolation method for *Sentinella* data of the FOPH.

A detailed description of the methods applied for this research component can be found in Chapter 8 i.e. Schmutz *et al.* (2017a).

3.2.6. Estimating health care costs of acute gastroenteritis and human campylobacteriosis in Switzerland

Own (preliminary) research results, official health statistics, expert opinions and official rates for medical services were used to estimate direct health care costs attributable to campylobacteriosis and AG in Switzerland. Four different patient management models (A-D) were developed based on expert opinions and data available from previous work: patients consulting a physician without stool testing (A), patients consulting a physician with negative *Campylobacter* stool test results (B), patients consulting a physician and having a positive *Campylobacter* stool test result (C) and hospitalized campylobacteriosis cases (D). Each model was divided in a

minimal and extended scenario accounting for the heterogeneity among patients' disease severity and needs for medical care.

Health care expenditures per patient for each scenario were estimated with official rates for consultations, hospitalisations, diagnostics and drugs from the Swiss medical tariff system (TARMED), the tariff list for diagnostics ("Analysenliste"), the list of pharmaceutical specialties ("Spezialitätenliste") and the diagnosis-related group-based hospital reimbursement system. Expenditures for model C were validated using real invoices from campylobacteriosis patients of the Swiss TPH travel clinic. Patient numbers for each of the models and scenarios were extrapolated based on surveillance data from the NNSID, official hospital statistics and estimates from previous studies. Total direct health care costs for Switzerland were then calculated as the sum of estimated patient numbers per scenario multiplied by health care expenditures per patient in each scenario.

A detailed description of the methods applied for this research component can be found in Chapter 9 i.e. Schmutz *et al.* (2017b).

3.3. Ethical considerations

All research was following the Essentials of Good Epidemiological Practice (Altpeter *et al.* 2005) and complies with the ethical principles stipulated in the Declaration of Helsinki. Ethical approval for projects was obtained from The Ethics Committee northwest/central Switzerland (EKNZ) if indicated by the Swiss Federal Act on Research involving Human Beings.

The EKNZ approved the projects "Time trends of positivity rates from *Campylobacter* and *Salmonella* testing over a decade in Switzerland" (Chapter 4) and "Estimating health care costs of acute gastroenteritis and human campylobacteriosis in Switzerland" (Chapter 9) (Ref-No.: EKNZ:2014-164 and EKNZ:2014-159). The two studies "A tradition and an epidemic: Determinants of the campylobacteriosis winter peak in Switzerland" (Chapter 4) and "Acute Gastroenteritis and Campylobacteriosis in Swiss Primary Care: The Viewpoint of General Practitioners" (Chapter 7) were commissioned by the FOPH and executed under the Swiss Epidemics Act (SR 818.101 EpG) and, hence, did not require additional ethical approval from the EKNZ. Access to European and Swiss surveillance data for the project "The recurrent campylobacteriosis epidemic over Christmas and New Year in Europe" (Chapter 5) was granted by TESSy, ECDC, Stockholm, Sweden and the FOPH, Bern, Switzerland according to the institutions' data sharing policies following formal requests. The study "Acute gastroenteritis in primary care: a longitudinal study in the Swiss Sentinel Surveillance Network, *Sentinella*" (Chapter 8) was conducted under the Swiss Epidemics Act (SR 818.101) and the ordinance on disease notification of humans (SR 818.141.1) not requiring ethical approval from an ethical committee.

4. ARTICLE 1: A tradition and an epidemic: determinants of the campylobacteriosis winter peak in Switzerland

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4.1. Abstract

Campylobacteriosis is the most frequently reported food-borne infection in Switzerland. We investigated determinants of infections and illness experience in wintertime. A case-control study was conducted in Switzerland between December 2012 and February 2013. Cases were recruited among laboratory-confirmed campylobacteriosis patients. Population-based controls were matched according to age group, sex and canton of residence. We determined risk factors associated with campylobacteriosis, and help seeking behaviour and illness perception. The multivariable analysis identified two factors associated with an increased risk for campylobacteriosis: consumption of meat fondue (matched Odds Ratio [mOR], 4.0, 95% confidence interval [CI] 2.3-7.1) and travelling abroad (mOR, 2.7, 95%-CI, 1.1-6.4). Univariable analysis among meat fondue consumers revealed chicken as the type of meat with the highest risk of disease (mOR, 3.8, 95%-CI, 1.1-13.5). Most frequently reported signs and symptoms among patients were diarrhoea (98%), abdominal pain (81%), fever (66%), nausea (44%) and vomiting (34%). The median perceived disease severity was 8 on a 1-to-10 rating scale. Patients reported a median duration of illness of 7 days and 14% were hospitalised. Meat fondues, mostly "*Fondue chinoise"*, traditionally consumed during the festive season in Switzerland, are the major driver of the epidemic campylobacteriosis peak in wintertime. At these meals, individual handling and consumption of chicken meat may play an important role in disease transmission. Laboratory-confirmed patients are severely ill and hospitalisation rate is considerable. Public health measures such as decontamination of chicken meat and improved food handling behaviour at the individual level are urgently needed.

4.2. Keywords

Campylobacter, notification system, case-control study, Switzerland, gastroenteritis, foodborne diseases

4.3. Introduction

In recent years, campylobacteriosis emerged as the most commonly reported zoonosis in Europe, including Switzerland [1, 2]. In 2012, the notification rate was 106 cases per 100,000 population corresponding to 8567 laboratory confirmed cases [3], the highest rate since campylobacteriosis became a notifiable disease in 1988 [1]. By registering only laboratory-confirmed cases, substantial underreporting is very likely.

Human *Campylobacter* infections generally lead to self-limiting, acute gastroenteritis with diarrhoea, abdominal pain, fever, vomiting and bloody stool as commonly reported symptoms [4]. Patients suffering of a severe infection and pregnant or immunocompromised patients require antibiotic treatment [5]. Rare but serious sequels of *Campylobacter* infections include reactive arthritis, febrile convulsions and Guillain-Barré syndrome [4] and contribute considerably to morbidity and economic costs of campylobacteriosis [6, 7]. Varying case-definitions, targeted age-groups and co-morbidities, methodologies, and follow-up periods result in a broad range of reported case-fatality rates. Risk factors for sporadic and outbreak-related *Campylobacter* infections have been extensively studied [8, 9]. Some 50-80% of sporadic human *Campylobacter* infections are attributable to chicken as a reservoir either through transmission via handling and consumption of poultry, eating undercooked poultry or via contact with live poultry [10-14]. Recent case-control studies identified chicken con-

sumption as source of infection for 24-29% of all cases [14]. Similarly, consuming chicken is an attributable risk exposure for 27% of campylobacteriosis cases in Switzerland [15]. Indirect evidence for an association between chicken consumption and human campylobacteriosis is provided by: i.) a significant reduction of campylobacteriosis case notifications after large-scale market-withdrawals of chicken due to dioxin-contaminated feed components [16] or an avian influenza outbreak [17] and ii.) congruent seasonality patterns of the incidence of campylobacteriosis in humans and *Campylobacter* colonisation of broiler flocks [18]. Other reported exposure risks originate from drinking unsafe water, consuming raw milk and unpasteurised dairy products, eating barbecued meat, travelling abroad and from contact with farm animals and pets [2, 8, 9]. Campylobacteriosis outbreaks in Europe are rare, accounting for about 2% of campylobacteriosis cases only [14, 19]. They are mostly associated with consumption of contaminated drinking water, raw milk and chicken products [9, 19, 20].

In temperate regions, seasonal patterns of human campylobacteriosis exist with an increased incidence during summer months [21, 22]. In Switzerland and Germany, seasonal patterns exhibit two distinct peaks: one in summer and one in winter [1, 23]. Reasons for this remain speculative: in Switzerland, suspected causes for both peaks include handling of raw and consumption of undercooked meat from barbecuing and from preparing a traditional meat fondue, a festive Christmas and New Year's dish, which implicates the handling of raw meat by the consumer at the table [1]. The objectives for this study were to investigate determinants of the campylobacteriosis winter peak in Switzerland and to elucidate illness

perception, symptomatology, and help seeking patterns of campylobacteriosis patients.

4.4. Methods

A case-control study recruiting prospectively laboratory-confirmed campylobacteriosis cases and population-based controls was conducted between December 2012 and February 2013.

The National Notification System for Infectious Diseases (NNSID) of the Swiss Federal Office of Public Health (SFOPH) covers entire Switzerland. *Campylobacter* infections must be mandatorily reported by diagnostic laboratories. Four private laboratories, covering entire Switzerland and diagnosing about one third of all notified cases, participated in case recruitment from 21st December 2012 until 24th January 2013.

Considering the seasonal nature of *Campylobacter* infections, the study commenced after the SFOPH enacted that the mandatory notifications of participating laboratories had to include person-identifiable data as stipulated by the Swiss Epidemics Act.

4.4.1. Cases

All cases reported by the four laboratories to the NNSID were screened for eligibility. Eligibility criteria for cases were age ≥5 years and Swiss residency. Cases were excluded if they reported antibiotic treatment four weeks prior to disease onset or were not speaking German, French or Italian.

4.4.2. Controls

Controls were selected from a random sample of the Swiss population obtained from the Federal Statistical Office. They were matched for sex, age group and canton of residence. Controls were excluded if they reported a diarrhoeal illness four weeks prior to the corresponding case's disease onset. In addition, the same exclusion criteria as for cases were applied.

4.4.3. Sample size

The study was designed to detect an effect size (odds ratio (OR)) of 2.5, with a power of 80% and a two-sided significance level of 0.05 assuming a case-to-control ratio of 1:1. Rejection rates were estimated at 50% for cases and 75% for controls. To achieve a sample size of 100 cases and 100 controls and to account for refusals and for exclusions after enrolment, sampling foresaw contacting 300 cases and 600 controls. All eligible controls were included, resulting in a case-to-control ratio ranging from 1:1 to 1:4.

4.4.4. Recruitment process

Within 24 hours upon receiving a positive laboratory report we sent an information letter together with a photo-illustrated questionnaire to the case by priority mail. The same package was mailed to four matched controls within 24 hours after completion of the case interview. Following the written notice cases and controls were contacted by telephone and, after giving verbal consent to participate, either interviewed immediately or a suitable appointment for the interview was fixed. If controls refused participation, additional controls were selected until at least one per case could be interviewed. Cases and controls were excluded after 15 unsuccessful call attempts

or if no telephone number was available in the telephone directory or upon request via postal mail. For participants <15 years, letters were sent to their parents and either parent was interviewed as surrogate.

4.4.5. Questionnaire

The questionnaire comprised a section on food- and non-food exposures and, for cases, a part on illness experience. It contained questions regarding food consumption, origin of meat, eating and hygiene behaviour, contacts to animals and humans, knowledge about food-borne pathogens, recent travel history, occupational exposure and co-morbidity. For both, cases and matched controls, exposure information was collected for the seven days preceding the onset of the case's disease, except for travel history (preceding two weeks). For case interviews, the questionnaire addressed morbidity, health seeking behaviour and treatment. Computer-assisted telephone interviews using LimeSurvey software were performed. In parallel, participants were encouraged to follow the interview questions in the photo-illustrated questionnaire.

4.4.6. Statistical analyses

Collected data were exported to Stata 10.1 (Stata Corporation). Pair-matched analyses were performed where applicable and matched odds ratios (mOR) are presented. Univariable conditional logistic regressions were performed. Variables with cells containing zero values in contingency tables were analysed using exact logistic regression.

For the multivariable conditional logistic regression we considered variables with $p \leq 0.2$ in the univariable analysis. In case of correlated predictor variables only the one which was biologi-

cally more plausible was kept in the model. In addition, we performed a subgroup analysis investigating risk factors among persons who reported fondue consumption.

The population attributable fraction (PAF) was calculated for each statistically significant risk factor of the multivariable model as difference of nationwide observed cases and expected cases in absence of the risk factor. Expected cases were calculated using the multivariable mOR, frequency of exposure among cases and controls and the sex-, age- and canton-specific prevalence of *Campylobacter* notifications during the study period.

Subsequent exploratory data analysis including additional subgroup and stratified analyses was conducted in order to assist in the interpretation and to generate new hypotheses. When conditional analysis was not possible the results are presented descriptively.

4.5. Results

4.5.1. Response rate and basic characteristics of study participants

A total of 303 campylobacteriosis case notifications were received by the study team. After exclusion of cases <5 years and non-Swiss residency, 289 cases and 898 controls were invited to participate in the study (Figure 4.1). We enrolled 180 (62%) cases and 324 (36%) controls of which 159 (55%) cases and 280 (31%) controls were included in the analysis. Case-to-control matching ratios were 1:1 for 72, 1:2 for 57, 1:3 for 26 and 1:4 for 4 cases, respectively. Participating cases represent-

ed 15% of all registered laboratory-confirmed campylobacteriosis cases during the study period.

The median number of call attempts was 2 for cases and 3 for controls. The median time period for cases between disease onset and interview was 15 days (range 5-63 days). Median age of participants was 38 years and the sex ratio was close to unity. Both study groups were consistent with regard to most socio-demographic characteristics (Table 4.1). An imbalance was observed in nationality as only 8 (5.0%) cases compared to 40 (14.3%) controls were not Swiss nationals.

4.5.2. Risk factors for campylobacteriosis during the festive season

4.5.2.1. Univariable conditional logistic regression analysis

Among foods consumed during the week prior to disease onset, meat consumption was identified as significant risk factor (mOR, 5.2, 95% confidence interval [CI], 1.2-23.3), but the only type of meat significantly associated with an increased risk was chicken (mOR, 2.5, 95%-CI, 1.5-4.1) (Figure 4.2). Eating raw or undercooked meat was associated with increased risk of disease (mOR, 1.6, 95%-CI, 1.0-2.6); however the effect was not statistically significant. Conversely, the consumption of raw vegetables was significantly associated with a decreased risk (mOR, 0.4, 95%-CI, 0.2-0.7). In addition, the consumption of dried and smoked meat (mOR, 0.6, 95%-CI, 0.4-0.9) and the consumption of ham (mOR, 0.6, 95%-CI, 0.4-1.0) were associated with a decreased risk.

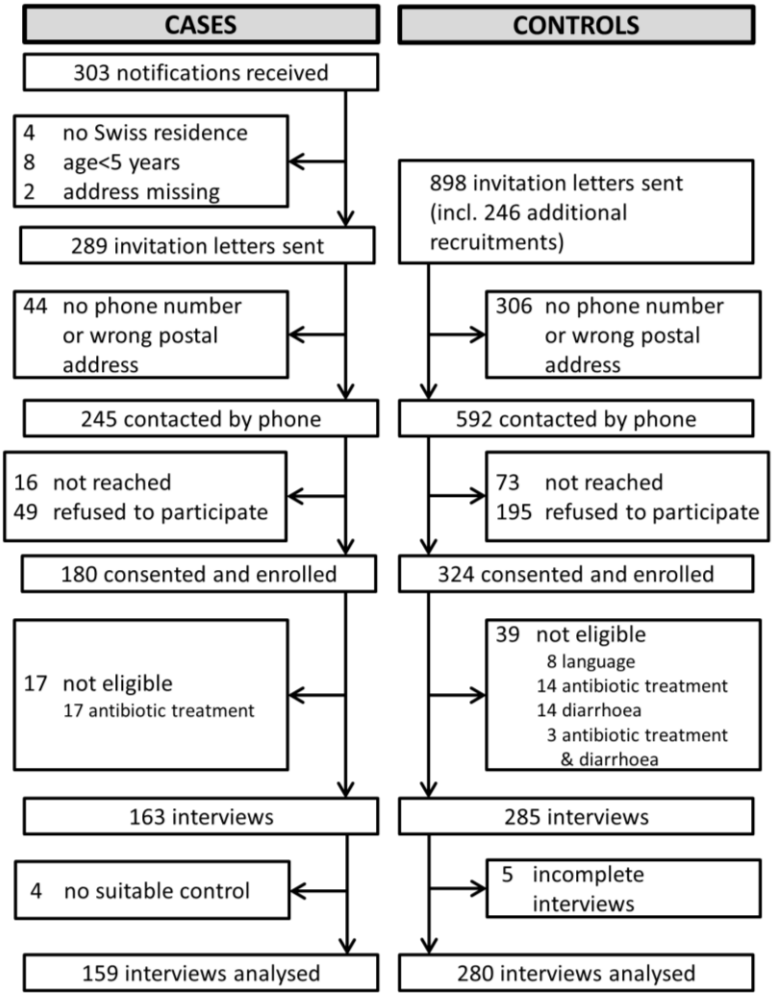

Figure 4.1: Study profile of cases and controls enrolled and recruited in the case-control study on *Campylobacter* infections in Switzerland, December 2012 – February 2013

Table 4.1: Demographic characteristics of 159 cases and 280 controls who participated in the case-control study on campylobacteriosis in Switzerland, December 2012 – February 2013

Characteristic	**Cases, n (%)**	**Controls, n (%)**
Sex		
Male	82 (51.6)	143 (51.1)
Female	77 (48.4)	137 (48.9)
Age groups (years)		
5-9	10 (6.3)	20 (7.1)
10-14	6 (3.8)	8 (2.9)
15-19	11 (6.9)	18 (6.4)
20-24	18 (11.3)	39 (13.9)
25-29	15 (9.4)	24 (8.6)
30-44	39 (24.5)	65 (23.2)
45-59	36 (22.6)	61 (21.8)
60-74	16 (10.1)	31 (11.1)
75+	8 (5.0)	14 (5.0)
Nationality		
Swiss	151 (95.0)	240 (85.7)
Foreign	8 (5.0)	40 (14.3)
Education[a]		
Low education	109 (68.6)	173 (61.8)
High education	50 (31.4)	107 (38.2)

[a]Low education implies none, compulsory and vocational education. High education implies high school degree, university degree or other higher education

Figure 4.2: Univariable conditional logistic regression analysis of selected risk factors for campylobacteriosis in winter times (December 2012 – February 2013) in Switzerland

[a] matched odds ratio

[b] confidence interval

[c] participants aged ≤15 or ≥65 years were excluded

The consumption of meat fondue was identified as a strong risk factor for disease (mOR, 3.9, 95%-CI, 2.4-6.4). The most frequently consumed meat fondue variant, the so-called *"Fondue chinoise"*, was also strongly associated (mOR, 2.9, 95%-CI, 1.8-4.7).

The univariable analysis showed no significant association of travelling abroad (mOR, 1.7, 95%-CI, 0.8-3.4) and campylobacteriosis. Having contact with children <5 was significantly associated with a decreased risk of illness (mOR, 0.5, 95%-CI, 0.3-0.8). No significant association of the disease with occupational contacts involving ill persons, animals and children, raw and cooked foods was found. The same observation was made for non-occupational contacts to animals. Swiss nationality was associated with a significantly increased risk for disease (mOR, 3.1, 95%-CI, 1.4-6.7). People with high education were less likely to suffer from disease (mOR, 0.7, 95%-CI, 0.4-1.1).

Among the fondue consumers, chicken showed again the strongest effect (mOR, 3.8, 95%-CI, 1.1-13.5) of all meat types (Figure 4.3). There was no noteworthy difference between fondue meals consumed at home, or outside home at friends or at restaurants. Five out of six participants who reported fondue consumption at other locations (e.g. at holiday or alpine huts) were cases. The consumption of previously frozen meat at a meat fondue was significantly associated with a decreased risk of disease (mOR, 0.1, 95%-CI, 0.0-0.6). The type of plate used for raw and cooked meat at a meat fondue was significantly associated with campylobacteriosis: both, using one plate with compartments and using two separate plates were associated with a decreased risk of disease (plate with compartments: mOR, 0.4, 95%-CI, 0.1-1.1; two plates: mOR, 0.2, 95%-CI, 0.1-0.6).

4.5.2.2. Multivariable conditional logistic regression analysis

While the mOR for meat fondue remained unchanged, the effect was lower for chicken consumption in general (mOR 1.4 *vs.* 2.5) and for Swiss nationality (mOR 2.1 *vs.* 3.1) (Figure 4.4). In contrast, the observed association with travelling abroad was stronger (mOR 2.7 *vs.* 1.7). The estimated PAFs for the significant risk factors of the multivariable model were 51.9% (95%-CI, 31.4-68.5%) for meat fondue and 13.5% (95%-CI, 1.1-33.5%) for travelling abroad.

4.5.2.3. Exploratory subgroup and stratified analyses

The stratified analysis by sex revealed a significant difference in odds for the consumption of chicken meat between females (crude OR [cOR], 4.9, 95%-CI, 2.0-13.6) and males (cOR, 1.4, 95%-CI, 0.7-2.9). Likewise, the consumption of meat fondue increased the odds for disease among females (cOR, 5.6, 95%CI, 2.9-10.8) significantly more compared to males (cOR, 1.8, 95%-CI, 1.0-3.3). Out of 26 cases who did not eat chicken six reported the consumption of raw or undercooked meat (23% in cases *vs.* 18% in controls), six reported meat fondue consumption with other meat types (23% *vs.* 15%) but only a single person (case *vs.* 10 controls) reported travels abroad.

4.5.3. Campylobacteriosis case characterisation

Most frequently reported disease onset dates were December 27^{th}/28^{th} and January 2^{nd}/3^{rd} (Figure 4.5). Median duration of illness was seven days (range 2.5 - 33). Only half of all patients (48%) reported full recovery.

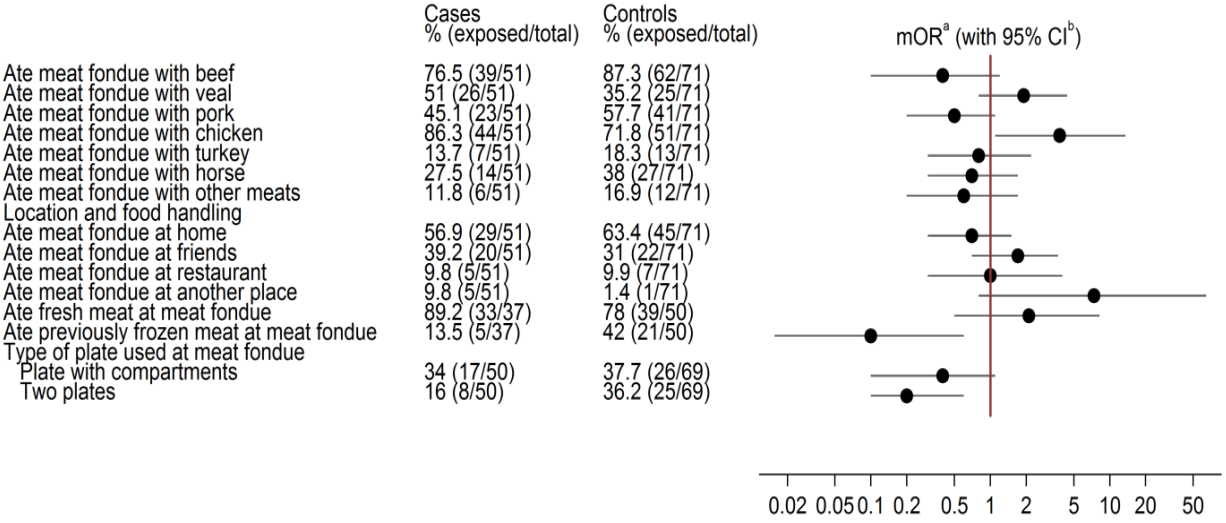

Figure 4.3: Univariable conditional logistic regression analysis of selected risk factors for campylobacteriosis related to the consumption of meat fondue in winter times (December 2012 – February 2013) in Switzerland

[a] matched odds ratio

[b] confidence interval

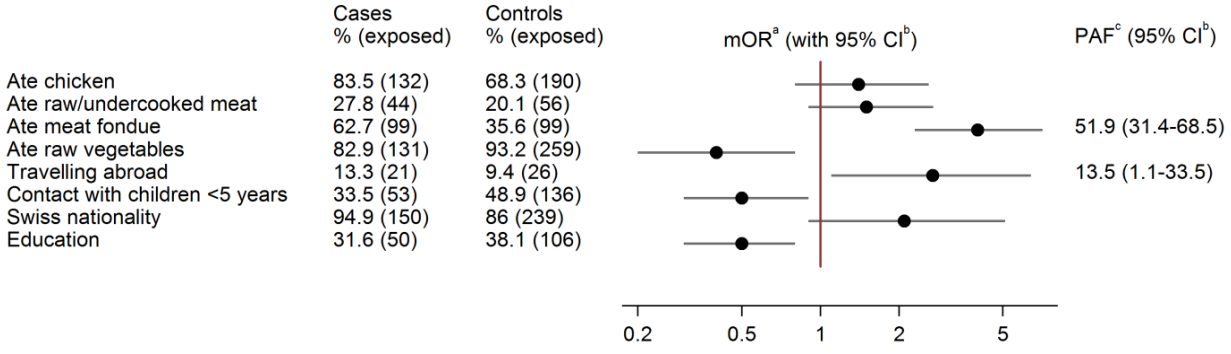

Figure 4.4: Matched multivariable conditional logistic regression analysis of selected risk factors for 158 cases and 278 controls in winter times (December 2012 – February 2013) in Switzerland

[a] matched odds ratio

[b] confidence interval

[c] population attributable fraction

Most commonly reported symptoms were diarrhoea, abdominal pain, fever, nausea, vomiting and headache (Table 4.2). Other reported symptoms included limb pain, shivering, fatigue, loss of appetite and vertigo. Irrespective of their sex, more than half of the patients rated the severity of their illness as ‘severe’ denoted by a median severity score of eight on a one-to-ten scale.

4.5.3.1. First health care seeking

Pharmacies and medical hotlines were consulted by 20% and 5% of the patients before seeing a physician, respectively. One third (33%) of all patients had approached a physician directly. More than half (54%) visited a physician within three days after symptoms onset. Most patients (63%) visited a general practitioner (Figure 4.5, Table 4.2). Emergency facilities were visited by 26% of patients.

4.5.3.2. Hospitalisation

The hospitalisation rate was 14% and did not differ between sexes, and was increased among patients ≥60 years (33%). Half of the hospitalisations lasted at least 3 nights.

4.5.3.3. Pharmacotherapy

With one exception, all patients reported drug treatment; about two third received antibiotics. Other medications were applied for symptomatic treatment. Among the 24% of all patients who received an infusion for rehydration or intravenous drug application, 42% were in outpatient treatment.

Table 4.2: Campylobacteriosis in Switzerland: Reported duration of illness, signs and symptoms, perceived severity, medical treatment and medication, December 2012-February 2013

	n (%) or Median (Range) (N=159)
Campylobacter-associated morbidity	
Duration of illness [days][a]	7 (2.5 – 33)
No recovery by the time of the interview	43 (27.0)
Perceived severity of illness[b]	8 (2 – 10)
Symptoms[c]	
Diarrhoea	156 (98.1)
Abdominal pain	128 (80.5)
Fever	105 (66.0)
Nausea	70 (44.0)
Vomiting	54 (34.0)
Headache	20 (12.6)
Help seeking behaviour	
Health care seeking before consulting a physician[c]	
None: Immediate consultation of a physician	52 (32.7)
Pharmacy	31 (19.5)
Medical hotline	8 (5.0)
Friends & family	68 (42.8)
Internet	23 (14.5)
Health guide	8 (5.0)
Other	10 (6.3)
Medical care seeking	
General practitioner (GP)	100 (62.9)
Emergency department	23 (14.5)
Emergency practice	19 (11.9)
Paediatrician	6 (3.8)
Medical specialist	4 (2.5)
Other	7 (4.4)

Table 4.2 continued

	n (%) or Median (Range) (N=159)
Reasons for medical care seeking[c]	
Severe symptoms	105 (66.0)
No amelioration	70 (44.0)
Need of a medical certificate	6 (3.8)
Other	44 (27.7)
Hospitalisation	
Total	23 (14.5)
Males[d]	13 (15.9)
Females[e]	10 (13.0)
Number of nights in hospital	3 (1 – 13)
Medication	
Consumed drugs	158 (99.4)
Drug classes[c]	
Antibiotic (Fluoroquinolones, Macrolides)	98 (61.6)
Antidiarrhoeal (Loperamide, Charcoal)	84 (52.8)
Probiotic (enterococci, saccharomyces)	73 (45.9)
Analgesic (Acetaminophen, Dipyrone, NSAIDs)	66 (41.5)
Antiemetic (Domperidone, Metoclopramide, Meclozine)	17 (10.7)
Spasmolytics (Butylscopolamine)	17 (10.7)
Acid blockers (Proton pump inhibitors)	5 (3.1)
Parenteral rehydration and/or drug application	38 (23.9)

[a] only those recovered at time of interview included (n = 116)
[b] N=158
[c] multiple answers possible
[d] N=82
[e] N=77

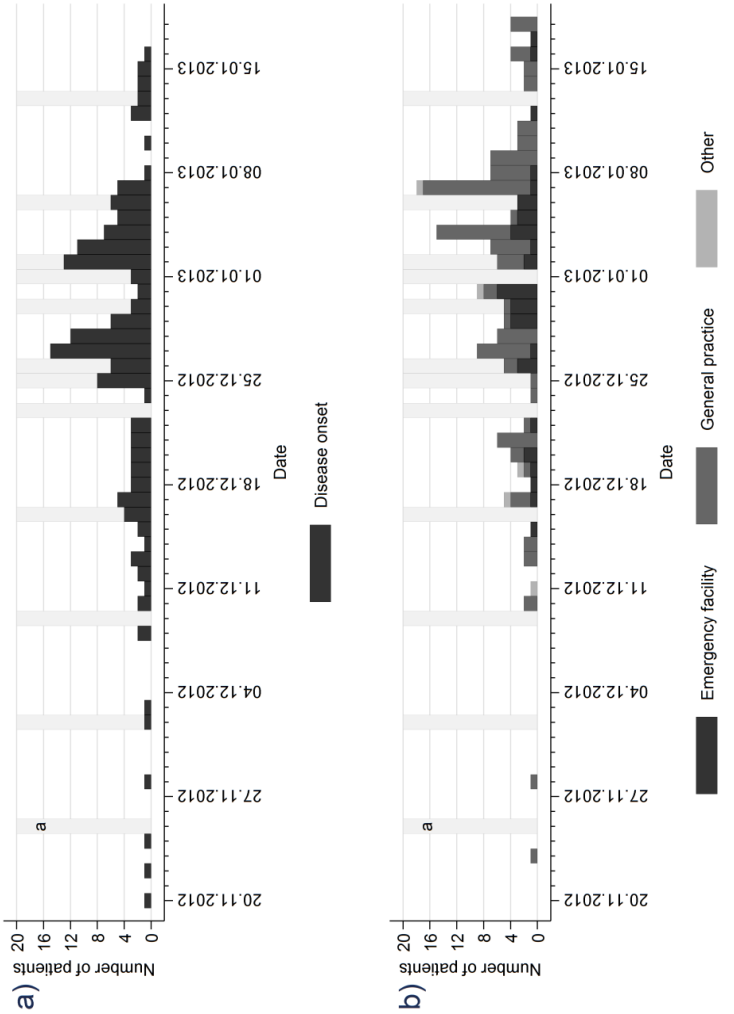

Figure 4.5: a) Daily numbers of reported disease onsets of campylobacteriosis patients and b) dates of consultations with a physician at an emergency facility or a general practice

4.6. Discussion

We assessed determinants for *Campylobacter* infections in wintertime in Switzerland with a case-control study design among laboratory-confirmed campylobacteriosis patients. A traditional meal (meat fondue), typically consumed at festive occasions in wintertime, was identified as the most important risk factor, especially if chicken meat was served. Furthermore, our findings suggest that the campylobacteriosis cases registered in the national disease registry are severely ill. The last investigation of determinants of campylobacteriosis in Switzerland dates back more than two decades and did not include the winter festive season [24].

4.6.1. Factors associated with increased risk of Campylobacter infections

Meat fondues, predominantly *"Fondue chinoise"*, are consumed traditionally in Switzerland during dinners around Christmas and New Year. In our study, disease onset dates peaked 2-3 days after those events. This is in line with the incubation period of 2-5 days [4]. More than 50% of *Campylobacter*-related gastroenteritis can be attributed to the consumption of meat fondue during the study period. The *"Fondue chinoise"* comprises sliced raw meat being individually handled and boiled in a family-shared broth hotpot. In contrast to chicken none of the other meat types consumed during fondue dishes were associated with *Campylobacter* infections. This is coherent with other studies identifying chicken as a risk exposure [11, 24-30]. This includes two outbreaks of *Campylobacter* infections in which meat fondue including chicken meat were the suspected source of infection [31]. Since Germans consume meat fondue with increased

popularity on New Year's Eve rather than at Christmas [32-34] *Campylobacter*-contaminated chicken could also be the cause for the peak of infections observed by Schielke et al. [23] in early January.

Further we observed that meat fondue eaters who put their raw and cooked meat on the same plate were more likely to suffer from campylobacteriosis. Conversely, the use of a compartmented plate or using two separate plates appeared to be protective in our study and has been previously recommended [35]. *Campylobacter* spp. are quickly inactivated after dipping the sliced chicken meat into the boiling broth. Therefore, on-the-plate cross-contamination of boiled meat from raw chicken meat juice is the most probable transmission route especially considering the low infectious dose of *Campylobacter* spp. [36]. We found women to have significantly higher odds than men for acquiring a *Campylobacter* infection after consumption of chicken meat or meat fondue. Among our study participants women consumed more often chicken at meat fondues than men which, however, does not explain the elevated risk.

The consumption of undercooked meat as a risk factor for campylobacteriosis is well known [11, 13, 27, 28, 37]. In our study the consumption of raw or undercooked meat was associated with campylobacteriosis especially in people not consuming meat fondue. We hypothesise that the strong effect of meat fondue consumption outweighs the known effect of raw or undercooked meat consumption and, therefore, is only statistically significant in the subgroup of people not consuming meat fondue. Travelling abroad was the only behavioural factor in the multivariable analysis significantly associated with increased odds for *Campylobacter* infections. This risk

factor has been described previously for Switzerland [24] and other countries [11, 25, 26, 28, 30]. Further, almost all acute gastroenteritis patients with travel history are tested for gastrointestinal pathogens and are more likely to be diagnosed (personal communication).

One can argue that meat fondue represents an intermediate variable on the pathway from chicken consumption to *Campylobacter* spp. infection. Intermediate variables, if included in the multivariable analysis, might bias the estimates - usually towards the null. Therefore, we re-ran the regression models omitting meat fondue-consumption: as expected, chicken consumption showed a higher odds ratio (2.3) compared to the full model. The point estimates for all other variables remained similar, with the exception of travelling abroad which was associated with a smaller effect.

4.6.2. Factors associated with reduced risk of Campylobacter infections

The finding that a reduced risk of disease is associated with having contact to children <5 years is difficult to interpret; especially because a high incidence is noticed for this age-class in the NNSID [1]. Persons having contact with young children may differ in general and food hygiene and dietary habits [38]. High education was associated with a reduced risk of disease. The association with gastrointestinal diseases in high-income countries is discussed controversially [38-41]. Another factor associated with a decreased risk was the consumption of raw vegetables. Similar findings are described from several European countries and elsewhere [13, 25, 27, 28, 42] linking the protective effects of the consumption of raw vegetables to high amounts of antioxidants and carotenoids which act as bacterial

growth inhibitors and generally increase immunity to infection. Several reports underscore that people who eat raw vegetables differ from others concerning cooking and eating preferences and behaviour [13, 25, 27, 28, 42]. The consumption of raw vegetables, especially during winter time, may reflect a generally healthy lifestyle [25, 27, 28, 42].

An exploratory subgroup analysis among meat fondue consumers indicates that consuming previously frozen meat is associated with a decreased risk of campylobacteriosis. Similar experiences were made in Iceland where the number of campylobacteriosis cases declined after freezing of meat originating from *Campylobacter*-infected broiler flocks [43]. In Switzerland, Baumgartner et al. [44] showed that chicken products were less contaminated with *Campylobacter* spp. after freezing, - a finding which is corroborated by the studies in Iceland [45] and Norway [46].

In summary, risk and preventive factors in this study point at contamination risks upstream at food production- and downstream at retail- and consumer sides. Consequently, potential preventive risk reduction measures could be applied upstream and downstream: upstream -, through decontamination at slaughter using peracetic acid [47] resulting in a decreased bacterial load at retail level or freezing of chicken meat before reaching retail [43, 45, 46]. Downstream risk prevention measures could include improving consumer awareness in handling raw chicken meat additionally to the current hygiene notice on Swiss chicken meat packages.

4.6.3. Illness perception and treatment of acute campylobacteriosis

Patients suffering from *Campylobacter* infection reported typical symptoms of an acute gastroenteritis and a high perceived severity of illness. Comparable studies for Switzerland are lacking; however, the pattern is coherent with experiences from other countries [13, 48-51]. The reported severity of illness appears to be slightly higher compared to others [48]. Compared to other countries the proportion of hospitalised patients (14%) was higher [13, 48] or slightly lower [52]. This variability could be due to differences in health systems, including differing notification criteria, case definitions and health care provider structure.

Although antibiotics are not generally recommended for treatment of campylobacteriosis more than 60% of our study patients received antibiotic treatment. In absence of information on the individual patient's medical history we cannot judge whether antibiotic use was medically indicated.

Generally, case-fatality rates in high-income countries range from 0.04-0.6% [2, 52-54]. We observed no death during our study. However, due to the similarity of epidemiological patterns in Europe *Campylobacter*-attributable mortality is likely to occur also in Switzerland [2, 54].

4.6.4. Strengths and limitations

We recruited all our cases from laboratory-confirmed campylobacteriosis patients registered in the NNSID. Patients with a mild course of disease are less likely to consult a physician or to be tested for campylobacteriosis and, hence, less likely to be notified. Participating laboratories were from the private sector

only; therefore, the hospitalisation rate and the proportion of patients approaching emergency departments and policlinics directly may be underestimated. Similarly, recruiting cases from private laboratories, serving mainly general practitioners, could explain the imbalance in nationalities. Swiss nationals more often consult their general practitioners while non-Swiss are more likely to approach emergency departments. As expected, patients volunteered more often to participate in the study and contacted back the study team after initial contacting failed. Cases may remember their exposures more accurately than controls, since they might have been reflecting about what caused their illness. Nevertheless, "don't know" was answered equally often by cases and controls. In addressing potential biases from recalling exposure risks we applied photo-illustrated questionnaires.

4.7. Conclusion

The study provides strong evidence that the consumption of a national festive dish ("*Fondue chinoise"*) is a risk factor for human campylobacteriosis in Switzerland. The main risks associated with this dish are probably twofold: firstly, chicken meat is frequently contaminated with *Campylobacter* spp. [44]. Secondly, the possibilities of and occasions for cross-contamination and ingestion of bacteria are manifold and the infection risk is exacerbated through individual food-handling at the table. Our findings, therefore, highlight the importance of food hygiene for chicken preparation and consumption at meat fondues. The steadily increasing number of notified campylobacteriosis cases, the high population attributable fraction for meat fondue and the previously unknown severity of illness and hospitalisation rate underline the relative importance for

Swiss public health over the festive season and point toward the necessity for public health interventions. Prevention measures could include decontamination of chicken meat at slaughter resulting in a decreased bacterial load at retail level, freezing of chicken meat before reaching retail and improving consumer awareness in handling raw chicken meat.

4.8. Acknowledgements

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4.9. Conflict of interest

This study was supported by the SFOPH with a view to understand campylobacteriosis and how the disease presents in the general population. Marianne Jost and Mirjam Mäusezahl-Feuz are on the staff of the SFOPH and participated in their capaci-

ties as public health specialists and their function as scientific collaborators within the organisation. The SFOPH played no part in the study design, data collection, analysis and interpretation of the results. Philipp Bless, Claudia Schmutz, Kathrin Suter, Jan Hattendorf and Daniel Mäusezahl are on the staff of the Swiss Tropical and Public Health Institute and received funding (incl. for a student practical for CS) from the SFOPH.

4.10. Ethical statement

The study was conducted under the Swiss Epidemics Act (SR 818.101 EpG). All participants were asked for oral informed consent before conducting the interview. The study was conducted in accordance with the Helsinki Declaration.

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5. ARTICLE 2: The recurrent campylobacteriosis epidemic over Christmas and New Year in European countries, 2006 - 2014

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5.1. Abstract

Objective: Campylobacteriosis is the most frequently reported foodborne disease in Europe with a notification rate of 71 per 100,000 population in the European Union in 2014. Surveillance data show a clear seasonality whereby case numbers peak during summer months in entire Europe and at the turn of the year, especially in Germany and Switzerland. A detailed description of European surveillance data by country at the turn of the year was missing so far. The objectives of the presented work were to describe national surveillance data of The European Surveillance System for 14 countries during winter times and to generate hypotheses for the observed seasonality of campylobacteriosis cases.

Results: The analysis included 317,986 cases notified between calendar weeks 45 and 8 of winter seasons 2006/2007 to 2013/2014. Winter peaks in weekly case notifications and notification rates were observed for Austria, Belgium, Finland, Germany, Luxembourg, The Netherlands, Switzerland and Sweden while for Denmark, France, Ireland, Italy, Norway and the United Kingdom no unusual increase was observed. Generally, weekly notification rates peaked in calendar week 1 or 2 after a strong decline in the last week of December and reached values of a multiple of the observed notification rates in the weeks before or after the peak e.g. up to 6.5 notifications per 100,000 population per week in Luxembourg. Disease onset of cases notified during winter peaks occurred predominantly in calendar weeks 52 and 1 and point towards risk exposures around Christmas and New Year. The consumption of meat fondue or table top grilling poses such a risk and is popular in many countries with an observed winter peak. Additionally, increased travel activities over the festive season could foster

campylobacteriosis transmission. Surveillance artefacts (e.g. reporting delays due to public holidays) should be excluded as causes for country-specific winter peaks before investigating risk exposures.

5.2. Keywords

Campylobacter, infectious disease surveillance, Europe, seasonality, The European Surveillance System (TESSy)

5.3. Introduction

Since 2005, human campylobacteriosis has been the most frequently reported foodborne bacterial gastrointestinal disease in Europe. Case numbers are increasing [1]. In 2014, around 237,000 cases were reported by 26 European Union (EU) member states corresponding to a notification rate of 71 per 100,000 population [1]. European campylobacteriosis surveillance data show a clear seasonal trend [2]. The number of notified cases starts to increase drastically in April and peaks during summer, between June and August [2]. The lowest numbers of cases are notified in February and March [2]. In the campylobacteriosis surveillance data of the EU, in particular of Germany, and of Switzerland, an additional seasonal peak between late December and early January, the so-called winter peak, has been described [1, 3, 4]. The monthly incidence in Germany peaks in January [3] and case numbers in Switzerland increase during the last week of December and the first week of January [4].

Our investigation of the winter peak in Switzerland identified the consumption of meat fondue as main risk factor, especially if served with chicken [5]. Meat fondue is traditionally con-

sumed on Christmas day and on New Year's Eve in Switzerland and is also a popular dish at New Year's Eve in Germany and Luxembourg [5, 6]. A detailed description of European *Campylobacter* surveillance data at the turn of the year is missing so far and hence, it is unknown in which other European countries winter peaks in notification data occur. This study analyses European country-specific surveillance data at the turn of the year from 2006 to 2014, to determine if winter peaks as observed in Switzerland and Germany also occur in other European countries and to generate hypotheses for the seasonal patterns.

5.4. Main text

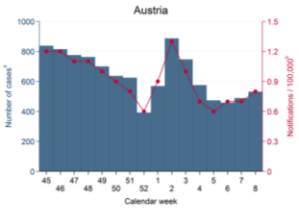
5.4.1. Analysis of Campylobacter surveillance data

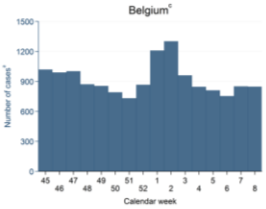
This study considered Switzerland, Germany and neighbouring countries (Austria, Belgium, France, Italy, Luxembourg, The Netherlands), countries of the British Isles (Ireland, United Kingdom) and Nordic countries (Denmark, Finland, Norway, Sweden). For EU member states, case-based notification data on laboratory-confirmed *Campylobacter* infections from 2006 to 2014 originated from The European Surveillance System (TESSy) - an indicator-based surveillance database for communicable diseases hosted by the European Centre for Disease Prevention and Control (ECDC) [7]. Surveillance data from the National Notification System for Infectious Diseases on laboratory-confirmed campylobacteriosis cases notified between 2006 and 2014 were used for Switzerland. Our previous analysis of Swiss notification data on *Campylobacter* showed that the winter peak is rather a short-term phenomenon and better observable in weekly than monthly notification data [4]. There-

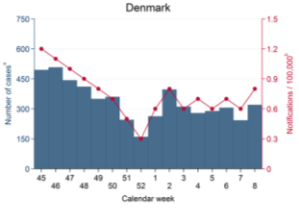
fore, we performed a descriptive analysis of country-specific weekly notification data focusing on the period of calendar weeks 45 to 8.

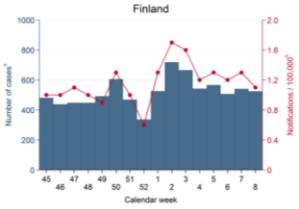
A total of 1,530,564 campylobacteriosis case notifications were received from TESSy. For 147 case notifications or 0.03% of all United Kingdom notifications no information on the week of notification was available. Hence, they were excluded from further analyses. In 2006 and 2007 German notification data were reported on a monthly basis leading to the exclusion of 118,142 case notifications. We additionally excluded 848 case notifications with a notification date in 2006 or 2014 but belonging to calendar week 52 of 2005 or calendar week 1 of 2015. For Italy no notification data from 2006 until mid-2008 were available. A total of 317,986 cases notified between calendar weeks 45 and 8 of the winter seasons 2006/2007 to 2013/2014 were analysed including 16,237 campylobacteriosis cases from Switzerland.

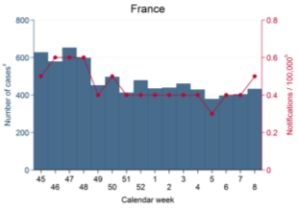
Weekly notification rates were calculated using annual country-specific population numbers as per 1st of January for each corresponding winter season from the Eurostat database [8]. The Dutch and French sentinel surveillance systems do not cover the whole population. We used the estimated population coverage for *Campylobacter* surveillance of 52% (The Netherlands) and 20% (France) [2] to calculate population numbers for the calculation of weekly notification rates. The population coverage of *Campylobacter* sentinel surveillance in Belgium and Italy is unknown and, hence, only case numbers were used. The sum of case numbers and the median of notification rates over all winter seasons are presented for each calendar week by country. Additionally, dates of disease onset or diagnosis were analysed to assess possible reporting delays.

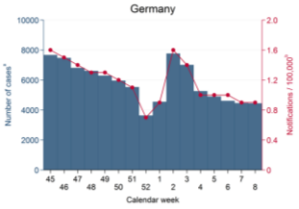

Austria
Number of cases*
Notifications / 100,000*
Calendar week


Belgium*
Number of cases*
Calendar week

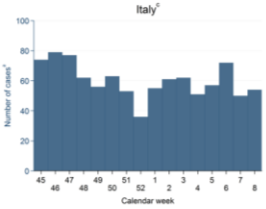

Denmark
Number of cases*
Notifications / 100,000*
Calendar week


Finland
Number of cases*
Notifications / 100,000*
Calendar week

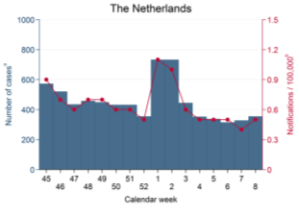

France
Number of cases*
Notifications / 100,000*
Calendar week

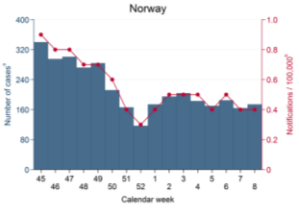

Germany
Number of cases*
Notifications / 100,000*
Calendar week

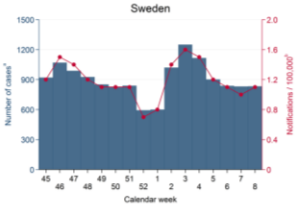

Ireland
Number of cases*
Notifications / 100,000*
Calendar week

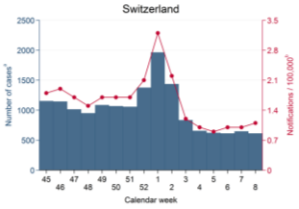

Italy*
Number of cases*
Calendar week


Luxembourg
Number of cases*
Notifications / 100,000*
Calendar week


The Netherlands
Number of cases*
Notifications / 100,000*
Calendar week


Norway
Number of cases*
Notifications / 100,000*
Calendar week


Sweden
Number of cases*
Notifications / 100,000*
Calendar week


Switzerland
Number of cases*
Notifications / 100,000*
Calendar week

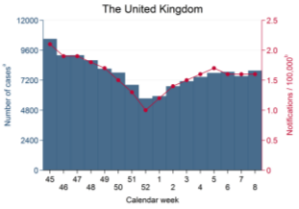

The United Kingdom
Number of cases*
Notifications / 100,000*
Calendar week

Figure 5.1: Number of case notifications and weekly notification rates per 100,000 population for campylobacteriosis in selected European countries, winter seasons 2006/2007–2013/2014.

[a]Sum of weekly notifications from winter seasons 2006/2007–2013/2014 (Germany and Italy: 2008/2009–2013/2014)

[b]Weekly notifications per 100,000 population = median of weekly notification rates from winter seasons 2006/2007–2013/2014 (Germany 2008/2009–2013/2014)

Table 5.1: Winter peaks of campylobacteriosis case notifications as median notification rate and sum of case notifications over all winter seasons, 2006/2007-2013/2014

Country	**Calendar week of peak**	**Median notification rate[a]**	**Sum of case notifications**
Austria	2	1.3	887
Belgium	2	n/a[b]	1302
Finland	2	1.7	719
Germany	2	1.5	8807
Luxembourg	2	2.9	116
The Netherlands	1	1.1	733
Sweden	3	1.6	1250
Switzerland	1	3.2	1964

[a]Rate per 100,000 population

[b]not applicable

In the Additional file 1 of Bless *et al.* (2017a) case numbers and notification rates per calendar week for each winter season and country are presented.

5.4.2. Seasonal patterns of campylobacteriosis

The sum of case notifications and the median of notification rates by calendar week over all years increased at the end of December or beginning of January for Austria, Belgium (case notifications only), Finland, Germany, Luxembourg, The Netherlands, Sweden and Switzerland and decreased towards the end of January (Figure 5.1). Winter peaks in terms of median notification rates were most pronounced in Luxembourg and Switzerland with peak rates of 2.9 and at 3.2 per 100,000 population, respectively (Table 5.1). Less pronounced winter peaks were observed in The Netherlands and Austria with peak rates of 1.1 and 1.3 per 100,000 population, respectively.

The sum of weekly case notifications in Belgium peaked in week 2. For the other countries (Denmark, France, Ireland, Italy, Norway and the United Kingdom) no unusual increase during the winter season was observed (Figure 5.1). A common characteristic of most countries was that the sum of case numbers and median notification rates were lowest at the end of December in week 52.

The weekly case numbers and notification rates of winter peaks varied in each country by year (Additional file 1 of Bless *et al.* (2017a)). The most distinct winter peak with a weekly notification rate of 6.5 per 100,000 population was observed in Luxembourg during the winter season 2013/2014 (Table 5.2).

Peak rates in other countries ranged from 1.8 in Germany and The Netherlands to 4.5 notifications per 100,000 population in Switzerland. From the beginning of the observation period in 2006/2007 to 2013/2014 peak case numbers and notification rates increased for Belgium, Germany, Luxembourg, The Netherlands, Sweden and Switzerland (Table 5.2). A more than

threefold increase was observed for Luxembourg and a twofold increase for Switzerland. For Austria and The Netherlands winter peaks in 2006/2007 had higher peak rates compared to the subsequent years but afterwards peak rates started to increase discontinuously. In Austria peak rates increased by 45% from 1.1 to 1.6 notifications per 100,000 population between 2011 and 2014. The highest rate of the winter peak 2007/2008 in The Netherlands was 0.7 per 100,000 population and increased to twice this rate in 2013/2014.

The Nordic countries Denmark and Norway exhibited no specific dynamics in the annual notification data on a regular basis (Additional file 1 of Bless *et al.* (2017a)). However, Danish weekly case numbers and notification rates showed irregular increases resembling a winter peak during some winter seasons. In Norway case numbers and notification rates generally decreased around calendar weeks 51 and 52 and were sometimes slightly increased in calendar weeks 1, 2, or 3.

Possible reporting delays were assessed for countries with observable winter peaks and for which dates of disease onset or dates of diagnosis were available (Austria, Belgium, Germany and Norway). Numbers of disease onset or diagnosis were summed up over all years per day and are depicted in Figure 5.2. In Austria, Germany and Norway the daily numbers of disease onset peaked in the first week of January and to a smaller extent already in the last week of December. Peaks of disease onset dates occurred a few days to one week before winter peaks observed in actual notification data. The number of diagnoses in Belgium started to increase at the end of December and decreased after the second week of January.

Table 5.2: Weekly peak notification rates over winter seasons and changes of weekly peak notification rates between 2006/2007 and 2013/2014 winter seasons

	Maximum weekly notification rate of all winter peaks			**Maximum weekly notification rate of winter peak 2006/2007**		**Maximum weekly notification rate of winter peak 2013/2014**		**Change of maximum weekly notification rates (2006/2007 to 2013/2014) [%]**
Country	Notification rate[a]	Calendar week	Year	Notification rate	Calendar week	Notification rate	Calendar week	
Austria	1.9	2	2007	1.9	2	1.6	3	-15.8
Finland	3.1	50	2007	1.4	3	1.7	3	+21.4
Germany	1.8	2	2014	1.7[b]	3[b]	1.8	2	+5.9
Luxembourg	6.5	3	2014	1.9	2	6.5	3	+242.1
Netherlands	1.8	1	2012	1.2	2	1.4	2	+16.7
Sweden	2.0	3	2008	1.5	3	1.5	3	0.0
Switzerland	4.5	1	2012	1.7	2	3.6	1	+111.8

[a] Rate per 100,000 population

[b] Winter peak 2008/2009

Our analysis of notification data shows that seasonal transmission of *Campylobacter* infection occurs prominently and distinctively during winter time in many European countries. Weekly notification rates can increase up to a multiple of the observed notification rates in the weeks before or after the winter peaks. In Switzerland and The Netherlands the notification rates already peaked in the first week of January whereas rates for the remaining countries peaked rather in week 2. So far this short-term phenomenon was described in the literature for Germany [3], Switzerland [4, 5] and Luxembourg [6]. For the EU the observation of a winter peak in January was reported for the first time for the years 2012 to 2014 [1].

Median notification rates over all winter seasons generally increase suddenly in the first week of January after a strong decline in the last week of December and do peak in January. The strong decline at the end of December, also observable in countries without a winter peak, could be due to limited access to health care services and reporting delays during public holidays at the end of the year. A study on campylobacteriosis notification data of England and Wales showed that the reporting rate is lower during weeks with a public holiday sometimes resulting in additional reporting in the following week [9]. Annual weekly notification rates of winter peaks showed an increasing trend over the recent years in most affected countries which could be related to the general increase of campylobacteriosis case notifications in Europe since 2005 [1, 2]. The analysis of Austrian, Belgian, German and Norwegian dates of disease onset and of diagnosis revealed that most notified cases show symptoms of campylobacteriosis in the last week of December and the first week of January. This observation was recently described for Germany [3].

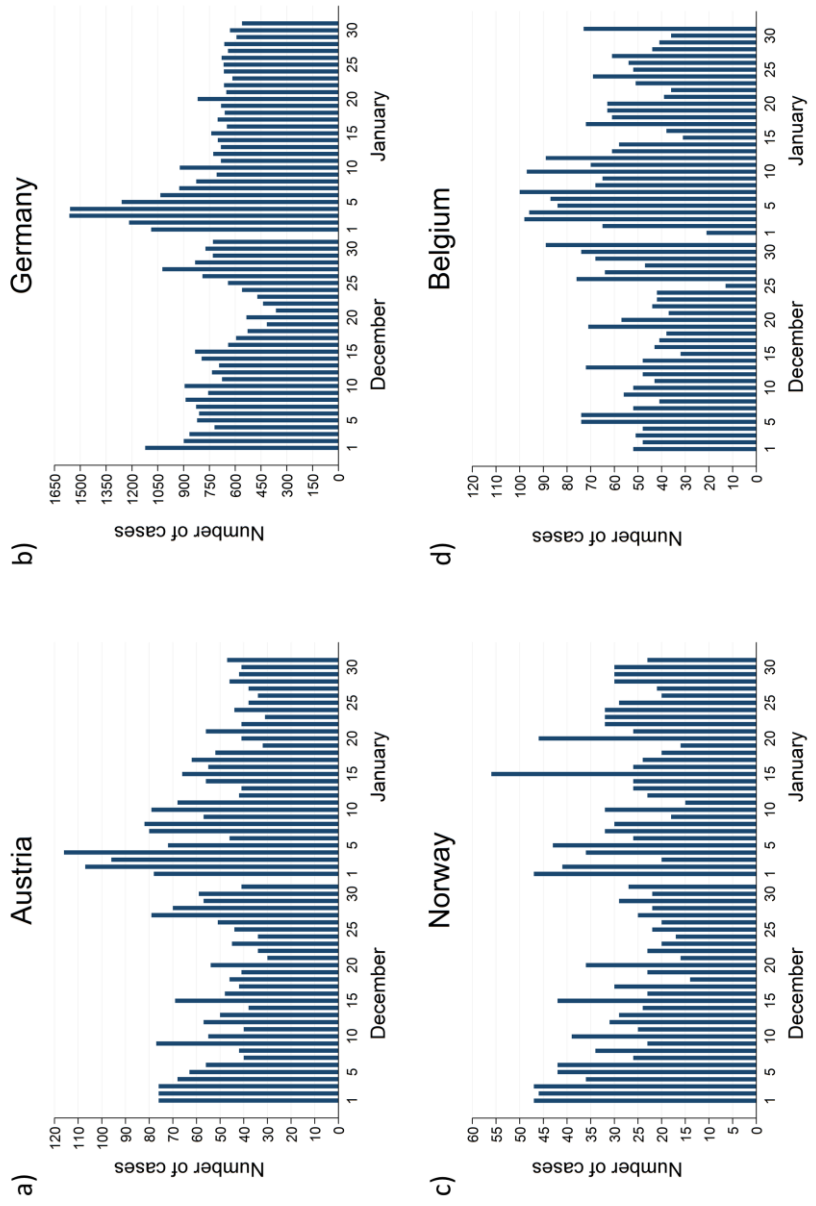

a)
Austria
Number of cases
0
10
20
30
40
50
60
70
80
90
100
110
120
1 5 10 15 20 25 30 1 5 10 15 20 25 30
December
January
b)
Germany
Number of cases
0
150
300
450
600
750
900
1050
1200
1350
1500
1650
1 5 10 15 20 25 30 1 5 10 15 20 25 30
December
January
c)
Norway
Number of cases
0
5
10
15
20
25
30
35
40
45
50
55
60
1 5 10 15 20 25 30 1 5 10 15 20 25 30
December
January
d)
Belgium
Number of cases
0
10
20
30
40
50
60
70
80
90
100
110
120
1 5 10 15 20 25 30 1 5 10 15 20 25 30
December
January

Figure 5.2: Sum of case notifications between 1st December and 31st January.

[a]Austria by daily disease onset, winter seasons 2008/2009–2013/2014
[b]Germany by daily disease onset, winter seasons 2008/2009–2013/2014
[c]Norway by daily disease onset, winter seasons 2006/2007–2013/2014.
[d]Belgium by daily diagnoses, winter seasons 2011/2012–2012/2013

Hence, winter peaks seen in surveillance data are likely delayed by a few days to one week compared to actual peaks of campylobacteriosis in the population when considering the "date used for statistics" of TESSy. These delays are likely caused by time needed for health care seeking, laboratory diagnostics and reporting. When taking into account an average incubation period for campylobacteriosis of 2-5 days, exposure to *Campylobacter* occurs likely around Christmas or New Year for notifications reported in the first two weeks of January [3, 5].

5.4.3. Possible reasons for the seasonal patterns

The sudden increases of weekly notification rates point towards a rapid change in exposure patterns or levels of exposures for campylobacteriosis in winter. Of particular interest appear food- and travel-related exposures around Christmas and New Year. In Finland and Sweden high proportions of travel-related cases (≥50%) are observed in annual surveillance data [1, 2]. Their winter peaks may be partially due to increased travel activities to foreign countries during Christmas and New Year holidays. In Switzerland, travelling abroad during the festive season was associated with almost three-time higher odds for contracting campylobacteriosis [5].

A recent study in Luxembourg identified the consumption of chicken in winter as risk factor for contracting campylobacteriosis and the authors hypothesised that it could be related to the traditional consumption of meat fondue during this time [6]. The consumption of meat fondue or table top grilling during the festive season is popular in Austria, Belgium, Germany, Luxembourg and The Netherlands. In Switzerland, the campylobacteriosis winter peak is associated with the frequent consumption of meat fondue at Christmas and New Year which increased the odds for contracting campylobacteriosis four-fold [5]. At these occasions, possibilities for *Campylobacter* transmission include cross-contamination of cooked meat and/or side dishes by raw poultry meat and individual meat preparation at the table [5, 10]. Hence, individuals are likely to contract campylobacteriosis around Christmas and New Year as a consequence of increased exposure levels to foodborne and travel-related risk factors.

5.5. Limitations

The "date used for statistics" provided by TESSy can vary between reporting countries and could mean the dates of disease onset, of diagnosis, of notification or any other date. The use of a non-standardised reporting date and differences in the national surveillance systems make it difficult to exactly compare the temporal trends of winter peaks among countries. Reporting delays and other surveillance artefacts affecting notification rates of observed winter peaks could not be excluded. Consequently, it should be evaluated whether these peaks represent a true epidemiological trend before investigating possible risk exposures. To our knowledge, there is no scientific evidence on the extent and significance of the consumption of meat fondue

or table top grilling for the investigated countries except for Switzerland [5].

5.6. Abbreviations

ECDC: European Centre for Disease Prevention and Control; EU: European Union; TESSy: The European Surveillance System.

5.7. Authors' contributions

All authors made substantial contributions to the conception and design of the study, data analysis and interpretation of results. PJB wrote the first draft of the manuscript and all authors critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

5.8. Acknowledgements

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5.9. Competing interests

The authors declare that they have no competing interests. Availability of data and materials The data that support the

findings of this study are available from TESSy, ECDC, Stockholm, Sweden and the Swiss Federal Office of Public Health, Bern, Switzerland but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

5.10. Disclaimer

The views and opinions of the authors expressed herein do not necessarily state or reflect those of ECDC. The accuracy of the authors' statistical analysis and the findings they report are not the responsibility of ECDC. ECDC is not responsible for conclusions or opinions drawn from the data provided. ECDC is not responsible for the correctness of the data and for data management, data merging and data collation after provision of the data. ECDC shall not be held liable for improper or incorrect use of the data. Ethics approval and consent to participate Access to routine surveillance data was granted by TESSy, ECDC, Stockholm, Sweden and the Federal Office of Public Health, Bern, Switzerland according to the institutions' data sharing policies following formal requests of the authors. The case-based data sets received by the authors contained no personal identifiers.

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5.12. References

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6. ARTICLE 3: Time trends of positivity rates from foodborne pathogen testing in Switzerland, 2003 - 2012

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6.1. Summary

Background: Campylobacteriosis and salmonellosis are important foodborne diseases in Europe, including in Switzerland. In 2014, notification rates for Switzerland were 92.9 per 100,000 population for campylobacteriosis and 15.2 per 100,000 population for salmonellosis. These notification rates originate from laboratory-based surveillance whereby positive test results are reported to the National Notification System for Infectious Diseases. Consequently, notification rates do not directly correspond to the disease burden among the population as the number of positive tests depends on patients' healthcare-seeking behaviour, stool sampling rates and other factors.

Methods: We assessed laboratory positivity rates (proportion of positive tests among all tests performed) of diagnostic tests for *Campylobacter* and *Salmonella* from five private laboratories in Switzerland between 2003 and 2012. We analysed demographic characteristics, temporal and spatial distribution of test numbers and positivity rates. Predictors for a positive test and disease seasonality were assessed with logistic regression analyses.

Results: A total of 135 122 (13 095 positive) *Campylobacter* tests and 136 997 (2832 positive) *Salmonella* tests were obtained with positive tests corresponding to 20.4% and 17.2% of notified campylobacteriosis and salmonellosis cases, respectively. The number of tests conducted annually increased for both pathogens by 51% from 2003 to 2012. Annual positivity rates of *Campylobacter* increased from 7.6 to 11.1% and rates of *Salmonella* decreased from 2.7 to 1.5%. The largest increases in annual *Campylobacter* positivity rates were observed for patients older than 85 years (+193.7%), followed by children

aged 5‑9 years (+131.9%). Positivity rates and test numbers for both diseases by month or calendar week showed a distinct seasonality, with peak rates for *Salmonella* occurring in autumn and for *Campylobacter* in summer and at the turn of the year. These findings were independent of patients' age and sex.

Conclusions: Both positivity rates and notification rates showed increasing trends for *Campylobacter* and decreasing trends for *Salmonella*, suggesting that these trends reflect changes in disease epidemiology at population level. The continuous assessment of positivity rates remains important to appropriately interpret changes observed in the notification system especially considering the increasing use of multiplex polymerase chain reaction test panels where multiple pathogens are tested simultaneously.

6.2. Keywords

Campylobacter, *Salmonella*, disease surveillance, denominator data, Switzerland, foodborne disease, seasonality, positivity, epidemiological trends, notification rate

6.3. Introduction

Human campylobacteriosis and salmonellosis are the most frequently reported foodborne bacterial infections in Europe. In 2014, notification rates in the European Union (EU) were 71.0 cases per 100,000 population (corresponding to approximately 236 900 cases) for campylobacteriosis and 23.4 cases per 100,000 population (approximately 88 700 cases) for salmonellosis [1]. In the same year, in Switzerland, the notification rate for *Campylobacter* infections was 92.9 cases per 100,000

population (approximately 7600 cases) and 15.2 cases per 100,000 population (approximately 1200 cases) for *Salmonella* infections [1]. During the mid-1990s, the annual number of notified human *Campylobacter* infections surpassed that of *Salmonella* infections in Switzerland [2]. This was owing to a reduction of human salmonellosis following the introduction of control measures in the egg and poultry industry, such as mandatory screening of layer hens, in the early 1990s [2]. So far, similar control measures for *Campylobacter* are lacking and campylobacteriosis is currently the most frequently notified foodborne disease in Switzerland [2].

In Switzerland, notifiable diseases are monitored by the Federal Office of Public Health (FOPH) through the National Notification System for Infectious Diseases (NNSID) [3, 4]. Laboratory-based surveillance of *Campylobacter* and *Salmonella* infections, as defined by the Epidemics Act of 1970 and its related ordinances, captured only those cases that tested positive [5–7]. Since the implementation of the new Epidemics Act at the beginning of 2016, the total number of tests conducted for these two pathogens, including the number of positive results, must be reported annually as aggregated numbers, stratified by month and test method [4, 8]. Hence, denominator data to help draw inferences from surveillance data about the epidemiological situation in the community have not been collected so far. The number of stool tests performed depends on the healthcare-seeking behaviour of patients with diarrhoea and the stool sampling rate of treating physicians [9–11]. As not all individuals affected by acute gastroenteritis seek medical care or have a stool sample examined for enteric pathogens, there are likely to be many undetected (at community level) and unreported (at healthcare level)

campylobacteriosis and salmonellosis cases [12, 13]. Hence, changes in notification rates do not necessarily reflect an epidemiological trend, but could be attributable to changes in healthcare-seeking behaviour or stool sampling rates. A more informed interpretation of surveillance data is made possible by calculating positivity rates (proportion of positive tests among all tests performed). Because positivity rate calculations also consider denominator data, they adjust for the number of tests [14, 15]. We analysed laboratory data for stool tests performed for *Campylobacter* spp. and *Salmonella* spp. by Swiss diagnostic laboratories over a 10-year period to better interpret the trends of campylobacteriosis and salmonellosis case notifications seen in the NNSID.

6.4. Materials and methods

6.4.1. Selection of diagnostic laboratories

The study aimed to include private diagnostic laboratories from all geographical and linguistic regions of Switzerland to reach an optimal representation of the campylobacteriosis cases reported to the NNSID between 2003 and 2012. Eleven private diagnostic laboratories, each reporting more than 1000 campylobacteriosis cases during that decade, were contacted and invited to provide data for the study. The case-based laboratory data requested comprised patients' demographic characteristics (sex, age, canton of residence, personal identification code assigned by laboratory) and test characteristics (pathogen tested, test result, date of test, test method) on all *Campylobacter* and *Salmonella* tests performed between 2003 and 2012.

6.4.2. Analysis of positivity rates

Datasets from individual laboratories were transformed uniformly, merged and analysed with STATA™ Version 13.1 (Stata Corporation; College Station, TX, USA). Firstly, double entries, repeated tests and tests for patients without Swiss residency were excluded. The following rules – based on disease durations and durations of organism excretion [16] – were applied to identify and exclude repeated tests: (i) control or follow-up tests, irrespective of result, following a positive result within 42 days for both, *Campylobacter* and *Salmonella*; (ii) negative tests following a negative result within 10 days (*Campylobacter*) or 21 days (*Salmonella*); and (iii) negative tests followed by a positive result within 10 days (*Campylobacter*) or 21 days (*Salmonella*). The patient population was characterised by sex, age, diagnostic laboratory, test year and residence by greater region (corresponding to the Nomenclature of Units for Territorial Statistics (NUTS) 2 level [17]). Age groups for statistical analyses were predefined. Residence by greater region was based on the patients' canton of residence (NUTS 3 level). Descriptive analysis of positivity rates - defined as positive tests divided by total tests performed - and exploratory logistic regression analyses of predictors for and seasonality of positive tests were performed. Characteristics of laboratory-confirmed cases of campylobacteriosis and salmonellosis were additionally compared with national surveillance data. Time trends of annual positivity rates were investigated using stratification and direct standardisation for age groups and sex. Thus, the population of individuals tested from 2003 to 2012 was used as the reference population. The seasonality of monthly and weekly positivity rates was assessed by calcu-

lating positivity rates from laboratory data from the whole observation period pooled by month or calendar week.

6.4.3. Univariable and multivariable regression models

In a first step, univariable logistic regression analyses were performed to estimate the effect of sex, age group, laboratory, residence by greater region, test week, test month and test year on the test result. Afterwards, a multivariable logistic regression model estimated the unconfounded effects of sex, age groups, laboratories, residence by greater region and test year on the test result. The effect of seasonal within-year variations on test outcome were investigated with a second multivariable logistic regression model including test month and adjustments for sex, age groups, laboratories, residence by greater region and test year. For this model, the test month with a positivity rate closest to the mean positivity rate of all test months was used as a baseline and test year was introduced as a random effect. The significance of variables in the multivariable models was assessed by likelihood ratio tests and the category of each variable with the most observations (except for test month) was used as a baseline to make the model more robust. Patients with missing information on the canton of residence were assigned the greater region of their corresponding laboratory.

6.4.4. Ethical statement

The study was approved by the local ethical committee "Ethikkommission Nordwest- und Zentralschweiz" [Ethical committee of Northwestern and Central Switzerland] (No.: EKNZ:2014-164).

6.5. Results

6.5.1. Exclusion of test results and representativeness

Eight laboratories agreed to participate in the study and five of them provided complete data for *Campylobacter* and *Salmonella* tests performed as requested. The eight laboratories conducted a total of 196 307 *Campylobacter* tests (17 694 positive) and 199 062 *Salmonella* tests (4163 positive) between 2003 and 2012. Excluding data from the three laboratories with incomplete data led to the exclusion of 43 530 (3345 positive) *Campylobacter* tests and 45 114 (640 positive) *Salmonella* tests. Among the remaining laboratories (A to E), removal of double entries, repeated tests and tests of non-Swiss residents led to the exclusion of a further 17 211 (1245 positive) *Campylobacter* tests and 16 499 (689 positive) *Salmonella* tests. Additionally, we excluded 444 (9 positive) *Campylobacter* tests and 452 (2 positive) *Salmonella* tests because of missing information on sex and/or age. In the detailed analysis, 135 122 (13 095 positive) *Campylobacter* tests and 136 997 (2832 positive) *Salmonella* tests were included. Culture-based test methods accounted for 98.7% of all *Campylobacter* and *Salmonella* tests conducted, and polymerase chain reaction (PCR) tests accounted for 1.3%. Positive tests included in the analysis corresponded to 20.4% and 17.2% of campylobacteriosis and salmonellosis cases, respectively, registered in the NNSID between 2003 and 2012 (Table 6.1 and Table 6.2).

Table 6.1: Comparison of campylobacteriosis cases from laboratory data and cases registered in the NNSID by test year, Switzerland, 2003-2012

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Proportion of NNSID cases reported by study laboratories in %	16.7	16.7	17.6	20.4	21.8	21.1	21.4	21.0	21.1	23.0
Proportion of NNSID cases by greater region reported by study laboratories in %										
Lake Geneva	1.5	2.5	2.0	3.5	3.0	3.0	4.0	4.0	3.5	4.0
Espace Mittelland	17.0	17.0	18.5	26.0	27.0	27.0	28.5	29.0	28.0	28.5
Northwestern Switzerland	26.0	22.5	23.0	25.0	27.5	26.0	27.0	25.0	27.0	33.0
Zurich	24.0	27.0	28.0	29.0	29.5	29.0	23.0	28.0	25.0	26.5
Eastern Switzerland	15.0	18.0	18.0	16.5	18.5	20.5	22.0	19.5	23.0	24.0
Central Switzerland	8.0	7.5	8.5	6.5	7.0	6.5	6.0	7.0	6.5	8.0
Ticino	45.5	47.0	44.0	63.0	69.5	54.5	60.0	52.5	57.0	58.0
Proportion of males in %										
Laboratories	56.6	55.4	53.5	57.7	55.2	53.7	55.8	53.0	54.6	54.9
NNSID	55.4	54.8	54.8	55.0	53.5	53.5	53.6	53.8	53.7	54.0
Median age in years										
Laboratories	34	34	34	35	35	36	37	37	39	36
NNSID	32	33	34	34	35	35	35	37	36	36

Table 6.2: Comparison of salmonellosis cases from laboratory data and cases registered in the NNSID by test year, Switzerland, 2003-2012

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Proportion of NNSID cases reported by study laboratories in %	15.6	15.9	15.7	16.7	17.7	16.4	17.4	19.0	21.0	19.8
Proportion of NNSID cases by greater region reported by study laboratories in %										
Lake Geneva	0.5	2.5	2.0	3.0	4.5	4.0	2.0	1.0	3.0	1.0
Espace Mittelland	14.5	18.0	14.0	19.0	19.5	19.0	18.5	20.5	28.5	21.0
Northwestern Switzerland	20.0	21.0	21.0	24.0	22.5	17.5	23.0	23.0	19.0	29.5
Zurich	19.0	17.5	18.0	22.0	23.5	21.5	23.0	25.0	14.0	24.5
Eastern Switzerland	9.5	11.0	16.5	12.5	14.5	14.0	17.0	23.0	19.5	18.5
Central Switzerland	6.0	6.5	3.5	7.5	3.5	4.5	4.5	12.0	3.0	10.5
Ticino	49.5	51.0	43.5	48.5	46.0	49.5	45.0	47.0	72.5	48.5
Proportion of males in %										
Laboratories	53.2	53.4	56.0	58.8	57.1	55.0	57.9	52.3	49.6	52.2
NNSID	52.1	49.6	53.1	56.2	54.3	51.4	53.0	52.4	51.2	52.5
Median age in years										
Laboratories	18	23	23	25	30	28	29	25	24	25
NNSID	25	25	26	25	27	28	27	27	28	26

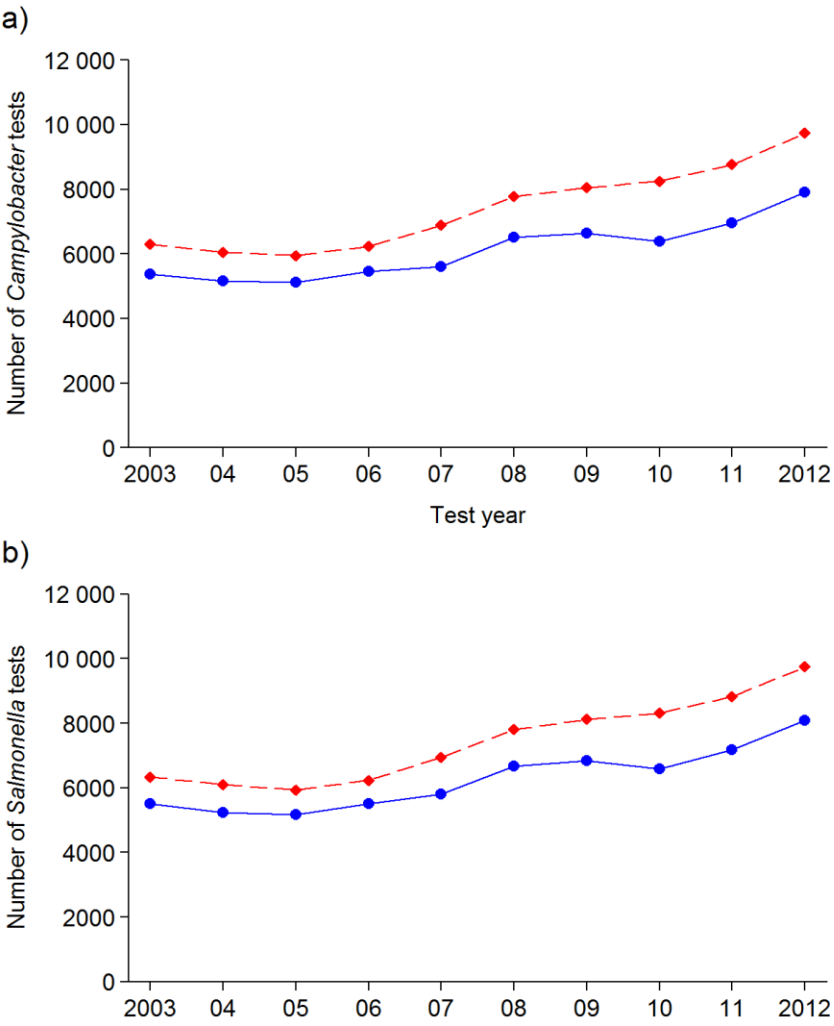


Figure 6.1: Number of stool tests for *Campylobacter* (a) and *Salmonella* (b) by sex in five diagnostic laboratories, Switzerland, 2003-2012.

6.5.2. Characteristics of the patient population and overview of tests performed

The annual number of tests performed increased by 51.1% from 2003 to 2012 (11 674 to 17 641 tests) for *Campylobacter* and by 50.7% (11 842 to 17 842 tests) for *Salmonella* (Figure 6.1). For both diseases, annual test numbers decreased by at least 6% for the age groups <5 years and 5–9 years, and increased by at least 31% in the older age groups. The median age of patients tested for *Campylobacter* was 42 years (range <1–108 years) and 41 years (range: <1‑108 years) for *Salmonella*. Patients' age differed significantly between laboratories and test years for both pathogens (Kruskal-Wallis test: p <0.01 for all four tests). Slightly more tests were conducted among females than among males for *Campylobacter* (54.8%) and for *Salmonella* (54.3%). The sex ratio differed between laboratories and test years for both pathogens (chi-square test: p<0.01 for all four tests). The patients' residence by greater region was associated with the geographical location of the laboratory that performed the test.

6.5.3. Annual positivity rates overall and by laboratory

Annual *Campylobacter* positivity rates standardised for age and sex increased by 46.1% from 2003 (7.6%) to 2012 (11.1%) (Figure 6.2). Annual standardised *Salmonella* positivity rates showed an inverse trend and decreased by 44.4% from 2003 (2.7%) to 2012 (1.5%). *Campylobacter* positivity rates stratified by laboratory (and standardised for age and sex) showed similar annual trends (supplementary Figure S1 of Bless *et al.* (2017b)). The annual positivity rates of laboratory C were remarkably lower throughout the investigated period compared with other laboratories.

Laboratory-specific *Campylobacter* positivity rates ranged from 3.8 to 9.4% in 2003 and continuously increased to 7.0‑13.2% in 2012. For *Salmonella,* annual positivity rates by laboratory differed only slightly between laboratories; the highest rates were observed for laboratory C, with two distinct peaks in 2007 and 2011. Overall, a decreasing trend was observed; positivity rates dropped from 2.1‑3.8% in 2003 to 1.2‑2.7% in 2012.

6.5.4. Annual positivity rates by sex and age groups

The annual *Campylobacter* positivity rates for males and females increased by 43.6% (from 9.4 to 13.5%) and by 45.2% (from 6.2 to 9.0%), respectively, from 2003 to 2012. In the same decade, annual *Campylobacter* positivity rates by age group increased for all age groups. The largest increase was observed for the age group ≥85 years (193.7%) followed by the 5‑9-year-olds (131.9%). Compared with 2003, annual *Campylobacter* positivity rates of sex-specific age groups were higher in 2012, except for females in the age group 10‑14 years (Figure 6.3a). Annual *Campylobacter* positivity rates were generally higher for males than for females over the entire observation period. For males and females in the age groups <5 years, 5‑9 years and ≥85 years, similar annual *Campylobacter* positivity rates were observed at the beginning of the decade but rates were later slightly higher for males in the age group ≥ 85 years and for females in the age groups <5 years and 5‑9 years.

Annual *Salmonella* positivity rates decreased from 3.3% to 1.6% (−51.5%) for males and from 2.5% to 1.2% (−52.0%) for females between 2003 and 2012. Annual positivity rates decreased for all age groups between 2003 and 2012 except for

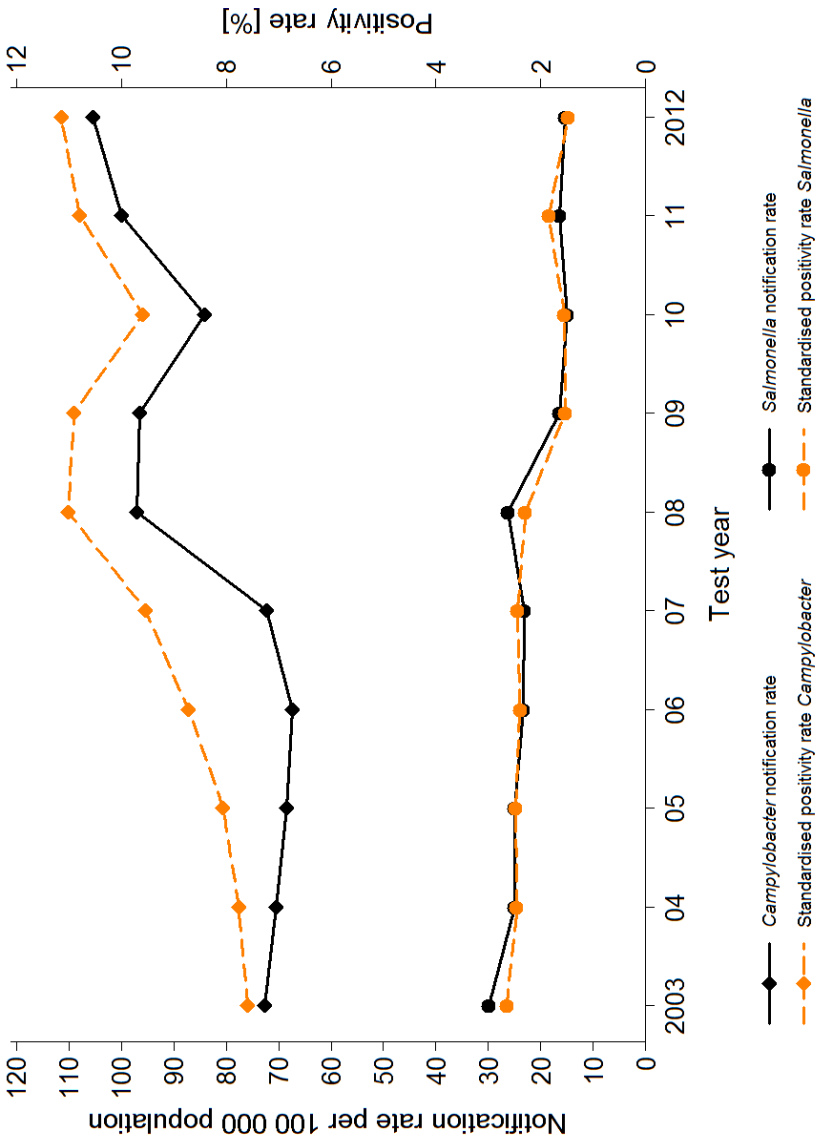

Positivity rate [%]
Notification rate per 100 000 population
Test year
2003
04
05
06
07
08
09
10
11
2012
0
2
4
6
8
10
12
0
10
20
30
40
50
60
70
80
90
100
110
120
Campylobacter notification rate
Standardised positivity rate Campylobacter
Salmonella notification rate
Standardised positivity rate Salmonella

Figure 6.2: NNSID notification rates and positivity rates (standardised for age and sex) of *Campylobacter* and *Salmonella*, Switzerland, 2003-2012.

NNSID data provided by the Federal Office of Public Health, Bern, Switzerland

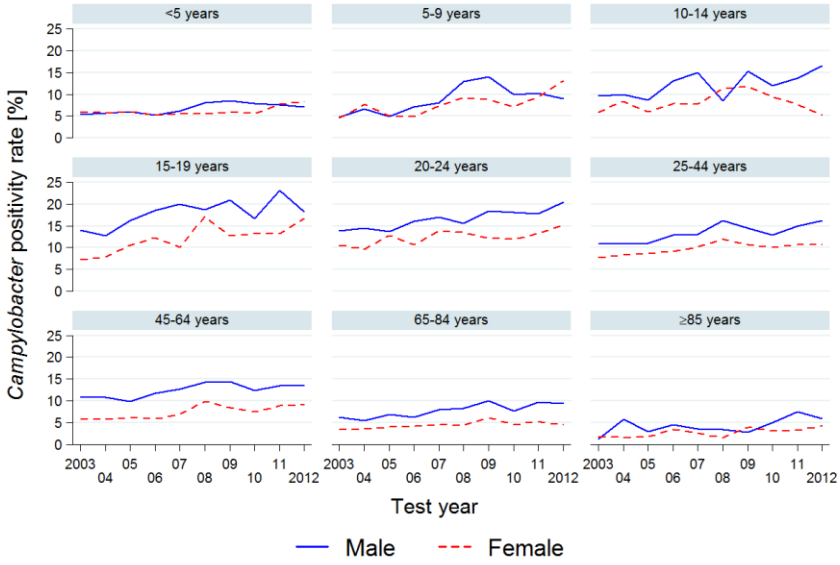
the age group 20‑24 years, for which the rate remained rather stable. The largest relative decrease of positivity rates was observed for the age groups 10‑14 years and ≥85 years, where rates decreased from 10.5 to 3.7% (−64.8%) and from 0.8 to 0.2% (−75.0%), respectively. Sex-specific *Salmonella* positivity rates were similar or slightly higher for males compared to females in all age groups although for some age groups, positivity rates varied strongly between years (Figure 6.3b).

6.5.5. Seasonal trends in stool sampling and positivity rates

The number of tests performed for *Campylobacter* and *Salmonella* started to increase in spring (Figure 6.4 panels a and c, Figure 6.5 panels a and c). Test numbers peaked in late August (calendar week 34) after a brief and strong temporary decline at the beginning of the month (calendar week 31). Afterwards, the number of tests decreased until the end of the year. Monthly test numbers were lowest in February for *Campylobacter* and *Salmonella*, even though calendar week 1 was the week with the fewest tests performed.

After a continuous increase during spring, monthly *Campylobacter* positivity rates peaked during summer months, with the highest monthly rate occurring in July (13.8%) (Figure 6.4 panels b and d). Likewise, monthly *Salmonella* positivity rates started increasing during the spring.

a)


<5 years
5-9 years
10-14 years
15-19 years
20-24 years
25-44 years
45-64 years
65-84 years
≥85 years
Campylobacter positivity rate [%]
0
5
10
15
20
25
2003
04
05
06
07
08
09
10
11
2012
Test year
Male
Female

b)

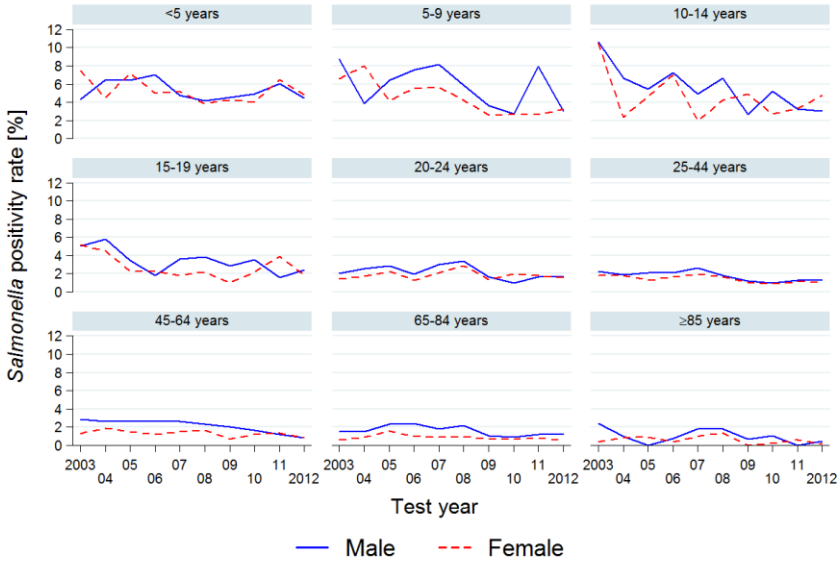

<5 years
5-9 years
10-14 years
15-19 years
20-24 years
25-44 years
45-64 years
65-84 years
≥85 years
Salmonella positivity rate [%]
0
2
4
6
8
10
12
2003
04
05
06
07
08
09
10
11
2012
Test year
Male
Female

Figure 6.3: Annual positivity rates of *Campylobacter* (a) and *Salmonella* (b) by age group and sex, Switzerland, 2003-2012.

They peaked twice, first in late summer (August) and then in the autumn, with the highest rate occurring in October (3.1%) (Figure 6.5 panels b and d).The highest weekly positivity rate for *Campylobacter* (17.3%) was in calendar week 1 (January), whereas the peak of weekly *Salmonella* positivity rates (3.5%) was in calendar week 43 (October). The lowest monthly positivity rates for *Campylobacter* and *Salmonella* were in February (5.3%) and March (1.1%), respectively. The seasonal trends of *Campylobacter* and *Salmonella* positivity rates were also observable for sex- and age-specific positivity rates although less pronounced in certain groups.

6.5.6. Regression analyses

In the univariable regression analyses, sex, age, laboratory, residence by greater region, test week, test month and test year all had a significant effect on the test result for both diseases. The multivariable regression analysis of predictors for a positive *Campylobacter* test showed higher odds of a positive test for males than for females (odds ratio [OR] 1.53, 95% confidence interval [CI] 1.47‑1.59) (supplementary Table S1 of Bless *et al.* (2017b)). Patients in the age groups 15‑19 years and 20‑24 years had higher odds for a positive test outcome compared with the age group 25‑44 years, whereas patients of other age groups had reduced odds. The patients' place of residence by greater region had similar odds for a positive test, except for patients from the Ticino region (OR 0.44, 95% CI 0.38‑0.52). From 2003 to 2008, the odds increased continuous-

ly and decreased slightly between 2009 and 2011 compared with 2012.

The regression model for seasonal within-year variations showed that the odds for a positive *Campylobacter* test was highest in July (OR 1.52, 95% CI 1.40‑1.65) and lowest in February (OR 0.55, 95% CI 0.49‑0.61) compared with May, which had a positivity rate closest to the monthly average (supplementary Table S2 of Bless *et al.* (2017b)). Significantly higher odds were also observed for June (OR 1.38, 95% CI 1.26‑1.50) and August (OR 1.24, 95% CI 1.14‑1.35) compared with May.

In the multivariable regression model for *Salmonella*, males had higher odds (OR 1.30, 95% CI 1.21‑1.40) of a positive test than females (supplementary Table S3 of Bless *et al.* (2017b)). The odds of a positive test outcome increased threefold for the age groups <5 years, 5‑9 years and 10‑14 years compared with the age group 25‑44 years. Greater region was no longer significantly associated with the outcome in the multivariable regression model. The odds of a positive test outcome steadily decreased during the study period compared with 2012. In the second multivariable model for seasonality, the highest odds of a positive *Salmonella* test were observed in October (OR 1.61, 95% CI 1.36‑1.90) and August (OR 1.44, 95% CI 1.23‑1.70) compared with November (supplementary Table S4 of Bless *et al.* (2017b)). The lowest odds (compared with November) were observed in March (OR 0.55, 95% C: 0.44‑0.68) and February (OR 0.57, 95% CI 0.46‑0.72).

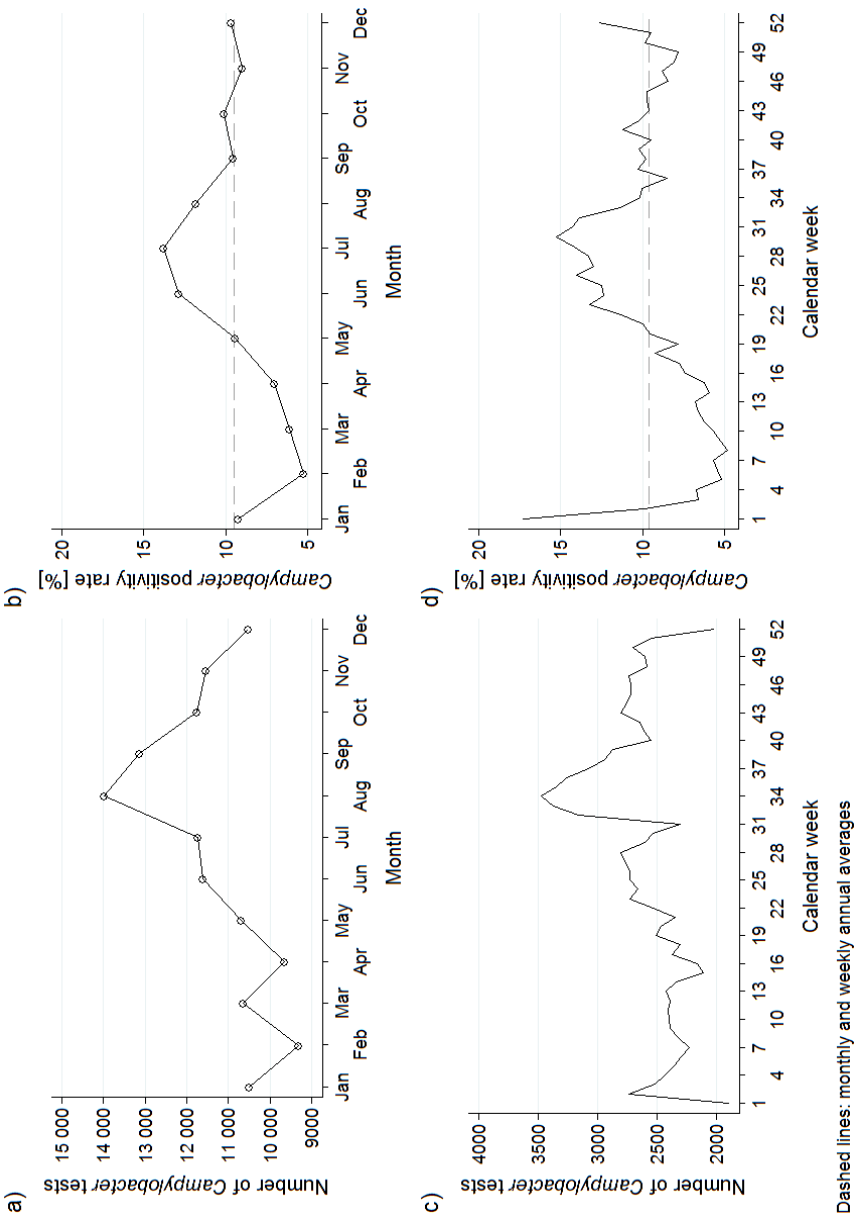


Figure 6.4: Seasonality of *Campylobacter* tests and positivity rates (pooled over study period) per month and calendar week, Switzerland, 2003-2012.

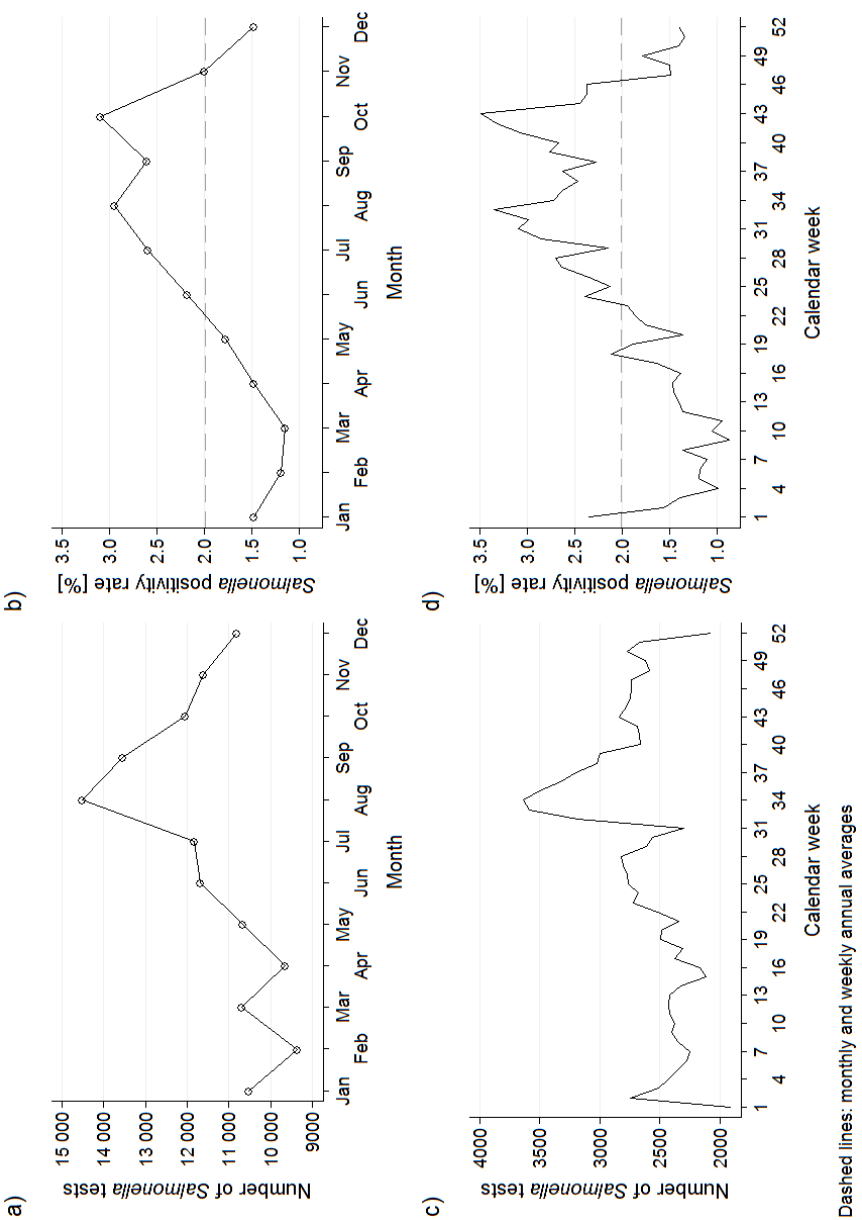


Figure 6.5: Seasonality of *Salmonella* tests and positivity rates (pooled over study period) per month and calendar week, Switzerland, 2003-2012.

6.6. Discussion

Annual *Campylobacter* positivity rates standardised for age and sex increased from 2003 to 2012, whereas standardised *Salmonella* positivity rates decreased. During the same time period, campylobacteriosis notification rates increased from 72.7 to 105.5 notifications per 100,000 population, whereas salmonellosis notification rates decreased from 29.8 to 15.4 per 100,000 population. *Campylobacter* positivity rates were generally higher for males than females in all age groups. Monthly and weekly *Campylobacter* positivity rates showed a distinct seasonality, with a peak during the summer months and again at the beginning of the year, which was independent of sex and age group. *Salmonella* positivity rates showed a similar seasonality, but peaked in autumn. Annual *Salmonella* positivity rates were similar or slightly higher for males than for females, with the highest rates observed in the younger age groups, <5, 5-9 and 10-14 years. The observed seasonality and annual trends of positivity rates for both pathogens are congruent with reports from other countries [14, 18].

6.6.1. Annual positivity rates in relation to NNSID notification rates

Annual positivity rates of *Campylobacter* and *Salmonella* standardised for age and sex and annual NNSID notification rates showed similar trends. Multiple testing, data duplication or simultaneous testing of several pathogens could potentially affect both numerator and denominator data in different ways. However, similar trends were observed for the standardised annual positivity rates presented here and for the crude, non-standardised positivity rates calculated from raw data from all

eight laboratories included in the study (supplementary Figure S2 of Bless *et al.* (2017b)).

The stool test data analysed for this study originated mainly from culture-based test methods, which used to be the standard diagnostic method for detecting *Campylobacter* and *Salmonella*. *Campylobacter*, *Salmonella* and *Shigella* are often tested simultaneously [19]. In terms of relative frequency, more positive *Salmonella* tests (18.9%) than positive *Campylobacter* tests (8.4%) were excluded, whereas the proportion of excluded duplicate and repeated tests was similar for negative *Campylobacter* and *Salmonella* tests (11.2 vs 10.2%). The proportion of negative *Salmonella* tests excluded dropped only slightly from 10.2 to 9.4% when the same time span used for excluding negative *Campylobacter* tests was applied. Hence, only laboratory-confirmed campylobacteriosis and salmonellosis patients differ with regard to repeated testing. In summary, reducing the number of tests per patient and disease episode to one test result is crucial for an accurate calculation of positivity rates whereas the temporal trend of positivity rates is not considerably affected.

The relative increase in standardised annual *Campylobacter* positivity rates (+46.1%) and the relative decrease in standardised annual *Salmonella* positivity rates between 2003 and 2012 (−44.4%) are close to the increase in notification rates of *Campylobacter* (+45.0%) and the decrease in notification rates of *Salmonella* (−48.4%). During the same time period, the number of tests performed for *Campylobacter* and *Salmonella* increased by around 51%. The proportion of cases diagnosed by participating laboratories among NNSID case notifications increased by 37.7% for campylobacteriosis and by 26.9% for salmonellosis over the study period.

The observed increase of test numbers in our study was partially due to a single laboratory (laboratory A), where the number of tests increased 3.5 times for *Campylobacter* and 3.8 times for *Salmonella* between 2003 and 2012. This laboratory was founded a few years before the study period. For the remaining laboratories (B, C, D, E), a smaller increase of 32.0% for *Campylobacter* tests and of 29.0% for *Salmonella* tests was observed. An increase in testing frequency has also been observed in other European countries [14, 20], except in the Netherlands, where testing frequency remained rather stable [21]. Testing frequencies are largely influenced by physicians' stool sampling behaviour and patients' healthcare-seeking behaviour [14, 22–25]. It is also possible that laboratories in the study increased their market shares.

The increase of *Campylobacter* notification rates is probably due to a combination of increasing test numbers and an upward epidemiological trend in the population, as suggested by the increase in positivity rates. The decrease of *Salmonella* notification rates presumably reflects an epidemiological trend in the population, as the notification rate decreased at the same time that testing frequency increased. The increase of campylobacteriosis cases in the population, together with the co-testing of *Salmonella* and *Campylobacter*, is probably responsible for the increase of *Salmonella* test numbers.

In summary, notification rates are influenced by both epidemiological trends in the population and test numbers. More infections in the population will lead to higher notification rates and fewer infections will lead to lower notification rates. On the other hand, increasing test numbers can lead to the detection of more cases in the population, i.e., higher notification rates without necessarily reflecting an increase in disease fre-

quency. Consequently, an observed increase in notification rates does not necessarily represent an actual increase of disease frequency in the population. A change in test numbers can be due to a number of factors such as changes in the prevalence of risk factors leading to testing, altered healthcare-seeking behaviour, and changes in physicians' testing practices, human susceptibility, and pathogenicity. Assessing the interplay of notification rates and test numbers by positivity rates provides more insights into the epidemiological situation in the population than one of these measures alone. Nevertheless, understanding underlying reasons for changes in one of these measures requires further investigation.

6.6.2. Positivity rates in relation to age and sex

A remarkable increase in *Campylobacter* positivity rates was observed for the age groups 5–9 years and ≥85 years (+131.9% and +193.7%). Test numbers for the age group 5–9 years decreased during the observation period (−6.1%), and they more than doubled for the age group ≥85 years (+131.5%). During the same time period, notification rates for the ≥85 years age group increased by 94.9% (47.2–92.0 per 100,000 population) and for the 5–9 years age group by 30.7% (55.3–72.3 per 100,000 population) [2]. It was found that adults and the elderly suffered increasingly more frequently from campylobacteriosis; this could be related to the frequent use of proton pump inhibitors and comorbidities in these age groups [2, 26, 27]. Others have also observed increasing test numbers among the elderly and related it to changes (increases) in healthcare-seeking and physicians' testing behaviour [14, 18, 24]. Additionally, the Swiss population aged ≥85 years increased by 29% from 2003 to 2012, which probably also contributed to the observed increase in test numbers [28].

Salmonella notification rates and annual sex-specific positivity rates showed similar decreasing trends. The strongest decreases in age-specific annual *Salmonella* positivity rates were observed for the age groups 10‑14 years and ≥85 years (−64.8% and −75.0%, respectively). At the same time, notification rates dropped by 55.4% (39.2‑17.5 per 100,000 population) for the 10‑14 year age group and by 55.6% (23.9‑10.6 per 100,000 population) for the ≥85 years group. It appears, therefore, that these decreases are true epidemiological trends. Age-specific *Salmonella* positivity rates tended to be slightly higher for males but did not remarkably differ between sexes. Similar observations have been made for corresponding NNSID data [2].

The increasing trend in *Campylobacter* positivity rates was similar for males and females. Also, male and female notification rates to the NNSID likewise increased during this time [2]. Both positivity rates and notification rates for *Campylobacter* were higher among males than among females in nearly all age groups. Higher positivity rates for males have also been observed by others [18]. Higher stool sampling rates have been reported for male patients in Canada [18] and for female patients in Wales [14]. Sex-specific differences in healthcare seeking or in risk exposures could account for this observation.

6.6.3. Seasonality of positivity rates and notification rates

Monthly and weekly *Campylobacter* and *Salmonella* positivity rates showed seasonal trends corresponding to the NNSID notification rates, which peaked during the summer months and, for *Campylobacter*, also at the beginning of the year [2]. Summer peaks of *Campylobacter* and *Salmonella* positivity rates have also been described previously [18]. Monthly and weekly

test numbers also peak in summer. The seasonal variation of test numbers could indicate seasonality of acute gastroenteritis, a temporal variation in the medical care-seeking behaviour of affected individuals and in the proportion of patients being tested. For instance, returning travellers are more likely to undergo stool diagnostics [24, 25, 29], leading to increased test numbers during the public school holiday season in the summer. The combination of high test numbers and high positivity rates in summer and autumn generates the observed peak in case numbers in the NNSID [2].

Peaks of *Campylobacter* and *Salmonella* notification rates during summer months are observed in most European countries [1, 2, 27, 30, 31]. The prevalence of *Campylobacter* in broiler flocks and the contamination of chicken meat with *Campylobacter* at retail are higher during summer months than during the rest of the year [31-34]. This probably explains the observed seasonality as poultry meat from broilers is the main source of *Campylobacter* infections in Switzerland [35-37]. However, it seems that the summer peak is not caused by a single common source of infection and is more likely driven by multiple sources of animal and environmental exposures and climatic conditions [27, 31, 38, 39]. An additional reason for the summer peak in Switzerland and parts of the EU could be related to the culture of barbequing during summer, which provides multiple occasions for disease transmission through undercooking of and cross-contamination by poultry and red meat [40-43]. Travel abroad is a known risk factor for contracting campylobacteriosis [42-45] - also in Switzerland [46, 47] - and a large proportion of notified *Salmonella* infections in Switzerland is travel-related [48]. Hence, travelling probably contributes to the observed seasonality of

campylobacteriosis and salmonellosis test numbers and case notifications in Switzerland.

The highest weekly positivity rate for *Campylobacter* was found in calendar week 1 when test numbers were lowest. Notification rates of campylobacteriosis in Switzerland show a strong annual increase over Christmas and New Year ("winter peak"). A similar peak in notification data at the beginning of January has also been observed in Germany [30] and in the *Campylobacter* surveillance data of The European Surveillance System [1]. In Switzerland, the major driver for the winter peak is frequent consumption of meat fondue at festive occasions around this time, especially if it includes chicken meat [47]. The low test numbers over the festive season in December and January are probably related to a different healthcare-seeking behaviour and restricted access to healthcare services during the holiday period. Therefore, the winter peak in *Campylobacter* notification rates is probably attenuated and does not reveal the full magnitude of the problem.

6.6.4. Strengths and limitations

In Switzerland, private diagnostic laboratories operate on a regional or national level and predominantly serve the practices of general practitioners and medical specialists. The study did not consider hospital-based laboratories as their patient profile generally differs from the patient profile in private practices at the primary care level. Hospitalised patients are likely to be more severely affected by acute gastroenteritis and to undergo more extensive diagnostic testing. Hence, their pre-test probability for a positive *Campylobacter* or *Salmonella* test result is different from that of patients consulting at primary care practices [18]. The catchment population of the participating

laboratories is not known. Therefore, it was not possible to describe the catchment population, adjust for potential changes therein or to estimate any population-based indicators like stool sampling rates. Similarly, we could not assess how well the data of the five participating laboratories represent the whole tested population in Switzerland, given the latter is not known. We could only assess the representativeness of the patient population by comparing "our" positively tested patients with all notified cases (and hence, supposedly, all positively tested patients in Switzerland; Table 6.1 and Table 6.2). From this comparison we conclude that estimated positivity rates are likely to represent accurately the epidemiological trends and situation in Switzerland as median age and the sex-ratio of cases identified in participating laboratories and in cases from the NNSID were comparable.

6.7. Conclusions

The study results support the assertion that the increase in notification rates of campylobacteriosis and the decrease in notification rates of salmonellosis are epidemiological trends in the population. These trends cannot be solely explained by changing test numbers. Still, we believe it is important to continuously assess test numbers or positivity rates to note changes in stool testing frequency that could lead to changes in case numbers seen in the notification system. This becomes especially important in the light of the increasing use of multiplex PCR panels where multiple pathogens are tested simultaneously and, hence, test numbers can change substantially [49]. The annual collection of test numbers of selected notifiable diseases as stipulated under the newly enforced Swiss Epidemics Act

will allow for continuous assessment of positivity rates in the future.

6.8. Acknowledgements

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6.10. Competing interests

The authors declare that they have no conflicts of interest.

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7. ARTICLE 4: Acute gastroenteritis and campylobacteriosis in Swiss primary care: the viewpoint of general practitioners

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7.1. Abstract

Acute gastroenteritis (AG) is frequently caused by infectious intestinal diseases (IID) including food- and waterborne pathogens of public health importance. Among these pathogens, *Campylobacter* spp. plays a major role. Many European countries monitor selected IIDs within disease surveillance systems. In Switzerland, the information on IIDs is restricted to limited surveillance data, while no data is available for AG. We conducted a qualitative study among Swiss general practitioners (GPs) to investigate the case management of AG and campylobacteriosis patients, the associated disease burden and the determinants leading to registration in the National Notification System for Infectious Diseases (NNSID). Interviews were conducted with a semi-structured questionnaire and underwent inductive content analysis based on Grounded Theory. The questionnaire was repeatedly adapted to capture emerging themes until the point of theoretical saturation. GPs perceived AG and campylobacteriosis of little relevance to their daily work and public health in general. According to GP self-estimates each consults about two cases of AG per week and diagnoses a median of five campylobacteriosis cases per year. A large proportion of AG cases receives telephone consultations only and gets medical advice from the practice nurse. Antibiotic therapy is considered useful and stool diagnostics are performed for about a fifth of consulting AG patients. Stool diagnostics ("test") and antibiotic therapy ("treat") are interrelated and follow four strategies: "Wait & See", "Treat & See", "Treat & Test", and "Test & See". AG case management is diverse and includes different triage steps. A small proportion of AG patients have stool diagnostics performed and only positive tested patients are reported to the NNSID. As a result

severe cases and cases with a history of travel abroad are overrepresented in the NNSID. The use of multiplex PCR panels in routine diagnostics likely leads to improved case management and higher case numbers in surveillance systems.

7.2. Keywords

campylobacteriosis, acute gastroenteritis, primary care, general practitioner, Switzerland

7.3. Introduction

Acute gastroenteritis (AG) is characterised by diarrhoea (watery, bloody), vomiting, fever, abdominal pain and cramps, nausea, and dehydration that occur in different combinations and with varying degrees of severity [1-3]. Those suffering from AG are frequently affected by infectious intestinal diseases (IID) caused by a wide range of gastrointestinal pathogens like viruses, bacteria and other parasites [1, 4, 5]. Food- and waterborne pathogens such as *Campylobacter* spp. and *Salmonella* spp., for example, are of particular public health concern as they can lead to disease outbreaks in addition to causing sporadic cases [6-8]. For this reason, many IID causing pathogens are monitored in most European Union (EU) countries and in Switzerland [9, 10]. The Swiss National Notification System for Infectious Diseases (NNSID) monitors a range of food- and waterborne pathogens including *Campylobacter* spp., *Salmonella* spp., *Shigella* spp. and enterohaemorrhagic *Escherichia coli* [9]. Among these, the most frequently notified IID in Switzerland is campylobacteriosis. Since 2006, a dramatic increase in case notifications has been observed, with an all-time high of almost

8500 notified cases in 2012 [11]. Increasing trends in case notifications were also observed in the European Union (EU) [10] e.g. England and Wales [12] or Germany [13] and in the United States of America (US) [14]. The NNSID is the only source of routine information on IIDs among the Swiss population, but it does not cover syndromic surveillance of AG, nor does any other surveillance system.

The overall aim of the NNSID is to allow for the early detection of disease outbreaks and health threats from infectious diseases to initiate timely interventions for disease control. Additionally, the system supports a continuous assessment of existing preventive measures. Only laboratory-confirmed cases of notifiable IIDs are reported to the NNSID. Reported case data include the patient's personal data (name or initials, address or place of residence, sex, age), the applied diagnostics, the diagnosing laboratory and the physician in charge [9]. However, except for enterohaemorrhagic *E. coli*, the NNSID does not collect associated clinical information such as onset of disease, signs and symptoms, progression of disease, case management, hospitalisations, risk exposures or risk factors for IIDs [9]. In addition to insufficient knowledge on the clinical presentation of IIDs, the actual burden of IIDs and AG at the primary care level and the population level are unknown. To assess the disease burden from laboratory-based surveillance data at both levels, it is crucial to know the patients' health care seeking behaviour and the physicians' case management including diagnostic practices. The lack of such information considerably impedes ability of the NNSID to capture minor epidemiological trends and interpretation of its data. The aims of this qualitative study among Swiss general practitioners (GPs), were to investigate the case management of AG and

campylobacteriosis patients, to assess the influence of patient's health care seeking behaviour and of GPs' clinical decision making on surveillance data and to collect estimates on the incidence of AG and campylobacteriosis at the primary care level.

7.4. Materials & Methods

7.4.1. Questionnaire development

We developed a semi-structured questionnaire for face-to-face interviews that was informed by the study objectives, expert opinions and relevant literature. The questionnaire was divided into two parts. The first part covered *GPs' perception of AG and campylobacteriosis;* that is, the perceived magnitude of the burden of AG and campylobacteriosis, incl. semi-quantitative estimates, relevance to public health, the clinical presentation (signs and symptoms) in daily practice, patients' health care seeking behaviour (motives and processes), and the patients' profile as it relates to risk behaviours and risk groups. The second part, *Case management*, focused on the case management of AG and campylobacteriosis by evaluating diagnostic practices and treatment approaches (incl. influencing factors and logic behind the action) and reasons for related decisions, like referral to a specialist or hospitalisation.

7.4.2. Interviewer training and pilot testing of questionnaire

Pilot and study interviews were conducted by three female social scientists (SF, MZ and SH) and one male epidemiologist (PJB), between May and August 2013. The interviewers received multiple trainings in qualitative interviewing techniques from a senior medical anthropologist (JMR). Pilot testing of the

questionnaire consisted of a preliminary interview with a key informant (senior GP), followed by five test interviews in German (four) and French (one). After the pilot, the questionnaire was re-structured accommodating the common procedure during the medical consultation with a patient with AG. The pilot indicated that the variety of determinants and approaches for symptomatic treatment are rather limited. Therefore, the questionnaire rather focused on examining the complex determinants and approaches for antibiotic therapy.

7.4.3. Recruitment of GPs and interview procedure

GPs who had managed campylobacteriosis patients in a previous case-control study [15] but were otherwise not actively engaged, were invited for an interview for the purpose of the current study. In addition to those 146 German-speaking and 29 French-speaking GPs of the case-control study [15] we purposely recruited six French-speaking GPs for the study to better represent the French-speaking area of Switzerland. GPs were invited with an information letter sent by postal mail. After the anticipated receipt of the information letter, GPs were contacted by telephone and the study and study objectives were described. Verbal informed consent was obtained and an appointment for the interview arranged. The interview was conducted at a place of the GP's choice, which was usually in his or her own practice. Interviews generally lasted for 20-40 minutes and were tape recorded and transcribed.

7.4.4. Data analysis

Data analysis followed the principles of inductive content analysis as required by Grounded Theory and was performed with Weft-QDA software (http://pressure.to/qda/). Upon comple-

tion, interviews were immediately transcribed and iteratively analysed, while data collection was ongoing. This approach allowed us (i) to capture emerging themes that could be included in subsequent interviews, (ii) to refine the question guide and (iii) to evaluate the saturation process. Codes for data analysis were continuously developed and assigned to GPs' narratives. All interviews were coded by a senior medical anthropologist (JMR). Theoretical saturation of themes and factors was eventually reached and study results were discussed at length by the research team. Semi-quantitative estimates of the perceived magnitude of AG and campylobacteriosis and the rates for requesting faecal specimens are given as the reported median and range.

7.4.5. Ethics statement

The work presented in this article and the previous case-control study [15] formed a project mandated by the Swiss Federal Government studying the epidemic increase of human *Campylobacter* spp. infections in Switzerland. Over the last decade notification rates for campylobacteriosis had not only steadily increased between 2005 and 2012 but also weekly notification rates peaked annually at the turn of the year. In 2011/2012 weekly notifications increased extraordinarily twofold compared to the previous and following weeks [11]. In concert with the general epidemiological trend this situation was categorised as an epidemic threat by the Federal Government. In response the Federal Office of Public Health (FOPH) commissioned the project for the winter 2012/2013 enforcing the Swiss Epidemics Act (SR 818.101 EpG). Projects conducted under the Epidemics Act do not require ethical approval. Hence, we did not seek approval from an ethical committee for the study but conducted the study in line with

the Declaration of Helsinki. Participating GPs provided verbal informed consent. They received an information letter of the FOPH and were subsequently contacted by telephone. During the telephone conversation interviewers explained again the purpose of the study and repeated the content of the information letter. GP's were subsequently formally asked to participate and their response check marked on the consent form. We did not obtain written informed consent as the interviews focused solely on GPs' professional views about the subject matter and not on any personal aspects or data of individual patients. The GPs' personal data were anonymised and they did not receive any financial compensation for their participation.

7.5. Results

7.5.1. Characteristics of participating GPs

In total, 69 GPs participated in the study (51 German-speaking and 18 French-speaking). The participation rate among GPs from the previous case-control study was 36.0% (63/175). Of the study participants, 13 (18.8%) were female and 56 (81.2%) were male. The majority (62) of interviewed GPs had specialised in general internal medicine, while five specialised in paediatrics, one in anaesthesia and one in urology. The latter two also provided primary health care. The median professional experience of GPs was 23 years (range: 3-39 years) and the median number of patients consulted per GP per week (as estimated by the GPs) was 138 (range: 32-300). Slightly more than half of the interviewed GPs (38/69) worked at a practice located in a semi-urban community, and practices located in

urban and rural communities accounted for 30.4% (21/69) and 14.5% (10/69) of the sample.

7.5.2. Perception of acute gastroenteritis and campylobacteriosis

Nearly all interviewed GPs considered AG in Switzerland to be of little relevance for the patient, uncommon in daily practice and of minor public health importance in Switzerland (Table 7.1). In contrast, GPs highlighted that AG plays an important role in travel medicine and patients with a travel history. Interviewed GPs estimated observing a median of 2 cases of AG per week (range: 0-10 cases per week) and a median of 5 (range: 0-52) laboratory-confirmed cases of campylobacteriosis each year. GPs highlighted that the real number of campylobacteriosis cases is higher than that indicated by laboratory-confirmed cases due to patients' health care seeking behaviour (not all AG patients contact a GP) and GPs' testing behaviour (not all AG cases are tested). The general perception was that, *Campylobacter* spp. has surpassed *Salmonella* spp. as the primary cause of bacterial diarrhoea in Switzerland, compared to the 1990s. Campylobacteriosis cases occur in waves or phases throughout the year and usually peak during the summer months and between December and January. GPs explicitly linked the summer peak to barbequing and the winter peak to traditional consumption of meat fondue (Table 7.1).

Table 7.1: Perception and burden of acute gastroenteritis and campylobacteriosis in Swiss primary care.

Participant	Quotes
SFY12	*"I have the impression that they [campylobacteriosis and AG] are not such a public health problem. Because I do, if I have them, if I discover them...I treat them. I don't have the impression that they…in any case for me…they are not a problem for me."*
MZ20	*"(...) Diarrheal diseases only become problematic when there is an electrolyte and fluid imbalance. Most at risk are children. (...) But all in all, it is not a problem. Diarrheal diseases are generally self-limiting."*
MZ20	*"So, first of all, I do not diagnose every campylobacter case or every bacterial diarrhoeal case. I only conduct targeted testing. I do not do routine testing in the case of diarrhoea. This means that I certainly miss some of the cases."*
SF02	*"Indeed. Before, the main problem was Salmonella. I have rarely seen Shigella. Very rarely. Nowadays, campylobacter is more common."*
SF01	*"In summer, it can be [observed] during the barbeque season, it [barbeque] is a fostering element."*
MZ01	*"One can see this after every festivity day. So after Christmas, people show up with campylobacter infections. This is due to the poultry. Fondue chinoise [meat fondue] is stretched out with poultry."* *"After the fondue chinoise season there are increasing campylobacter infections, yes."*
PJB16	*"Mostly it is fondue chinoise or barbeques. That is the classic. Nowadays it is rarely eggs or sauces compared to earlier times, but fondue chinoise is really classic.*

GPs agreed on the basic signs of bacterial AG, particularly for campylobacteriosis: symptoms like abdominal pains and cramps or fever appear abruptly and the patient feels and presents as very ill (Table 7.2). Nausea and vomiting were also mentioned but occur less frequently. Some GPs also mentioned pain in the limbs and headache. Campylobacteriosis was seen as a self-limiting disease, easy to treat, and generally not dangerous for peoples' health (Table 7.1). However it can lead to a severe, painful and disturbing health condition that prevents people from working (Table 7.2). GPs recognised the importance of AG and campylobacteriosis for vulnerable patients such as infants, the elderly, or individuals suffering from comorbidities. Campylobacteriosis can affect anyone, independently of age, sex or socio-economic status. However, young adults and middle-aged people appear to be affected more frequently than the rest of the population, and especially more frequently than vulnerable groups. The perceived risk factors for contracting campylobacteriosis mentioned were: handling and eating raw or undercooked poultry, travelling and eating "unsafe" food, eating out in canteens or restaurants, barbecuing, consuming meat fondue with poultry or ready-to-eat salads and working in the food sector. Campylobacteriosis patients are generally unable to work for several days to more than one week (Table 7.2). The patient's general condition is the main criterion for sickness certification and duration of sick leave. Other medical factors linked to occupation (physical or nonphysical activities; activities that can put others at risk) or social factors (like pressure by the employer or the patients themselves) also play a role.

7.5.3. Health care seeking behaviour and medical encounters at the primary care level

GPs reported on patients' individual health care seeking behaviour. Individuals affected by AG consult their GP within several hours to days after the onset of symptoms. Factors accounting for prompt or delayed patient consultation included perceived severity, pain and distress, past experiences, attitude towards coping with disease, health insurance deductible or the need for a medical certificate. Up to 60% of all AG-related enquiries lead to telephone consultations only, without a face-to-face consultation at the practice.

Table 7.2: Clinical presentation and risk groups for campylobacteriosis.

Participant	**Quotes**
PJB17	*"It's [symptoms of campylobacteriosis] for sure relatively fast appearing diarrhoea, watery diarrhoea, nausea, frequently fever. So they are really doing badly for a few days."*
MZ13	*"They [campylobacteriosis cases] mostly have fever. But it is mostly not very high. Whereby this also occurs for viral infections....The patients have also a bad general condition. Blood [in stool] I don't see so often. (...) The patients simply feel bad. When one only has a gastro-intestinal flu, one doesn't feel fit. One also has to run to the toilet all the time. But somehow, people with campylobacter really look very bad. (...)They are very pale and almost collapse."*
MZ01	*"Campylobacteriosis goes across all the social strata, all generations, across everything."*
PJB21	*"No, it [the risk group] is less children, mostly age groups from 20-25 to 60-65 years, this middle group. Less so children and older people."*

Table 7.2 continued

Participant	Quotes
PJB16	*"Until they [the patients] start to improve a little after three to four days, until they are healthier again it goes approximately one week. Then they return to work, except if they have a physical work, then, it might need a little bit longer. But people working in the office or students can go back to work after a week – still a little impaired, not completely normal yet. Then it gradually improves."*
PJB14	*"Independent of the stool test, the patient is anyway ill for three to five days and can't go for work. For patients working in the food sector, maybe even ten to fourteen days. The employers don't really like it because it is a long time."*
PJB05	*"Another reason [for treating with antibiotics] is the importance of the working position of the patient. Some really need to go to work, others do not. Some ask for it [antibiotics]."*

Thus, practice nurses play a key role in evaluating the severity of disease, filtering patients for consultations at the practice and providing appropriate medical advice on the telephone. Several physical (e.g. severity), psychosocial (e.g. anxiety, mutual trust), and situational (e.g. GPs' workloads) factors can favour either telephone or face-to-face consultations. After the first consultation and with appropriate measures taken, most GPs either schedule a follow-up appointment (usually by phone but sometimes at the medical practice) or ask patients to call if the symptoms do not improve. The follow-up serves as a means for evaluating the course of disease and for establishing further actions if needed. GPs' workloads can be an obstacle to routine follow-up. Medical treatment is either concluded pas-

sively, i.e. patients do not contact the GP again, or actively at a follow-up consultation.

7.5.4. Diagnostic and treatment approaches

Routine consultation of an AG patient starts with history taking, including assessment of potential risk exposures followed by a clinical examination and point-of-care diagnostics (e.g. C-reactive protein (CRP) level). Faecal specimens for diagnostic purposes (mainly stool-cultures for *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp.) are requested for a median of 18% (5-60%) of AG patients depending on the general condition, fever, blood in faeces, elevated CRP level e.g. >100 mg/l, prolonged disease duration, relevant co-morbidities, patient's occupation and a positive history of ingesting risky food or of travel (Table 7.3).

Table 7.3: Diagnostic approaches for AG cases among Swiss GPs.

Participant	Quotes
MZ23	*"For each patient, I first make an anamnesis. I ask him since when has he had it. When did it start? Have you eaten something special? Have you done something special? Have you been abroad? Just the anamnesis. After this, the first impression of the patient. When there is massive diarrhoea, you can see that the patient is suffering. An important symptom is fever. Febrile diarrhoea has to be looked at differently. (…) Then I usually take CRP and blood status. Harmless diarrhoea has mostly a CRP of 20 to 40. But campylobacter have often 100, 120. Sometimes, they also have a leucocytosis. And when I have a suspicion, I request a stool examination."*
MZ19	*"Fever, bad general condition and when the patient himself says that he feels bad. Then I do a blood test, so*

Table 7.3 continued

Participant	Quotes
	CRP and leucocytes. I only check stool bacteriology when the values are clearly increased."
PJB06	*"An anamnesis revealing a risk situation. I say it like this, did he have a risk situation, did he eat eggs, or poultry products or mozzarella or such products somewhere, so farmer products (...) or does he have fever?"*
MZ16	*"In fact, there are two reasons for which one generally makes a stool examination: If the patient really feels ill and miserable. (...) As a general rule, I then give Imodium. When the patient has taken it correctly, and it doesn't work, then I might do a stool test. Then there is a second group: Patients who were abroad. For these patients, it is possible that I primarily do a stool test. (...) Then there is a third group, where I primarily do a stool examination. When the patients come from an old people's home and one knows that there are already several people who fell ill."*

Symptomatic treatment of AG, including antimotility drugs and oral rehydration therapy for simple cases or intravenous rehydration therapy for severe cases, is very common (Table 7.4). Antibiotic therapy plays only a secondary role due to the self-limiting nature of most AG cases. Nevertheless, antibiotic therapy is considered useful but prescribed cautiously. Its indication depends on disease severity, general condition, fever, inflammation parameters, occupation and partially on stool diagnostic results (Table 7.5). GPs mostly prescribe ciprofloxacin and to a lesser extent erythromycin or specific classes of antibiotics, depending on the stool diagnostic result. Most GPs were concerned about potential antibiotic resistance of gastrointestinal bacteria. However, only some remembered

experiencing this problem in their medical practice (Table 7.5). GPs were aware that frequent prescription of antibiotics is positively associated with the occurrence of antibiotic resistance. However, many also consider antibiotic therapies as very helpful for individual treatment, even if not medically indicated, to shorten disease duration or to ameliorate symptoms, for example.

Table 7.4: Symptomatic treatment approaches for AG cases among Swiss GPs.

Participant	**Quotes**
MZ11	*"So primarily, I administer probiotics. At first, I focus on nutritional establishment and [recommend] the intake of fluids with light meals and without any dairy products for two, three days. Like this, one manages the patient slowly. This is standard for me."*
PJB18	*"There is the "solution of thirds". (...) one third orange juice, one third black tea and one third mineral water, heavily sugared. (...) It contains everything, potassium in the orange juice, bicarbonate in the mineral water and you have fluid and sugar. (...) [it] is a cheap electrolyte solution."*
PJB02	*"And then only if...someone has 12 stools per day, I also give antidiarrhoeals. This is something that relieves the symptoms. But otherwise, in the first 3 days, cleaning of the intestine belongs to the body's self-healing processes."*
PJB06	*"So what I mean, what I sometimes do, I give someone an infusion. When somebody is prone to collapsing and has low blood pressure with nothing risky otherwise. Then we do an infusion here or at home. This I indeed like to do, I like to offer this."*
PJB21	*"They do essentially get better and the fever decreases faster if one gives an infusion and puts the fluid balance a little back in order."*

Table 7.5: Prescription of antibiotic therapy for AG cases and the perception of antibiotic resistance.

Participant	Quotes
MZ23	*"If somebody feels really sick and has a high fever, I may give him antibiotics quicker than recommended. (...) But on the other hand...if somebody has a fever of 39 degrees for two days and diarrhoea, you don't leave him to wait for another two, three days. With these cases, I am relatively easy in giving antibiotics."*
PJB17	*"The indication of antibiotics is generally not due to the test result campylobacter, but rather due to the symptomatology"*
MZ18	*Interviewer: "When do you give antibiotics?"* *"If there is extremely high fever and there are extremely high inflammation values, a CRP of 100 or higher."*
PJB14	*"If I don't know the pathogen yet, I empirically give ciprofloxacin."* *Interviewer: "And after you get the test result?"* *"If it is Campylobacter jejuni, I change to a macrolide"*
MZ15	*"In fact, I almost always treat with ciprofloxacin. I attended a tropical course. There I have heard that resistances are building slowly and that erythromycin products would be better. But up to now, I have always had good experiences with ciprofloxacin."*
PJB02	*"The resistance problem is known. Often there is a quinolone-resistance and then macrolides have to be used. It is only a matter of time until resistances also appear there."*
PJB18	*"Yes I had one single case that did not react to it [ciprofloxacin] ...with campylobacter. There, I had to do a second culture with an antibiotic resistance profile. Then it worked, indeed with azithromycin and not with ciprofloxacin."*

7.5.5. The interplay of stool diagnostics and antibiotic therapy

Initiating stool diagnostics ("Test") is interrelated with antibiotic therapy ("Treat") and follows four distinct approaches to acting and reacting in specific medical, social and physical situations (Table 7.6). GPs can lean towards "Treat & See", "Treat & Test" or "Test & See", and some can "Wait & See" longer than others. Few respondents openly refused an individual approach or adhered to one of these approaches only. The approaches "Wait & See" and "Treat & Test" appeared to be preferred.

Table 7.6: Diagnostic and antibiotic therapy approaches among Swiss GPs.

Approach	**Quotes**
Wait & See	PJB08: *"Waiting doesn't mean omitting. Watchful waiting as it is called. It is a pleasant fact that, in general, a lot of problems that we are confronted with in general medicine are self-limiting. For this reason, I do not have to make a big effort concerning diagnostics. One decides based on the evidence (observing the course of the disease) and says: 'Come again in two days'. Mostly they have to come again for a medical certificate. Or I tell the patient to report within a certain period if it doesn't improve."*
	MZ18: *"Basically, one goes ahead step by step. First, one observes. One waits. One leaves it open. One only does a stool culture when diarrhoea persists. Not for every patient."*
	Interviewer: *"So the self-healing tendency plays a role?"*
	MZ18: *"Exactly. One waits, often for one week or so. But when the pains are extreme or it takes longer, then we take a stool culture."*

Table 7.6 continued

Approach	Quotes
Treat & See	MZ17: *"I am convinced that for 99% of the cases, we don't know the disease agent. We treat with a broad spectrum antibiotic. I cannot make a throat smear for every patient with sore throat (...). I think this is not the objective of a general practitioner."* Interviewer: *"So in the end you treat blindly. So, independent of a test result."* MZ18: *"Yes, exactly. This is in our science not unusual. One applies a broad spectrum antibiotic. (...) For a lung infection, for example, you of course do not know whether a patient has this or that bacterium. This is of no interest to me in the general practice. And in general, it does not help the patient either. If you make a culture then you have the result maybe next Wednesday or Thursday. When you must send the sample you have to consider that the patient has pains and inflammation values for the next four, five days. What is the examination good for? It costs the patient money. In the deductible-system the patient pays, without any use."*
Treat & Test	MZ03: *"And then there is such a thing ... there is such a cookbook rule, if there is bloody diarrhoea, or febrile diarrhoea. After doing stool bacteriology I give mostly ciprofloxacin. I say: "You go home first, then you fill the container, and then you swallow these tablets". And this has shown quite good results. (...) And I say he should not take the tablets beforehand, otherwise we do not know what it is and we have no diagnosis, if it does not get better. (...) And I know it [test result] within four days. "Usually you [the patient] get better. But if you do not feel better, we know which bug it is."* MZ15: *"Mostly, one also does a CRP, in order to determine whether it is a bacterium or a virus. (...)*

Table 7.6 continued

Approach	Quotes
	Depending on the result of the blood examination, I give him [the patient] a tube to take home. I always say then that it costs a lot of money. If you feel better, we don't need to send it. One has to treat anyway before one has the result. (...) it is practically always blind treatment. It is rare that the laboratory calls and we have not yet treated. It is then rather a confirmation that something is there. I, in fact, almost always treat with ciprofloxacin. (...) When I have the impression that the patient does not necessarily want to know it, I take the stool sample and I start treatment. When he gets better, we don't send it." MZ19: *"When a patient comes with this psycho-social pressure, for example he has to work, then you do give him antibiotics. Then I don't wait until I receive the results. I treat immediately."*
Test & See	PJB03: *"When the patient says he hasn't improved at all, the test result is there, maybe against expectation…of campylobacter, and he says: 'I don't get better at all', he has still stomach cramps, diarrhoea and so on, then I treat him"* Interviewer: *"So it might take some time until you get the test result. What is the influence of this in your treatment?"* PJB23: *"Generally none. In the first phase, the treatment is independent of the stool sample."* Interviewer: *"In the first phase. What do you do then with a positive result?"* PJB23: *"Let's say it is salmonella or campylobacter positive, it doesn't mean that they get ciprofloxacin. It simply means that one keeps an eye on them. I look how fast they recover and follow-up after a week, checking inflammation indicators."*

Table 7.6 continued

Approach	Quotes
	Interviewer: *"So a positive test result doesn't always indicate an antibiotic use or so?"* PJB23: *"No. (...) A young healthy person can overcome these diseases without antibiotics, they are not necessary. Second, there is a risk that we will have more chronic carriers if we give antibiotics. For salmonella this is known, they recover faster but they remain longer carriers, really for a long time and this is what I want to avoid."*

Wait & See: This approach seems to be the standard starting point for most AG episodes. It is based on the principle that symptoms of AG including campylobacteriosis disappear after two to five days. It is mostly applied when the episode is recent and mild, or if the patient is in good general condition. Practice nurses evaluate the patient by telephone and decide if there is a need for a consultation or if the patient should wait out the disease's progression. Diet, rehydration and symptomatic treatment recommendations are provided at this stage.

Treat & See: Few GPs reported treating AG with antibiotics without requesting a faecal specimen. The underlying logic is that there is no need to know the exact cause of AG for a successful treatment, particularly if there is indication of a bacterial infection, such as an elevated CRP level. Other reasons were: the costs of stool diagnostics, wish to reduce the duration of suffering and infeasibility of requesting a faecal specimen (if the patient has to travel or the episode occurs just before the weekend, for example). The approach is a pragmatic

one, focused on patients' wellbeing and against the perceived norm for cautious use of antibiotics.

Treat & Test: Antibiotic therapy starts before knowing the stool diagnostic result but after faecal specimen collection. It can then be modified upon receiving diagnostic results. This approach implies that empirical treatment usually works and that stool diagnostics are helpful for the post-diagnostic adaptation of antibiotic therapy. GPs' responses indicate the need to start antibiotic therapy immediately due to social (e.g. the patient has to work) and medical considerations (e.g. bad general condition). Reasons for applying this approach include the possibility of redirecting treatment if indicated, and considering public health aspects (e.g. if the patient works in the food sector or in health care).

Test & See: This approach implies that antibiotic therapy only starts if indicated and after knowing the stool diagnostic result. However, antibiotics are only indicated if bacterial pathogens are identified and symptoms persist or the patient's general condition deteriorates. Then the approach transforms to "Test and Treat" and the patient receives the pathogen-specific antibiotic therapy. GP's applying this approach seek to avoid unnecessary and empirical 'best-guess' antibiotic therapies.

7.5.6. Referrals

Generally, GPs manage AG patients themselves at their practices. Complex cases of AG are referred to a specialist (gastroenterologist, specialist for infectious diseases, specialist in tropical and travel medicine) or a hospital. Reasons for referring a patient to a specialist include the development of persistent or chronic gastroenteritis (e.g. diarrhoea persists several weeks, prolonged blood in faeces) or no response to the

usual treatments. A specialist in travel medicine is specifically approached if gastrointestinal problems persist after travelling abroad. Hospitalisation of AG patients is rather uncommon. Hospital referrals occur in case of bad general condition, severe dehydration, fear of sepsis, suspicion of diverticulitis or appendicitis or if vulnerable patients suffer from severe AG. They also occur in cases where patients cannot manage at home due to lack of social support (e.g. elderly people living alone) or travel (e.g. tourists staying in a hotel).

7.6. Discussion

A qualitative study among 69 GPs in Switzerland on the clinical presentation and case management of acute gastroenteritis and campylobacteriosis showed that GPs see around two patients with AG per week and a median of 5 campylobacteriosis cases per year. However, AG patients can also treat themselves at home, sometimes with medical advice from the practice nurse. Campylobacteriosis and AG are perceived as having little relevance for general public health, daily clinical practice and the average patient. Case management in the form of antibiotic therapy and stool diagnostics follows four approaches: "Wait & See", "Treat & See", "Treat & Test" or "Test & See". GPs request faecal specimens for stool diagnostics from 18% of AG patients and prefer empirical antibiotic therapy before stool diagnostic results are available over result-based antibiotic therapy.

7.6.1. The burden of acute gastroenteritis and campylobacteriosis

GPs generally observe that, among causes of IIDs, *Campylobacter* spp. has surpassed *Salmonella* spp. in the last

20 years. This is confirmed by the trends of campylobacteriosis and salmonellosis case numbers reported to the NNSID [11]. Similar trends in notification rates were observed in the EU [10] e.g. Wales [16] whereas in the US the incidence of *Salmonella* spp. remained higher than for *Campylobacter* spp. [14, 17]. NNSID data also support GPs' impressions that young adults and middle-aged people are more frequently affected [11]. More prevalent exposure risks among these groups, such as traveling abroad, eating out and preparing food themselves, as stated by GPs, could be responsible for increased case numbers. However, data to support this assumption are not yet available for Switzerland.

The described seasonality of campylobacteriosis cases is reflected in the NNSID data [11]. Two distinct peaks of campylobacteriosis, one during summer months and one shorter peak over the festive season in December and January, lead to more primary care attendance. The summer peak of campylobacteriosis case notifications is observable throughout Europe [10]. The winter peak has been described in detail for Switzerland and Germany and is also observable in European notification data [10, 11, 13]. GPs associated the frequent consumption of meat fondue over the festive season in winter with increased campylobacteriosis case numbers. Indeed, meat fondue consumption was found to be the major risk factor for the winter peak of campylobacteriosis in Switzerland, as it is tradition to consume it at Christmas and New Year times [15]. The association of the summer peak with the barbeque season is plausible as barbequing meat provides many occasions for undercooking and re- and cross-contamination [18]. Studies in Switzerland [19] and Germany [20] showed higher *Campylobacter* spp. contamination rates of chicken meat

during summer months. Additional drivers for infection could also be more frequent recreational water activities or travels in summer, both risk factors that have been previously described for campylobacteriosis [18, 21-23]. GPs also observed that consultations due to AG occur in a clustered manner, with alternating case-free weeks and then several cases occurring in a single week. This might be due to small, local epidemics of viral IIDs. Switzerland does not have routine syndromic surveillance of AG, which would allow investigations of temporal and seasonal AG trends. This would be desirable, as other European countries such as France have had positive experiences with routine syndromic surveillance of AG [24].

7.6.2. The influence of patients' health care seeking behaviour on NNSID case numbers

Many AG affected individuals do not contact a GP at all or only get advice by telephone, depending on their health care seeking behaviour. GPs are aware that this leads to an underestimation of the IID burden at the primary care level and has - together with case management approaches - an influence on NNSID case numbers. This has already been described for other disease surveillance systems [5, 25, 26]. However, patients suffering from a bacterial gastrointestinal infection appear to be more likely to consult a GP than patients with a viral gastrointestinal infection [5, 27]. In the Netherlands, national GP guidelines recommend telephone consultations by practice nurses to deal with simple AG cases to reduce the number of consultations and stool diagnostics [28]. In Switzerland, the active promotion of telephone consultations for patients with mild AG could help to reduce health care expenditures, which are among the highest in the world [29]. According to study GPs, severely affected patients often directly consult the emer-

gency department of a hospital, whereas the average AG case is dealt with at the practice and is rarely referred to a specialist or hospital. This is comparable with other findings reporting 8.5% of GPs hospitalising an AG patient during the seven days preceding the interview [30]. However, hospitalised AG patients suffering from an IID are likely to undergo intensive diagnostics and, hence, will not be missed by the NNSID if diagnosed with a notifiable disease.

7.6.3. The influence of diagnostic approaches on NNSID case numbers

The GPs' self-estimated proportion of requesting faecal specimens for 18% of patients is comparable to other studies where rates vary between 4.3% and 50% [25, 28, 31-33]. Individual rates differed strongly among the GPs interviewed. The observed heterogeneity seems to be rather common and has also been observed among English GPs [31]. It is likely related to GPs' individually perceived usefulness of stool diagnostic results for case management and the patient populations they serve. This highlights the need to systematically estimate the faecal specimen testing rate to assess the disease burden of notifiable IIDs at the primary care level from NNSID case numbers.

The determinants for requesting a faecal specimen, as found by this study, are similar to those found in other studies [28, 30-32, 34-36] and are consistent with published recommendations on the clinical management of AG cases [4, 37]. Additionally, our study showed that factors related to the health system (e.g. health insurance deductible or duration of stool diagnostics) also influence the decision to perform stool diagnostics. An important determinant for performing stool diagnostics was the

patient's CRP level. An elevated CRP level is considered indicative of a bacterial infection, making distinct stool diagnostics more likely. Arguments for this criterion were the limited treatment possibilities for viral causes of AG and the need to know the bacterial cause for targeted antibiotic therapy. Requesting a faecal specimen based on a positive travel history, as observed in our study, may not always be appropriate as stool diagnostics are not recommended for watery or traveller's diarrhoea due to the low yield of recognising pathogenic bacteria (e.g. enterotoxigenic *E. coli*) in the sample [37]. In accordance with others [32, 34], we observed that mainly severely affected patients or patients with a history of travelling abroad undergo stool diagnostics in Switzerland, likely leading to a high proportion of severe and imported cases in the NNSID. Imported and domestic cases cannot be distinguished in the NNSID for most IIDs as laboratory reports do not include any information on exposure. Hence, the possible overrepresentation of imported cases should be considered when interpreting NNSID data as they are of less relevance for assessing national disease transmission and interventions. To improve the interpretation of NNSID data it would be advisable to include patients' recent travel history on case notifications to differentiate between imported and domestic cases, similarly to other European countries [10]. The preference of severe cases for stool diagnostics also explains the perceived high severity of disease by notified cases (7 on a rating scale from 1 = not severe, to 10 = very severe) and the high antibiotic prescription rate (61.6%) found in our case-control study on determinants of campylobacteriosis in Switzerland [15].

When the study was conducted, the first diagnostic laboratories had introduced multiplex polymerase chain reaction (PCR) panels for IIDs in routine diagnostics. Up until then, the routine stool diagnostics applied to AG patients were stool-cultures for *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. [38]. Only a few of the interviewed GPs had already deliberately ordered stool diagnostics with this new diagnostic tool. Multiplex PCR panels will likely affect case numbers in the NNSID if they are routinely deployed by Swiss GPs. They have a higher detection rate of IIDs in faecal specimens compared to conventional methods due to a higher sensitivity and the wide range of IIDs tested simultaneously [39-41]. Greater sensitivity will likely lead to increased case numbers of the routinely tested and notifiable IIDs (*Campylobacter* spp., *Salmonella* spp. and *Shigella* spp.) within the NNSID. Similarly, stool diagnostics for other specific notifiable IIDs, e.g. enterohaemorrhagic *E. coli,* were mainly requested for AG patients with a certain suspicion such as blood in faeces. More tests will be conducted for these IIDs because faecal specimens investigated by multiplex PCR panels are tested for the same range of IIDs independent of the suspected cause which could lead to the detection of more cases.

7.6.4. "Treat & See" and "Treat & Test" for targeted antibiotic therapies

The GPs in our study considered stool diagnostics and antibiotic therapy useful for managing AG cases. The "Wait & See" approach, including symptomatic treatment, is the approach applied most often to AG case management among Swiss GPs. This is in line with published case management guidelines for simple AG cases [1, 4, 37, 38]. From a public health perspective, the "Treat & See" and "Treat & Test" approaches are

questionable as both can lead to untargeted antibiotic therapies. Similar to the "Wait & See" approach, the "Treat & See" approach additionally contributes to the underreporting of IID cases in the NNSID.

Studies showed that in a large proportion of faecal specimens from AG patients no or viral pathogens are identified and, hence, disease is likely not caused by bacteria [42-45]. The aforementioned approaches bear a high probability of incorrectly treating those patients with antibiotics. In the era of increasing antibiotic resistance among gastrointestinal bacterial pathogens, untargeted antibiotic therapy should be avoided. Additionally, antibiotic therapy needs to be carefully considered for its potentially counter-productive effects for bacterial infections such as *Escherichia coli* O157:H7, for example [46, 47]. Timely antibiotic therapy is desirable to reduce disease duration and to increase the wellbeing of the patient in cases of severe AG (e.g. with febrile dysentery with an indication of a bacterial cause such as an elevated CRP level or based on food history) [4, 36, 37].

A major reason for applying the "Treat & See" and "Treat & Test" approaches is the perceived long duration until culture-based stool diagnostic results are available. Therefore, fast molecular diagnostics for IIDs such as multiplex PCR panels would enable the physician to initiate timely and targeted antibiotic therapy and are desirable [36, 39]. When these are widely deployed, "Test & See" could become the preferred approach to AG case management over "Wait & See". The fast availability of diagnostic results will also permit a shift to "Test and Treat", including a specific and timely treatment approach based on stool diagnostic results. GPs in our study were prone to change their treatment approach based on the stool diagnos-

tic results. However, immediate antibiotic therapy will remain the therapy of choice for severely affected patients to assure the wellbeing of the patient.

Swiss surveillance data shows that *Campylobacter* spp. is the most frequent bacterial cause of IIDs [11]. But around 50% of tested *Campylobacter* spp. isolates from humans are resistant to fluoroquinolones according to Swiss study and surveillance data [48, 49]. Therefore, the prescription of ciprofloxacin (fluoroquinolone) for AG cases with a suspected bacterial cause, as mentioned by interviewed GPs, is questionable. Azithromycin (macrolide) would be the drug of choice for treating campylobacteriosis and is also appropriate for treating salmonellosis and shigellosis [4, 37]. A similar level of resistance of *Campylobacter* spp. to fluoroquinolones is observed in EU countries, but varies considerably between countries. As a result, the European Food Safety Authority and the European Centre for Disease Prevention and Control no longer consider fluoroquinolones appropriate for routine empirical treatment of human campylobacteriosis [50]. In summary, empirical antibiotic therapy for the treatment of AG patients should be avoided whenever possible and macrolides (e.g. azithromycin or erythromycin) are recommended for empirical treatment if it is indicated for the wellbeing of the patient.

7.6.5. Discussion of research approach

A wide range of GPs was accessible through the previously conducted case-control study [15] and provided an ideal and unique opportunity to assess the case management of AG and campylobacteriosis patients and the associated disease burden at the primary care level. A qualitative research approach was

chosen due to the lack of information on AG and campylobacteriosis at the primary care level in Switzerland and the unknown willingness of GPs to participate. This allowed researchers to collect information on all aspects of interest nearly independent of the participation rate, but limited the possibilities for quantifying some of the results. Semi-quantitative estimates on the disease burden by GPs allowed a first assessment of the unknown disease burden at the primary care level. Such estimates of disease burden should be interpreted with caution as they are influenced by several factors. The progression of the interview, the time point of the interview in regard to disease seasonality or the GP's importance alluded to the disease can lead to over- or underestimation. The large sample of 69 GPs from the German- and French-speaking parts of Switzerland increased the geographical and paradigmatic variation represented, leading to an improved saturation of investigated themes. Additionally, interviewers followed-up on various topics with different levels of detail during the interviews due to different backgrounds of interviewers, resulting in even wider variation and fast theoretical saturation. We lack interviews with GPs from the Italian-speaking part of Switzerland but we assume that – due to the minor differences between French- and German-speaking GPs – differences in case management and disease burden would only slightly differ from our study results. It might appear that the study generated only general knowledge, but it is the first and largest study to date providing a comprehensive overview of the applied case management, disease burden and determinants leading to disease notification in Switzerland.

7.7. Conclusions

The health care seeking behaviour of AG patients leading to primary care attendance, and GPs' varying case management approaches including triage steps and stool diagnostic frequency need to be taken into account when interpreting NNSID data. Patients severely affected by AG or who travelled abroad are more frequently seeking care and are hence, overrepresented among campylobacteriosis cases notified in the NNSID. As a result, the NNSID monitors the epidemiological situation of notifiable IIDs of more severe disease expressions rather than the entire spectrum of notifiable IID suffering in the Swiss population. The current transition from routine culture-based stool diagnostics to routine multiplex PCR panels in diagnostic laboratories will likely counter act such a skewed epidemiological data situation. This expectation is mainly driven by the higher sensitivity of these molecular diagnostics and by a possible increase in the number of stool diagnostics conducted due to faster availability of diagnostic results. Therefore, the anticipated increase in case numbers will not necessarily reflect an epidemiological trend in the Swiss population and should be considered when communicating NNSID data to stakeholders. Knowledge on which diagnostic methods are available and actually applied is important for public health authorities to accurately interpret NNSID data, particularly during the transition period. Consequently, further research should be conducted on the impact of routine multiplex PCR panels on the composition and number of cases registered in the NNSID and possible changes in case management including antibiotic therapies.

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8. ARTICLE 5: Acute gastroenteritis in primary care: a longitudinal study in the Swiss Sentinel Surveillance Network, *Sentinella*

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8.1. Abstract

Purpose: Acute gastroenteritis (AG) leads to considerable burden of disease, health care costs and socio-economic impact worldwide. We assessed the frequency of medical consultations and work absenteeism due to AG at primary care level, and physicians' case management using the Swiss Sentinel Surveillance Network "Sentinella".

Methods: During the one-year, longitudinal study in 2014, 172 physicians participating in "Sentinella" reported consultations due to AG including information on clinical presentation, stool diagnostics, treatment, and work absenteeism.

Results: An incidence of 2146 first consultations due to AG at primary care level per 100,000 inhabitants in Switzerland was calculated for 2014 based on reported 3.9 thousand cases. Physicians classified patients' general condition at first consultation with a median score of 7 (1=poor, 10=good). The majority (92%) of patients received dietary recommendations and/or medical prescriptions; antibiotics were prescribed in 8.5%. Stool testing was initiated in 12.3% of cases; more frequently in patients reporting recent travel. Among employees (15-64 years), 86.3% were on sick leave. Median duration of sick leave was four days.

Conclusions: The burden of AG in primary care is high and comparable with that of influenza-like illness (ILI) in Switzerland. Work absenteeism is substantial, leading to considerable socio-economic impact. Mandatory infectious disease surveillance underestimates the burden of AG considering that stool testing is not conducted routinely. While a national strategy to reduce the burden of ILI exists, similar comprehensive prevention efforts should be considered for AG.

8.2. Keywords

Acute gastroenteritis; sentinel surveillance; primary health care; Switzerland; antibiotics; infectious intestinal diseases

8.3. Background

Acute gastroenteritis (AG) is a common disease in humans worldwide. Case definition varies between studies and countries but mostly includes signs and symptoms of diarrhoea, vomiting, nausea, abdominal cramps or pain, fever, and blood or mucus in the stool [1-5]. AG can be caused by a wide variety of pathogens ranging from viruses and bacteria to protozoa and other parasites [5]. A study in Austria identified norovirus, *Clostridium difficile* and rotavirus as the most frequent aetiological agents in patients consulting general practitioners (GPs) due to AG [4]. Norovirus, rotavirus, sapovirus and *Campylobacter* spp. were the most common organisms among cases of infectious intestinal disease (IID) presenting to the GP in the United Kingdom [6].

Bacterial pathogens causing AG which have to be reported to the National Notification System for Infectious Diseases (NNSID) include positive laboratory tests for *Campylobacter* spp., *Salmonella* spp., and *Shigella* spp. as well as clinical and laboratory reports of positively tested patients with *Listeria monocytogenes* and enterohaemorrhagic *E. coli* (EHEC). None of the above mentioned viral causes of AG are notifiable in Switzerland [7]. As a result, the NNSID underestimates the true burden of AG because of non-notifiable pathogens causing AG. Additionally, not every patient suffering from AG presents to a physician (under-ascertainment) and, the physician does not always initiate stool

diagnosis to investigate the aetiology of the illness (underreporting) [8, 9]. Hence, what is seen in the Swiss mandatory notification system represents only an incomplete picture of the burden of disease due to AG. The determinants of under-ascertainment or underreporting have been described for several countries but not for Switzerland: In the UK, it is estimated that every case of IID reported to national surveillance represents 9.5 cases presenting to a GP or 147 cases in the community [6]. In the Netherlands, 8% of patients with an IID visited a physician [10]. Van Cauteren *et al.* [11] estimated that of 115 community cases of campylobacteriosis and 20 community cases of salmonellosis one case is reported to the surveillance system in France. However, it has to be noted that the French surveillance systems are voluntary for these two pathogens.

Swiss routine surveillance data suggest an increasing frequency of campylobacteriosis and a decreasing frequency of salmonellosis [12]. More than half of campylobacteriosis patients in a case-control study approached a physician within three days after onset of symptoms and 14.5% were hospitalised [13]. A subsequent qualitative survey among primary care physicians described case management approaches including treatment strategies and stool diagnostic testing behaviours from the physicians' perspective for patients with AG [8]. Four main approaches were identified of which only two – the "test & wait" and the "test & treat" approaches – include stool specimen testing and, hence, would result in case registration in the mandatory disease surveillance system in case of a positive test outcome. Healthcare costs for AG in Switzerland were estimated at €29-45 million annually [14].

In Switzerland, we lack data on under-ascertainment and under-reporting. Under-ascertainment refers to people not seeking healthcare and, hence, not being captured by the surveillance system as defined by Gibbons *et al.* [9]. Under-reporting is defined as people seeking healthcare but not being reported because of under-diagnosis – not diagnosing or misdiagnosing the infection or pathogen – or under-notification – failure to report positive diagnoses [9].

This study within the Swiss Sentinel Surveillance Network, Sentinella, aimed at understanding the lower levels of the burden of illness pyramid and addressing the incidence of AG in a broader context. Specifically, the study aimed at understanding determinants of under-diagnosis by (i) estimating the incidence and burden of AG seen at the primary care level, (ii) describing the physicians' case management (diagnostics, treatment) of AG patients and (iii) estimating the work loss due to AG of cases presenting to a physician.

8.4. Methods

A one-year, longitudinal study in Sentinella, during the year 2014, was conducted asking physicians to report cases of AG on a weekly basis (later referred to as data from the "weekly questionnaire"). A questionnaire about disease characteristics, stool testing, and treating strategies was completed for a subset of cases (later referred to as "supplementary questionnaire").

8.4.1. Study setting

Sentinella is a voluntary surveillance system and research network of primary care physicians existing since 1986 which is operated and funded by the Federal Office of Public Health

(FOPH). Physicians are organised in six geographical regions, each having its representative within the Sentinella steering committee. The steering committee, consisting of physicians and researchers of academic primary care institutes, meets regularly to set the research priorities and to decide on submitted projects. Our study was accepted to run in 2014.

During the Sentinella-year 2014, 172 physicians (47% general practitioners, 37% internists and 16% paediatricians; thereafter referred to as "Sentinella-physicians") covering entire Switzerland were active in the network. In Switzerland, 6930 physicians were practicing in the ambulatory sector with the main specialty "general internal medicine" (summarising general practitioners and internists) or "paediatrics" in 2014 according to the Swiss medical association FMH [15]. Among these, 86% were practicing in general internal medicine and 14% in paediatrics.

8.4.2. Case definition

A case of AG was defined as (a) a patient consulting a Sentinella-physician for the first time during the illness episode and suffering from diarrhoea (at least 3 watery or pasty stools daily; for at least 24 hours but 14 days the longest) likely due to an infectious cause or (b) a patient consulting a Sentinella-physician for the first time during the illness episode with vomiting and abdominal cramps without significant diarrhoea, likely due to an infectious cause. Patients were excluded if diarrhoea was due to a known gastrointestinal disease (e.g. Crohn's disease, ulcerative colitis, coeliac disease), medication intake (e.g. antibiotics) or food intolerance. Also patients with persistent diarrhoea (>14 days) or if vomiting was due to pregnancy were excluded.

8.4.3. Data collection

Sentinella-physicians reported basic data on patients suffering from AG on a weekly questionnaire, and more detailed data for a subsample of patients through a supplementary questionnaire which were available in German and French. German versions of the weekly (part on AG only) and supplementary questionnaires are available online (see electronic supplementary material 1 of Schmutz *et al.* (2017a)). The questionnaires were piloted with 10 general practitioners.

The weekly questionnaire included information on sex, date of birth, stool testing and hospitalisation of all AG patients (see case definition) seen in the corresponding week. The supplementary questionnaire contained additional questions on employment status, date(s) of symptom onset and consultation(s), signs and symptoms until first consultation, general condition, antibiotic and symptomatic treatment, stool testing, sick leave, hospitalisation, sequelae, and selected risk exposures in the seven days preceding symptom onset.

Weekly questionnaires were available on paper and electronically according to the Sentinella standard procedure (method chosen by physician). More than half of the Sentinella-physicians reported electronically, all others reported on paper. Supplementary questionnaires were available on paper only. While weekly paper questionnaires were sent to the FOPH once a week by postal mail according to routine procedures, Sentinella-physicians were asked to send the supplementary questionnaire as soon as they considered the corresponding case as "completed". Weekly electronic questionnaires were entered directly into the Sentinella-database by the Sentinella-physician.

Information available on Sentinella-physicians included the physicians' specialty and location of practice. Sentinella-physicians additionally reported the total number of daily physician-patient contacts (PPCs) on the weekly questionnaire. A PPC is defined as each consultation independent of place (in practice or as domiciliary visit) and time (during or off consultation-hour or on emergency service) and serves as denominator for calculating disease incidence rates.

8.4.4. Subsample for supplementary questionnaire

We expected that each Sentinella-physician would report around two AG cases per week based on the pilot testing and discussions with physicians. Assuming that 150 physicians report during 48 weeks, 14,400 cases were expected during the 1-year-study period. In order to reduce the anticipated work load for Sentinella-physicians but still reaching an appropriate sample size allowing for estimates with acceptable precision we decided to apply the supplementary questionnaire to a subsample of cases. The targeted subsample size was set at 4800 cases (one third of all cases). A sampling scheme was defined whereby every Sentinella-physician had to complete supplementary questionnaires during four consecutive weeks four times a year (=16 weeks per physician per year). We randomly assigned each Sentinella-physician a sampling pattern with sampling periods distributed equally over the year, hence not allowing for two consecutive sampling periods.

Case numbers in the first half of the study period were lower than expected necessitating the sampling scheme to change to full sampling. Starting from week 25 (starting on 14.06.2014) supplementary questionnaires had to be completed for every AG patient until the end of the study.

8.4.5. Data entry and analysis

Weekly questionnaires on paper forms and all supplementary questionnaires were entered into the electronic Sentinella-database at the FOPH. Ten percent of supplementary questionnaires were randomly selected for double entry to assess data quality. Double entries of questionnaires were compared and discrepancies were eliminated by re-checking against the original paper forms.

Cases of Sentinella-physicians who reported PPC for less than 75% of the weeks during the study period, i.e. <39 of 52 weeks were excluded from data analysis. This rule and cut-off value for regularly reporting physicians is standard for analyses of Sentinella data. Additionally, cases not fulfilling the case definition or cases where the Sentinella-physician spontaneously indicated a final diagnosis not in agreement with infectious AG were excluded from the analysis of supplementary questionnaire data.

Data of weekly questionnaires were analysed descriptively. We calculated the average number of cases per Sentinella-physician and week and the number of initial consultations due to AG per 1000 PPCs per week. Additionally, we estimated the incidence and total number of first consultations due to AG at the primary care level for 2014 in Switzerland by the standard extrapolation of the Sentinella system which is described elsewhere [16].

Due to the mid-study change in the sampling scheme of supplementary questionnaires, analyses of the supplementary questionnaire data were weighted according to the sampling probability: information from the supplementary questionnaire of cases reported during the first half of the study period was

analysed using a sampling weight of 3.25 (as each physician was required to submit a supplementary questionnaire for each case seen during 16 of 52 weeks; 1/(16/52)=3.25) while information reported during the second half had a sampling weight of 1 (supplementary questionnaire required for every case). Point-estimates including 95% confidence intervals (CI) and interquartile ranges (IQR) for medians are reported for weighted analyses. Data from supplementary questionnaires were analysed descriptively and differences were assessed for significance by weighted, univariable logistic regression. For all analyses involving employment status, only patients aged 15-64 years were considered. Data was analysed and represented graphically using Stata 13.1 (StataCorp.). Maps were created using ArcGIS 10.2.1 for desktop (Environmental Systems Research Institute, Inc., Esri).

8.5. Results

8.5.1. Physician and patient characteristics

In total, 3867 cases of AG were reported on weekly questionnaires by 172 participating Sentinella-physicians. After exclusion of cases reported by not regularly reporting Sentinella-physicians (130 cases) and for other reasons (3 cases), 3734 cases were used for analyses of weekly questionnaires. 2200 cases were retained for the analyses of supplementary questionnaires. The detailed inclusion process is described in Figure 8.1.

Out of 172 physicians registered in the Sentinella system in 2014, 154 of the regularly reporting physicians reported at least one case of AG on the weekly questionnaire. Over the whole

study period, individual physicians reported up to 400 cases (median: 17, IQR: 7-29).

A total of 144 physicians submitted at least one supplementary questionnaire of a case fulfilling the case definition (Figure 8.1). The subsample of cases with supplementary questionnaires was comparable to cases reported on weekly forms in terms of basic patient characteristics (Table 8.1).

Median age of AG cases was 21 years (IQR: 5-41 years). Children, adolescents and young adults (age groups <1, 1-4, 5-9, 10-14, 15-19 and 20-29 years) were overrepresented among AG cases consulting a physician compared to the frequency of those age groups in the general Swiss population for both genders (Figure 8.2). In the age group of 10-14 year olds, males were more frequent than females. In adults, female cases aged 20-29 years were most frequently reported while in males the 30-44 year age group predominated.

8.5.2. Burden of AG at primary care level

Each week, 15-139 cases (median: 69, IQR: 54-80) were reported (Figure 8.3). Case numbers were highest during the first weeks of the year (maximum in week 4) and decreased thereafter. A median rate of 5.4 first consultations due to AG per 1000 PPCs per week (IQR: 4.6-6.7) was observed. The notifications correspond to 2146 first consultations due to AG at primary care level per 100,000 inhabitants or 174,610 first consultations due to AG in Switzerland in 2014 using the standard extrapolation method of the FOPH for Sentinella data. Incidence (of first consultations) by Sentinella-region is displayed in Figure 8.4.

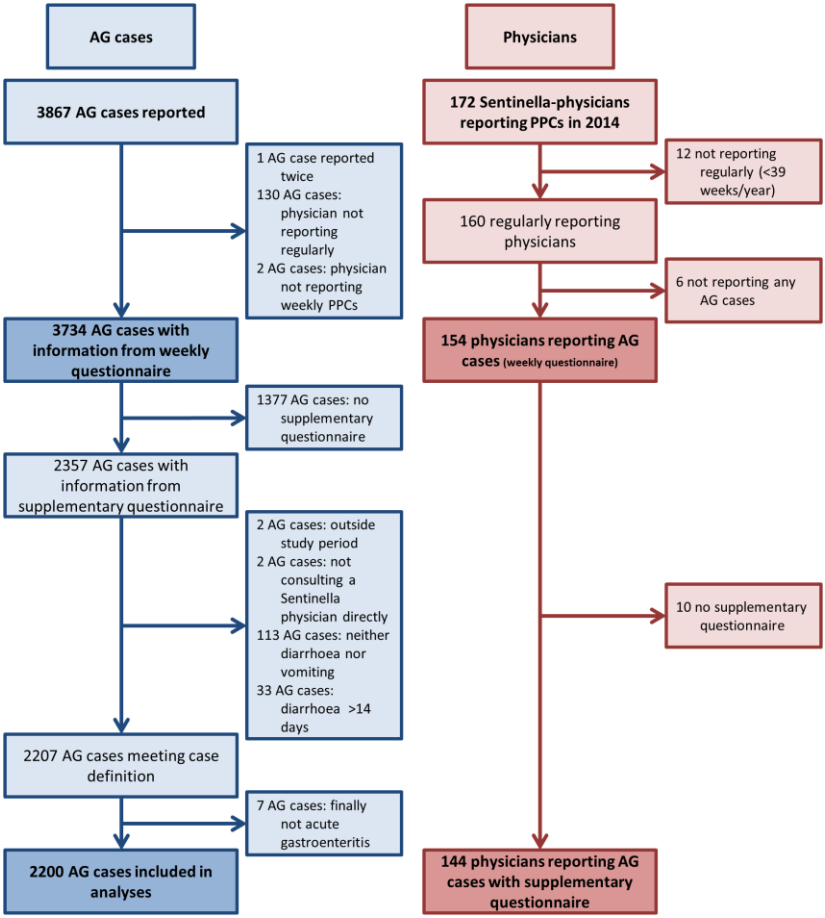

Figure 8.1: Study profile of notified cases and reporting physicians. Acute gastroenteritis study, Swiss Sentinel Surveillance Network, 2014.

AG acute gastroenteritis

PPC physician–patient contact

Table 8.1: Basic characteristics of acute gastroenteritis cases reported on the weekly and supplementary questionnaires by physicians from the Swiss Sentinel Surveillance Network in 2014

	Weekly form	Supplementary questionnaire
Cases included in analysis (N)	3734	2200
Proportion of male cases, % (95%-CI)	50.2	50.6 (48.0-53.3)
Median age, years (IQR)	21 (5-41)	22 (6.0 [95%-CI: 2.6-9.4] – 43.0 [95%-CI: 38.1-47.9])
Physicians' area of specialisation		
General medicine, % (95%-CI)	35.3	37.5 (29.9-45.8)
Internal medicine, % (95%-CI)	26.7	27.6 (21.1-35.4)
Paediatrics, % (95%-CI)	38.0	34.9 (25.7-45.3)
Stool testing initiated, % (95%-CI)	10.9	12.3 (10.1-14.8)
Hospitalised, % (95%-CI)	2.0	2.7 (1.9-3.7)

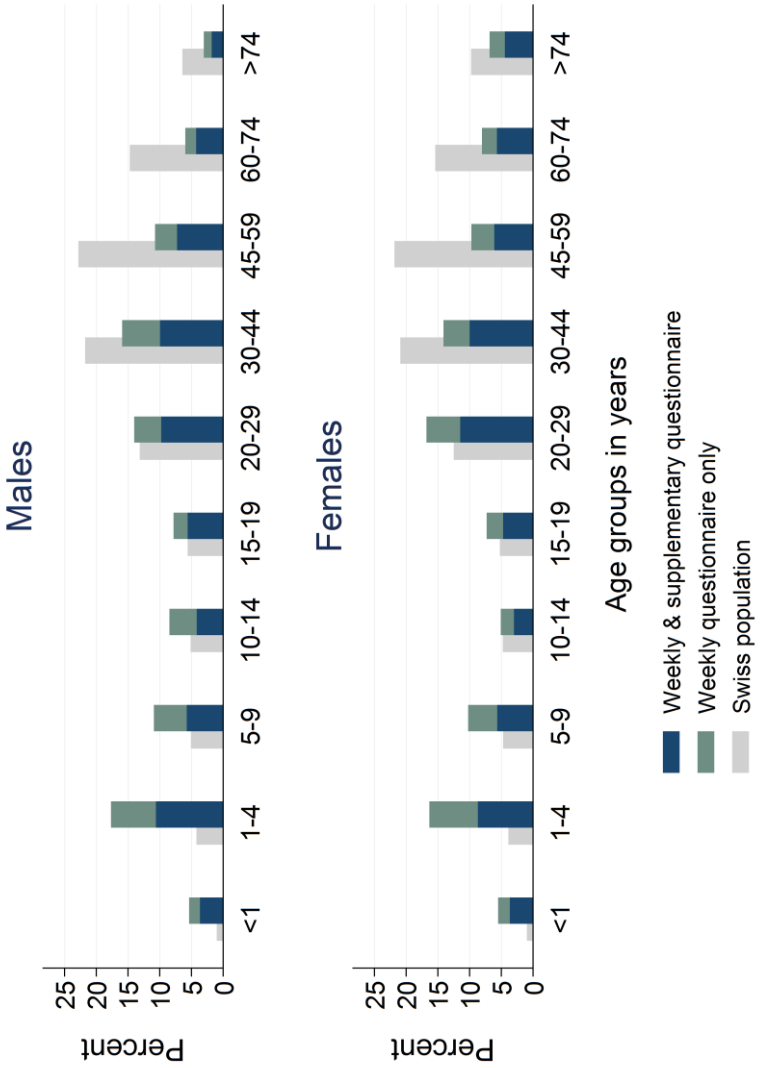

Figure 8.2: Age distribution by sex among acute gastroenteritis cases reported by Sentinella-physicians on weekly and/or supplementary questionnaires, Swiss Sentinel Surveillance Network, 2014.

Age distribution of Swiss population (official numbers, [17]) added for comparison

8.5.3. Health care seeking and clinical presentation

The median time from symptom onset to first consultation was 2 days (95%-CI: 2.0-2.0, IQR: 1.0 [95%-CI: 1.0-1.0] – 3.0 [95%-CI: 2.4-3.6]). The majority of patients (87.9% [95%-CI: 85.6-89.9]) suffered from diarrhoea (Table 8.2). Loss of appetite was reported for 63.5% (95%-CI: 58.4-68.4), abdominal pain or cramps for 61.1% (95%-CI: 57.0-65.1), nausea for 60.4% (95%-CI: 56.6-64.1) and vomiting for 57.5% (95%-CI: 54.3-60.7) of patients. Less frequently reported signs and symptoms included flatulence, fever, dehydration and headache.

The majority of patients consulted the Sentinella-physician only once (79.6%, 95%-CI: 76.5-82.4) (Table 8.2). The median general condition of cases as reported by Sentinella-physicians at the time of first consultation was 7 (95%-CI: 6.5-7.5, IQR: 5.0 [95%-CI: 4.5-5.5] – 9.0 [95%-CI: 8.5-9.5]) on a rating scale from 1 (poor) to 10 (good). Overall, 86.3% (95%-CI: 83.1-89.0) of employed patients were unable to work. The odds for a good general condition (7 or above) was lower for employed patients compared to unemployed patients although not significantly (Odds ratio [OR] 0.76, 95%-CI: 0.52-1.11, p=0.159).The median duration of sick leave was 4 days (95%-CI: 3.8-4.2, IQR: 3.0 [95%-CI: 3.0-3.0] – 5.0 [95%-CI: 4.5-5.5]). For all except 7 cases the duration of sick leave was below 15 days.

The hospitalisation rate was 2.7% (95%-CI: 1.9-3.7). The highest hospitalisation rate was observed for the >74 year age group (11.5%, 95%-CI: 6.4-19.9) whereas for the remaining age groups the rates were below 4%. For 2.0% (95%-CI: 1.4-2.9) of patients Sentinella-physicians reported sequelae, like dehydration, diverticulitis, or colitis. No deaths due to AG were reported.

Initial consultations per 1000 PPCs per week
10
8
6
4
2
0
Number of notifications per week
160
140
120
100
80
60
40
20
0
1
3
5
7
9
11
13
15
17
19
21
23
25
27
29
31
33
35
37
39
41
43
45
47
49
51
Sentinella-week

Figure 8.3: Acute gastroenteritis cases reported by physicians from the Swiss Sentinel Surveillance Network in 2014 (28.12.2013 – 26.12.2014): weekly case numbers (bars) and number of initial AG consultations per 1000 physician–patient contacts (PPCs, "consultations") per week (line)

Vertical, dashed line: date of change of sampling scheme (from subsample of cases with supplementary questionnaires to supplementary questionnaire for every reported case)

8.5.4. Stool diagnostics and results

Sentinella-physicians reported the initiation of stool specimen testing in 12.3% (95%-CI: 10.1-14.8); in 11.6% (95%-CI: 9.5-14.1) of cases they indicated that the sample was actually sent off (Table 8.3). The odds for stool testing did not differ between sexes ([female vs. male]: OR=1.13, 95%-CI: 0.84-1.50, p=0.423) but differed by age group (p<0.001): The proportion of stool testing was generally higher among older age groups. Paediatricians initiated stool testing less frequently (OR=0.32, 95%-CI: 0.18-0.55, p<0.001) than general practitioners. The odds of initiating stool testing did not differ significantly for internists compared to general practitioners (OR=1.13, 95%-CI: 0.71-1.78, p=0.610).

Even though the questionnaire explicitly asked for the main reason for initiating stool testing, multiple answers were given for 31.0% (95%-CI: 24.9-37.8) of cases. The three most frequent reasons mentioned were protracted course of disease (29.4%, 95%-CI: 21.9-38.2), poor general condition (11.5%, 95%-CI: 6.9-18.4) and due to a specific symptom (9.5%, 95%-CI: 4.6-18.6) when excluding those with multiple answers. When considering also multiple answers, staying abroad before

symptom onset was the third most frequent reason (data not shown).

Travelling within the seven days preceding symptom onset was reported for 9.0% (95%-CI: 7.4-10.8) of cases. Patients with recent travel history were significantly more likely to undergo stool testing than patients not reporting any recent travels (OR=3.60, 95%-CI: 2.47-5.33, p<0.001). Among patients with recent travel history, 30.0% (95%-CI: 22.7-38.6) were tested while for patients without travel to a foreign country in the seven days preceding the symptom onset this proportion was 10.6% (95%-CI: 8.6-13.0). "Staying abroad" was indicated as the main reason for testing for 40.8% (95%-CI: 24.4-59.6) of patients with a travel history. Protracted course of disease was the second most often mentioned reason for stool testing among patients with travel history abroad (17.4%, 95%-CI: 7.2-36.2).

A positive test result was reported for more than one third (35.9%, 95%-CI: 29.2-43.2) of tested patients while for the remaining 64.1% (95%-CI: 56.8-70.8) of patients test results were negative or not specified. The most frequently identified pathogen was *Campylobacter* spp. (50.8%, 95%-CI: 39.2-62.3) followed by norovirus (10.9%, 95%-CI: 5.0-21.9), and *Blastocystis* spp. (9.6%, 95%-CI: 4.0-21.1) (Table 8.3). Other pathogens identified included rotavirus, *Clostridium* spp., *Entamoeba* spp., pathogenic *E. coli*, *Candida* spp., *Salmonella* spp., *Giardia* spp., microsporidia, adenovirus, *Aeromonas* spp. and hepatitis E virus. Two pathogens were identified in 11.5% (95%-CI: 5.4-22.9) of the 98 cases with a positive stool test result.

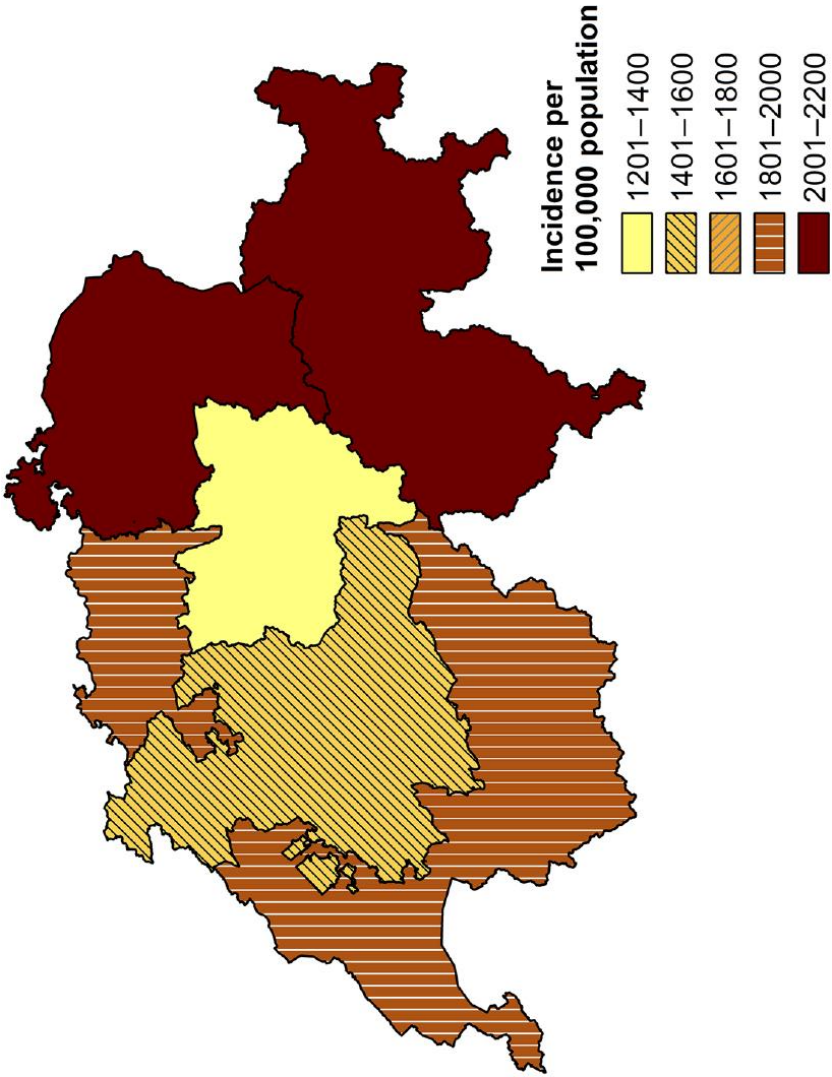

Figure 8.4: Calculated incidence of first consultations due to acute gastroenteritis at primary care level in Switzerland by Sentinella-region, based on standard extrapolation. Swiss Sentinel Surveillance Network, 2014

Note: an outlier (one physician reporting 400 cases) was excluded from this extrapolation by region

Source of map shapefile: Swiss Federal Office of Topography

Table 8.2: Characteristics of cases with acute gastroenteritis at first consultation and number of consultations as reported by primary care physicians from the Swiss Sentinel Surveillance Network, 2014.

	Number of cases [n]	**Percent [%]**	**(95% confidence interval)**
Signs and symptoms until first consultation[a] (N=2200)			
Diarrhoea	1940	87.9	(85.6-89.9)
Diarrhoea with blood and/or mucus	249	10.8	(8.5-13.7)
Loss of appetite	1345	63.5	(58.4-68.4)
Abdominal pain/cramps	1329	61.1	(57.0-65.1)
Nausea	1296	60.4	(56.6-64.1)
Vomiting	1227	57.5	(54.3-60.7)
Flatulence	896	40.6	(35.6-45.7)
Fever	530	25.0	(22.3-27.9)
Dehydration	183	8.5	(6.6-11.0)
Headache	68	3.2	(2.1-4.8)
General condition at first consultation (according to physicians' impression) (N=2115)			
Poor – 1	1	0.09	(0.01-0.6)
2	28	1.1	(0.7-1.9)
3	95	4.6	(3.3-6.4)

Table 8.2 continued

		Number of cases [n]	Percent [%]	(95% confidence interval)
General condition at first consultation (according to physicians' impression) (N=2115)				
	4	177	8.4	(6.2-11.4)
	5	237	10.7	(7.9-14.4)
	6	228	10.1	(8.3-12.3)
	7	318	15.8	(13.6-18.2)
	8	476	23.9	(20.6-27.5)
	9	356	16.5	(13.5-20.1)
Good –	10	199	8.7	(6.3-12.0)
Number of consultations (N=2200)				
	1	1742	79.6	(76.5-82.4)
	2	365	16.4	(14.0-19.2)
	3	75	3.2	(2.4-4.2)
	4	18	0.8	(0.4-1.5)

[a] multiple answers possible

Table 8.3: Frequency of and reasons for prescription of stool diagnostics among acute gastroenteritis patients consulting primary care physicians from the Swiss Sentinel Surveillance Network, 2014.

	Number of cases [n]	Percent [%]	(95% confidence interval)
Stool test initiated (N=2176)	286	12.3	(10.1-14.8)
Stool test performed (N=2176)	272	11.6	(9.5-14.1)
Main reason for stool testing (N=197)			
Protracted course of disease	62	29.4	21.9-38.2
Poor general condition	23	11.5	6.9-18.4
Specific symptom	19	9.5	4.6-18.6
Stay abroad before symptom onset	18	7.8	4.5-13.1
Comorbidity	10	5.3	2.5-10.7
Outbreak investigation	8	5.3	1.6-16.4
Occupation	10	3.8	1.8-8.1
Resident/patient institution	2	2.0	0.5-8.0
Age	2	1.3	0.3-6.2
Contact to animals	1	1.0	0.1-6.8
Contact to ill persons	1	0.3	0.04-2.3
Other reasons (e.g. elevated CRP level, leucocytosis, recent antibiotic therapy)	20	10.5	6.5-16.6
Reason not specified	21	12.2	6.4-22.2
Pathogens identified[a] (N=98)			
Campylobacter spp.	57	50.8	(39.2-62.3)
Norovirus	8	10.9	(5.0-21.9)

Table 8.3 continued

	Number of cases [n]	Percent [%]	(95% confidence interval)
Pathogens identified[a] (N=98)			
Blastocystis spp.	6	9.6	(4.0-21.1)
Rotavirus	5	8.9	(2.9-24.2)
Clostridium spp.	7	7.3	(2.9-17.2)
Entamoeba spp.	4	5.4	(1.7-15.8)
Pathogenic *E. coli*	6	5.3	(2.0-13.1)
Candida spp.	3	4.8	(1.4-15.6)
Salmonella spp.	6	3.8	(1.7-8.2)
Other (*Giardia* spp., adenovirus, *Aeromonas* spp., hepatitis E)	4	4.0	(1.2-12.5)

[a]Two pathogens were identified in 11.5% (95%-CI: 5.4-22.9) of the 98 cases with a positive stool test result

8.5.5. Approaches for symptomatic and antibiotic therapy

In 92.0% (95%-CI: 89.8-93.8) of cases, Sentinella-physicians gave dietary recommendations, or prescribed symptomatic and/or antibiotic treatment. Most commonly, patients were advised to care for fluid replacement by the intake of sufficient tea, broth etc. (58.3%, 95%-CI: 53.0-63.3) (Table 8.4). Distinct rehydration therapies such as electrolyte solution (11.4%, 95%-CI: 7.8-16.4) and infusion therapies (1.7%, 95%-CI: 1.1-2.6) were less frequently prescribed. Symptomatic treatment included probiotics (45.9%, 95%-CI: 39.1-52.8), antiemetics (45.4%, 95%-CI: 40.5-50.4), antidiarrhoeals (28.8%, 95%-CI: 23.6-34.6), analgesics (16.3%, 95%-CI: 12.8-20.5), and spas-

molytics (15.0%, 95%-CI: 11.5-19.2). Antibiotics were prescribed in 8.5% (95%-CI: 6.5-11.0) of cases (Table 8.4).

The Sentinella-physicians initiated stool testing and prescribed antibiotics at the first consultation in 33 cases (unweighted results, Table 8.5). Stool diagnostics revealed presence of a pathogen susceptible to antibiotics in 20 of these cases. No antibiotics were prescribed in 22 cases even though a pathogen which is theoretically susceptible to antibiotics was identified.

The majority of patients receiving antibiotics was treated with quinolones (60.2%, 95%-CI: 48.5-70.9), followed by macrolides, metronidazole, aminopenicillin, trimethoprim/ sulfamethoxazole, cephalosporin and tetracycline (Table 8.4). Two or more antibiotic classes were reported to be used for 8.5% (95%-CI: 4.6-15.2) of cases. No antibiotic class was reported for 1.6% (95%-CI: 0.6-4.4) of cases treated with antibiotics.

Main reasons for the prescription of antibiotic therapy included (suspicion of) bacterial gastroenteritis (41.1%, 95%-CI: 25.0-59.5), duration of illness (9.0%, 95%-CI: 3.4-19.6), a specific symptom (7.2%, 95%-CI: 3.4-14.8) and others (Table 8.4). Sentinella-physicians mentioned several reasons for 23.9% (95%-CI: 16.6-32.2) of the patients despite being asked to indicate only the main reason. When considering also multiple answers, "poor general condition" was the third most frequently mentioned reason for antibiotic therapy (data not shown).

Similar to stool testing, antibiotic prescription was associated with age ($p<0.001$) and with the physicians' specialty ($p<0.001$) but not with sex ($p=0.511$) (data not shown). Again, children and adolescents were less frequently treated with antibiotics compared to adults. Among the >74-year-old age group,

one fifth of cases received antibiotics (20.0%, 95%-CI: 12.8-29.7). Nearly three-quarter of the antibiotic therapies were prescribed at the first consultation (71.3%, 95%-CI: 60.5-80.1). These patients had a lower general condition according to physicians' impression (median: 5.0, 95%-CI: 4.0-6.0, IQR: 4.0 [95%-CI: 3.0-5.0] – 7.0 [95%-CI: 6.0-8.0]) than patients receiving antibiotics later on (median 7.0, 95%-CI: 6.0-8.0, IQR: 5.0 [95%-CI: 4.0-6.0] – 8.0 [95%-CI: 7.0-9.0]) and also suffered slightly more frequently from fever (44.7%, 95%-CI: 34.5%-55.4 *vs.* 38.9%, 95%-CI: 24.0-56.2). However, both differences were not statistically significant. Patients with a recent history of travel had significant higher odds to undergo antibiotic therapy (OR=1.75, 95%-CI: 1.06-2.88, p=0.029).

Table 8.4: Frequency of prescription of antibiotic and symptomatic treatment, and reasons for prescription of antibiotic therapy among acute gastroenteritis patients consulting primary care physicians from the Swiss Sentinel Surveillance Network, 2014.

	Number of cases [n]	Percent [%]	(95% confidence interval)
Antibiotic therapy prescribed (N=2089)	195	8.5	(6.5-11.0)
Antibiotic class prescribed[a] (N=195)			
Quinolone	123	60.2	(48.5-70.9)
Macrolide	30	15.0	(9.3-23.3)
Metronidazole	21	12.8	(7.7-20.5)
Aminopenicillin	22	11.6	(6.3-20.5)
Trimethoprim/sulfamethoxazole	7	4.5	(1.5-12.7)
Cephalosporin	5	3.1	(1.1-8.6)
Tetracycline	1	0.3	(0.0-2.4)
Not specified	5	1.6	(0.6-4.4)
Main reason for prescription of antibiotics (N=195)			
Bacterial gastroenteritis	64	41.1	25.0-59.5
Duration of illness	12	9.0	3.4-19.6
Specific symptom	10	7.2	3.4-14.8
Expecting attitude of patient	6	4.5	1.7-11.6
Poor general condition	6	3.6	1.3-9.2
Immunosuppression	3	3.2	0.9-11.0
High, prolonged fever	5	3.1	1.0-9.3

Table 8.4 continued

	Number of cases [n]	Percent [%]	(95% confidence interval)
Main reason for prescription of antibiotics (N=195)			
Polymorbidity	4	2.7	0.8-8.5
Preventively	3	2.3	0.6-8.5
Other reasons (e.g. elevated CRP level, leucocytosis, co-infection)	22	13.3	7.9-21.6
Reason not specified	14	9.9	5.2-18.2
Recommended symptomatic treatment[a] (N=1909)			
Fluid replacement with tea, broth	1089	58.3	(53.0-63.3)
Probiotics	875	45.9	(39.1-52.8)
Antiemetics	851	45.4	(40.5-50.4)
Antidiarrhoeals	584	28.8	(23.6-34.6)
Analgesics	330	16.3	(12.8-20.5)
Spasmolytics	287	15.0	(11.5-19.2)
Rehydration solution	201	11.4	(7.8-16.4)
Intravenous rehydration	36	1.7	(1.1-2.6)

[a] multiple answers possible

Table 8.5: Time point of prescription of stool testing and antibiotic treatment among acute gastroenteritis patients consulting primary care physicians, Swiss Sentinel Surveillance Network, 2014.

Note: unweighted results. Cases with missing information on (date of) antibiotic prescription and/or (date of) stool test were excluded.

	No antibiotics prescribed	**Antibiotic prescribed at first consultation**	**Antibiotic prescribed at follow-up consultation**
No stool test initiated	1713	70	11
Stool test initiated at first consultation	68	33	7
thereof with positive result for a pathogen susceptible to antibiotic therapy[1]	12	20	5
thereof with positive result for a pathogen not susceptible to antibiotic therapy[1]	4	1	
Stool test initiated at follow-up consultation	56	3	22
thereof with positive result for a pathogen susceptible to antibiotic therapy[1]	10	2	11

Table 8.5 continued

	No antibiotics prescribed	Antibiotic prescribed at first consultation	Antibiotic prescribed at follow-up consultation
Stool test initiated at follow-up consultation	56	3	22
thereof with positive result for a pathogen not susceptible to antibiotic therapy[a]	4		1

[a] Not considering possible antibiotic resistances and treatment recommendations

8.6. Discussion

This study underscored that acute gastroenteritis is common in Swiss primary care: extrapolated annual consultation numbers (175,000 first consultations) are comparable to those of influenza-like illness (ILI) during an influenza season (varying between 107,000 and 276,000 ILI cases in the last three seasons [18-20]). The majority of patients is symptomatically treated and does not require multiple consultations. However, most episodes of AG lead to a sick leave of several days, though the physician-assessed general state of the patients is considered as "fairly good". Stool specimen testing is not systematically conducted and antibiotic therapy is applied to less than 10% of patients.

8.6.1. Multiple factors influence physicians' decision making

Sentinella-physicians reported more than one reason for stool testing in a third of cases despite being explicitly asked for the main reason in the questionnaire. This suggests that a combination of factors plays a role in decision-making. The same holds true for the prescription of antibiotic treatment where in around a quarter of cases several reasons were mentioned albeit physicians were asked to indicate the main reason. The reasons mentioned most frequently for stool testing – namely protracted course of disease, poor general condition, due to a specific symptom and a history of recent travel – are in line with findings from other studies: three of the aforementioned four factors (all except "specific symptom") were also mentioned by GPs participating in a qualitative study in Switzerland [8] and in a study from Northern Ireland and the Republic of Ireland [21]. The Irish study further reported that stool testing is frequently prescribed if the illness is associated with an outbreak or if the physicians suspect a link with a particular consumed food item or food premises (pub, restaurant, take away). Similarly, a qualitative study among GPs in the UK found that long duration of illness, recent travel, blood in the stool, patient being unwell and exclusion of an infectious cause were the reasons mentioned most frequently for stool testing [22]. Factors most strongly associated with requesting a stool culture were bloody diarrhoea, diarrhoea lasting more than 3 days, and a diagnosis of AIDS in a postal survey among physicians in the United States [23].

Considering that protracted course of disease and poor general condition were mentioned most frequently as main reasons for stool testing in our study, the difference in reported general condition at the time of first consultation among tested and

untested patients seems rather small (median 7.0, 95%-CI: 6.5-7.5, IQR: 5.0 [95%-CI: 4.5-5.5] – 8.0 [95%-CI: 7.5-8.5] *vs.* median 8.0, 95%-CI: 7.5-8.5, IQR: 6.0 [95%-CI: 5.5-6.5] – 9.0 [95%-CI: 8.5-9.5]). One explanation for this is that a "protracted course of disease" does not necessarily equate with a poor general condition but simply reflects the lack of improvement of symptoms with an average or fairly good general condition. Most of the aforementioned studies [8, 21, 22] acknowledge that decisions for testing are subjective and depend on the physicians' experiences and attitudes.

AG, whether of viral or bacterial origin, is usually self-limiting [5]. Antibiotics are mainly recommended for severely affected patients and are most effective if given early [5, 24, 25]. "Bacterial gastroenteritis" was most frequently mentioned as main reason for antibiotic therapy in our study. We cannot judge whether this reasoning was based on laboratory results or on physicians' experience. However, only two cases with positive stool test results for pathogens not susceptible to antibiotics were prescribed antibiotics in our study. The second most common reasoning for antibiotic treatment, namely duration of illness, was also reported by Swiss GPs in an extensive qualitative assessment [8]. A study from Poland concluded that factors associated with antibacterial drug administration included the work environment of the physician (working in large practices and hospital wards favoured antibiotic prescription compared to small practices), presence of fever, or mucus or blood in stool, age of the patient and (rural/urban) residence [26]. Presence of fever, or mucus or blood in stool could also be a factor leading to antibiotic therapy in our study as the third most frequent mentioned main reason for antibiotic prescription was suffering from a specific symptom.

Some 62% of all cases with a laboratory-confirmed *Campylobacter* infection received antibiotic treatment in our study. This finding is important in the context of antibiotic resistance development. More than half of those patients received quinolones and one third was treated with macrolides – a finding confirming results from an earlier qualitative study among Swiss GPs [8]. Given antibiotic resistance levels for fluoroquinolones as high as 55.3% for human *Campylobacter* isolates in Switzerland in 2014 [27], these studies' findings underscore the need for changes in prescription practise in Switzerland. A similar level of resistance (60.2%) was observed in Europe in 2014 [28]. Consequently, the European Food Safety Authority and the European Centre for Disease Prevention and Control do no longer recommend fluoroquinolones for the empirical treatment of human campylobacteriosis.

8.6.2. Physicians' case management impacts on the mandatory surveillance system

A stool test was performed only for 11.6% of patients consulting a Sentinella-physician due to AG. Of these, 19.8% (95%-CI: 15.1-25.6) had a positive result for a notifiable pathogen. Hence, a very small proportion of 2.3% (=11.6%*19.8%) of AG patients consulting a Sentinella-physician were actually reportable to the mandatory reporting system. This is in line with Swiss physicians' typical treatment pattern for AG of "wait & see", which can be followed by a "treat & see" approach or a desirable (from the perspective of the NNSID) "test & see" or "test & treat" approach based on illness progression [8]. Considering the (main) reasons mentioned for stool testing, patients with a prolonged duration of illness and patients reporting recent travel abroad are likely overrepresented among

notified cases. The proportion of patients with stool testing varies substantially between countries: it was found to be 4.3% or 9.1% in France [29], 6% in Italy [30], 7% in Ireland [31], 12% in the Netherlands [32], 19% in the US [33] and 25% in Denmark [34].

The pathogen most often identified through stool testing in this study (*Campylobacter* spp.) is also the pathogen most frequently reported to Swiss national surveillance. Norovirus, which is not notifiable in Switzerland but in several countries of the European Union, was the second most common identified pathogen.

8.6.3. Mild disease with high socio-economic burden

Physicians rated the general condition of AG patients as relatively good. Nevertheless, a high proportion of 86.3% of employed patients was not able to work due to the illness. Sick leave is considerable with a median of 4 days. The risk of transmission seems to play a subordinate role as a reason for inability to work. Similar findings were reported in a French study where 79% of working patients were on sick leave for a median duration of 3 days [35]. In a Danish study, only 35% of patients with AG reported having missed work or school as a result of illness [34]. However, this Danish study was a population-based study in which only 13% of patients were seen by a physician and/or hospitalised. In our study, we did not observe a difference in time from symptom onset to consultation between employed and unemployed patients (data not shown). This indicates that the need of a medical certificate is unlikely to be a main reason for consultation.

It is well known that some pathogens causing AG are easily transmitted from human-to-human, especially viruses, and con-

tact with diarrhoea patients has been described as a risk factor for AG previously [35, 36]. In our study, 28.6% (95%-CI: 24.9-32.6) of the patients had contact to other people suffering from similar signs and symptoms in the seven days preceding symptom onset. Thus, it is possible that these patients had a common source of infection or transmitted the disease among each other.

In summary, our findings suggest that AG is a common, but generally mild disease which results, however, in a high social and economic burden. The overall financial burden due to AG (including losses in productivity) is likely a multiple of the healthcare costs estimated for Switzerland in the range of €29-45 million annually [14].

8.6.4. Sentinella is invaluable to investigate current public health issues

All information for this study was derived from physicians in the Swiss Sentinel Surveillance Network. This study was specifically set up by the FOPH to clarify current epidemiological questions about gastroenteritis in Switzerland, using a national primary care sentinel surveillance platform.

We consider it a strength of the study to have obtained information on diagnosis and treatment directly from treating primary care physicians. However, the actual duration of sick leave might have been longer or shorter than reported or certified by the physician. Similarly, we could not record the overall duration of the illness as in this study we could not send out follow-up questionnaires at the end of an AG episode.

A limitation of our study is the change in sampling scheme for supplementary questionnaires for the second half of the study

period, especially considering that AG is subject to seasonal variation. However, we believe that changing to full sampling and using weighted analyses to adjust for the change in sampling scheme resulted in more reliable data than continuing without changing the sampling scheme and obtaining far less supplementary questionnaires.

We expected to observe a seasonality of case reports considering the literature [4, 36], results of a previous study [8] and surveillance data [12], with a peak of AG in winter (December-March) and during summer (June-September). Instead we found a decreasing number of initial consultations per 1000 PPCs over the year which we assume is partially due to reporting fatigue of the Sentinella-physicians partaking in the study. This is supported by a survey conducted among Sentinella-physicians in which they were asked about the time required for participating in the sentinel network – in total and for the different research topics. Physicians indicated that the study on AG was comparatively time-consuming although the majority indicated that the total amount of time required for notifying was acceptable [37].

8.7. Conclusion

Not to our complete surprise, this study has shown that acute gastroenteritis is a common disease in Switzerland with consultation frequencies comparable to influenza-like illnesses. AG presented to physicians lead to substantial sick leave in the employed, resulting in considerable socio-economic costs due to productivity loss.

Furthermore, as suspected, the study confirms that the National Notification System for Infectious Diseases captures – if at all

– only a fraction of the scope of the problem (see introduction for currently notifiable diarrhoea-causing pathogens). Hence, the Swiss Sentinel Surveillance Network, Sentinella, represents a very important complementary surveillance instrument to grasp principal dynamics of infectious disease epidemiology at the primary care level.

The FOPH and the Federal Food Safety and Veterinary Office, being responsible to maintain population health and food safety in Switzerland, are currently lacking effective tools for pinpointing and a comprehensive national programme addressing the control of foodborne diseases and AG. While there are efforts to increase food safety and consumer hygiene including campaigns to increase awareness for food and kitchen hygiene among consumers in Switzerland, prevention measures to reduce contamination at food production or retail level are incomplete. Overall, there is an imbalance in national disease prevention and control efforts for AG considering that national strategies to reduce the burden of seasonal influenza – an infection with a disease burden comparable to AG – exist since many years.

8.8. Acknowledgements

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8.9. Ethical statement

This study was conducted under the Swiss Epidemics Act (SR 818.101) and the ordinance on disease notification of humans (SR 818.141.1).

8.10. Conflict of interest

This study was funded by the Federal Office of Public Health, Bern, Switzerland [grant numbers 13.004570, 14.000710 and 15.007090]. MJ and MM are on the staff of the Federal Office of Public Health and participated in their capacities as public health specialists and their function as scientific collaborators within the organisation.

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9. ARTICLE 6: Estimating healthcare costs of acute gastroenteritis and human campylobacteriosis in Switzerland

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9.1. Abstract

Rising numbers of campylobacteriosis case notifications in Switzerland resulted in an increased attention to acute gastroenteritis (AG) in general. Patients with a laboratory-confirmed *Campylobacter* infection perceive their disease as severe and around 15% of these patients are hospitalized. This study aimed at estimating healthcare costs due to AG and campylobacteriosis in Switzerland. We used official health statistics, data from different studies and expert opinion for estimating individual treatment costs for patients with different illness severity and for extrapolating overall costs due to AG and campylobacteriosis. We estimated that total Swiss healthcare costs resulting from these diseases amount to €29–45 million annually. Data suggest that patients with AG consulting a physician without a stool diagnostic test account for €9.0–24.2 million, patients with a negative stool test result for *Campylobacter* spp. for €12.3 million, patients testing positive for *Campylobacter* spp. for €1.8 million and hospitalized campylobacteriosis patients for €6.5 million/year. Healthcare costs of campylobacteriosis are high and most likely increasing in Switzerland considering that campylobacteriosis case notifications steadily increased in the past decade. Costs and potential cost savings for the healthcare system should be considered when designing sectorial and cross-sectorial interventions to reduce the burden of human campylobacteriosis in Switzerland.

9.2. Keywords

Acute gastroenteritis, campylobacteriosis, healthcare costs, Switzerland.

9.3. Introduction

Since 1995 *Campylobacter* spp. has been the most frequently reported gastrointestinal bacterial pathogen in humans in Switzerland [1] and since 2005 in the European Union (EU) [2]. An estimated 9.25 million cases of campylobacteriosis occurred in 2009 in the 27 EU member states, of which around 2% were reported [3]. Havelaar et al. estimated the 'true' incidence rate of campylobacteriosis in these countries at 30–13,500/100,000 population (350/100,000 in Switzerland).

In Switzerland, positive test results for *Campylobacter* spp. have to be notified by diagnostic laboratories to the Federal Office of Public Health (FOPH) since 1988 [4]. In 2012, 8480 campylobacteriosis cases were registered within the National Notification System for Infectious Diseases (NNSID), which is the highest number reported so far [1]. This corresponds to a notification rate of 105 cases/100,000 resident population in Switzerland. The extent to which campylobacteriosis contributes to the public health burden of acute gastrointestinal illness is unknown. In The Netherlands, about twice the population size of Switzerland, approximately 4.8 million cases of gastroenteritis occur annually, whereby 220,000 patients need medical consultation [5].

A study among 69 general practitioners (GPs) concluded a rising awareness of campylobacteriosis as a public health problem in Switzerland (Supplementary material of Schmutz *et al.* (2017b)). Despite its mostly self-limiting nature, the health burden of campylobacteriosis in the Swiss population may be significantly higher than figures from the NNSID indicate. Severe cases and complications such as Guillain–Barré syndrome, reactive arthritis and post-infectious irritable bowel syndrome

amplify the burden of disease and in particular the economic burden [6–8].

The estimated economic burden (equating healthcare costs at large, including, e.g. loss of productivity and/or transportation and other direct and indirect non-healthcare costs) of gastrointestinal infections or foodborne illnesses in high-income countries varies between €14 (Australia [9]) and €1305 (United States [10]) per case in the community ([9–20] in Table 9.1). Thereby, healthcare costs account for €3–155/case in the community [9–20]. This wide range is partially due to heterogeneity in case definitions and definitions of economic burden. The yearly costs for gastroenteritis due to 14 food-related pathogens and associated sequelae in The Netherlands were estimated at around €468 million [11].

For campylobacteriosis, the estimated economic burden per case varies, ranging from €117 (The Netherlands [17]) to €6141 (United States [12]) ([8, 10–12, 17, 20, 26] in Table 9.2). Healthcare costs of campylobacteriosis cases were estimated at €8/case in New Zealand, €82–280 in The Netherlands and €163–253 in the United States ([8, 10–12, 20] in Table 9.2). These numbers are difficult to compare as case definitions and cost items included vary between studies. For example, sequelae due to campylobacteriosis were considered in some studies while in others they were not. Campylobacteriosis-associated acute gastroenteritis (AG) accounts for approximately 108 000 cases/year in The Netherlands, causing annual societal costs of about €81.5 million (including sequelae) [11]. In the EU, campylobacteriosis cases account for expenditures of public health systems and for productivity losses of around €2.4 billion/year according to the European Food Safety Au-

thority [28]. The economic burden highlights the importance of this widespread and common disease.

A quantification of healthcare costs due to AG and/ or campylobacteriosis in Switzerland is lacking so far. Due to the rising number of campylobacteriosis case notifications in recent years, we conducted several studies which aimed at generating a better understanding of the epidemiology of campylobacteriosis in Switzerland. We investigated epidemiological determinants [29], described time trends in notification data [1], the campylobacteriosis-associated illness experience from the patients' perspective [29, 30], the case management strategies of GPs and laboratory positivity rates of *Campylobacter* spp. (Supplementary material of Schmutz *et al.* (2017b)). In concert, these studies indicate that campylobacteriosis is causing a considerable burden of disease which considerably impacts the health system in Switzerland and is likely associated with high costs.

The aim of this study was to estimate the total annual costs for the medical treatment of campylobacteriosis in Switzerland. However, given that available data do not systematically distinguish campylobacteriosis from AG we focused this analysis on available data of both conditions. To the best of our knowledge, this is the first study estimating healthcare costs due to AG and campylobacteriosis in Switzerland.

Table 9.1: Overview of selected studies estimating the cost-of-illness of gastrointestinal or foodborne illnesses

First author, year [ref.]	Nation	Year	Pathogens/disease considered (community cases, unless specified otherwise)	Cases per year	Costs included[a]					Exchange rate used (€1 = …)[c]	Direct healthcare cost, per case (in €)	Direct healthcare cost, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
					Direct healthcare cost	Patient costs (e.g. travel costs)	Productivity losses	Others[b]						
Hoffmann, 2015 [10]	United States	2013	15 foodborne pathogens including long-term disabilities; only domestically acquired and foodborne cases	8 914 713	X		X	X		USD 1·34	155[d]	1384	1305[d]	11 636
Mangen, 2015 [11]	Netherlands	2011	14 foodborne pathogens; including sequelae	4810000	X	X	X			EUR 1	31[d]	147	97[d]	468
Scharff, 2012 [12]	United States	2010	All domestically acquired, foodborne illnesses	47 780 778	X		X	X		USD 1·33	75	3568[d]	806–1227	38 506–58 589
Friesema, 2012 [13]	Netherlands	2009	Gastroenteritis	4 600 000	X	X	X			EUR 1	14[d]–32[d]	63–147	133–151	611–695
Gauci, 2007 [14]	Malta	2004/05	Infectious intestinal disease	164 471	X	X	X			Lm 0·44[e]	72[d]	12	108	17
Abelson, 2006 [15]	Australia	2004	Gastroenteritis due to foodborne illnesses	5 400 000[f]	X		X	X		AUD 1·69	22[d]	118	111[d]	598
Majowicz, 2006 [16]	City of Hamilton, Canada	2001	Acute gastroenteritis	619 334[g]	X		X			CAD 1·39	17[d]	11[d]	66	40
Van den Brandhof, 2004 [17]	Netherlands	1999	Gastroenteritis	4 476 399	X	X	X			EUR 1	14	61	77	345
Roberts, 2003 [18]	England	1994	Infectious intestinal disease	9 400 000[h]	X	X	X			GBP 0·66 (year 1999)	16[d]–44[d]	153–412	109[d]–120	1028–1128
Hellard, 2003 [9]	Australia	1999	Highly credible gastroenteritis	15 173 430	X		X			AUD 1·65	3[d]	46	14[d]	208

Table 9.1 continued

First author, year [ref.]	Nation	Year	Pathogens/disease considered (community cases, unless specified otherwise)	Cases per year	Costs included[a]				Exchange rate used (€1 = …)[c]	Direct healthcare cost, per case (in €)	Direct healthcare cost, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
					Direct healthcare cost	Patient costs (e.g. travel costs)	Productivity losses	Others[b]					
Lindqvist, 2001 [19]	Municipality of Uppsala, Sweden	1999	Foodborne illnesses	500 000[j] (Sweden)	X		X		SEK 8·81	117	58[d]	246	123
Scott, 2000 [20]	New Zealand	1999	Foodborne infectious disease	119 320	X	X	X	X	NZD 2·01	9[d]	1·0	229	27
Karve, 2014 [21]	United States	2010/11	Acute gastroenteritis; only cases consulting a physician, visiting emergency department and inpatient care setting	6 668 944[j]	X				USD 1·36	472[d]	3151	472	3151

[a] Categories represent only a very broad classification of costs included in the studies. Certain items may be included in different categories, depending on the study. For example, transportation cost was sometimes considered as 'direct healthcare cost' (when covered by the health system) and sometimes included in 'patient costs'.
[b] For example, food recalls, or intangible costs for reduced quality of life (intangible costs are monetary representations of pain, suffering and fear which can be obtained through willingness-to-pay studies [22]), or value of statistical life for premature deaths.
[c] Average exchange rates of the calendar year when the study was conducted (as indicated in the column 'year') were used and extracted from [23].
[d] Calculated based on yearly case numbers and either costs per case (for calculating yearly costs) or yearly costs (for calculating costs per case) as reported in the original publication.
[e] Exchange rate as indicated in the original publication (1 Maltese lira = €2·29).
[f] According to Hall *et al.* 2005 [24].
[g] Calculated based on a population size of 490 290 and 126 320 cases/100 000 population as reported in the original publication.
[h] Calculated based on total yearly costs (£742·8 million) divided by total costs per case (£79) as reported in the original publication, rounded to the next 100 000.
[i] According to Norling, 1994 [25].
[j] Sum of estimated annual episodes of acute gastroenteritis in physician's office (5 337 473), emergency department (1 032 064) and inpatients (447 580) as reported in the original publication.

Table 9.2: Overview of selected studies estimating the cost-of-illness of campylobacteriosis

First author, year [ref.]	Nation	Year	Pathogens/disease considered (community cases, unless specified otherwise)	Sequelae considered	Cases per year	Costs included[a]					Exchange rate used (€1 = …)[c]	Direct healthcare cost, per case (in €)	Direct healthcare cost, yearly (in million €)	Total costs per case (in €)	Total yearly costs (in million €)
						Direct healthcare cost	Patient costs (e.g. travel costs)	Productivity losses	Others[b]						
Hoffmann, 2015 [10]	United States	2013	*Campylobacter* spp.; only domestically acquired and foodborne cases	GBS	845 024[f]	X		X	X		USD 1·34	253[d]	213	1710	1445
Mangen, 2015 [11]	Netherlands	2011	*Campylobacter* spp.	GBS, ReA, IBS, IBD	108 000	X	X	X			EUR 1	280[d]	30	757	82
Scharff, 2012 [12]	United States	2010	*Campylobacter* spp.; only domestically acquired and foodborne cases	GBS, ReA	845 024[e]	X		X	X		USD 1·33	163	138[d]	1392–6141	1177–5189
Gellynck, 2008 [26]	Belgium	2004	*Campylobacter*-associated gastroenteritis and sequelae	GBS, ReA, IBD	55 000	X	X	X			EUR 1	n.a.	n.a.	497[d]	27
Mangen, 2005 [8]	Netherlands	2000	*Campylobacter* spp. and sequelae	GBS, ReA, IBD	79 000	X	X	X			EUR 1	82[d]	6·5	261[d]	21
Van den Brandhof, 2004 [17]	Netherlands	1999	*Campylobacter* spp.	Not considered	79 000[f]	X	X	X			EUR 1	n.a.	n.a.	117[d]	9
Scott, 2000 [20]	New Zealand	1999	Proportion of foodborne *Campylobacter* spp.	GBS, ReA, HUS	75 345	X	X	X	X		NZD 2·01	8[d]	0·6	265	20
Roberts, 2003 [18]	England	1994	*Campylobacter* spp.	Not considered	n.a.	X	X	X			GBP 0·66 (year 1999)	n.a.	15	n.a.	106

GBS, Guillain–Barré Syndrome; HUS, haemolytic uraemic syndrome; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; n.a., not available; ReA, reactive arthritis.

[a] Categories represent only a very broad classification of costs included in the studies. Certain items may be included in different categories, depending on the study. For example, transportation cost was sometimes considered as 'direct healthcare cost' (when covered by the health system) and sometimes included in 'patient costs'.

[b] For example, food recalls, or intangible costs for reduced quality of life (intangible costs are monetary representations of pain, suffering and fear which can be obtained through willingness-to-pay studies [22]), or value of statistical life for premature deaths.

[c] Average exchange rates of the calendar year when the study was conducted (as indicated in the column 'year') were used and extracted from [23].

[d] Calculated based on yearly case numbers and either costs per case (for calculating yearly costs) or yearly costs (for calculating costs per case) as reported in the original publication.

[e] According to Scallan *et al.* 2011 [27].

[f] Assumed, according to Mangen *et al.* 2005 [8].

9.4. Methods

We developed patient management models and estimated their frequency and associated costs from the perspective of the healthcare system.

9.4.1. Typology of patients: patient management models

Cost estimation was based on four different patient management models for AG which were derived from a broad expert consultation across a purposive enquiry among practitioners in private general and specialized practices (four), clinics and university hospitals (four), authors opinions and data available to them: (i) patients consulting a physician without stool testing (patient management model A), (ii) patients consulting a physician with negative *Campylobacter* stool test results (patient management model B), (iii) patients consulting a physician and having a positive *Campylobacter* stool test result (patient management model C), and (iv) hospitalized campylobacteriosis cases (patient management model D).

9.4.2. Population figures as basis for modelling: sources and approach

The number of notified campylobacteriosis cases occurring each year in Switzerland was retrieved from the NNSID [1]. A study assessing the trend in *Campylobacter* positivity rates was conducted (thereafter referred to as the 'Positivity study'). This study used data of eight Swiss diagnostic laboratories on *Campylobacter* tests performed between 2003 and 2012. Positivity rates, defined as the proportion of *Campylobacter*-positive to total number of *Campylobacter* tests, were calculated. The number of *Campylobacter* tests performed in

Switzerland was estimated based on the preliminary positivity rate of 2012.

In 2013, a qualitative study among 69 GPs was conducted in Switzerland (thereafter referred to as the 'Swiss GP study'). Using a semi-structured questionnaire, physicians were interviewed about their case management strategies for and general perception of AG and campylobacteriosis. From this study, GPs' estimates on the proportion of AG patients with a stool test prescribed were available.

In 2014, the Swiss Sentinel Surveillance Network decided to study AG for 12 months; 170 participating GPs reported all cases consulting due to AG. This study (thereafter referred to as the 'Sentinella study') also provides estimates on the proportion of patients with a stool test.

The results used for cost estimates from the 'Positivity', the 'Swiss GP' and the 'Sentinella study' are preliminary. Short summaries of these studies including the preliminary results used for estimating healthcare costs can be found in the Supplementary material of Schmutz *et al.* (2017b). Final results of all these studies will be published separately.

We used the number of hospitalizations due to the ICD-10 code 'A04.5 *Campylobacter* enteritis' as reported in official hospital statistics published by the Federal Statistical Office [31]. We compared this number with estimates based on the hospitalization rate found in our case-control study on determinants of campylobacteriosis [29] and the number of campylobacteriosis case notifications from the NNSID [1].

9.4.2.1. Population-level estimates

The number of campylobacteriosis cases registered at the FOPH was assumed to correspond to the number of patients in management models C and D in the whole of Switzerland. The number of hospitalizations in Switzerland (patient management model D) was extracted from official hospital statistics (hospitalizations due to *Campylobacter* enteritis, ICD-10 code A04.5) [31].

Patients in management model D

= cases hospitalized due to ICD-10 code A04.5

Patients in management model C

= cases in NNSID − patients in management model D

The proportion of positive to total number of campylobacteriosis tests was used to estimate the number of patients in management model B based on notified cases (hence, cases with a positive test result).

Patients in management model B

$$= \frac{\text{cases in NNSID}}{\text{positivity rate } (= \frac{\text{positive tests in } x \text{ labs}}{\text{all tests in } x \text{ labs}})} - \text{cases in NNSID}$$

The proportion of patients with stool testing (as opposed to consultation without stool testing) was used to estimate case numbers for patient management model A.

Patients in management model A

$$= \left[\frac{patients\ in\ management\ model\ B\ +\ cases\ in\ NNSID\ (=\ all\ tested)}{proportion\ of\ patients\ with\ stool\ test}\right] - \text{all tested}$$

The data sources used for the extrapolation from individual to population-based costs are summarized in Figure 9.1a.

9.4.3. Healthcare expenditures

Healthcare costs for each of the patient management models were estimated by combining associated medical standard procedures with publicly available respective rates for accounting. We extrapolated these individual case management costs to estimate healthcare costs associated with AG and campylobacteriosis in Switzerland in 2012.

9.4.3.1. Sources of cost data

We used different sources in order to calculate healthcare expenditure due to *Campylobacter* infections: from the Swiss GP study, based on expert opinions and using preliminary results of the Sentinella study, treatment schemes and standard approaches for case management (including number and duration of consultations, laboratory tests performed and medications prescribed) were identified. Consultation costs of GPs were calculated using the number of points from the publicly available Swiss medical tariff system, TARMED (as of June 2012) [32] and a point value of €0.7138 which is used in the canton of Bern [33]. Similarly, points for laboratory diagnostics were extracted from the official tariff list ('Analysenliste'; as of January 2012) using a point value of €0.83 applied throughout Switzerland [34]. Costs for medications were extracted from the list of pharmaceutical specialities ('Spezialitätenliste', version of 1 January 2012) [35]. Calculation of hospitalization costs was based on the flat rates of the Swiss diagnosis-related group-based (DRG-based) hospital reimbursement system and a base rate which is applied by several regional hospitals in the canton of Bern, both for 2012 [36, 37]. Costs in Swiss francs

were converted to Euros using an exchange rate for the Euro of €0.83 per Swiss franc (average exchange rate January 2012–December 2012) [23]. The cost estimation process for the patient management models is presented in Figure 9.1b.

We obtained primary cost data from invoices for consultations of *Campylobacter*-positive patients, covering all patient consultations between 2011 and 2013 at the Swiss TPH travel clinic. This part of the study was approved by the local ethical committee (Ethikkommission Nordwest- und Zentralschweiz ref. no. EKNZ: 2014–159).

9.4.4. Data analysis

9.4.4.1. Costs per patient treated

Differentiating by patient management model (models A–D), we evaluated the costs for consultations, medication, laboratory tests and hospitalization until conclusion of medical treatment. For all patient management models we defined two scenarios to account for some of the heterogeneity of the patients and the case management strategies within a given model: a minimal and an extended or prolonged scenario. The proportions of patients treated with the minimal and the extended scenario were estimated based on results of the case-control (e.g. proportion of patients treated with antibiotics) [29] and the Sentinella study (e.g. number of consultations; Supplementary material of Schmutz *et al.* (2017b)). Afterwards, experts were asked whether they considered the estimated proportions reasonable. The two scenarios do not imply any chronology of the steps involved.

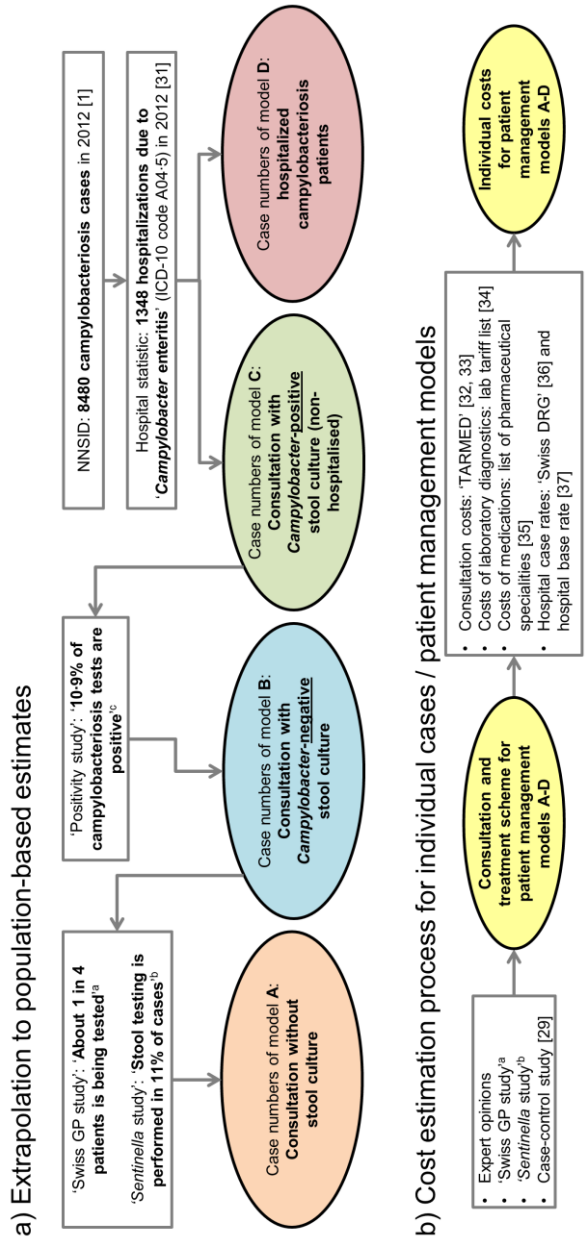
a) Extrapolation to population-based estimates
'Swiss GP study': 'About 1 in 4 patients is being tested'a
'Sentinella study': 'Stool testing is performed in 11% of cases'b
'Positivity study': '10-9% of campylobacteriosis tests are positive'c
NNSID: 8480 campylobacteriosis cases in 2012 [1]
Hospital statistic: 1348 hospitalizations due to 'Campylobacter enteritis' (ICD-10 code A04-5) in 2012 [31]
Case numbers of model A: Consultation without stool culture
Case numbers of model B: Consultation with Campylobacter-negative stool culture
Case numbers of model C: Consultation with Campylobacter-positive stool culture (non-hospitalised)
Case numbers of model D: hospitalized campylobacteriosis patients
b) Cost estimation process for individual cases / patient management models
Expert opinions
'Swiss GP study'a
'Sentinella study'b
Case-control study [29]
Consultation and treatment scheme for patient management models A-D
Consultation costs: 'TARMED' [32, 33]
Costs of laboratory diagnostics: lab tariff list [34]
Costs of medications: list of pharmaceutical specialities [35]
Hospital case rates: 'Swiss DRG' [36] and hospital base rate [37]
Individual costs for patient management models A-D

Figure 9.1: Overview of data sources used for (a) extrapolation of treatment costs and (b) for cost estimation for acute gastroenteritis and campylobacteriosis patients

[a]Qualitative study about case management of campylobacteriosis patients among 69 general practitioners in Switzerland (Supplementary material).

[b]Study on acute gastroenteritis conducted within the Swiss Sentinel Surveillance Network *'Sentinella'* (www.sentinella.ch) in 2014 (Supplementary material).

[c]Study on laboratory positivity rates of *Campylobacter*, *Salmonella* and *Shigella* diagnostic tests in Switzerland (Supplementary material).

Estimates for patient management model C were validated using real patient records of the Swiss TPH travel clinic. Patient invoices were entered in an electronic database and analysed using Stata v. 13 (StataCorp., USA). Costs for laboratory tests or medication not primarily associated with AG were excluded, i.e. tests for *Echinococcus*, *Filaria*, flavivirus and *Plasmodium*, vaccines for rabies and tetanus, and electrocardiograms. Laboratory tests performed in external laboratories were invoiced by these laboratories and could, hence, not be considered in our analysis. However, we added costs for one positive stool test for *Campylobacter* spp. as patients were selected based on having laboratory-confirmed campylobacteriosis.

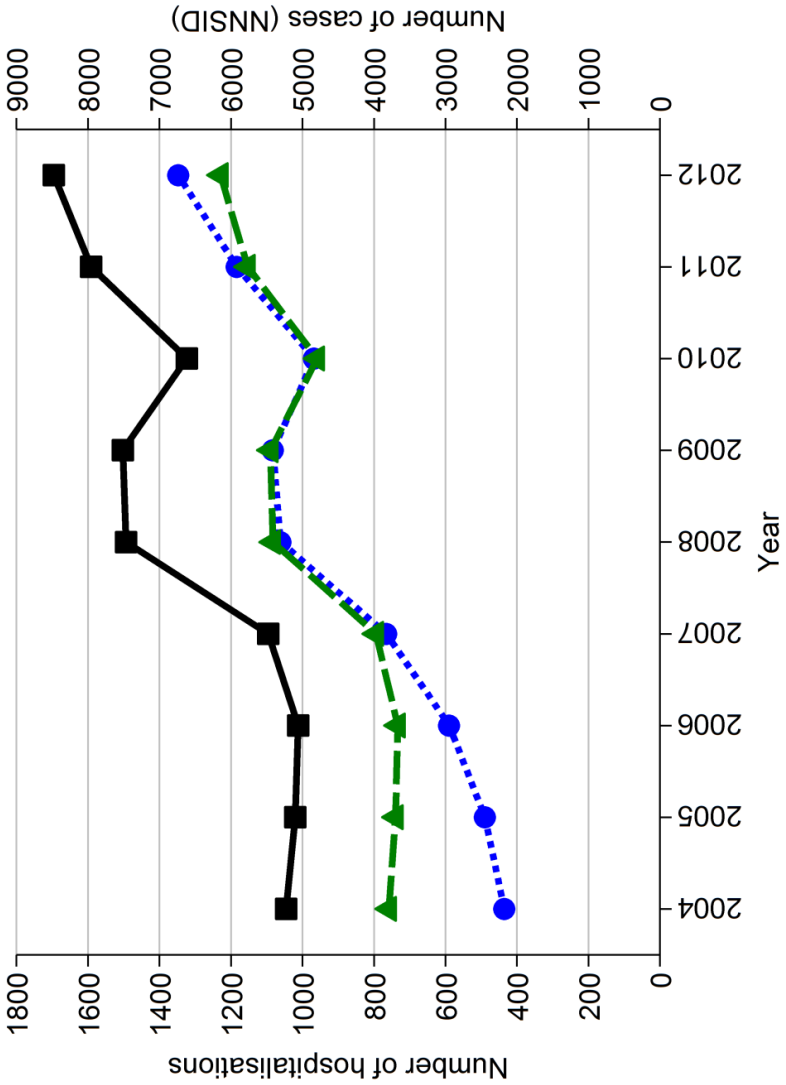
Number of hospitalisations
0
200
400
600
800
1000
1200
1400
1600
1800
Number of cases (NNSID)
0
1000
2000
3000
4000
5000
6000
7000
8000
9000
2004
2005
2006
2007
2008
2009
2010
2011
2012
Year

Figure 9.2: Number of hospitalizations due to ICD-10 code A04.5 '*Campylobacter* enteritis' in Switzerland from 2004 to 2012 (blue dotted line with circles, left axis, [31])

Number of hospitalizations extrapolated from results of a case-control study in Switzerland [29] assuming hospitalization of 14.5% of cases registered in the National Notification System for Infectious Diseases (NNSID) (green dashed line with triangles, left axis)

Number of case notifications from the NNSID [1] (black solid line with squares; right axis).

9.5. Results

9.5.1. Frequency of different patient management models in Switzerland

In the NNSID, 8480 cases of campylobacteriosis were registered in 2012 [1]. Preliminary results from the Positivity study showed that 10.9% of all campylobacteriosis tests were positive (Supplementary material of Schmutz *et al.* (2017b)). Consequently, we estimated that 77 798 tests for *Campylobacter* spp. were made in 2012, of which 69 318 had a negative test result (patient management model B). Estimates of the Swiss GP study indicated that one in four AG patients has a stool test performed (Supplementary material of Schmutz *et al.* (2017b)), suggesting that 233 394 patients consult a physician each year without further stool testing (patient management model A). However, preliminary results from the Sentinella study suggest that only 11% (420/3794) of patients had stool testing performed (Supplementary material of

Schmutz *et al.* (2017b)). In this case a total of 629 457 patients would be in patient management model A.

The number of hospitalizations due to '*Campylobacter* enteritis' (ICD-10 code A04.5) as reported in the official Swiss hospital statistics increased steadily since 2004. In 2012, 1348 hospitalizations were reported which is the maximum so far (Figure 9.2). For comparison, 14.5% (23/159) of interviewed patients in the recent case-control study, with laboratory-confirmed campylobacteriosis, reported hospitalization due to their illness [29]. Considering the case notification numbers of 2012 (8480 cases), this proportion would result in 1230 hospitalizations (patient management model D). Patient management model C includes all notified cases except those being hospitalized (1348), resulting in 7132 patients annually in Switzerland.

9.5.2. Individual case management costs for AG and campylobacteriosis patients

The costs per case are highly variable ranging from €30 (patient management model A) to €4828 (patient management model D). The cost items attributed to the different patient management models and scenarios and associated costs are presented in . (For a list of unit costs see Supplementary Table S2 of Schmutz *et al.* (2017b))

The healthcare costs of 41 patients with laboratory-confirmed *Campylobacter* spp. infection were analysed. Costs for those 19 male and 22 female patients aged between 1 and 72 years were in the range of €179–1033 (median €464). The number of consultations varied between 1 and 8 per patient (median 2), the number of blood samples taken between 0 and 4 (median 1) and the time between the first and the last consultation between 0 (only one consultation) and 65 days (median 3). Consultation

costs and costs for laboratory testing of real patient data were higher than estimated costs for patient management model C (Supplementary Table S3 of Schmutz *et al.* (2017b)).

9.5.3. Healthcare costs due to AG and campylobacteriosis

Total healthcare costs for the management of the four different patient management models combined in Switzerland in 2012 were estimated at €29.5–44.7 million (). Costs for the different patient management model groups (A–D) were €9.0–24.2, €12.3, €1.8 and €6.5 million, respectively (Supplementary Figure S1 of Schmutz *et al.* (2017b)).

Costs separated by type/provider were: €11.1–20.6 million for GPs' services (including medical assistants), €7.7–9.1 million for laboratory diagnostics, €4.4–8.6 million for medications and €6.4 million for hospitalizations (Supplementary Figure S2 of Schmutz *et al.* (2017b)).

Table 9.3: Health care costs associated with the management of acute gastroenteritis and campylobacteriosis for four patient management models with two scenarios each. (Values reflect costs in Euro)

	Patient management model A Consultation without stool test		Patient management model B Consultation with negative stool culture[e]		Patient management model C Consultation with positive stool culture[a]		Patient management model D Hospitalization	
Minimal scenario	10 min consultation[b]	19·02	15 min consultation[b]	31·69	15 min consultation[b]	31·69	15 min consultation[b]	31·69
	1 medication[c]	10·79	Stool culture[a] (negative)	64·74	Stool culture[a] (positive)	128·65	Hospital stay (DRG G67B[a])	4727·36
			Taking blood sample	5·85	Taking blood sample	5·85		
			Haemogram[d] and CRP	18·26	Haemogram[d] and CRP	18·26		
			1 medication[c]	10·79	1 medication[c]	10·79		
			5 min reviewing patient file	12·68	5 min reviewing patient file	12·68		
			5 min telephone cons.	12·68	5 min telephone consultation	12·68		
Total, minimal scenario		**29·81**		**156·68**		**220·59**		**4759·06**
Extended scenario	+ Taking blood sample	5·85	+ Antibiotic	24·90	+ Antibiotic	24·90	+ 5 min reviewing patient file	12·68
(costs additional to minimal scenario)	+ Haemogram[d] and CRP	18·26	+ Pharmacy fees[f]	6·27	+ Pharmacy fees[f]	6·27	+ Taking blood sample	5·85
	+10 min second consultation[b]	19·02	+10 min second consultation[b]	19·02	+10 min second consultation[b]	19·02	+ Haemogram[d] and CRP	18·26
							+ 15 min second consultation[b]	31·69
Total, extended scenario		**72·93**		**206·87**		**270·78**		**4827·53**
Proportion of patients requiring extended scenario:	**20%**		**40%**		**65%**		**50%**	
Data sources								
Expert opinion	x		x		x		x	
TARMED[g] [32]	x		x		x		x	
List of pharmaceutical specialities [35]	x		x		x		x	
Official laboratory tariff list [34]	x		x		x		x	
Flat rates of Swiss DRG, version 1.0 [36]							x	
Swiss GP study[h]	x		x		x			
Sentinella study[i]	x		x		x			

Table 9.3 continued

	Patient management model A Consultation without stool test	Patient management model B Consultation with negative stool culture[a]	Patient management model C Consultation with positive stool culture[a]	Patient management model D Hospitalization
Swiss TPH travel clinic			x	

CRP, C-reactive protein; NNSID, National Notification System for Infectious Diseases.

[a] Stool culture includes *Campylobacter*, *Salmonella* and *Shigella*.

[b] Or telephone consultation of same duration.

[c] Of the following medications: antidiarrhoeal, antiemetics, probiotics; average price of those medications: €10·79 (13 CHF).

[d] Including erythrocytes, leucocytes, haemoglobin, haematocrit, thrombocytes, and ⩾5 subpopulations of leucocytes.

[e] For a patient with *Campylobacter* enteritis (ICD-10 code A04·5), aged ⩾1 year, with a length of stay between 2 and 11 nights, the DRG group 'G67B' is assigned. Cost weight: 0·573, base rate (applied by several regional hospitals in Bern): €8250·20 (9940 CHF) [37]. Quote from Swiss DRG version 1.0 [36] defining code 'G67B': [*translated from German*] 'Oesophagitis, gastroenteritis and other diseases of the digestive organs with a complex diagnosis or age <1 year or gastrointestinal bleeding, with very severe or severe complications or comorbidities or age >74 years or peptic ulcer disease with severe complications or comorbidities or age >74 year, hospital occupancy > 1 day, without complicating diagnosis, without dialysis'.

[f] Fees include check of the prescription which can be invoiced once per item prescribed ('Medikamenten-Check'; €3·57, CHF 4·30) and check of the purchase which can be invoiced once per patient, per day and per provider ('Bezugs-Check'; €2·70, CHF 3·25) [49].

[g] Costs vary among cantons; median costs are used (tariff point value €0·7138 or 0·86 CHF, e.g. canton Bern) [33].

[h] Qualitative study about case management of campylobacteriosis patients among 69 general practitioners in Switzerland (Supplementary material).

[i] Study on acute gastroenteritis conducted within the Swiss Sentinel Surveillance Network '*Sentinella*' (www.sentinella.ch) in 2014 (Supplementary material).

Table 9.4: Estimated health care costs for the treatment of acute gastroenteritis and campylobacteriosis in Switzerland. Costs for individual cases are based on resource use estimates presented in Table 9.3.

	Patient management model $A_{Sentinella}$	Patient management model $A_{Swiss\ GP}$	Patient management model B	Patient management model C	Patient management model D
Estimated number of cases (*n*)	**629 457**	**233 394**	**69 318**	**7132**	**1348**
In minimal scenario	503 566	186 715	41 591	2496	674
In extended scenario	125 891	46 679	27 727	4636	674
Consultation	€11 969 523	€4 438 134	€4 359 611	€448 552	€42 722
Laboratory diagnostics	€0	€0	€5 753 394	€1 047 762	€0
Medication	€6 791 841	€2 518 321	€747 941	€76 954	€0
Hospitalization	€0	€0	€0	€0	€6 372 487
+Consultation	€3 129 858	€1 160 517	€527 246	€88 156	€33 845
+Laboratory diagnostics	€2 298 770	€852 359	€0	€0	€12 307
+Medication	€0	€0	€864 154	€144 488	€0
Healthcare costs by patient management model	**€24 189 992**[a]	**€8 969 331**[a]	**€12 252 346**[a]	**€1 805 913**[a]	**€6 461 362**[a]
Total healthcare costs	**€29 488 953–44 709 613**[a]				

[a] Totals do not always add up because of rounding.

9.6. Discussion

This study provides for the first time an assessment of total Swiss healthcare costs due to AG and campylobacteriosis by estimating the individual costs of four types of patient management models and their frequency: patients suffering from AG and seeking medical care without being tested (model A); patients seeking medical care and having a *Campylobacter*-negative stool test (model B); patients seeking medical care and having a *Campylobacter*-positive stool test (model C); and patients with a severe course of campylobacteriosis requiring hospitalization (model D).

Cases of campylobacteriosis increased in the last decade 1.5-fold, implying a contemporarily relevant public health problem. We estimated that in Switzerland, each year 311 192–707 255 patients consult a physician due to AG or campylobacteriosis, leading to annual healthcare costs ranging from €29 to €45 million.

The calculations were based on several assumptions as this study provides the first estimates of healthcare costs due to AG and campylobacteriosis in Switzerland. The country has no central database which is based on diagnostic codes and where healthcare costs from outpatient care are systematically recorded. Therefore, we tried to cross-validate our estimates whenever possible by combining different data sources. The real patient data which we used for comparison with cost estimates for patient management model C originated from our own institution's (Swiss TPH) travel clinic. These real patient data suggested higher costs for laboratory-confirmed, ambulatory patients than we used for our calculations. Possibly consultation time in returning travellers was longer because of the travel anamnesis and laboratory tests were more extensive.

Nevertheless, returning travellers are likely to be overrepresented also in the patients with AG seen by GPs. When using the median total costs of the real patient data of the travel clinic for patients in management model C, the costs for this group would be €3.3 million (instead of €1.8 million; Supplementary Figure S1 and S2 of Schmutz *et al.* (2017b)). Hence, we believe the cost estimates used for patient management model C are conservative.

Some physicians reported performing a second stool test after a positive result for certain patient groups (e.g. working in the food sector) before allowing the patients to return to work. A few experts claimed that the consultation times we applied in our models were rather short. They suggested consultation times of 5–10 min longer for selected (but not for all) consultations. The case-control study [29] found that about 10% of campylobacteriosis patients in outpatient treatment received intravenous therapy, which was not considered in our models. Furthermore, patients requiring hospitalization may be transferred to the hospital by ambulance causing additional costs. Taking all these points into account, we believe that our estimates reflect rather conservative approximations.

9.6.1. Healthcare costs of laboratory-confirmed campylobacteriosis patients

Campylobacteriosis cases as registered in the NNSID were estimated to cost around €8.3 million/year (patient management models C and D). The majority of these costs are attributable to hospitalizations. Comparison of our estimates with actual patient data suggests that our estimates (at least for patient management model C) underestimated actual costs occurring in the health system. The number of hospitalizations

due to '*Campylobacter* enteritis' (ICD-10 code A04.5) matches well with the calculated number of hospitalized patients using the official notification data together with the hospitalization rate found in the case-control study (1348 vs. 1230 cases). The hospitalization costs, which are based on DRG flat rates, include all costs occurring during the hospital stay. This flat rate is independent of the length of stay as long as it is within 2–11 nights (for DRG code G67B, according to DRG v. 1.0 [36]).

9.6.2. Healthcare costs of AG patients

The costs for AG patients without laboratory-confirmed campylobacteriosis varied significantly depending on the proportion of stool testing we used to calculate patient numbers for patient management model A. The proportion of stool testing is highly variable also in other countries: it was found to be 12% in The Netherlands [38], 19–44% in the United States [39, 40] and 27% in England [41]. Even though our estimate of 11% from the Sentinella study is lower compared to the proportions reported in other countries we believe that this number is more accurate than the semi-quantitative estimates obtained from the Swiss GP study. Moreover, the figure from the Sentinella study represents the proportion of patients for which the physician initiated stool testing. It is likely that not all patients actually provided a stool specimen. Hence, using the proportion of actually completed stool tests would increase case numbers in model A and our cost estimates. Additionally, our calculation for patient management model A is based on the estimated number of tests for *Campylobacter* spp. This may in fact underestimate the total number of stool tests as in some instances physicians might only test their patients for viruses, for example. In this case, the number of patients in management models A and B would be even larger.

Apart from *Campylobacter* both *Salmonella* and *Shigella* infections are notifiable in Switzerland. Usually, basic stool bacteriology involves testing for these three pathogens [42]. Under this assumption and ignoring the chance of mixed infections, all *Salmonella*- or *Shigella*-positive patients were assigned to management model B (patients with *Campylobacter*-negative stool test). This leads again to a rather conservative estimate of costs since stool cultures with a positive result are more expensive than negative stool cultures (€64.74 vs. €128.65) [34]. Additionally, salmonellosis and shigellosis patients may also need hospitalization and those patients are, therefore, more likely to create costs similar to those estimated for campylobacteriosis patient management models C and D. In 2012, 1243 cases of salmonellosis and 159 cases of shigellosis were reported [43, 44]. Moreover, AG patients with viral infections and patients without an identified causative agent might be hospitalized. The hospitalization costs for these patients were not considered in our study.

Patients consulting a physician not at all or only by phone and patients seeking help in a pharmacy have not been considered in this study. Up to 60% of gastroenteritis patients calling the medical practice are managed by phone, according to the Swiss GP study (Supplementary material of Schmutz *et al.* (2017b)). Individual (healthcare) costs for these patients may be low. However, the high quantity of these patients might still lead to considerable costs.

9.6.3. Comparison of cost estimates for Switzerland with estimates of other countries

Various studies have been conducted in several countries to estimate costs for gastrointestinal infections or campylobac-

teriosis (Table 9.1 and Table 9.2). However, comparison of costs is very difficult due to varying case definitions used, heterogeneity in costs included, differences in health systems and health-system use and time. We estimated that a case of laboratory-confirmed campylobacteriosis costs on average €975 (average per case for models C and D). The extent of underreported campylobacteriosis infections – defined as infections in individuals who seek healthcare but whose infection is not captured by the surveillance system [45] – is unknown for Switzerland. The multiplication factor due to underreporting of campylobacteriosis was estimated at 1.3 in the UK [46] and at 2.0–5.6 in The Netherlands [6, 47]. Applying the same factors to Swiss data would result in 2544–39 008 additional campylobacteriosis cases. Assuming that underreporting was due to under-diagnosis (as opposed to under-notification), these cases are automatically included in our patient management model A (where model A represents all consulting AG patient without stool diagnostics.) Hence, costs in model A attributable to under-diagnosed campylobacteriosis cases would range between €0.98 and €1.50 million. Total costs attributable to campylobacteriosis would then range between €8.4 and €9.8 million in Switzerland (representing 19–33% of total AG costs) or €206–759/case. Healthcare costs per case are higher than Dutch (€82–280/case, Table 9.2) or US estimates (€163–253/case). However, the latter two were based on the yearly estimated number of campylobacteriosis cases in the population while we considered only campylobacteriosis cases presenting to the GP or being hospitalized.

On average, a case of AG (including campylobacteriosis) in Switzerland was estimated at €63–95. Again, our cost estimates are based on cases presenting to the GP while estimates from

other countries usually are presented for cases in the community. Hence, values are not comparable even though our cost estimates are within the range of cost estimates from other countries (€3–155 [9–20], Table 9.1).

9.6.4. Unknown socioeconomic burden

We only assessed direct healthcare costs for AG and campylobacteriosis. The average hospital stay of three nights and the median disease duration of 7 days of campylobacteriosis patients which were found in the case-control study [29] suggest that the socioeconomic burden due to productivity loss and home care is a multiple of the healthcare costs. Additionally, we neither considered costs arising from complications of the disease (e.g. Guillain–Barré syndrome, reactive arthritis or irritable bowel syndrome) nor did we include out-of-pocket expenses for medications of patients not consulting a physician or costs arising of patients consulting the physician exclusively by phone. This further underscores the conservative nature of our overall healthcare cost estimated at €29–45 million.

The disease burden and economic consequences are further increased by years of life lost due to premature mortality. The ICD-10 codes A02 'other *Salmonella* infections' and A04.5 '*Campylobacter* enteritis' were recorded only for four patients in 2011 as the main cause of death (Swiss Federal Statistical Office, personal communication). When considering also secondary causes of deaths, 104 deaths were registered in 2011. For influenza it was shown that mortality is underreported in official statistics [48]. We assume that such underreporting is also the case for deaths due to campylobacteriosis (and salmonellosis).

AG and campylobacteriosis cause a marked public health problem generating considerable costs. To our knowledge, this is the first study investigating healthcare costs due to AG and campylobacteriosis in Switzerland. Further research is needed for more accurate cost estimation. In order to reduce the financial burden and suffering of patients, there is a need for implementing health policy measures, sectorial and intersectorial public health interventions and increasing awareness in the population at all levels.

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9.8. Declaration of Interest

None.

9.9. References

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10. General discussion

Human campylobacteriosis and acute gastroenteritis (AG) due to infectious intestinal diseases (IID) received little attention in Switzerland so far. Despite campylobacteriosis case notifications are increasing since 2005 and show a distinct winter peak whose determinants are unclear. The aim of this doctoral research is to contribute to a better understanding of the epidemiology of human campylobacteriosis and AG and to improve the interpretation of routine surveillance data from the Swiss National Notification System for Infectious Diseases (NNSID). The six research components conducted appropriately addressed this aim and the underlying objectives from a human and health system's perspective along the burden-of-illness pyramid (see Chapter 3).

The case-control study identified the consumption of meat fondue especially if consumed with chicken meat as a major risk factor for contracting campylobacteriosis in Switzerland over Christmas and New Year (Chapter 4). Hence, its consumption is largely responsible for the winter peak of cases observed in the NNSID. Moreover, the consumption of meat fondue is likely to play a similar role in other European countries with a winter peak in surveillance data (Chapter 5). An analysis of laboratory positivity rates from *Campylobacter* and *Salmonella* infections confirmed the epidemiological observations made in the NNSID and thereby increased the validity of surveillance data from the NNSID (Chapter 6).

The disease burden and presentation of campylobacteriosis and AG, and determinants of the NNSID at the primary care level were investigated by a mixed methods approach (Chapter 7 and 8). The qualitative study among general practitioners (GPs)

generated knowledge on health care seeking, clinical presentation and case management of patients suffering from campylobacteriosis and AG in Switzerland (Chapter 7). The following quantitative study within the Sentinel Surveillance Network *Sentinella* showed that the disease burden of AG due to IID is comparable to the burden of influenza-like illnesses (ILI) and estimated determinants of the burden-of-illness pyramid such as stool testing rates (Chapter 8). Finally, the generated knowledge on case management and disease burden together with official rates for consultations, hospitalisations, diagnostics and drugs was used to estimate health care costs of campylobacteriosis and AG in Switzerland (Chapter 9).

The following chapter compiles and discusses the estimated disease burden and health care costs of campylobacteriosis and AG along the burden-of-illness pyramid in Switzerland (addressing general objective 1). Subsequently, the usefulness and validity of the disease burden measured by the NNSID and implications of current and upcoming diagnostic practices and methods on measuring the disease burden by the NNSID are highlighted (addressing general objective 2). The need for an assessment of IID and AG at the community level to even better understand the disease and economic burden along the burden-of-illness pyramid is emphasised. Additionally, a future monitoring of non-notifiable IID and AG is proposed. The presentation and case management of patients suffering from campylobacteriosis and AG at the primary care level is discussed considering specifically the increasing resistance to antibiotics among bacterial IID and changes in diagnostic methods to come (addressing general objective 1 and 2). The current control measures and prevention campaigns for campylobacteriosis in Switzerland are reviewed in the light of

determinants assessed to acquire a *Campylobacter* infection (addressing general objective 1). Finally, promising interventions to reduce the burden of campylobacteriosis in the future are highlighted.

10.1. Campylobacteriosis and acute gastroenteritis along the burden-of-illness pyramid

10.1.1. Disease burden and health care costs

Results of the *Sentinella* study showed that around 175,000 cases of AG consulted at the primary care level in Switzerland in 2014 (Chapter 8). This is comparable to the consultation numbers due to ILI during an influenza season (107,000 – 276,000 ILI cases during the seasons 2013 - 2016) which is estimated by the same method as the burden of AG (BAG 2014, 2015a, 2016). The study on health care costs estimated that between 311,192 and 707,255 cases of AG and campylobacteriosis occur annually at the primary care level (Chapter 9).

The estimated 175,000 to 707,255 cases correspond to a primary care attendance rate due to AG of 21 to 87 cases per 1000 person-years. These estimates are close to estimates from the UK (18 per 1000 person-years), the Netherlands (13.0 per 1000 person-years) and France (110 per 1000 person-years) (Havelaar *et al.* 2012, Tam *et al.* 2012c, van Cauteren *et al.* 2012). Yet, it is remarkably lower than estimates from Germany (395 per 1000 person-years), Italy (389 per 1000 person-years), Poland (266 per 1000 person-years) and Norway (200 per 1000 person-years) (Kuusi *et al.* 2003, Baumann-Popczyk *et al.* 2012, Scavia *et al.* 2012, Wilking *et al.* 2013). This comparison should be interpreted with caution as consultation rates originate from studies with different study designs and case

definitions. All remarkably higher consultation rates originate from retrospective studies which relied on self-reporting of AG episodes by participants, often with a 4-week recall period. The *Sentinella* study and the study estimating the rate for the UK used a prospective study design generating similar results (21 and 18 consultations per 1000 person-years).

Retrospective study designs on disease burden are prone to a special recall bias known as "telescoping" (Wheeler *et al.* 1999). Thereby, participants believe that a disease episode occurred more recently than it actually did. This recall bias can lead to an overestimation of the disease burden in the recall period and is maybe more prevalent among AG cases consulting a physician than cases not consulting. Another possibility is that AG cases consulting a physician are likely to better remember their disease episode. Hence, they could be more likely to report their episode than cases with a mild episode not leading to a consultation. This would point towards an underestimation of cases with a mild episode leading to an overestimation of the proportion of cases consulting a physician.

Estimating case numbers by two different approaches (*Sentinella* study and study on health care costs) provided the possibility to cross-validate individual estimates. The difference between the two estimates can partially be explained by the different methods used to estimate case numbers. Annual AG case numbers at the primary care level in the *Sentinella* study were calculated based on consultation and population numbers stratified by temporal and spatial determinants and also patient characteristics (sex, age) (Altpeter *et al.* 2013). The estimation of health care costs used annual rates (stool test, positivity and hospitalisation rates) and case numbers from the

NNSID without stratification by temporal, spatial or patient characteristics to calculate case numbers for the different case models. Yet, the analysis of positivity rates showed that test numbers and positivity rates vary among sex, age groups and over the year (Chapter 6). Similarly, stool testing rates are pathogen-specific and depend on patient characteristics such as age or exposure to risk factors (Chapter 7 and 8).

The estimated case numbers of the *Sentinella* study are likely also influenced by reporting fatigue. Participating physicians indicated in a survey that the reporting of AG cases is comparatively time-consuming and hence, could have had reported less cases leading to a lower number of estimated cases. Another important fact is that the upper estimate of the study on health care costs (707,255 cases) is based on the stool testing rate estimated from the quantitative *Sentinella* study. This stool testing rate (11.6%) is significantly lower than the one of the qualitative GP study (25.0%) used to calculate the lower estimate (311,192 cases). It can be assumed that the stool testing rate of the quantitative *Sentinella* study is more reliable given the methodological advantages of the study design to quantitatively assess outcomes.

It is difficult to judge which of the two estimates reflects the true disease burden better as both approaches have their limitations. Assuming the stool testing rate from the *Sentinella* study reflects the reality better, the true burden of AG at the primary care level per year is likely between the 175,000 cases of the *Sentinella* study and the 707,255 cases of the study on health care costs (upper estimate).

It also needs to be added that a considerable proportion of the cases observed at the primary care level were admitted to hospital. The *Sentinella* study and the case-control study showed

that 2.7% of AG patients and 14.5% of campylobacteriosis patients needed to be hospitalised during their illness (Chapter 4 and 8). Among elderly patients (>60 years) even 7.0% of AG patients and 33.0% of campylobacteriosis patients were admitted to a hospital. The majority of health care costs associated with campylobacteriosis cases notified in the NNSID were attributable to hospitalisations (€6.5 million). The health care costs caused by AG and campylobacteriosis patients admitted to hospitals should therefore not be neglected. The disease burden and health care costs at the hospital level could even increase in the future considering that the Swiss population is ageing.

The study on health care costs estimated the costs due to AG and campylobacteriosis at the primary care level in Switzerland at €29–45 million per year. A considerable proportion of these costs can be attributed to campylobacteriosis: €1.8 million to campylobacteriosis patients at the primary care level and €6.5 million to hospitalised campylobacteriosis patients. A comparison of the estimated health care costs due to AG and campylobacteriosis in Switzerland with other (neighbouring) countries can be found in Chapter 9. Yet, such a comparison is challenging given varying case definitions used, heterogeneity in costs included, differences in health systems and health-system use and time.

The approach used to estimate health care costs relied on estimated case numbers, official rates for health care services and expert opinions. The estimation of case numbers was based on determinants of the burden-of-illness pyramid (stool testing, positivity and hospitalisation rates) which are influenced by temporal and spatial factors and patient characteristics as mentioned before. A possible new estimation of health care costs

for AG and campylobacteriosis using the same approach should thus consider stratifying the calculation of case numbers by temporal, spatial and patient characteristics. Estimated health care costs per case were based on official rates and expert opinions. Only health care costs for patients with campylobacteriosis were validated with real patient data from the Swiss TPH's Department of Medicine. Hence, assessing the health care costs per case management model with real patient data is recommended for a future assessment. More accurate estimates for case numbers and health care costs per case will lead to a more precise estimate of health care costs due to AG and campylobacteriosis in Switzerland.

In summary, the studies conducted showed that the burden of AG and campylobacteriosis at the primary care level and in hospitals in Switzerland is considerable and results in substantial health care costs requiring public health action to reduce the associated burden.

10.1.2. Usefulness and validity of the disease burden of campylobacteriosis and salmonellosis measured by the National Notification System for Infectious Diseases

The rise in campylobacteriosis and the decrease in salmonellosis case notifications in the NNSID between 2003 and 2012 as observed by Schmutz *et al.* (2016) could be confirmed as real epidemiological trend in the population by the analysis of positivity rates (Chapter 6). During the same time period, the number of tests conducted for *Campylobacter* spp. and *Salmonella* spp. increased and the rise in campylobacteriosis case numbers can be interpreted as an actual rise in the number of cases combined with increased testing. In contrast, the decline in salmonellosis case

notifications represents a strong decrease of human salmonellosis in Switzerland as case numbers decreased even in the light of increasing test numbers i.e. lower positivity rates (positive tests / total test numbers). Similar trends observed in case notifications for both diseases on the European level seem to confirm the observations made (EFSA and ECDC 2016).

The new Epidemics Act was implemented together with a new ordinance on the reporting of infectious diseases in Switzerland at the beginning of 2016 (Die Bundesversammlung 2012, EDI 2015). The ordinance requires all medical laboratories to report annually the total number of tests conducted for *Campylobacter* spp. and *Salmonella* spp. including the number of positive results as aggregated numbers, stratified by month and test method. This summary measure of denominator data allows now for a continuous but basic temporal assessment of positivity rates to interpret trends in the NNSID. Yet, the aggregated numbers do not allow calculating age- or sex-specific positivity rates for an accurate interpretation of NNSID data stratified by age or sex.

The analysis of positivity rates showed once again the need of analysing denominator data (total number of tests conducted) for the interpretation of trends in NNSID case numbers (cf. Schmutz *et al.* (2013)). The importance of analysing denominator data for the interpretation of trends in passive surveillance systems has also been highlighted by others (van Pelt *et al.* 2003, Janiec *et al.* 2012, Franklin *et al.* 2015). Why denominator data is important could be directly shown by the qualitative GP study (Chapter 7) and the *Sentinella* study (Chapter 8). They showed that the primary care level is very important for two determinants of the burden-of-illness pyramid. First, in many primary care practices the GP or a nurse filters patients

and provides them with medical advice at the telephone decreasing the number of patients that are seen by the GP. Second, the decision to conduct a stool test or not is strongly influenced by disease progression, reported exposure to risk factors (e.g. travel abroad) and the GP's personal experiences and opinions. Analysing positivity rates helps detecting changes among these determinants which can affect the number of cases registered in the NNSID in different ways.

Hence, cases of notifiable IID registered in the NNSID represent the more severe cases and risk groups rather than the average individual affected by IID. This is also supported by the case-control study conducted among campylobacteriosis cases registered in the NNSID (Chapter 4). Cases in this study rated the disease severity with a median of 8 on a rating scale from 1 (very mild) to 10 (very severe). As a result, the information on and about mild and short episodes of notifiable IID does simply not reach the NNSID. This leads to a clear underestimation of the incidence of notifiable IID at the primary care level and in the Swiss population as a whole by the NNSID. IID case numbers observed in the surveillance system represent only the tip of the iceberg of cases occurring in the community (Allos *et al.* 2004).

10.1.3. Influence of diagnostic practices and methods on the disease burden measured by the National Notification System for Infectious Diseases

In Switzerland physicians generally order basic stool culture for *Campylobacter*, *Salmonella* and *Shigella* for their patients suffering from AG with a suspected bacterial infection e.g. based on increased C-reactive protein levels (Chapter 7). Stool tests for viral or parasitic causes were often only ordered with a

distinct suspicion about an exposure during an outbreak or for travelling abroad. In 2011, the first diagnostic laboratories in Switzerland started to offer stool-based multiplex PCR panels for the detection of gastrointestinal pathogens in routine diagnostics which are commonly used today (Hächler and Stephan 2015). These PCR panels are able to detect a wide range of gastrointestinal pathogens including viruses, bacteria and parasites with a high sensitivity and specificity (Binnicker 2015, Spina *et al.* 2015).

Notification rates of EHEC in Switzerland increased 2.5-fold from 2014 (1.5 per 100,000 population) to 2015 (3.5 per 100,000 population), while the notification rate of the haemolytic-uremic syndrome remained rather stable (BAG 2015b, Hächler and Stephan 2015). Multiplex PCR panels for gastrointestinal pathogens often include EHEC (Binnicker 2015, Spina *et al.* 2015) and, hence, every patient suffering from AG and undergoing stool testing with PCR panels will be tested for EHEC independent of the clinical suspicion. This likely increases EHEC notification rates due to its detection in cases where previously only basic stool culture was ordered by the physician and performed (Hächler and Stephan 2015).

Hence, it should be taken into account that the introduction of multiplex PCR panels as routine diagnostic for gastrointestinal pathogens likely increases test numbers for pathogens that are not the primarily suspected cause of disease from a clinical point of view. This could lead to an increase of pathogen-specific notification rates. As a result, positivity rates of gastrointestinal pathogens will likely decrease due to increased test numbers and a lower pre-test probability. It is likely that positivity rates of *Campylobacter* spp., *Salmonella* spp. and *Shigella* spp. in Switzerland will only be slightly affected by

this phenomenon as these pathogens belonged already previously to standard stool diagnostics. Since the introduction of the new Epidemics Act in 2016, it is possible to assess these developments in Switzerland as the monthly number of tests conducted (incl. test results) for *Campylobacter* spp. and *Salmonella* spp. must be reported to the FOPH (Chapter 1.6.3). Such assessments are highly recommended for an appropriate interpretation of NNSID data considering the current changes in the diagnostic sector.

Most recent European notification rates declined for *Campylobacter* and slightly increased for *Salmonella* from 2013 to 2015 (EFSA and ECDC 2016). Therefore, an important question from an epidemiological point of view is to understand if such increases or decreases in notification data are real trends requiring public health action or just an artefact of the transition from single and often culture-based methods to multiplex molecular diagnostics (Langley *et al.* 2015, Marder *et al.* 2017). The assessment of corresponding positivity rates is a solid method to investigate this issue. Further should be considered that physicians' testing behaviour and patient's health care seeking likely have a much bigger influence on surveillance data than diagnostic technologies (Cronquist *et al.* 2012, Doorduyn *et al.* 2012, Janiec *et al.* 2012, Langley *et al.* 2015). Diseased individuals that do not seek health care or do not get tested have no chance to be recorded by the surveillance system.

10.1.4. Monitoring the disease burden of non-notifiable infectious intestinal diseases and AG in Switzerland

Laboratory-confirmed infections by bacterial IID (*Campylobacter* spp., *Salmonella* spp., *Shigella* spp., *Vibrio*

cholerae, *Listeria* spp., EHEC) are monitored on a regular basis by the NNSID (Chapter 1.6.3). Viral or parasitic IID are not regularly monitored by the NNSID. They have only to be reported to the cantonal health department if an excess of case numbers (more than expected in time and place) i.e. an outbreak are observed by physicians or diagnostic laboratories (EDI 2015). The consequences thereof are twofold: (i) only obvious outbreaks are detected and (ii) conclusive estimates on the national burden of viral and parasitic IID are lacking for Switzerland so far.

In contrast, Germany monitors a subset of viral and parasitic IID causing AG by a similar mandatory notification system as in Switzerland (RKI 2016). France as another example monitors AG (and other diseases) at the population level through the sentinel system *French GPs Sentinelles network* and results of this national surveillance are made available for the public on the network's website (Flahault *et al.* 2006, Réseau Sentinelles 2017). The National Outbreak Reporting System (NORS) in the US monitors AG outbreaks of any cause and provides valuable information of the aetiological agents involved (Hall *et al.* 2013). Additionally, the laboratory surveillance Network "CaliciNet" collects norovirus sequences and epidemiologic outbreak data and allows investigating spatial and temporal trends and identifying and linking clusters of norovirus outbreaks in the US (Vega *et al.* 2011). Switzerland does not have any surveillance data on AG or single viral and parasitic IID while other countries do. So there is a clear potential for expanding the surveillance of AG and IID in Switzerland.

The surveillance of ILI during the influenza season has already been part of the *Sentinella* network since many years. The *Sentinella* study provides solid evidence that AG could also be

monitored through the network (Chapter 8). A possible routine monitoring of AG within *Sentinella* would profit from the methodologies developed for ILI (e.g. estimation of national disease burden) and could be based on an already existing system likely not generating considerable additional costs. Hence, the *Sentinella* network would provide an excellent system to monitor the burden of AG at the Swiss primary care level similar to the *French GPs Sentinelles network*. Also this network monitors cases of ILI and AG side by side based on the clinical presentation of cases. Information gained from such a surveillance of AG could include its incidence and presentation at primary care level and stool testing and hospitalisation rates. Integrating AG monitoring into *Sentinella* would allow assessing spatial and temporal trends of AG on a regular basis and thereby provide valuable epidemiological information (e.g. for outbreak detection) for cantonal and federal health authorities.

The *Sentinella* study showed that the *Sentinella* network is currently only of limited value - if at all - for the surveillance of specific IID (Chapter 8). A major limitation is that only around 12% of cases suffering from AG undergo stool testing in daily practice. This limits the detection rate of specific IID if they are tested at all and results in small case numbers of laboratory-confirmed IID. Hence, reliable estimates for the disease burden of specific IID at the primary care level can currently not be made from the *Sentinella* Network especially not for rather rare IID. A solution could be to increase the number of physicians participating in *Sentinella* as currently a small proportion (2.5%) of all physicians practicing in the ambulatory care sector participate. This would likely result in an increased number

of laboratory-confirmed IID cases making estimates of the primary care burden more reliable.

Another possibility to improve the surveillance of specific IID within *Sentinella* would be to test all or a defined proportion of consulting AG cases for a defined set of IID. This would likely increase case numbers of laboratory-confirmed IID for the estimation of the primary care burden and allow determining the aetiology of AG at the primary care level. Diagnostic costs associated with such an approach are presumably too high for routine surveillance (3,900 AG cases were reported in the *Sentinella* study). However, a one-time assessment for research purposes i.e. assessing the aetiology of AG at the primary care level would be desirable as this has not been done within the *Sentinella* study.

Compared to other European countries or the US (Flahault *et al.* 2006, Vega *et al.* 2011, Hall *et al.* 2013, RKI 2016), surveillance data on viral IID of public health importance such as norovirus or rotavirus are currently lacking in Switzerland. In Germany the viral and parasitic IID norovirus, rotavirus, giardiasis and cryptosporidiosis are also notifiable besides some bacterial IID (RKI 2016). This allows Germany to investigate unusual observations in the epidemiology of these IID in more detail e.g. the sudden increase of human norovirus infections at the end of 2016 (Niendorf *et al.* 2017). The introduction of a mandatory reporting for selected viral and parasitic IID in Switzerland would: (i) increase the knowledge on how these diseases present in the population and (ii) allow a better detection of outbreaks caused by these diseases than with the current procedures i.e. reporting of unusual observations by physicians and laboratories.

The identification of infectious causes of AG in stool was done by pathogen-specific diagnostics with different methodologies until the development of multiplex PCR panels for IID at the end of the 2000s (Chapter 1.5.3). Today, human stool specimens can be tested for a variety of IID with a single test. Multiplex PCR panels for the diagnosis of IID are becoming increasingly popular. The Swiss NNSID could profit of this development by including so far non-notifiable IID in the mandatory reporting system which are part of such panels. These non-notifiable IID are now tested with such panels anyway while in the past specific single tests had to be conducted. At least norovirus and rotavirus could be easily monitored in Switzerland as they are part of most commercially available multiplex PCR panels (Binnicker 2015, Spina *et al.* 2015). In summary, it would be clearly beneficial for Switzerland to monitor some currently non-notifiable IID given the resulting knowledge gain and the recent developments in the diagnostic sector. Yet, the increasing use of multiplex PCR panels likely leads to a decrease in the number of pathogen isolates available for outbreak investigations or antimicrobial susceptibility testing which needs to be considered for corresponding surveillance systems (Langley *et al.* 2015).

10.1.5. Case management of patients suffering from acute gastroenteritis and campylobacteriosis

Results of the *Sentinella* study showed that around 12% of AG patients consulting at the primary care level have a stool test performed compared to a median of 18% in the qualitative GP study (Chapter 7and 8). From the perspective of the NNSID i.e. surveillance it would be much more beneficial if every patient would get tested. This way, notified cases would likely be more representative for the primary care level. Yet, conventional

diagnostic methods such as stool cultures or single PCRs can fail to detect an infectious agent in more than 50% of faecal specimens from AG patients (Huhulescu *et al.* 2009, Karsten *et al.* 2009, Tam *et al.* 2012b). Hence, such an approach is only of limited benefit as there are considerable costs associated with stool diagnostics (Chapter 9).

As discussed earlier, multiplex PCR panels for the detection of IID in faecal specimens advance and are now frequently offered for routine diagnostics. They have the potential to replace culture, microscopy and antigen methods for the detection of IID in the clinical setting due to the faster availability of results and the lower labour costs (Schreckenberger and McAdam 2015, Rochat *et al.* 2017). This could lead to an increase in the number of AG patients tested for IID. However, these panels are not beneficial to every AG patient (passage and non-viable pathogens) and their deployment or not should be carefully considered by the physician in charge (Schreckenberger and McAdam 2015, Rochat *et al.* 2017).

The treatment by antibiotic therapy is only recommended for very severe cases of AG with e.g. inflammatory and invasive bacterial IID while symptomatic treatment incl. oral rehydration therapy or antidiarrhoeals belongs to the standard treatment approach for AG patients (DuPont 2009, 2014, Zollner-Schwetz and Krause 2015). The vast majority of AG patients consulting at the Swiss primary care level requires supportive symptomatic treatment and around 1 out of 10 patients is additionally treated with antibiotics (Chapter 7 and 8). A Polish study found that 15.6% of AG cases visiting a GP received antibiotic therapy (Stefanoff *et al.* 2013). Close to two-third of laboratory-confirmed and registered campylobacteriosis cases are treated with antibiotics in Switzerland

(Chapter 4). Cases suffering from severe campylobacteriosis are more likely to be tested and hence, are more likely to be registered in the NNSID. This puts the antibiotic treatment rate of campylobacteriosis cases into perspective.

In Switzerland, roughly 60% of AG patients and 50% of campylobacteriosis patients receiving antibiotic therapy are treated with quinolones (Chapter 8). This practice is highly questionable as human *Campylobacter* isolates show high levels of resistance to fluoroquinolones in Switzerland and Europe in general (FOPH and FSVO 2016, EFSA and ECDC 2017). Niederer *et al.* (2012) also showed that in Switzerland resistance to quinolones is higher among *Campylobacter* isolates from travel-associated cases (56%) than from domestic cases (39%). The ECDC does not anymore recommend fluoroquinolones for the empirical treatment of campylobacteriosis due to the high level of resistance (EFSA and ECDC 2017). AG – if clinically indicated – and campylobacteriosis are nowadays best treated with azithromycin (macrolide) (Zollner-Schwetz and Krause 2015). Considering that mostly elderly suffer from severe campylobacteriosis the treatment with effective antibiotics is important to reduce morbidity among the elderly (Chapter 4 and 8).

The Strategy on Antibiotic Resistance Switzerland calls for a prudent use of antibiotics: they should be used carefully and if really indicated (The Federal Council 2015). The results of the studies conducted indicate that there is likely a potential to further reduce the use of antibiotics for the case management of patients suffering from AG and bacterial IID. Consequently, antibiotic treatment practices for AG and campylobacteriosis patients in Switzerland should be re-considered and routine antibiotic resistance testing for bacterial IID would be advisa-

ble for an effective case management. The development of national guidelines for the case management of AG and campylobacteriosis cases appears to be necessary given these circumstances.

The high rate of resistance against quinolones among *Campylobacter* spp. highlights the need for a routine antibiotic resistance monitoring of bacterial IID. In Switzerland, antibiotic resistance monitoring of *Campylobacter* spp. and *Salmonella* spp. (and many other human pathogens) is already done by the Swiss Centre for Antibiotic Resistance in Bern (FOPH and FSVO 2016). The centre compiles the results from antibiotic resistance testing of the major diagnostic laboratories and hospitals in Switzerland resulting in a comprehensive and representative overview. Similarly, the ECDC collects antibiotic resistance monitoring data of EU member states and publishes the results of the monitoring in an annual report (EFSA and ECDC 2017). National guidelines for the case management of AG and campylobacteriosis could be adapted based on this surveillance if necessary.

Antibiotic resistance is currently assessed by the phenotype of bacterial isolates which are collected during the application of conventional diagnostic methods such as stool cultures (Platts-Mills *et al.* 2013). So how can isolates of IID for antibiotic resistance monitoring be acquired if the future diagnostic of choice could shift to multiplex PCR panels? A possibility is the antimicrobial susceptibility testing of isolates gained from stool samples tested positive by multiplex PCR panels. A recent study showed that this is a very promising approach and isolates for antimicrobial susceptibility testing could be recovered from 71% of stool samples tested positive for *Campylobacter jejuni*, *Salmonella* spp., *Shigella* spp.,

enteroinvasive *Escherichia coli* and *Yersinia enterocolitica* by multiplex PCR (van Lint *et al.* 2016).

In the future, the detection of antibiotic resistance genes by PCR or WGS together with knowledge on the phenotypic expression could provide a very fast tool for the identification of clinically relevant antibiotic resistance (Platts-Mills *et al.* 2013). Yet, this approach will still rely on the relationship of genes and phenotypic expression and hence, will likely complement and not replace phenotypic testing (Platts-Mills *et al.* 2013).

10.2. Control measures to reduce the burden of human campylobacteriosis in Switzerland

Human campylobacteriosis is a known public health problem in Switzerland since many years but received little attention so far. The FSVO launched the so-called "*Campylobacter* platform" to tackle the problem by a One Health approach in December 2008 (FVO 2009). The multi-sectoral platform consisted of federal and cantonal authorities, researchers, scientist and the poultry industry and *"was established to identify and close any gaps in knowledge, to re-launch the control of Campylobacter and finally to reduce the disease burden in humans"* (FVO 2009). In 2016, the platform was abolished and the focus lies now on distinct interventions to reduce the disease burden (BLV 2016b).

Studies initiated by the platform included the case-control study on risk factors for contracting campylobacteriosis of this thesis (Chapter 4) and others (Kittl *et al.* 2011, Kittl *et al.* 2013a, Jonas *et al.* 2015). These studies collectively showed that the majority of human campylobacteriosis cases in Swit-

zerland is related to the poultry reservoir confirming results from other studies from Europe (EFSA Panel on Biological Hazards 2010, Domingues *et al.* 2012). Specifically, the case-control study of this thesis could epidemiologically proof that the consumption of meat fondue – especially if consumed with chicken meat – is an important risk factor for a *Campylobacter* infection in Switzerland over Christmas and New Year when case notifications show a distinct increase (Chapter 4). Also in other European countries an increase in the number of notified cases is observed at this time and the consumption of meat fondues or table top grillings appears to be a considerable risk factor given the increasing use of inexpensive poultry meat (Chapter 5).

Bearth *et al.* (2013, 2014b, a) showed that poultry consumers in Switzerland are generally well aware of the microbial contamination of poultry meat (e.g. *Campylobacter*) and associated mitigation measures for the preparation of poultry meat. However, food safety behaviour especially regarding the avoidance of cross-contamination is often insufficient due to misconceptions and knowledge gaps. Exact adherence to mitigation measures is even lower at special occasions such as barbecues or meat fondues.

The Swiss poultry industry's own efforts to tackle the problem included implementing stricter biosafety measures to prevent the infection of flocks on broiler farms or hygiene measures to prevent the contamination of chicken meat with *Campylobacter* at the slaughter and processing levels (FVO 2009). Unfortunately, these efforts were of rather limited success. Campylobacteriosis case numbers notified to the NNSID continued to rise during this time (Schmutz *et al.* 2016). Consequently, measures to reduce the exposure to

Campylobacter spp. targeting the slaughter, processing, preparation and consumption of chicken meat were promoted by the platform:

- Freezing of chicken liver from campylobacter-positive flocks
- Process hygiene criterion for the *Campylobacter* load on broiler carcasses
- Hygiene note on the packaging of fresh chicken meat products
- Information campaign on the safe preparation and consumption of chicken meat for consumers

As already mentioned, several studies proved that the major source for human campylobacteriosis in Switzerland is chicken meat. Hence, control measure to reduce the human campylobacteriosis burden need to focus on the transmission of *Campylobacter* spp. along the farm-to-fork chain i.e. from broiler farms over slaughter and retail levels to the consumer level.

10.2.1. Control measures along the poultry production chain

Biosafety measures e.g. ante-rooms and disinfection for boots for personnel aim at preventing the introduction of pathogens such as *Campylobacter* spp. into broiler flocks (Wagenaar *et al.* 2013). Fly screens at possible entry points for flies e.g. ventilation systems lead to a reduced prevalence of campylobacter-positive flocks, too (Hald *et al.* 2007). But even with the application of strict biosecurity measures broiler flocks can become campylobacter-positive until slaughter as *Campylobacter* spp. is present all over in the environment of broiler houses

(Wagenaar *et al.* 2013). The implementation of stricter biosecurity measures by the Swiss poultry industry did also not have the desired effects as previously mentioned (FVO 2009).

A vaccine preventing the colonisation of broilers by *Campylobacter* spp. would be an ideal solution to reduce the disease burden in humans (Wagenaar *et al.* 2013, Johnson *et al.* 2017). Several vaccine candidates are currently tested but until today there is no vaccine on the market to reduce the load of *Campylobacter* spp. in broilers (Johnson *et al.* 2017). Trials with a vaccine candidate for broilers are on the way in Switzerland (Malcisbo AG 2017). Yet, the development is still at the beginning and further trials will have to be conducted to prove effectiveness on the farm level.

Another approach would be to eliminate *Campylobacter* spp. from broiler flocks by phage therapy with specific bacteriophages but this approach still needs further research before it can be applied on broiler farms (Janez and Loc-Carrillo 2013). Broiler carcasses after slaughter or chicken meat before packaging can already be treated with bacteriophages in some countries (Endersen *et al.* 2014). However, different risk assessments suggest that a reduced prevalence of *Campylobacter* spp. among broiler flocks does only lead to a minor reduction of the incidence in humans (Golz *et al.* 2014).

Since January 2014, only chicken liver originating from campylobacter-negative flocks can be sold fresh in Switzerland while the one from positive flocks needs to be frozen prior to be sold at retail (EDI 2016a). Freezing chicken meat has been proven several times to be effective in lowering the quantitative load of *Campylobacter* on the meat and thereby reducing the risk for consumers (EFSA Panel on Biological Hazards 2011).

Additionally, a process hygiene criterion for the *Campylobacter* load on broiler carcasses at the end of the slaughter process (after chilling) was introduced with the new hygiene ordinance at the beginning of May 2017 including a transition period until 30 April 2018 (EDI 2016a). The limit for the process hygiene criterion is 2.5 $\log_{10}$ colony-forming units (CFU) of *Campylobacter* per gram (g) of broiler skin and applies to the arithmetic mean of the $\log_{10}$ of a minimum of 5 pooled samples (10g of neck skin and 10g of breast skin per carcass from 3 carcasses per flock) per day. If the measured value is above the limit the slaughterhouses have to adopt measures such as improvements of slaughter hygiene, measures for germ reduction, and reviewing the process control, the origin of broilers and biosafety measures on the farms of origin. Distinct control measures are not mandatory at the slaughter stage and chicken meat producers can decide by themselves how they want to reduce contamination levels of *Campylobacter* spp. as long as they reach acceptable contamination levels.

The EU adapted a similar process hygiene criterion incl. the adoption of measures for improvement if the criterion is not met which enters into form as from 1 January 2018 (The European Commission 2017). The proposed limit of 3 $\log_{10}$ CFU/g could lead to a public health risk reduction of more than 50% if carcasses comply with this limit (EFSA Panel on Biological Hazards 2011, The European Commission 2017). The Swiss limit is even lower (2.5 $\log_{10}$ CFU/g) and a decrease of campylobacteriosis case numbers can theoretically be expected within the coming years.

Reducing the faecal leakage from and avoiding cross-contamination of carcasses during the slaughter process and

subsequent carcass processing steps are important points for low loads of *Campylobacter* spp. on chicken meat (Golz *et al.* 2014). Possibilities for the decontamination of carcasses at the end of the slaughter process include chemical decontamination (e.g. by lactic acids, acidified sodium chlorite, peracetic acid), freezing of broiler carcasses or irradiation (e.g. gamma rays) (EFSA Panel on Biological Hazards 2011, Golz *et al.* 2014). Most effective is irradiation leading to a risk reduction of 100% while chemical decontamination leads to a 50-90% risk reduction in regard to public health (EFSA Panel on Biological Hazards 2011). According to the federal law, only the chemical decontamination of bovine carcasses with lactic acids is currently allowed in Switzerland (EDI 2016c). Yet, it is in the responsibility of the FSVO to approve processes and chemicals for broiler carcass decontamination such as irradiation or chemical decontamination by acidified sodium chlorite or peracetic acid (Der Schweizerische Bundesrat 2016, EDI 2016c).

In summary, it appears to be most feasible today to decrease the *Campylobacter* spp. load on chicken meat below the limit of the hygiene criterion by chemical decontamination or irradiation at the end of the slaughter process. Especially considering that the implementation of stricter biosecurity measures on farms by the Swiss poultry industry was not successful in the past. Unfortunately Swiss consumers' preferences and acceptance are currently not well compatible with chemical decontamination. The Swiss and also the European consumers are rather opposed to the so-called "Chlorhühnchen" (Jordan and Stockley 2010, Baumgartner *et al.* 2012). Yet, in the absence of vaccines or phage therapies to eliminate *Campylobacter* spp. from broiler flocks, chemical decontami-

nation or irradiation seems the only promising way to reduce the burden of campylobacteriosis in Switzerland. An additional benefit of these decontamination methods would be the reduction of antibiotic resistant bacteria e.g. extended-spectrum beta-lactamase-producing *E. coli* which are frequently found on Swiss chicken meat (FOPH and FSVO 2016). Additionally, contamination limits for imported chicken meat should be considered in Switzerland despite imported chicken meat is significantly less contaminated with *Campylobacter* spp. than domestic chicken meat (Baumgartner and Felleisen 2011).

10.2.2. Prevention measures at the consumer and household level

The ordinance on food of animal origin obliges the producers in Switzerland to put a hygiene note on the correct handling of fresh poultry meat products on their packaging since January 2014 (EDI 2016b). The note informs the consumer that the fresh poultry meat products need to be thoroughly cooked before consumption and how they can be handled in a hygienic manner at home.

The information campaign "Richtig zubereiten - sicher geniessen" (Prepare properly – enjoy safely, see www.sichergeniessen.ch) is run by the FSVO and partners from the meat industry and retail business since 2016 (BLV 2016a). It covers all aspects in regard to the storage and preparation of raw foods such as meat, eggs, fish or seafood. The aim is to better prevent foodborne diseases especially campylobacteriosis by making 4 basic rules for kitchen hygiene known countrywide (heat properly, separate properly, wash properly, cool properly).

Further, the FSVO currently runs an annual campaign for the safe preparation and consumption of meat fondue before the festive season at the turn of the year which is similar to the campaign "Richtig zubereiten - sicher geniessen". One of the main recommendations is the use of two separate plates for raw and cooked meat to avoid cross-contamination (BLV 2017) which is supported by the case-control study results of this thesis (Chapter 4). Also before the barbeque season during summer the main hygiene messages of the campaign are communicated to the public.

10.2.3. Impact of measures implemented on the number of notified campylobacteriosis cases

All the aforementioned measures along the farm-to-fork chain are earliest in place since 2014 and the process hygiene criterion for the *Campylobacter* load on broiler carcasses – a very promising control measure – only since 2017[5]. The number of notified campylobacteriosis cases slightly increased from 2014 (7647 cases) to 2016 (7810 cases) with less notified cases in 2015 (6705 cases) (BAG 2017b). The campylobacteriosis winter peak that is observed around the turn of the year and which is related to the consumption of meat fondue was less pronounced in 2016/2017 compared to 2014/2015 and 2015/2016 (BAG 2017a). There is no direct evidence that this can be attributed to the campaign for the safe preparation and consumption of meat fondue and the information campaign "Richtig zubereiten - sicher geniessen" by the FSVO. Yet, an

[5] Introduction of process hygiene criterion 1 May 2017 with a transition period until 30 April 2018

impact of these campaigns appears to be likely. The results of the case-control study of this thesis received nationwide media attention (see Appendix 14.3) which likely also contributed to the risk awareness of the Swiss population.

However, it is too early to make a reliable statement on the influence of all the measures on the human disease burden of campylobacteriosis. A successful implementation of these measures should theoretically lead to a decrease in campylobacteriosis case numbers observed within the NNSID in the coming years. This effect was also observed when control measures for salmonellosis (e.g. mandatory screening of layer hens) were implemented in the 1990s (Schmutz *et al.* 2016). The success of the control measures for *Salmonella* spp. in the poultry sector showed that Switzerland has the potential to control zoonotic diseases with a One Health approach. A reduction of campylobacteriosis case numbers should also be possible with the control measures implemented for campylobacteriosis.

Costs and benefits of the cross-sectorial approach to *Campylobacter* mitigation by the *Campylobacter* platform were assessed for the first time by Babo Martins *et al.* (2017). Costs for the overall mitigation activities – mainly commissioned research and surveillance activities in humans and animals – between 2009 and 2013 were estimated at 1.85 million CHF (370,000 CHF per year) (Babo Martins *et al.* 2017). The estimated human disease burden of campylobacteriosis in Switzerland increased from 1609–2756 DALYs in 2008 to 1751–2852 DALYs in 2013 (Babo Martins *et al.* 2017). As mentioned before, *Campylobacter* control measures targeting the food chain are in place earliest since 2014. A cross-sectorial economic assessment using the same methodological framework should be performed again in the

coming years to assess the cost and benefits of control measures implemented along the farm-to-fork chain.

Case notifications at the end of 2019 should be compared with the previous years as the process hygiene criterion for *Campylobacter* spp. will then be in place nationwide for more than a year[6] and case numbers could be already declining. When assessing the impact of measures implemented by the analysis of NNSID case notifications positivity rates and diagnostics applied (culture methods vs. PCR) should be considered (Chapter 10.1.3). Unfortunately the NNSID does not collect any information that would allow distinguishing between autochthonous and travel-associated campylobacteriosis cases. This would be ideal to gather a better picture of the impact of the control measures applied on NNSID case numbers.

Currently, 40 to 84% of human campylobacteriosis cases in Switzerland originate from the poultry reservoir (Kittl *et al.* 2011, Kittl *et al.* 2013a, Jonas *et al.* 2015). If control measures are successful, the proportion of chicken-associated cases will likely decrease and hence, a decline in case numbers can be expected. Sources of infections should be assessed in the future by genetic source attribution studies as already previously done in Switzerland. Although the majority of human campylobacteriosis cases in Switzerland currently originates from the poultry reservoir other sources of infection such as raw milk or contaminated drinking water should not be neglected. These sources will likely require more attention to decrease the dis-

[6] Introduction of process hygiene criterion 1 May 2017 with a transition period until 30 April 2018

ease burden in Switzerland further if the control measures in the poultry sector have the desired effect.

10.3. Strengths and limitations of the research conducted

Each research component was conducted in the most appropriate way considering given financial, administrative, personal and temporal limitations. They were often implemented within running systems such as the NNSID or *Sentinella* which was often not straightforward and required reasonable compromises for implementation. On the other hand, this allowed gaining reliable and valid results for and insights into these systems for public health authorities and researchers. Major strengths and limitations of the chosen research approach are outlined below and detailed strengths and limitations of individual research components can be found in the corresponding result chapters (Chapter 4 to 9).

The case-control study (Chapter 4), the analysis of TESSy surveillance data (Chapter 5), the analysis of positivity rates (Chapter 6) and the estimation of health care costs (Chapter 9) (partially) relied on notified and laboratory-confirmed campylobacteriosis cases. These cases represent only a subgroup of campylobacteriosis cases as cases with mild disease progression are less likely to consult a physician or to be tested for campylobacteriosis and, hence, less likely to be notified. Therefore, generated research results are often highly reliable for laboratory-confirmed cases while the results might not always be directly transferable to cases with mild disease.

Laboratory-confirmed cases for the case-control study and laboratory data for the analysis of positivity rates originated from private laboratories which operate on a regional or national

level and predominantly serve the practices of GPs and medical specialists. The catchment population of the participating laboratories was not known and hospital-based laboratories were not included. As a result, the hospitalisation rate and the proportion of patients approaching emergency departments and policlinics directly as estimated by the case-control study may be underestimated. An estimation of stool sampling rates and an assessment of the representativeness of the patient population could not be done given the aforementioned circumstances. Cases included in the analysis of positivity rates and notified cases were comparable and hence, estimated positivity rates are likely to represent accurately the epidemiological trends and situation in Switzerland.

A mainly descriptive approach was chosen for the analysis of positivity rates and for the analysis of TESSy surveillance data. This approach produced reliable and solid descriptive results for the understanding of *Campylobacter* transmission dynamics and the disease presentation at the laboratory and surveillance level. However, more sophisticated analysis by a time-series model taking into account endemic and epidemic behaviours and seasonality of laboratory and surveillance data would have been an option, too. This was previously done for Swiss campylobacteriosis notification data but results were similar to another descriptive analysis (Wei *et al.* 2015, Schmutz *et al.* 2016). In summary, using a time-series model like suggested would likely not have added new insights compared to the approaches applied.

The combination of a qualitative and a quantitative study at the primary care level (Chapter 7 and 8) provided an ideal and unique opportunity to assess the presentation and case management of campylobacteriosis and AG patients and the

associated disease burden at the primary care level. First, a qualitative approach was chosen due to the lack of knowledge on AG and campylobacteriosis at the primary care level in Switzerland. This first approach generated valuable results for the planning, design and content of the following quantitative approach. Yet, it only allowed for first semi-quantitative estimates on the disease burden and important determinants for the NNSID such as the stool testing rate by GPs. The disease burden and determinants for the NNSID at the primary care level were subsequently quantified by the quantitative study within *Sentinella*. The combination of these approaches allowed to cross-validate study results increasing their reliability and significance.

The estimation of health care costs due to campylobacteriosis and AG (Chapter 9) was the first of its kind done so far for Switzerland. Only direct health care costs of campylobacteriosis and AG were considered. Costs associated with patients not consulting at the primary care level, hospitalisations due to other IID than campylobacteriosis or sequela (e.g. Guillain–Barré syndrome, reactive arthritis or irritable bowel syndrome) were not considered as corresponding information was often lacking. The calculations performed were based on several assumptions and own (preliminary) research results leading to a rather wide range of estimated costs. Estimates were cross-validated whenever possible by combining different data sources e.g. official hospital statistics or real patient data from the Swiss TPH's travel clinic. As a result, the estimated costs are rather conservative i.e. likely underestimate the real health care costs for campylobacteriosis and AG.

11. Conclusion

This is the first comprehensive assessment of the epidemiology of human campylobacteriosis and AG in Switzerland considering also related data from the NNSID. The consumption of meat fondue especially if consumed with chicken meat and travelling abroad are important drivers for the observed campylobacteriosis peak around the turn of the year. The consumption of meat fondues or table top grillings is likely to play a similar role in other European countries with increased case numbers during this period of time. Human campylobacteriosis and AG cause a considerable disease burden in the primary care setting and at the hospital level. Epidemiological trends of campylobacteriosis are accurately reflected by surveillance data from the NNSID. The number of annually notified campylobacteriosis cases remains on a high level although the *Campylobacter* problem figures high on the agenda of the Swiss authorities and poultry industry since many years. This high disease burden within the Swiss health system results in substantial health care costs. Yet, the exact burden of AG and campylobacteriosis in the community and the specific disease burden of other IID than campylobacteriosis remain largely unclear. Hence, there is a clear need to assess the presentation and disease and economic burden of AG and IID at the community level given the unknown situation at this level of the burden-of-illness pyramid.

Swiss public health authorities should regularly re-assess determinants of the burden-of-illness pyramid (health care seeking, stool testing and positivity rates) to strengthen the surveillance of IID by the NNSID especially considering the ongoing changes in diagnostics applied and test numbers obtained. Additionally, the sentinel surveillance network

Sentinella would provide an ideal tool for the routine surveillance of AG at the Swiss primary care level. Yet, it is currently not suitable for the surveillance of specific IID.

Laboratory-confirmed campylobacteriosis cases and many AG patients suffer from a severe course of disease and a considerable proportion - especially elderly - requires hospitalisation and/or antibiotic therapy. Around 60% of AG patients and 50% of campylobacteriosis patients receiving antibiotic therapy are treated with quinolones although more than 50% of *Campylobacter* spp. – the most common cause of bacterial AG in Switzerland - are resistant to fluoroquinolones. Public health authorities in partnership with medical associations should consider developing national case management guidelines including antibiotic therapy recommendations for patients suffering from AG and IID.

11.1. Recommendations

- The epidemiology and disease and socioeconomic burden of AG and IID at the community level in Switzerland should be assessed e.g. by a population-based longitudinal study.
- Sporadic cases of viral IID – at least due to norovirus and rotavirus – should be notifiable and reported to the NNSID as surveillance data on viral IID of public health importance is lacking so far.
- AG at the primary care level should be monitored through the *Sentinella* network similar to ILI. This would allow a regular assessment of the burden and epidemiology of AG which are not well known so far.
- If the current control measures do not lead to the desired reduction of human campylobacteriosis in Switzerland stricter or additional control measures along the food chain need to be considered e.g. a lower limit for the process hygiene criterion or mandatory chemical decontamination or irradiation.

12. Outlook

The research approach applied in this PhD was not conceptualised to assess the presentation and the disease and socioeconomic burden of AG, campylobacteriosis and other IID at the community level in Switzerland. The *Sentinella* study provides only an estimate for the disease burden at the Swiss primary care level (Chapter 8). Many cases suffering from AG or IID will not contact a GP during their course of illness but are also significantly contributing to the overall national disease and socioeconomic burden. To know how AG and IID present at the community level is crucial to strengthen the interpretation of surveillance data from the NNSID and to estimate the overall national disease and socioeconomic burden of IID.

A longitudinal population-based study would be the ideal study design to close this knowledge gap. A study protocol for such a study was developed within the Household Health Systems Research Group during this PhD and funding from the FOPH and FSVO was already in parts received to conduct the study. The findings of this PhD work in concert with the forthcoming results and lessons learnt from the said population-based cohort study on AG will soon contribute to an even better understanding of the epidemiology and the disease and socioeconomic burden of AG and IID in Switzerland.

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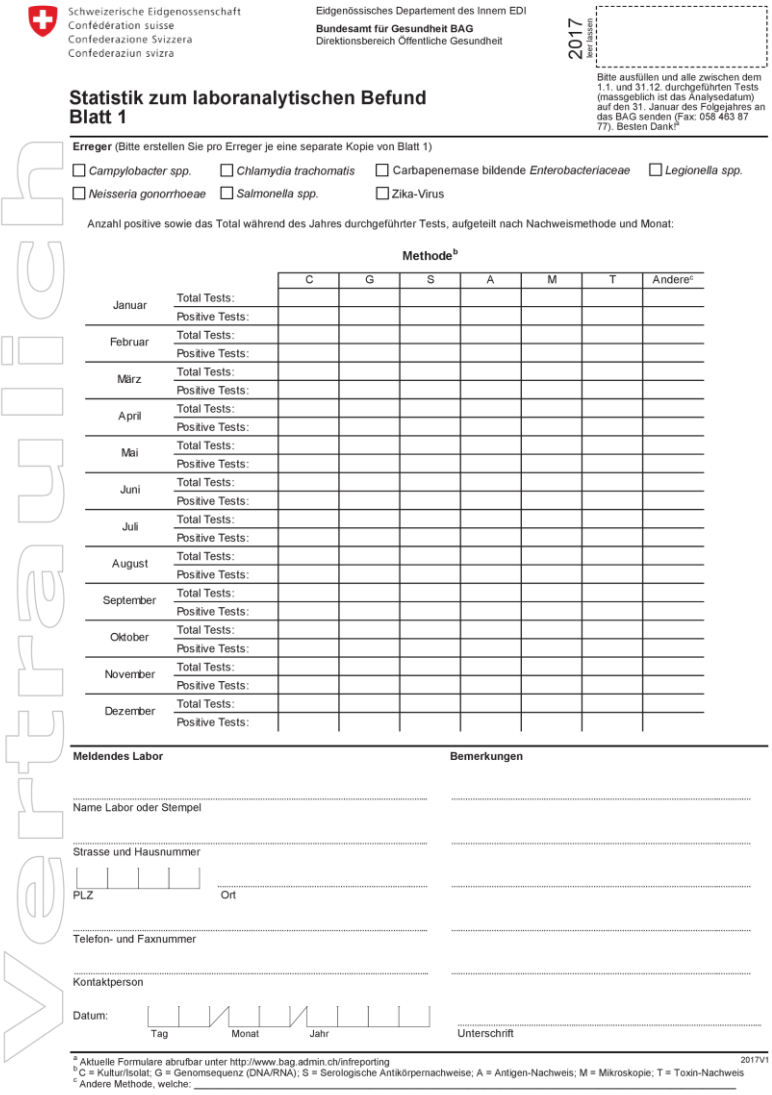
14. Appendices

14.1. Reporting form for laboratory statistics



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2017
bleer lassen

Bitte ausfüllen und alle zwischen dem 1.1. und 31.12. durchgeführten Tests (massgeblich ist das Analysedatum) auf den 31. Januar des Folgejahres an das BAG senden (Fax: 058 463 87 77). Besten Dank[a]

Statistik zum laboranalytischen Befund
Blatt 1

Erreger (Bitte erstellen Sie pro Erreger je eine separate Kopie von Blatt 1)

☐ *Campylobacter spp.* ☐ *Chlamydia trachomatis* ☐ Carbapenemase bildende *Enterobacteriaceae* ☐ *Legionella spp.*
☐ *Neisseria gonorrhoeae* ☐ *Salmonella spp.* ☐ Zika-Virus

Anzahl positive sowie das Total während des Jahres durchgeführter Tests, aufgeteilt nach Nachweismethode und Monat:

Methode[b]

		C	G	S	A	M	T	Andere[c]
Januar	Total Tests:							
	Positive Tests:							
Februar	Total Tests:							
	Positive Tests:							
März	Total Tests:							
	Positive Tests:							
April	Total Tests:							
	Positive Tests:							
Mai	Total Tests:							
	Positive Tests:							
Juni	Total Tests:							
	Positive Tests:							
Juli	Total Tests:							
	Positive Tests:							
August	Total Tests:							
	Positive Tests:							
September	Total Tests:							
	Positive Tests:							
Oktober	Total Tests:							
	Positive Tests:							
November	Total Tests:							
	Positive Tests:							
Dezember	Total Tests:							
	Positive Tests:							

Meldendes Labor

Name Labor oder Stempel

Strasse und Hausnummer

PLZ Ort

Telefon- und Faxnummer

Kontaktperson

Datum: Tag Monat Jahr

Bemerkungen

Unterschrift

[a] Aktuelle Formulare abrufbar unter http://www.bag.admin.ch/infreporting 2017V1
[b] C = Kultur/Isolat; G = Genomsequenz (DNA/RNA); S = Serologische Antikörpernachweise; A = Antigen-Nachweis; M = Mikroskopie; T = Toxin-Nachweis
[c] Andere Methode, welche: _____

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Statistik zum laboranalytischen Befund Blatt 2

Francisella tularensis

Total aller während des Jahres durchgeführter Tests: .....

Davon Anzahl **positive** Tests: .....

Davon Anzahl **negative** Tests: .....

HI-Virus

Total aller während des Jahres durchgeführter Tests[b]: .....

Davon Anzahl **reaktive** Tests: .....

Davon Anzahl **bestätigt**[c] **positive** Tests: .....

Meldendes Labor

Name Labor oder Stempel

Strasse und Hausnummer

PLZ Ort

Telefon- und Faxnummer

Kontaktperson

Datum: Tag Monat Jahr

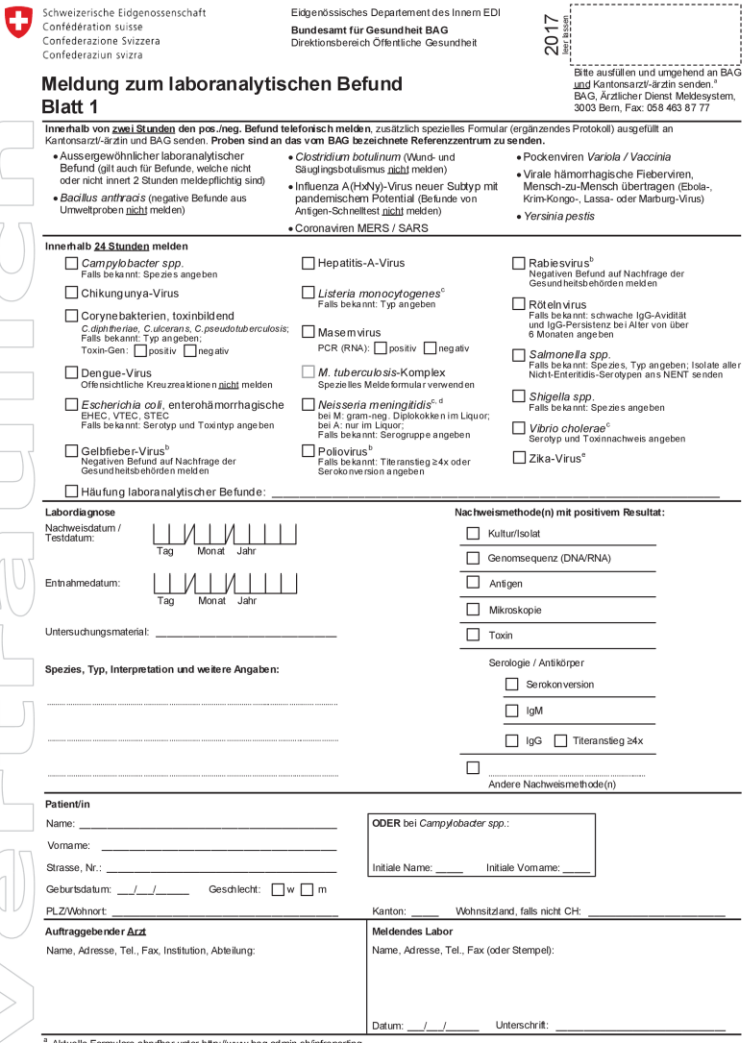
Bemerkungen

Unterschrift

[a] Aktuelle Formulare abrufbar unter http://www.bag.admin.ch/infreporting
[b] ohne Tests im Rahmen der Blutspende
[c] In einem Bestätigungslabor (gemäss HIV-Testkonzept)

2017V1

14.2. Reporting form for laboratory diagnoses of notifiable diseases



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BAG Blatt 1

Bitte ausfüllen und umgehend an BAG und Kantonsarzt/-ärztin senden.[a]
BAG, Ärztlicher Dienst Meldesystem, 3003 Bern, Fax: 058 463 87 77

Meldung zum laboranalytischen Befund
Blatt 1

Innerhalb von zwei Stunden den pos./neg. Befund telefonisch melden, zusätzlich spezielles Formular (ergänzendes Protokoll) ausgefüllt an Kantonsarzt/-ärztin und BAG senden. **Proben sind an das vom BAG bezeichnete Referenzzentrum zu senden.**

- Aussergewöhnlicher laboranalytischer Befund (gilt auch für Befunde, welche nicht oder nicht innert 2 Stunden meldepflichtig sind)
- *Bacillus anthracis* (negative Befunde aus Umweltproben nicht melden)
- *Clostridium botulinum* (Wund- und Säuglingsbotulismus nicht melden)
- Influenza A(HxNy)-Virus neuer Subtyp mit pandemischem Potential (Befunde von Antigen-Schnelltest nicht melden)
- Coronaviren MERS / SARS
- Pockenviren *Variola / Vaccinia*
- Virale hämorrhagische Fieberviren, Mensch-zu-Mensch übertragen (Ebola-, Krim-Kongo-, Lassa- oder Marburg-Virus)
- *Yersinia pestis*

Innerhalb 24 Stunden melden

- ☐ *Campylobacter spp.* — Falls bekannt: Spezies angeben
- ☐ Chikungunya-Virus
- ☐ Corynebakterien, toxinbildend — *C.diphtheriae, C.ulcerans, C.pseudotuberculosis*; Falls bekannt: Typ angeben; Toxin-Gen: ☐ positiv ☐ negativ
- ☐ Dengue-Virus — Offensichtliche Kreuzreaktionen nicht melden
- ☐ *Escherichia coli*, enterohämorrhagische — EHEC, VTEC, STEC; Falls bekannt: Serotyp und Toxintyp angeben
- ☐ Gelbfieber-Virus[b] — Negativen Befund auf Nachfrage der Gesundheitsbehörden melden
- ☐ Hepatitis-A-Virus
- ☐ *Listeria monocytogenes*[c] — Falls bekannt: Typ angeben
- ☐ Masernvirus — PCR (RNA): ☐ positiv ☐ negativ
- ☐ *M. tuberculosis*-Komplex — Spezielles Meldeformular verwenden
- ☐ *Neisseria meningitidis*[c, d] — bei M: gram-neg. Diplokokken im Liquor; bei A: nur im Liquor; Falls bekannt: Serogruppe angeben
- ☐ Poliovirus[b] — Falls bekannt: Titeranstieg ≥4x oder Serokonversion angeben
- ☐ Rabiesvirus[b] — Negativen Befund auf Nachfrage der Gesundheitsbehörden melden
- ☐ Rötelnvirus — Falls bekannt: schwache IgG-Avidität und IgG-Persistenz bei Alter von über 6 Monaten angeben
- ☐ *Salmonella spp.* — Falls bekannt: Spezies, Typ angeben; Isolate aller Nicht-Enteritidis-Serotypen ans NENT senden
- ☐ *Shigella spp.* — Falls bekannt: Spezies angeben
- ☐ *Vibrio cholerae*[c] — Serotyp und Toxinnachweis angeben
- ☐ Zika-Virus[e]

☐ Häufung laboranalytischer Befunde: _____

Labordiagnose

Nachweisdatum / Testdatum: ☐☐/☐☐/☐☐☐☐ (Tag / Monat / Jahr)

Entnahmedatum: ☐☐/☐☐/☐☐☐☐ (Tag / Monat / Jahr)

Untersuchungsmaterial: _____

Spezies, Typ, Interpretation und weitere Angaben:

.....

.....

.....

Nachweismethode(n) mit positivem Resultat:

- ☐ Kultur/Isolat
- ☐ Genomsequenz (DNA/RNA)
- ☐ Antigen
- ☐ Mikroskopie
- ☐ Toxin

Serologie / Antikörper

- ☐ Serokonversion
- ☐ IgM
- ☐ IgG ☐ Titeranstieg ≥4x

☐ _____ Andere Nachweismethode(n)

Patient/in

Name: _____

Vorname: _____

Strasse, Nr.: _____

Geburtsdatum: __/__/_____ Geschlecht: ☐ w ☐ m

PLZ/Wohnort: _____ Kanton: _____ Wohnsitzland, falls nicht CH: _____

ODER bei *Campylobacter spp.*:

Initiale Name: _____ Initiale Vorname: _____

Auftraggebender Arzt

Name, Adresse, Tel., Fax, Institution, Abteilung:

Meldendes Labor

Name, Adresse, Tel., Fax (oder Stempel):

Datum: __/__/_____ Unterschrift: _____

[a] Aktuelle Formulare abrufbar unter http://www.bag.admin.ch/infreporting.
[b] Proben sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[c] Isolate sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[d] Nur von normalerweise sterilem Material (Blut, Liquor, Gelenkflüssigkeit; *kein* Urin).
[e] Proben von Schwangeren sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.

2017V1.1

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Bitte ausgefüllt innerhalb 1 Woche an BAG und Kantonsärztin/-arzt senden.[a]
BAG, Ärztlicher Dienst Meldesystem, 3003 Bern, Fax: 058 463 87 77

Meldung zum laboranalytischen Befund
Blatt 2

Innerhalb einer Woche melden

- ☐ *Brucella spp.* — Falls bekannt: Spezies angeben
- ☐ *Chlamydia trachomatis* — Nur Befunde aus Proben des Genitaltrakts melden
- ☐ *Coxiella burnetii* — Nur akute Infektionen melden; bei S: nur Angaben zu spezifischen IgG und IgM gegen Antigene der Phase II
- ☐ Carbapenemase bildende Enterobacteriaceae — Falls bekannt: Spezies, Genotyp, Carbapenemase Klasse A, B, D, Colistin-Resistenz angeben
- ☐ *Francisella tularensis*
- ☐ *Haemophilus influenzae*[d] — Falls bekannt: Typ angeben
- ☐ Hanta-Virus — Falls bekannt: Typ angeben
- ☐ Hepatitis-B-Virus — ☐ Anti-HBc-IgM ☐ HBs Ag ☐ HBe Ag
- ☐ Hepatitis-C-Virus — ☐ Anti-HCV mit pos. Bestätigungstest ☐ Core-Antigen
- ☐ HIV — Spezielles Meldeformular verwenden
- ☐ Influenzavirus, saisonal — Falls bekannt: Typ/Subtyp angeben
- ☐ *Legionella*[c]
- ☐ *Neisseria gonorrhoeae*
- ☐ *Plasmodium spp.* — Falls bekannt Spezies angeben
- ☐ Prionen[f] — ☐ Histologie ☐ PrP^{SC}-Nachweis ☐ 14-3-3 Proteine im Liquor bei CJD-Verdacht
- ☐ *Streptococcus pneumoniae*[c, d] — Falls bekannt: Typ angeben
- ☐ *Treponema pallidum* — ☐ VDRL/RPR[g] ☐ TPHA/TPPA[g] ☐ FTA-Abs ☐ EIA/ELISA/CLIA/ECLIA (weitere Methoden unten angeben)
- ☐ *Trichinella spiralis* — Falls bekannt: Spezies angeben
- ☐ West-Nil-Virus (WNV)[b] — Falls bekannt: Unterscheidung WNV/Kunjin; Falls WNV: Abstammungslinie I oder II angeben
- ☐ Zeckenenzephalitisvirus

Labordiagnose

Nachweisdatum / Testdatum: ___/___/_____ (Tag Monat Jahr)

Entnahmedatum: ___/___/_____ (Tag Monat Jahr)

Untersuchungsmaterial: _____

Spezies, Typ, Interpretation und weitere Angaben:

.....

.....

.....

Nachweismethode(n) mit positivem Resultat:

- ☐ Kultur/Isolat
- ☐ Genomsequenz (DNA/RNA)
- ☐ Antigen
- ☐ Mikroskopie
- ☐ Toxin

Serologie / Antikörper

- ☐ Serokonversion
- ☐ IgM
- ☐ IgG ☐ Titeranstieg ≥4x
- ☐ ..... Andere Nachweismethode(n)

Patient/in

Initiale Name: ____ Initiale Vorname: ____

Geburtsdatum: ___/___/_____ Geschlecht: ☐ w ☐ m

PLZ/Wohnort: _____ Kanton: ____ Wohnsitzland, falls nicht CH: _____

ODER bei HBV, HCV, *Legionella spp.* und Prionen:

Name: _____ Vorname: _____

Strasse, Nr.: _____

Auftraggebender Arzt

Name, Adresse, Tel., Fax, Institution, Abteilung:

Meldendes Labor

Name, Adresse, Tel., Fax (oder Stempel):

Datum: ___/___/_____ Unterschrift: _____

[a] Aktuelle Formulare abrufbar unter http://www.bag.admin.ch/infreporting.
[b] Proben sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[c] Isolate sind an das vom BAG bezeichnete Referenzzentrum weiterzuleiten.
[d] Nur von normalerweise sterilem Material (Blut, Liquor, Gelenkflüssigkeit; *kein* Urin).
[f] Proben sind bei Verdacht auf vCJK an das vom BAG bezeichnete Labor zu senden.
[g] Positive VDRL/RPR allein oder mit negativen spezifischen Tests (TPHA/TPPA, FTA-Antikörper) nicht melden.

2017V1.1

14.3. Selected articles in Swiss media

Durchfall hat immer Saison

Aktualisiert am Dienstag, 29. Dezember 2015, 9:11 Uhr

3 Kommentare

Campylobacter-Infektionen zählen weltweit zu den häufigsten Ursachen von Durchfallerkrankungen durch Lebensmittel. Das Bakterium hat nicht nur während der Grillzeit im Sommer Hochsaison – auch im Winter ist es für eine Häufung der Erkrankungen verantwortlich.

Verunreinigtes Pouletfleisch zählt zu den Hauptursachen für heftige Darmleiden. FOTOMONTAGE/COLOURBOX

Audio		
1	Keine schädlichen Keime auf dem Schneidebrett	3:10 min
2	«Das Geflügelfleisch beim Fondue Chinoise ist schuld»	3:03 min
3	Hygiene-Tipps fürs Grillieren	4:09 min

Jährlich werden in der Schweiz 7000 bis 8000 Durchfallerkrankungen durch Lebensmittel verzeichnet. Eine **Forschungsarbeit des Swiss TPH** belegt: Der häufigste Grund für eine Ansteckung ist rohes Fleisch, im speziellen Geflügelfleisch, das mit dem Campylobacter-Bakterium kontaminiert ist.

In der Studie stellte sich heraus, dass der Konsum von Fleischfondue (z.B. Fondue Chinoise) das Risiko einer Ansteckung erhöht – insbesondere, wenn dabei frisches Geflügelfleisch verwendet wird. Es zeigte sich auch, dass die Hälfte der Patientinnen und Patienten mindestens eine Woche krank war. Rund 15 Prozent der Erkrankten mussten stationär im Spital behandelt werden.

Source: https://www.srf.ch/sendungen/puls/alltag-umwelt/durchfall-hat-immer-saison, Accessed 22 November 2017

Das Poulet versaut uns die Feier

MYSTERIÖS ⇢ Über die Weihnachtstage erkranken jedes Jahr Tausende Schweizer. Jetzt ist das Rätsel gelöst. Schuld ist der Feiertagsschmaus.

Es ist der Feiertags-Klassiker schlechthin, das Fondue Chinoise. Zu Hunderttausenden sitzen Herr und Frau Schweizer über die Weihnachtstage mit Freunden und Familie gemütlich am festlich gedeckten Tisch. Und schlemmen. Nicht selten endet der fröhliche Abend aber unschön: Mit üblen Bauchkrämpfen auf dem Topf.

Jahr für Jahr erkranken in den Weihnachtsferien 7000 bis 8000 Schweizer an einer Campylobacter-Infektion. Diese auffällige Häufung brachte Experten und Ärzte ins Grübeln.

Nun hat das Schweizerische Tropen- und Public Health-Institut aus Basel das Rätsel gelöst. Und den Übeltäter entlarvt: Es ist das Fondue Chinoise. Genauer: Das rohe Poulet.

Die Forscher befragten für die Studie Personen, die zwischen Dezember 2012 und Februar 2013 an einer Campylobacter-Infektion erkrankt waren. Sie hätten dabei die Infektion als schwere Erkrankung beschrieben, die im Schnitt sieben Tage gedauert habe.

Das Bundesamt für Gesundheit (BAG) hat auch schon Tipps parat, damit die nächste Weihnachtsfeier ohne unschöne Abstecher auf die Toilette über die Bühne geht: **Getrennte Teller für rohes und gekochtes Poulet.** Damit soll das Infektionsrisiko um den Faktor fünf sinken. Zudem soll man zuvor gefrorenes Fleisch verwenden. **pbe**

Bleiben gesund
Weil sie beim Fondue Chinoise das Poulet weglassen.

Fotos: Dukas (2), ddp images, Panos Pictures/VISUM, AFP

Source: Blick am Abend, 04.07.2014, page 7